Effect of Airway Pressure Release Ventilation (APRV) with Pressure Support (PS) on Indices of Oxygenation and Ventilation in Patients with Severe ARDS: A Cohort Study

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Abstract

***Background*: Airway pressure release ventilation (APRV) is an alternative approach to the "open-lung" ventilation strategy and has recently emerged as an alternative ventilatory strategy in patients with severe ARDS.**

***Aims*: Our objective was to assess the effect of APRV+ low level pressure support (PS) on indices of oxygenation and ventilation in patients with severe ARDS.**

***Methods*: During the study period we recorded oxygenation and ventilation data (for up to 96 hours) as well as the use of sedative and vasopressor agents in patients in our MICU with severe ARDS (PaO_2/FiO_2<150) who we switched to APRV+PS from low tidal volume assist-controlled (AC) ventilation. Vd/Vt was measured by volumetric capnography. Patients were followed until hospital discharge or death.**

***Results*: Twenty-two patients with severe ARDS secondary to sepsis were studied. The patients were on AC for 4±3.5 days prior to conversion to APRV. The PaO_2/FiO_2 increased (134±48 to 210±87 mmHg; p=0.03) while the Vd/Vt fell significantly (66±10 to 54±10%; p=0.01) by 24 hours. These changes were maintained throughout the study period. The total daily dose of sedative and vasopressor agents decreased by 46% and 55% respectively by 24 hours. While these patients were critically ill with a high anticipated mortality, 12 (54%) survived to hospital discharge.**

***Conclusion*s: APRV+PS improves oxygenation and V/Q mismatching in patients with severe ARDS allowing a decrease in the use of sedative agents. While the survival benefit of APRV could not be assessed in this study, APRV should be considered in the ventilatory strategy of patients with severe ARDS.**

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Key words: Acute respiratory distress syndrome (ARDS), airway pressure release ventilation (APRV), respiratory dead space, oxygenation, ventilation.

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Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) first described by Ashbaugh and colleagues in 1967, is characterized by the abrupt onset of hypoxemia (PaO_2/FiO_2<300) with the presence of bilateral alveolar infiltrates on chest radiography. (1,2) Two decades ago, the mortality from ALI was as high as 70% but has since declined to 30-40%. (3-5) Advanced age, multi-system organ dysfunction (MSOF) and severe persistent hypoxia are associated with a poor outcome. (6) The preferred mode of ventilation in patients with ARDS/ALI is controversial

as the traditional goals of normalizing arterial oxygen and carbon dioxide (CO_2) tensions may exacerbate lung injury and worsen outcome. (6,7) A landmark study published by the ARDSNet group (NIH ARDS Network) in 2000 demonstrated that volume-assisted ventilation (AC) with a small tidal volume (6 ml/kg of predicted body weight) was associated with a significant reduction in 28 day all cause mortality as compared to AC ventilation with traditional tidal volumes (12 ml/kg of predicted body weight). (8) Such an approach is now considered the standard of care. (6,7,9) While sepsis and MSOF remain the most common cause of death in patients with ARDS up to 20% of deaths are attributable to progressive respiratory failure. (5) A number of interventions have been attempted in this group of patients including inhaled nitric oxide, nebulized prostacyclin and surfactant, recruitment maneuvers, liquid ventilation and prone positioning with little evidence that these interventions improve outcome. (6,7,10,11) Airway pressure release ventilation (APRV) has recently emerged as an alternative ventilatory strategy in patients with severe ARDS. (12-14)

APRV is a relatively recent innovation, first described by Stock and colleagues in 1987, and commercially available since the mid 1990's. (15) APRV can be classified as a pressure-limited, time-cycled mode of mechanical ventilation that allows the patient unrestricted spontaneous breathing during the application of continuous positive airway pressure. (16-18) It is an alternative approach to the "open-lung" ventilation strategy. (18) Although recruitment maneuvers may be effective in improving gas exchange and compliance, these effects are not sustained; APRV may be viewed as a nearly continuous recruitment maneuver. (16) The ventilator maintains a high-pressure setting for the bulk of the respiratory cycle (PHigh), which is followed by a periodic release to a low pressure (PLow) (19) (**Figure 1**). The periodic releases aid in carbon dioxide elimination (CO_2). The release periods (TLow) are kept short (0.7-1 s); this prevents derecruitment and enhances spontaneous breathing during THigh. (18,20) The advantages of APRV over volume controlled ventilation include an increase in mean alveolar pressure with alveolar recruitment, the hemodynamic and ventilatory benefits associated with spontaneous breathing and the reduced requirement for sedation. While the benefits of APRV have been reported in trauma and surgical patients, (14,21-24) there is little data on the use of the mode of ventilation in medical ICU (MICU) patients. (25) Our objective was to assess the effect of APRV+low level pressure support (PS) on indices of oxygenation and ventilation in MICU patients with severe ARDS.

Methods

This study was carried out in the MICU at Thomas Jefferson University Hospital in Philadelphia, PA during the months of September 2007 to July 2008. All patients with ARDS in our ICU were ventilated according to the ARDSnet low tidal volume strategy. (8) At the discretion of the attending intensivist, patients with ARDS with a PaO_2/FiO_2 which remained less than 150 after 72 hours of ventilation using the ARDSnet low-tidal volume protocol were switched to our APRV protocol. (8) As this was a non-randomized study there was no control group. This study was approved by Thomas Jefferson University IRB who waived the need for informed consent as patients were treated according to approved hospital protocols. Puritan-Bennet 840 ventilators were used for both modes of ventilation. Our assist-controlled (AC) ventilation protocol aimed at maintaining the plateau pressure (Ppl) <30 cmH_2O with a tidal volume (TV) of approximately 6 ml/kg predicted body weight (PBW). PBW was calculated using the patients' sex and height. (8) PEEP and FiO_2 were titrated according to the ARDSnet low-tidal volume protocol. (8) Based on our preliminary experience and that reported in the literature, the initial APRV settings were as follows: PHigh 25 cmH_2O (or 75% Ppl on AC), PLow 5 cmH_2O (or 75% of AC-PEEP, if AC-PEEP>10 cmH_2O), release rate of 12/min, TLow "locked at" 1 s, PS of 5 cmH_2O above PHigh, with a fractional inspired oxygen concentration (FiO_2) equivalent to that on the AC mode. (19) Patients remained on APRV ventilation throughout the rest of their ICU course. The ventilatory goals on both AC and APRV were to maintain an arterial oxygen saturation greater than 88% and an arterial pH between 7.2 and 7.4.

Sedation on AC ventilation was titrated using a sedation protocol (lorazepam and fentanyl) to achieve a Ramsay Sedation Scale (RSS) level of 3-4 with ventilator synchrony. (26) Our sedation protocol included daily awakenings and spontaneous breathing trials. (27) Sedation in the APRV

mode was titrated (reduced) to achieve a RSS level of 2 with the patient having 1-2 spontaneous (PS assisted) breaths at each PHigh (**Figure 1**). Vasopressors were titrated to maintain a mean arterial pressure greater than 65 mmHg. Once the patients were hemodynamically stable with a FiO_2 ≤0.5 we initiated weaning by sequentially reducing the PHigh by 2 cmH_2O and increasing the TLow by 0.2 s at a time interval not greater than 4-6 hours. This process was continued until the patients were breathing on continuous positive airway pressure (CPAP)+PS whereupon the patients were extubated.

De-identified patient data including demographics, clinical diagnoses, ventilator days, ICU days and outcome were recorded. The following variables were collected at baseline on AC (T0) and repeated at 2 hrs (T1), 6 hrs (T2) and 24 hrs (T3) after switching to APRV and then 24 hourly for 3 days (up to 96 hrs; T4-7): ventilator settings, mean airway pressure (MAP), minute ventilation (MV), release and spontaneous volumes on APRV, arterial blood gas values, PaO_2/FiO_2 and Vd/Vt. We also recorded use of sedatives and vasopressors agents until the patient was extubated, switched to another ventilatory mode or died. Tidal volumes, release volumes and spontaneous volumes were expressed as milliliters per PBW (ml/kg PBW). The Vd/Vt was measured by volumetric capnography (NICO Respironics; Wallingford, CT). An arterial blood gas sample was obtained when the mean expired CO_2 variability on the NICO monitor (which uses minute-to-minute measurement averaging) was <1 mmHg within a 5 minute period. The expired CO_2 was measured at the Y-adapter of the ventilator circuit. The Vd/Vt was calculated using the Enghoff modification of the Bohr equation as follows: $Vd/Vt=(PaCO_2-PeCO_2)/PaCO_2$. (28)

Continuous data was described as the mean (±SD) while categorical data was expressed as n (%). Baseline differences between survivors and non-survivors were compared using non-paired Students' T test. The oxygenation and ventilation data were compared with a repeated measure one-way ANOVA and the Kramer-Tukey adjustment method was used for multiple comparisons. All tests were two sided with a p value <0.05 considered statistically significant. Data analysis was conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Twenty-two patients were included in this study. The patients' mean age was 51±15 years; 13 were male (60%). All patients had sepsis with 12 (68%) having pneumonia. The patients were on AC for 4±1.5 days prior to conversion to APRV. Their SOFA score at T0 was 11±3.5. Three patients were extubated by 48 hours and 7 by 96 hours. Four patients had died by 96 hours. Twelve patients (54%) survived to hospital discharge. Of the non-survivors 6 (60%) had metastatic cancer. All of the non-survivors died of MSOF. The SOFA score (T0) was 8.9± 2.7 in the survivors compared to 13.1± 2.9 in the non-survivors (p=0.02). The time course of the patients' ventilatory and oxygenation parameters between T0 and T6 were presented in **Table 1**. Notably between T0 and T3, MAP and PaO_2/FiO_2 increased significantly while the minute ventilation and Vd/Vt decreased significantly. The $PaCO_2$ remained constant over the study period despite a decrease in minute ventilation. The total daily dose of sedatives and vasopressor agents between decreased by 46% and 55% respectively after 24 hours of APRV (between T0 and T3).

Discussion

In this study we demonstrated a significant improvement in oxygenation with decreased V/Q mismatching (increased PaO_2/FiO_2 and decreased Vd/Vt) in a cohort of patients with severe ARDS who were switched from volume-controlled ventilation to APRV with low level PS. The mortality rate in our series was 46% which is in keeping with previous studies in unselected patients with ARDS. (3-5,29) One would have anticipated a higher mortality, as the patients included in this study had severe hypoxemia having "failed" the standard ARDSnet low tidal volume strategy. Furthermore, 60% of the patients who died had metastatic malignancy. The baseline (T0) PaO_2/FiO_2 and Vd/Vt in our patients were 134 mmHg and 66% respectively. These indices are predictive of a poor outcome. (29,30) Indeed, Kallet and colleagues demonstrated that a Vd/Vt greater than 60% was almost always associated with a fatal outcome. (31) While we believe that APRV may improve the outcome of patients with severe ARDS, this was an uncontrolled, non-randomized study and hence the survival advantage of APRV cannot be determined from our study.

APRV has a number of theoretical advantages over low-tidal volume AC ventilation, most notably the reduced requirement for sedative agents and the ability of patients' to take spontaneous breaths throughout the respiratory cycle. (18) Lung protective strategies using both volume and pressure controlled ventilation are usually poorly tolerated requiring deep sedation. Remarkably, we have found that APRV is extremely well tolerated by patients allowing sedation to be discontinued in many patients. This is a very important issue as the increased use of sedation has been associated with a longer duration of mechanical ventilation as well as an increased incidence of ventilator associated pneumonia, delirium and an increased mortality. (27,32,33) APRV uses an active exhalation valve that allows spontaneous breathing throughout the respiratory cycle. Due to the short release time (TLow) the spontaneous breaths occur almost exclusively during the PHigh. (18,20) Both experimental and clinical studies have demonstrated that the addition of spontaneous breaths to APRV recruits dependent lung regions, increases end-expiratory lung volume, decreases V/Q mismatching, and improves oxygenation, cardiac function (cardiac index) and organ blood flow. (21,25,34-38) These studies have demonstrated that spontaneous breathing recruits dependent lung segments (which are preferentially perfused). Permanent alveolar recruitment with APRV is therefore achieved by the combination of the high inflation pressure (PHigh), short release time (which prevents derecruitment) together with spontaneous respiratory efforts. In the studies cited above, the spontaneous breaths were unassisted. Habashi and colleagues have suggested that the cardio-respiratory benefits of spontaneous breathing during APRV are mitigated by the addition of PS. (12,13) Others have suggested that *"it cannot be ruled out that the proven physiological effects of unassisted spontaneous breaths during APRV may be attenuated or even eliminated when each detected spontaneous breathing effort is assisted with PSV during APRV"*. (39) In our early experience with APRV in patients with severe ARDS, we noted a very dramatic fall in minute ventilation (with an acute rise in CO_2) when patients were switched to APRV without low level PS (5 cmH_2O). Furthermore, the patients became tachypneic and quite agitated. We speculated that this was due to the increased work of breathing through the ventilator circuitry at high lung volumes. Furthermore, without low level PS the spontaneous tidal volumes were very low (approximately 50-80 ml vs. about 200 ml with 5 cm H_2O PS) and this was presumably associated with CO_2 rebreathing. Wrigge and colleagues studied the effect of automatic tube compensation (ATC) during APRV in 14 patients with ALI. (40) These authors reported that the addition of ATC increased minute ventilation, oxygenation and end-expiratory lung volumes without affecting cardiovascular function. While the patients in the study by Wrigge and colleagues appeared to have tolerated APRV without support of their spontaneous breaths they were markedly less sick than our patients (baseline PaO_2/FiO_2 of 273±68 vs 134±48 mmHg). Furthermore, their oxygenation and ventilatory parameters improved with the addition of ATC. This suggests that the notion that the benefits of APRV are lost when spontaneous breaths are supported may be incorrect. (12,13) In our preliminary work, we found that low-level PS (ie 5 cmH_2O) was better tolerated by our patients than ATC. We therefore used a PS of 5 cmH_2O in our current APRV protocol.

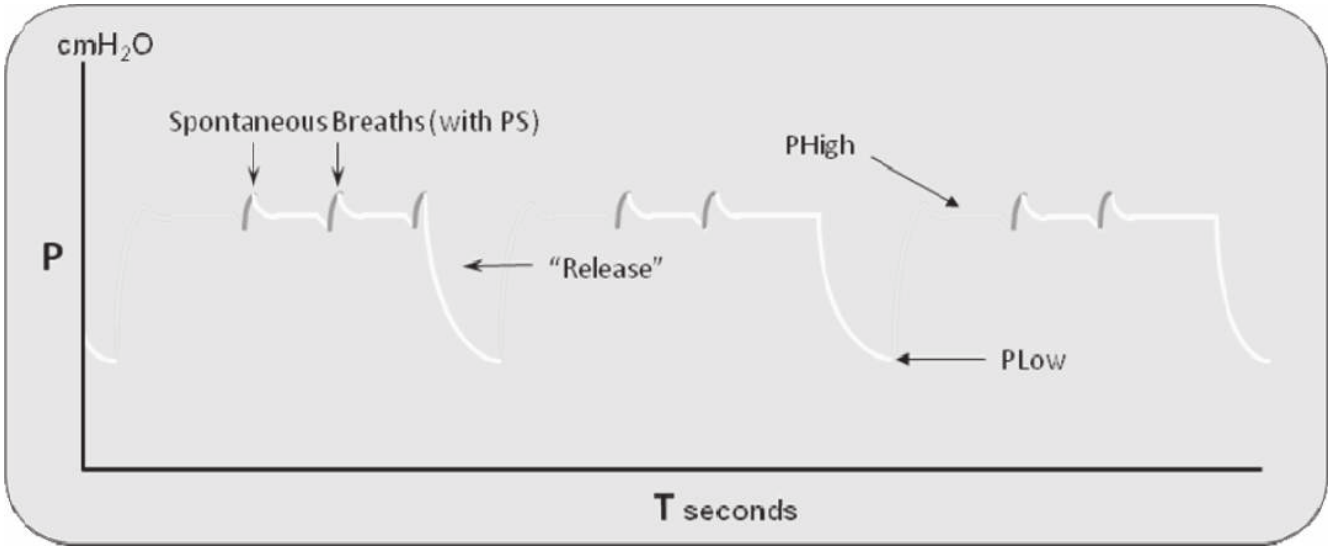
Although the ARDnet protocol specifies a tidal volume of 6 ml/kg PBW we observed that the tidal volume in our patients on the "ARDSnet protocol" was 8.0±1.4 ml/kg PBW. (8) This observation is in keeping with the practice reported in other major teaching centers where less than 50% of patients with ARDS are ventilated with a tidal volume of <6.5 ml/kg PBW. (41-43) Interestingly, although we did not target a specific tidal volume, the release volume on APRV was 7.9±1.4 ml/kg PBW.

In our study we demonstrated a significant decrease in the Vd/Vt (from 66±10 to 54±10%; p=0.01) with an increase in oxygenation when our patients were switched from low-tidal volume AC ventilation to APRV with low level PS. Vd/Vt has been demonstrated to be the single best predictor of outcome in patients with ARDS and is considered a global assessment of abnormal gas exchange and not simply a measure of respiratory dead space. (30,31,44) Unlike the experience with high-frequency oscillatory ventilation (HFOV) in ARDS, the improvement in oxygenation and ventilatory function in our patients was maintained with time. (45) It should be noted that while the minute ventilation fell, the PCO_2 stayed constant. The change in ventilatory strategy was associated with a significant decrease in the use of sedative and vasopressor agents. Our study therefore extends the data on the benefits of APRV in surgical patients to medical patients with severe ARDS. We believe that APRV should be considered as an alternative lung-protective strategy in patients with severe ARDS.

Table 1. Time Course of the Patients' Ventilatory and Oxygenation Parameters from Baseline (AC) to 96 Hours after APRV

Variable	T0 (BL)	T1 (2hr)	T2 (6hr)	T3 (24hr)	T4 (48hr)	T5 (72 hr)	T6 (96)	Difference T0-T3
(Mean±SD)	n=22			n=22	n=19	n=17	n=11	Diff (95% CI); p value
Mean airway pressure (cmH_2O)	17±5	22±4	21±5	21±4	21±4	20±4	22±5.3	-4 (-7 to -1); 0.05
Minute ventilation (l/min)	13.5±4.0	10.5±2.8	10.0±3.1	9.5±2.6	9.7±2.0	10.0±1.7	8.8±2.3	4.0 (1.3 to 6.7); 0.0002
Tidal Volume (ml/kg PBW)	8.0±1.4	-	-	-	-	-	-	-
$PEEP_H$	-	24.7±5.3	24.7 ±6.0	25.0 ±5.3	24.0 ±4.8	23.1 ±5.5	21.2 ±7.7	-
Release volume (ml/kg PBW)	-	7.9±2.6	7.8±2.1	8.2±1.8	8.8±2.3	7.0±2.5	7.0±2.5	-
Spontaneous volume (ml/kg PBW)	-	3.6±2.7	3.3±3.0	2.6±2.4	3.5±2.2	3.9±2.7	3.5±2.5	-
PaO_2/FiO_2 (mmHg)	134±48	167±66	174±66	210±87	218±93	216±94	187±91	-75 (-148 to -2); 0.03
$PaCO_2$ (mmHg)	44±9	43±8	42±8	41±10	42±9	43±9	43±6	3 (-4 to 11); 0.9
Vd/Vt (%)	66±10	56±11	54±11	54±10	55±10	50±10	52±11	12 (1.5 to 23); 0.01

Figure 1. Cartoon of "Idealized" Pressure-Time Waveform of Patient on APRV with PS



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