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Case Report

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Airway Pressure Release Ventilation Does Not Protect Against Acute Respiratory Distress Syndrome Development in Surgical Critical Care Patients

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ABSTRACT

Background:

Acute respiratory distress syndrome(ARDS) is a challenging disease process with high mortality. Airway pressure release ventilation(APRV) has been shown to potentially protect against development of ARDS.

Methods:

Observational study of all ventilated patients admitted to the surgical intensive care unit(SICU) at a single, tertiary center. Patients were assigned to APRV or conventional ventilation(CV). ARDS was defined using the Berlin definition. Primary outcomes included development of ARDS between ventilation modalities, ability of APRV to protect against ARDS in septic patients and ability of APRV to decrease mortality. Univariate and multivariate logistic regression models were utilized. Statistical significance was defined as $p<0.05$.

Results:

268 total patients enrolled. 141(52.6%) developed ARDS. 119(44.4%) patients were on APRV and 149(55.6%) were on CV. ARDS development was not statistically different between these two cohorts(p=0.732). 108(40.3%) patients were septic with 49(45.4%) on APRV and 59(54.6%) on CV. 33(67.3%) of APRV and 37(62.7%) of CV septic patients developed ARDS suggesting APRV is not protective against development of ARDS in this cohort(p=0.616). APRV use did not protect against 30-day mortality with rates of 53.5% versus 46.5% for patients on APRV versus CV respectively(p=0.191).

Conclusion:

APRV does not appear to be protective against development of ARDS, even in septic patients. APRV is not superior to CV in decreasing mortality.

Introduction:

Acute Respiratory Distress Syndrome (ARDS) was originally described by Ashbaugh et al in 1967.[1] Since that time, ARDS has gone through a variety of definitions including the longest standing accepted definition from the American-European Consensus Conference (AECC) in 1994.[2] Recently, the definition of ARDS was again updated and revised to address many of the limitations of the 1994 AECC definition.With an incidence of 1.5 to 8.3 per 100,000 person-years[3] and an excess cost of $150,000 per case, ARDS is a hospital-acquired phenomenon in which 67% of patients develop within the first 30 hours of hospital admission.[4] Emr et al showed that when placed on mechanical ventilation, up to 25% of all patients with normal lungs will develop ARDS.[5] Numerous studies have been conducted to examine ways to reduce the incidence of ARDS development and subsequent mortality. Despite a better knowledge of this disease process and better ventilation management strategies, the mortality rate from ARDS remains relatively unchanged.[6,7]Airway pressure release ventilation (APRV) was first described in 1987 by Stock and Downs as a modified form of continuous positive airway pressure (CPAP) to enhance oxygenation by augmenting alveolar recruitment.[8] Its major advantages over other modes of conventional ventilation (CV) include the preservation of spontaneous unassisted ventilation throughout the entire ventilatory cycle and maintenance of a relatively long lung inflation time.[9,10] Multiple prospective studies in animal models have demonstrated an ARDS preventative effect with APRV in shock and traumatic conditions as well as normal lungs.[4,5,11,12] APRV use as a protectant against lung injury remains controversial in current clinical practice despite a theoretical benefit of early alveoli stabilization. We hypothesize APRV with protect against the development of ARDS compared to CV in the surgical critical care population.

Methods:

This was an Institutional Review Board approved, prospective observational cohort study. All patients admitted to the surgical intensive care unit (SICU) and requiring ventilatory support at a single tertiary, 805-bed academic hospital were included in the study over a 6-month period. Patients were assigned to receive APRV or conventional ventilation (CV) based on which subdivision of the SICU the patient was admitted. This was completely random based on bed availability, assigned through the SICU nurse manager. Conventional ventilation was defined as any method of ventilation other than APRV including continuous mandatory ventilation, synchronized intermittent mandatory ventilation, pressure support ventilation and noninvasive mechanical ventilation. We do not utilize oscillatory ventilation strategies in our SICU therefore this population was excluded by default. Acute respiratory distress syndrome was defined using the new Berlin definition.[13] Baseline demographics including age, race and sex where defined for our cohort. Primary outcomes included the development of ARDS while utilizing APRV versus CV, the ability of APRV to protect against the development ARDS in the subset of septic patients and 30-day mortality rates for patients on APRV versus CV. Secondary outcomes evaluated the differences between the number of ventilator hours between APRV and CV patients. Furthermore, SICU length of stay (LOS) in days was examined between these two cohorts. In the CV group, ventilator management was at the discretion of the treating critical care board-certified physician. All CV patients were managed with lung protective strategies with tidal volumes between 6 – 8mL/kg in accordance with the ARDSnet trial of 2000.[14] This was regardless of whether or not the patient developed ARDS. Management of APRV was standardized by using an existing algorithm created for SICU patients at our institution based on prior literature review

Figure 1: Protocol for weaning ventilator from patients receiving APRV

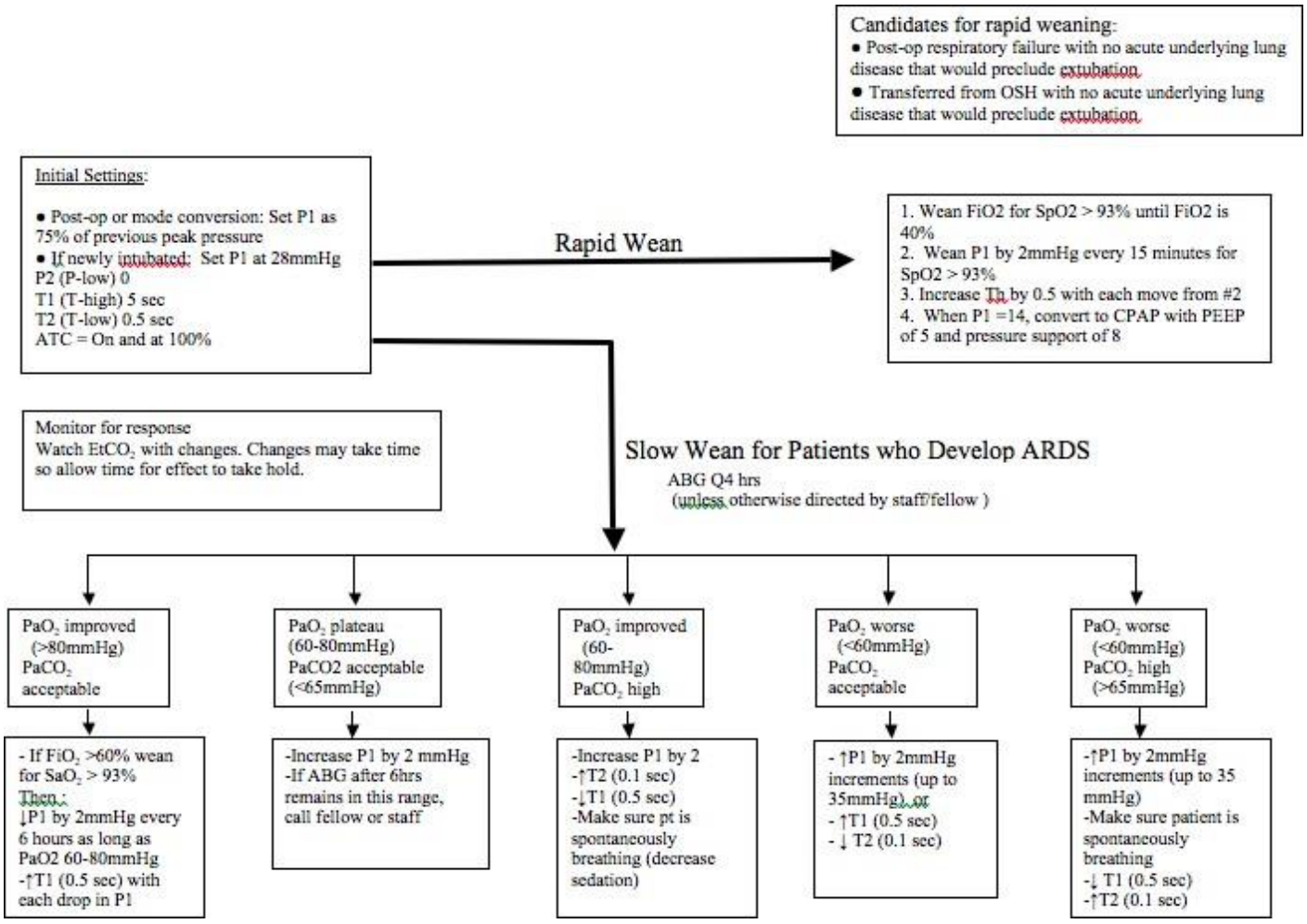

Figure 1:

This figure demonstrates the weaning protocol used to wean all patients placed on APRV. The "Rapid Wean" was for those patients who did not develop ARDS and the "Slow Wean" was used for those patients who did develop ARDS. ARDS was defined using the Berlin definition.[13]Exclusion criteria included patients less than 18 years of age, any patient not maintained on their initial ventilatory mode (APRV versus CV) for the entire required respiratory support period prior to extubation and any patient on the ventilator that had undergone a pneumonectomy as these patients can not be classified into an ARDS category based on the Berlin definition.[13]Univariate analyses were carried out using chi-square tests for categorical variables, and using two-group independent t-tests for continuous variables. Univariate logistic regression models were utilized to produce crude odds ratios and multivariable logistic regression models were used to produce adjusted odds ratios, both with 95% confidence intervals. Statistical significance was set at $p<0.05$. All analyses were done using SAS 9.4 (SAS Institute Inc, Cary, NC).

Results:

A total of 268 ventilated patients were enrolled in the study. 155 (57.8%) patients were male, 99 (36.9%) patients were black, 147 (54.9%) were Caucasian and 22 (8.2%) were of other race. The average age was 57.9(±17.7) years. 119 (44.4%) patients were assigned to APRV as their mode of ventilation and 149 (55.6%) were assigned to CV. A total of 141 (52.6%) patients developed ARDS and 127 (47.4%) patients did not develop ARDS while on the ventilator. There was no statistical significance detected in terms of developing ARDS between those patient placed on APRV versus CV. This comparison is demonstrated in

Table 1. Using logistic regression modeling, the odds of developing ARDS when placed on APRV, as the mode of ventilation, was 1.09 (95%CI of 0.67 to 1.76, p=0.73) comparatively.

Table 1: Incidence of ARDS

Variable		No ARDS (N=127)	ARDS (N=141)	P-Value
APRV	No	72 (56.7%)	77 (54.6%)	0.732
	Yes	55 (43.3%)	64 (45.4%)	

Table 1: No statistical difference for the development of ARDS between patients placed on APRV versus those not placed on APRV

The septic patients were selected out by standard definition: presence of at least two systemic inflammatory response syndrome criteria and a source of infection.[15] Of our 268 total patients, 108 (40.3%) were met the criteria for the diagnosis of sepsis and 160 (59.7%) did not. Of the 108 patients who developed sepsis, 49 (45.4%) were placed on APRV and 59 (54.6%) were placed on CV. A total of 33 (67.4%) patients on APRV and 37 (62.7%) patients on CV developed ARDS (p=0.616). This results shows APRV is not pulmonary protective against the development of ARDS in this subset of septic patients (**Table 2**).

Table 2: ARDS Development in the Subset of Septic Patients on APRV vs CV

	CV (N=59)	APRV (N=49)	P-Value
No ARDS (N=38)	22 (37.3%)	16 (32.7%)	0.616
ARDS (N=70)	37 (62.7%)	33 (67.4%)	

Table 2: All 108 septic patients included in study. There is no statistical difference in the development of ARDS between those patients on APRV and those on CV.

Overall, 43 (16%) patients died in our study. Of those 43 patients, 31 (72.1%) had ARDS (p=0.005). In our study, patients who developed ARDS had 2.97 times the odds of death than patients without ARDS (95% CI 1.42, 6.20) (p=0.004). APRV use did not appear to protect against 30-day mortality with an incidence of death of 53.5% versus 46.5% patients for patients placed on APRV versus CV respectively (p=0.191). Using multivariate regression analysis, APRV was not superior to CV in mortality prevention with an odds ratio of death of 1.24 (95% CI 0.59, 2.61)(p=0.576) for all APRV patients and an odds ratio of death of 1.01 (95% CI 0.39, 2.60)(p=0.983) for those APRV patients who developed ARDS comparatively. In review of our secondary outcomes, APRV did not show superiority in terms of decreasing in the number of ventilator hours compared with CV. Furthermore, APRV was not superior to CV in terms of decreasing overall length of stay in the SICU. These comparisons can be seen in.

Table 3: Ventilator Hours and SICU Length of Stay

	No APRV (N=149)	APRV (N=119)	P-Value
Ventilator Time (Hours)	133.4 ±211.9	102.4 ±138.1	0.197
SICU Length of Stay (Days)	10.8 ±9.9	10.2 ±9.7	0.440

Table 2: There is no statistically significant difference seen in mean ventilator hours or mean SICU length of stay between patients managed with conventional ventilation versus APRV.

Discussion:

Since its commercial availability in the mid-1990s,[16] APRV has not been a widely utilized strategy in clinical practice in North America.[9] It is often considered an alternative rescue mode for the difficult-to-oxygenate patients who have already developed ARDS.[9] Recently, APRV has been gaining popularity due to a large body of literature demonstrating that it not only helps in patients who have already developed ARDS but may also prevent the development of ARDS in

ventilated patients. APRV has many advantages when compared to CV, one of which is achievement of a higher alveolar recruitment.[17] APRV is considered an "open lung approach" to ventilation, a concept of maximizing and maintaining alveolar recruitment throughout the entire ventilatory cycle to avoid over-distension on inspiration and alveolar collapse on exhalation.[9,18,19] This affects pulmonary and systemic blood flow in a salutatory fashion resulting in a significant reduction of hypoxic pulmonary vasoconstriction.[20,21,22,23] By decreasing hypoxic pulmonary vasoconstriction, there is a subsequent decrease in right ventricular pressure, increased venous return to the heart which in turn increases cardiac output by increasing the stroke volume.[17] The end result of this physiology is improved end-organ perfusion.Furthermore, APRV allows the patient to breathe spontaneously throughout the ventilatory cycle. Spontaneous ventilation has been associated with increased oxygenation, increased end-expiratory lung volumes and an increased CT-guided aeration index.[17,21] This spontaneous ventilation increases aeration and lung volume from the dependent lung regions rather than overdistension of already compliant regions,[10,21] which supports the theory of a lung protective role for APRV.[17] Finally, APRV has also been shown to be more comfortable not only for the patients, but also for the families of these patients.[22,23] These patients require less sedation and are able to be more interactive with their own patient care as well as family members at the bedside which has shown to result in shorter ventilator and ICU days, improved overall patient outcomes, and increased family comfort.[17,23]Acute respiratory distress syndrome (ARDS) is defined as acute hypoxemic respiratory failure with bilateral pulmonary infiltrates that is associated with both pulmonary and non-pulmonary risk factors.[3,24] There are two main processes that contribute significantly to the development of ARDS: high permeability pulmonary edema and alveolar instability from the repetitive expansion and collapse of alveoli with tidal ventilation causing atelectrauma.[4,25,26,27] Healthcare providers often do not recognize the progression to ARDS until diagnostic criteria are met. In many cases, physicians have initiated the disease process by the use of inappropriately high tidal volumes.[5] Since the Acute Respiratory Distress Syndrome Network study in 2000,[14] ventilator management therapies have shifted to widespread use of lower tidal volume strategies.ARDS has not typically been identified as a disease in progression but rather has historically been viewed as being present or absent. Appropriate therapy is therefore implemented only after all the features of the disease are present.[28] Unfortunately, this is often too late for effective therapy. As previously stated, ARDS is often a hospital-acquired condition with 67% of ARDS patients developing this devastating disease within the first 30 hours of hospital admission.[4] Therefore, before patients even start showing signs of respiratory distress, they are in subclinical progression of the disease beginning shortly after the initial insult.[4] In the surgical population, this insult can often be the surgery itself. Because of the nature of this disease process, multiple recent studies have focused on using APRV to prevent the development of ARDS by maintaining alveolar stability, which prevents the injurious process of atelectrauma, and reduces pulmonary edema formation.[4,25,29,30] Studies to date have only demonstrated a protective effect of APRV in animal modes (rats or pigs) with no validation in human patients.[4,5,11,12] To our knowledge, this study is one of the first attempts to validate the protective effects of APRV in a cohort of human patients, specifically those in the surgical critical care patient population. In our prospective, observational examination of 268 ventilated patients in the SICU, we found that APRV did not protect against the development of ARDS when compared to use of CV. Although this contradicts our original hypothesis, APRV was not shown to be a superior ventilator modality compared to CV in preventing ARDS. Furthermore, our study failed to show a pulmonary protective effect for the subset of septic patients, a finding that is contradictory to the previously published animal studies. One theory for our results is that surgical and trauma patients typically have higher intravenous volume status or more fluid shifts than non-surgical patients given the nature of the surgery or traumatic injury. Fluid volume status of surgical and trauma patients may have more impact on the development of ARDS then the actual ventilation mode itself. This may be why our findings contradict the animal model studies that do not reflect this clinical variant. A second theory, which was not well addressed in the animal models, is that the development of ARDS may be directly related the type or severity of the

insult (traumatic or surgical), however, additional studies are needed to confirm these theories.There have been several studies comparing APRV to CV in humans with ARDS, however most are weakened by the small number of patients and short time of observation.[9,23] Although these studies consistently show improvement in oxygenation using APRV, none of them have shown improvement in mortality with the APRV group.[9] The mortality from ARDS remains unacceptably high with rates ranging anywhere from 23%[31] to as high as 68.8%[32] with the majority of studies quoting rates between 30% and 40%.[4,7,33,34,35] Although our overall mortality rate is low (16%), of the 43 patients that died in our study, 31 (72.1%) met criteria for the diagnosis of ARDS, further confirming ARDS is still a major cause of mortality in the ICU, even when clinical care strategies are implemented to reduce its development. Our study is, however, consistent with previous literature that demonstrated no decrease in overall 30-day mortality when using APRV compared to CV. A recent prospective study by Maxwell et al examined 63 adult trauma patients requiring ventilation for greater than 72 hours. APRV had a similar safety profile as low tidal volume ventilation but there was no difference in overall mortality rates between the APRV and CV groups.[36] Finally, our study showed no statistical difference between APRV and CV in terms of ventilator hours or SICU LOS. This is actually contrary to previous literature showing shorter ventilator and ICU days for the APRV cohort.[17,23] It would make sense that APRV would result in shorter ventilator days due to the fact these patients usually require less sedation theoretically resulting in shorter ICU LOS, however this is not what our study demonstrated. Further studies are required to provide a more direct rationale for the differences between this study and those studies done previously.There are several limitations to our study. First, this study was a prospective, observational study from a single academic center comparing ventilated patients managed by various critical care physicians with varying degrees of APRV knowledge and comfort. A larger, prospective multi-institutional, multi-continental double-blinded study is needed to better validate our results. Second, although the Berlin definition has addressed many of the limitations of the American-European Consensus Conference definition as well as improved the predictive validity,[13] defining ARDS in the clinical setting still requires a certain degree of subjectivity on behalf of the diagnosing clinician. It has been demonstrated that experts' ability to clinically separate ARDS from other heterogeneous causes of respiratory failure is limited.[37,38] The Berlin definition may also be "over-sensitive" for surgical critical care patients who demonstrate a different intravenous volume status and likely more variation in fluid shifts compared to patients in other critical care units. Third, our study was limited to surgical critical care patients only. Additional studies are required to examine the effects of APRV in other critical care cohorts to see if there are similar or different findings. Fourth, our study did not provide a specified weaning protocol for CV, only for APRV. Most treating physicians at our institution wean from CV when FIO2 reaches 50% and the Tobin Index is < 80. Additional studies should, however, include a protocol for weaning CV as there can be variations in clinical management. Finally, we grouped all forms of mechanical ventilation other than APRV as "conventional ventilation." Future studies should contrast separate modes of mechanical ventilation against APRV for a better comparison analysis.

Conclusion:

Our study is an initial attempt to compare Airway Pressure Release Ventilation to conventional ventilation in human subjects. We demonstrated that APRV is not protective against the development of ARDS in ventilated surgical critical care patients, nor is it protective against ARDS development in septic patients compared to those patients managed with CV. Furthermore, APRV does not improve mortality rates among those patients that develop ARDS, which is consistent with current literature. Finally, APRV and CV are similar in terms of ventilator hours and SICU LOS. Overall, APRV appears to have the same efficacy and safety as CV, suggesting either modality can be used with similar outcomes. Although we cannot recommend the use of APRV as a protective mode of ventilation against the development of ARDS based off these study results, we do recommend mastering one or two specific ventilation modalities using lung protective methods when managing ventilated patients in the intensive care unit. Given the proven beneficial physiologic profile and non-inferiority of APRV, our institution continues to

support the use of APRV as both a primary and rescue modality for all ventilated patients. Further studies are, however, required to validate the results of this analysis.

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Statement of Information Access:

Drs. Zachary Bauman, DO and Jill Watras, MD had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions and Conflicts of Interest:

All authors contributed substantially to this research project. There are no conflicts of interest or financial interests to disclose for any of the contributing authors. All authors involved in this research collectively designed, conducted and interpreted the data. Furthermore, all authors reviewed and approved the decision to submit this manuscript for publication. The institution providing the patient population and data collected was Henry Ford Hospital in Detroit, MI.

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