Original Research

A Pilot Study of Patients With COVID–19-Related Respiratory Failure Utilizing Airway Pressure Release Ventilation (APRV)

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ABSTRACT

Background: Pneumonia leading to acute respiratory distress syndrome (ARDS) is one of the devastating consequences of coronavirus disease 2019 (COVID-19). Airway pressure release ventilation (APRV) has been described as beneficial in acute lung injury and ARDS. We hypothesized that utilizing APRV would be advantageous in the COVID-19 ARDS population. **Methods:** Prospective, observational, single-center study. Data were extracted on demographics, vasopressors, sedatives, analgesics, and oxygenation (PaO2/FiO2). A generalized linear mixed models analysis was performed to compare low tidal volume ventilation (LTV) with APRV for patients who required intubation due to ARDS from COVID-19 and who were managed with at least 48 consecutive hours of APRV in our surgical intensive care unit (SICU). **Results:** Twelve patients met criteria; two were on APRV mode from admission to the SICU and were not included in the study. Ten patients were analyzed and were primarily male (70%), average age of 64.5 ± 12.9 years, and 70% were obese (average body mass index of 30.6 ± 8.0 kg/m^2). There were no smokers in the sample, but two patients presented with underlying lung pathology. APRV was shown to significantly increase the PaO_2/FiO_2 ratio by 30% (5% to 61%) ($p = 0.05$) and was associated with up to a 12% (–26% to 5%) reduction in the level of F_iO_2 and reduction in the use of vasopressor support (–59% [–83% to –2%]), sedatives (–15% [–29% to 2%]), and analgesics (–16% [–38% to 12%]). **Conclusions:** This pilot study showed that APRV was associated with decreases in FiO_2, vasopressors, sedatives, and analgesic requirements with an increase in PaO_2/FiO_2 ratio. In the current pandemic, where providers are grappling with ways to manage COVID-19 ARDS, APRV may be the optimal ventilator mode. Prospective randomized studies are required to validate whether use of APRV in the COVID-19 population leads to improved oxygenation and a subsequent decrease of ventilator days and length of stay.

Keywords: acute respiratory distress syndrome, airway pressure release ventilation, COVID-19, respiratory failure

INTRODUCTION

A mysterious disease erupted in late December 2019 thought to have originated in Wuhan, China.[1] It has rapidly evolved to create the first worldwide pandemic of the 21st century. The disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been termed "coronavirus disease 2019" (COVID-19) and quickly progressed into a pandemic that changed our way of life. As of July 20, 2020, the number of cases worldwide, according to the Johns Hopkins Coronavirus Resource Center COVID-19 Dashboard Web site by the Center for Systems Science and Engineering at Johns Hopkins University, was more than 14.5 million with 607,187 deaths and counting. In the United States, the number of people who tested positive was 3,794,355 and the death toll stood at 140,716. With the number of hospitalizations skyrocketing and a mortality rate of 3.4%, interventions that can prolong life are urgently needed. To date, no treatment modality has been shown

to be consistently effective. In fact, it appears that supporting the individual through the course of the disease may be the best opportunity for survival.

Patients with COVID-19 present with a variety of symptoms ranging from mild: loss of smell and taste, gastrointestinal upset, to severe: acute respiratory failure requiring intubation. Although the mechanism of lung injury remains unclear, the typical presenting symptom is that of refractory hypoxia. The pneumonia caused by COVID-19 meets the Berlin criteria for acute respiratory distress syndrome (ARDS), and radiographic studies support this theory. Gattinoni et al.[2] suggest that the relative compliance of early-phase COVID-19 ARDS is marked by normal lung mechanics compared with severity of hypoxemia with later stages more consistent with typical ARDS with lower lung compliance. The prevailing symptom of acute hypoxemia renders the patient incapable of tissue oxygenation. In China, a study by Zhou et al.[3] demonstrated a 16.8% rate of intubation in hospitalized patients, whereas Richardson et al.[4] reported a 20.2% rate in 5700 patients in the United States. The significant need for ventilator support in these patients mandates the understanding of the best options. We hypothesized that particular vent modalities may prove more beneficial than others in patients requiring intubation.

Airway pressure release ventilation (APRV) is a mode of ventilation that was first described by Stock et al.[5] and Downs and Stock[6] in 1987 as a means to oxygenate the lungs. It prevents significant fluctuations in airway pressure (P_{aw})[7–9] and thus is thought to decrease the risk of barotrauma.[6–10] A patient is able to maintain spontaneous breathing throughout this mode and is not constrained by the traditional forms of ventilation, which can lead to dyssynchrony and a need for sedation.[11] Moreover, APRV has been demonstrated to have a 70% reduction in neuromuscular blocking agents (NMBAs) and a 40% reduction in sedation requirements, as compared with traditional ventilation.[12,13] This in turn may reduce the risk of aspiration, and long-term neurological dysfunction. Often used as a rescue mode in severe hypoxemia and ARDS, multiple studies have demonstrated the improvement of oxygenation using APRV.[7–9,11,14,15] We hypothesized that patients suffering from COVID-19 ARDS would have improved oxygenation and a potentially shorter duration of mechanical ventilation.

METHODS

After institutional review board approval at NYU Winthrop Hospital (IRB #s20–00469), we collected data on all patients intubated for respiratory failure from COVID-19 and transferred to the surgical intensive care unit (SICU) under the care of the surgical intensivist, and who were transitioned to APRV settings after at least 24 hours of no improvement of oxygenation on low tidal volume (LTV) ventilation. Ventilator settings and adjunct ARDS treatments (e.g., prone positioning) were at the discretion of the surgical intensivist. All vents were Draeger Infinity c500. In general, P_{high} was set at 2 cm H_2O above the plateau pressure from LTV ventilation and the P_{low} set at 0 cm H_2O. The T_{high} was set at 5.0 seconds and the T_{low} at 0.5 seconds and adjusted to achieve an end-expiratory flow equal to 75% of the peak expiratory flow rate.[4,12] Settings were modified based on patient response by changing the P_{high} by 2 cm H_2O and the T_{high} by 0.5 seconds. The T_{low} was rarely changed once the initial settings were established.

Patients were observed for at least 48 hours and monitored for signs of hypoxia and tolerance. Data extracted included demographics, patient characteristics, FiO_2, PaO_2/FiO_2, and qualitative number of vasopressors, sedatives, and analgesics used. Patients were observed for failure to tolerate ventilator mode. Each patient had these outcomes measured daily while on the ventilator, transition to another mode of ventilation, initiation of extracorporeal membrane oxygenation (ECMO), or death, or for a period of 21 days.

Demographics and clinical characteristics such as body mass index (BMI) and comorbidities were summarized using mean ± SD or frequency (percentage) as appropriate. Generalized linear mixed models for repeated measures were used to analyze outcomes using appropriate distribution and link function based on the distribution of each outcome. The models included ventilator mode as the fixed effect, a subject-specific random intercept, and an autoregressive correlation structure. Ventilator mode was also added as a random effect to account for individual uncertainty of being assigned to a ventilator. SAS PROC GLIMMIX was used to implement these models. All analyses were performed using SAS 9.4 (SAS Inc, Cary, NC).

RESULTS

Patient Characteristics

Patients were observed for a period of 21 days. Of 12 patients who met criteria, two were only on APRV and therefore could not be compared with LTV. Data for the remaining 10 patients were analyzed. The average age of patients was 64.5 (±12.9) years with 30% women and with an average BMI of 30.6 (±8.0) kg/m^2. Two patients had underlying lung disease, chronic obstructive pulmonary disease, and another in whom the pathology was not defined, and three patients were considered immunocompromised. Most of the patients observed (70%) had a history of essential hypertension and all presented from home (Table 1).

Pulmonary Function Data

Oxygen requirements decreased with all patients on APRV with a concomitant qualitative reduction in the use of vasopressor (–59% [–83% to –2%]), sedation (–15% [–29% to 2%]), and analgesic (–16% [–38% to 12%]) medications. Importantly, the PaO_2/FiO_2 ratio, a

Table 1.—Demographics and clinical characteristics

Variables	Descriptive Statistics
Age, y, mean ± SD	64.5 ± 12.9
Female sex	3 (30)
BMI (kg/m^2), mean ± SD	30.6 ± 8.0
Time to ventilation (h), median (IQR)	23 (7–52)
SNF or LTAC	0 (0)
COPD	1 (10)
Moderate/Severe asthma	0 (0)
Current smoker or vape	0 (0)
Other lung pathology	1 (10)
HTN	7 (70)
CAD	1 (10)
DM	2 (20)
CKD	2 (20)
ESRD on HD or PD	1 (10)
Liver disease	1 (10)
Immunocompromised	3 (30)

Data are presented as n (%) unless otherwise noted
BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes; ESRD, end-stage renal disorder; HD, hemodialysis; HTN, hypertension; IQR, interquartile range; LTAC, long-term acute care; PD, peritoneal dialysis; SNF, nursing home

marker of ARDS severity, was seen to increase by up to 30% (5% to 61%) with vent mode conversion to APRV (Table 2). Ventilator dyssynchrony was noted to improve in all patients. Four patients were initially treated with paralytics while on LTV, which was discontinued when transitioned to APRV. Only one patient on APRV was transiently treated with NMBA, for an episode of acute hypoxia and agitation also requiring increased sedation. Three patients who had required prone positioning while on LTV did not subsequently need to be in prone position once the ventilator mode was converted to APRV.

Physiologic Variables

Patients admitted to NYU Winthrop Hospital for COVID-19 respiratory failure routinely have measures of D-dimers, ferritin, and other inflammatory markers measured on admission and at various times in the course of the disease process. At the start of the patient surge in New York, there was no clear protocol with respect to the timing of laboratory draws. Values were drawn at physician discretion and patient status. Patients on APRV did not demonstrate any patterns with respect to the usual inflammatory markers seen in patients with COVID-19 ARDS (Table 3).

DISCUSSION

In this single-center, observational pilot study at NYU Winthrop Hospital, a 591-bed tertiary care American College of Surgeons–verified Level 1 Trauma Center, the use of APRV was associated with a rapid decrease in oxygen requirements and an increase in the PaO2/FiO2 ratio in intubated patients suffering from COVID-19 ARDS.

The term "acute respiratory distress syndrome" was developed in 1967 by Ashbaugh et al.[16] to describe a constellation of symptoms leading to decreased oxygenation. In ARDS, gas exchange is inhibited in large part due to ventilation-perfusion mismatch and shunting.[17,18] Although a goal of less than 31% death rate has been set, mortality in patients with ARDS remains at approximately 40%.[19] Patients with ARDS suffer from inability to oxygenate caused by the inflammatory processes in the lung resulting in interstitial and alveolar edema, decrease in alveolar surfactant and subsequent decreased compliance.[17,20,21]

Patients with ARDS present with heterogeneous lung with atelectasis and de-recruited lung.[22] In a study by Gattinoni et al.[10] of 68 patients, on average, 24% of lung could not be aerated. The ability to recruit lung tissue was strongly associated with the response to positive end-expiratory pressure (PEEP)[10]; however, increased PEEP can lead to static overdistention, further injuring already damaged lung.[23,24] Further, methods for optimizing oxygenation have focused on recruitment of alveoli and do not always consider the recruitment/de-recruitment phenomenon that occurs, which compounds and leads to a worsening of ARDS.[19] The ARDS net method of LTV ventilation is designed to obtain maximal recruitment of collapsed lung; however, this is

Table 2.—Comparing outcomes between APRV versus other ventilator modes using repeated measures data

Model Outcome	Independent Variable	Estimate (SE)†	Percent Increase or Decrease (95% CI)‡	*p* Value†
Total sedatives¶	APRV vs. other	−0.16 (0.09)	−15% (−29% to 2%)	0.10
Total analgesics¶	APRV vs. other	−0.18 (0.15)	−16% (−38% to 12%)	0.26
Total pressors¶	APRV vs. other	−0.90 (0.45)	−59% (−83% to −2%)	0.08
AM FiO2§	APRV vs. other	−0.11 (0.08)	−10% (−23% to 5%)	0.20
PM FiO2§	APRV vs. other	−0.13 (0.09)	−12% (−26% to 5%)	0.17
AM PaO2/FiO2§	APRV vs. other	0.01 (0.15)	1% (−25% to 36%)	0.93
PM PaO2/Fi02§	APRV vs. other	0.26 (0.11)	30% (5% to 61%)	0.05

†Estimated via generalized linear mixed models (GLMM) for repeated measures data
‡Computed from the model estimates
¶GLMM assumed data followed a Poisson distribution
§GLMM assumed data followed a log-normal distribution
Note: These models do not consider time because time did not have linear continuity
APRV, Airway pressure release ventilation; CI, confidence interval

Table 3.—Laboratory markers between ventilator modes

Variable	APRV Median (Q1–Q3)†	Other Median (Q1–Q3)†	*p* Value‡
Creatinine (mg/dL)	1.6 (0.5–3.2)	1.0 (0.7–3.3)	0.99
Ferritin (ng/mL)	2006 (1227–2674)	1779 (1125–3050)	0.53
CRP (mg/L)	169.0 (40.3–262.7)	186.2 (177.5–236.7)	0.78
LDH (IU/L)	527.3 (392.8–655.0)	510.5 (414.0–612.0)	0.73
D-dimer (ng/mL)	1836 (1187–4457)	2252 (1547–5391)	0.443

†Median (25^{th} percentile–75^{th} percentile) values were computed as within patient then between patients per ventilator mode
‡*P* values are from Generalized Linear Mixed Models (GLMM) for repeated measures data
APRV, Airway pressure release ventilation; CRP, C-reactive protein; LDH, lactate dehydrogenase

not necessarily accomplished or maintained by airway recruitment maneuvers.[10,25]

In APRV, tidal volume (V_t) is "inherently" set by the patient based on the compliance of the lung itself. Alveoli recruitment occurs over several hours, and collapse of these alveoli does not occur due to the short release time, typically between 0.5 to 0.7 seconds.[26] Previous studies have shown benefits with APRV on pulmonary function that include improved oxygenation and ventilator tolerance.[1,19,26] Plateau pressures decrease with a rise in mean airway pressure (P_{aw}) leading to improved oxygenation and respiratory compliance when compared with LTV ventilation.[7,9] APRV maximum pressures P_{high} are set for a period of time (T_{high}), with a release (P_{low}) for a brief period (T_{low}). In APRV, alveoli are never fully collapsed, which is thought to preserve against barotrauma. A randomized controlled trial (RCT) performed by Hirshberg et al.[27] failed to demonstrate the lung protective effects of APRV. In that study, V_t was reported to be too large (as much as 12 mL/kg) and highly variable. The investigators had previously set a V_t goal of 6 mL/kg, and the study was terminated early, although there was no difference identified in patient groups, citing risk of barotrauma. Several studies have suggested alternate mechanisms,[28,29] and laboratory data have shown the presence of an increased inflammatory response demonstrated by the presence of interleukin-6 when alveoli recruit and de-recruit, so-called "dynamic strain", further supporting an alternate mechanism of lung injury.[19]

Hemodynamic effects have also been demonstrated to improve due to the patients' inherent ability to breathe.[19] Because a patient is allowed to respire spontaneously, there is a physiologic decrease in intrathoracic pressure, leading to improved venous return and hemodynamics.[4,26,30] In a study by Zhou et al.,[31] patients treated with APRV when compared with patients treated with LTV had both shorter ventilation days and improved oxygenation, leading to decreased intensive care unit (ICU) stay. These results were noted even when controlling for sedation requirements. In our study, there was a trend toward decreased use of vasopressor support, although this was not statistically significant.

The COVID-19 pandemic has had a crushing impact on global health and the worldwide economy. Treatment of patients has strained health systems, leading to shortages in every aspect: hospital beds, ventilators, staff, and notably in medications to support victims. Routinely, methods of analgesia and sedation are altered to accommodate drug shortages. The use of APRV, therefore, is a logical step that can serve to alleviate the use of these medications (Table 2). The management of patients who deteriorate to intubation includes heavy sedation, prone positioning, and in some cases paralysis. Patients who are proned are subject to pressure ulcers and endotracheal tube obstruction,[32] whereas those with tracheostomies can have these airways dislodged. Moreover, heavy sedation is required to keep patients comfortable while in this position. In our experience, one patient was proned shortly after initiating APRV, but this was subsequently not required. Other patients who previously required prone positioning did not need to have this performed after APRV mode of ventilation was initiated.

Our study has several limitations. It is an observational pilot study with a potential for bias. There was not a defined protocol for initiation of APRV or for consequent ventilator management. The group of surgical intensivists have similar practice patterns, but the manipulation of ventilator settings was subject to variation based on the surgeon intensivist preference and experience. In addition, the surgical intensivist team did not initially manage patients. At the peak of the pandemic in Nassau County, there was an urgent need for ICU beds. We created a system of different-tiered ICUs where the sickest patients went to a Tier 1 ICU with 24/7 intensivists and the ability to do ECMO and/or continuous renal replacement therapy (CRRT) if needed. Tier 2 ICU also had 24/7 intensivists, but ECMO and CRRT could not be performed and patients did not require titration of vasoactive medications and were more stable. Many patients were transferred to the lower-tiered units once they were better stabilized (i.e., no longer requiring heavy sedation or vasopressor support and lower oxygen settings). Notably, one patient transferred to the SICU for initiation of ECMO did not ultimately require ECMO after a few days trial of APRV. At the peak of the crisis, there was a large turnover of patients, and some

individuals were transferred out of the SICU and the care of the surgical intensivist as they became more stable. These patients were placed back on LTV modes of ventilation, making any further interpretation of data difficult.

Because of the observational nature of this study, we could not assess for other mitigating factors that may or may not have contributed to the results. Nevertheless, when RCTs are not feasible, a well-designed observational study may be key.[33] The observational method allows for direct observation of a clinical tool without manipulation.[34] An observational study without randomization would be most appropriate as we aim to better understand how best to mitigate the impact of SARS-CoV-2 on lung pathophysiology.

CONCLUSIONS

Although the overwhelming presentation of patients was that of lung failure, we are fully aware that SARS-CoV-2 affects multiple systems in a variety of ways, including creating a hypercoagulable state that is as yet not well understood. In patients who experience severe respiratory failure, the management of lung failure is the key focus in patient care. In our study, APRV provided an opportunity to safely oxygenate patients while allowing for spontaneous breathing and decreased need for sedation and paralysis, which may be harmful when used liberally. APRV requires knowledge of the mode of ventilation and implementation of a protocol. Briefly, we propose a similar method to that used by Zhou et al.,[31] in which we set the P_{high} at the last plateau pressure and the P_{low} is set at 5 cm H_2O. The release phase T_{low} is adjusted to terminate the peak expiratory flow rate of $\geq$50% with the T_{high} calculated based on the T_{low} and release frequency. We set the initial FiO_2 at 100%. A blood gas is performed and if the appropriate response occurs, we titrate the FiO_2 to maintain a saturation of $\geq$92% until the level reaches 40%. The vent settings are then "dropped" and "stretched" by 2 cm H_2O (P_{high}) and no more than 1 second (T_{high}). If the patient does not demonstrate a response or fails to tolerate, the reverse is done. With the increasing need for interventions that shorten and/or cure the disease caused the by SARS-CoV-2 virus, it is important that all clinical and laboratory research be made available to the public as soon as feasible. The report of our small clinical study allows for a more formalized protocol to assess fully the impact of APRV on patient outcome. At this time, the management of these patients is that of support. Our experience suggests that this may be done in a manner that is more beneficial and less injurious to the intubated patients with COVID-19.

APRV mode provides a unique opportunity to allow for oxygenation with limited barotrauma and the possibility of fewer ventilator days, and shorter ICU length of stay. An RCT is indicated to fully understand the full benefit of this mode of ventilation compared with LTV for ARDS in intubated patients with COVID-19.

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