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Comparison of airway pressure release ventilation with low tidal volume ventilation in patients with acute respiratory failure

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ABSTRACT

Background and aims : Acute respiratory failure (ARF) frequently requires invasive mechanical ventilation. Though low tidal volume ventilation has improved outcome of these patients, mortality is still high. We aimed to assess whether the use of Airway Pressure Release Ventilation (APRV) results in better oxygenation compared to Low Tidal Volume (LTV) ventilation in patients with ARF.

Methods : Patients with ARF requiring mechanical ventilation were randomized into either APRV or LTV ventilation. PaO_2 and PaO_2/FiO_2 ratio were recorded and compared between the groups for the assessment of effect on oxygenation.

Results : Two hundred and two patients were included in the study with 101 patients in each group. Baseline oxygenation status, APACHE II scores, and demographic parameters were similar in both the groups. PaO2 values at the time of admission (73.73 ± 22.23 mmHg in APRV group and 75.13 ± 20.43 mmHg in LTV group; p = 0.643), at 24 hours (176.21 ± 50.70 vs 180.62 ± 53.19 mmHg; p = 0.547) and at 72 hours (208.17 ± 61.20 vs 211.36 ± 50.89 mmHg; p = 0.688) were similar between the groups. The mean values of PaO2/FiO2 ratio at 0, 24, and 72 hours were 178.67 ± 55.51 vs 186.09 ± 53.34, 285.87 ± 69.08 vs 290.95 ± 63.56, and 288.95 ± 71.51 vs 283.78 ± 59.13 mmHg respectively in APRV and LTV groups.

Conclusion : Both APRV and LTV modes improved oxygenation and had similar effects on oxygenation in patients with ARF.

Keywords : *acute respiratory failure, airway pressure release ventilation, low tidal volume ventilation, oxygenation.*

INTRODUCTION

Acute respiratory failure (ARF) is defined by the sudden onset of severe impairment of pulmonary gas exchange and is characterized by the inability of the lungs to meet the body's metabolic needs for the transport of oxygen (O_2) into the blood and/or removal of carbon dioxide from the blood.[1] More than half of the patients admitted to the ICU with stays of more than 48 hours have ARF at some point during their hospitalization[2]. And the overall mortality rates are well above 34%.[2-5] Many of these patients need ICU admission for respiratory support. With the overwhelming mortality reduction observed in ARDSNet trial,[3] positive pressure ventilation in the form of low tidal volume ventilation has been the mainstay of therapy for these patients. Despite these developments and advances, mortality in patients with ARF is still very high (35 to 46%).[4] Lately Airway Pressure Release Ventilation (APRV) has shown promising results. APRV has the following theoretical advantages:[5] a) minimizes ventilator-induced lung injury, b) improves hemodynamic profile, c) provides benefits from spontaneous breathing, d) decreases work of breathing, e) decreases need for sedation/neuromuscular blocker. Moreover, recent studies have compared APRV to ARDS net protocol ventilation and found improved efficacy and safety with APRV.[6,7] Animal models and retrospective human data have suggested that APRV may even prevent the development of ARDS.[8-10] However, despite its theoretically attractive advantages and positive results, APRV is still not routinely used in clinical practice. We aimed to assess whether APRV results in better oxygenation compared to Low Tidal Volume (LTV) ventilation in patients with acute respiratory failure requiring endotracheal intubation and mechanical ventilation.

METHODS

This was a quantitative, interventional, randomized clinical trial enrolling all eligible patients with ARF admitted to the ICU of TUTH between 2015 December to 2017 January. All patients, more than 16 years of age, requiring intubation and positive pressure ventilation for more than 72 hours were included. Exclusion criteria were: a) pregnancy, b) presence of bronchopleural fistula, c) immunocompromised state, d) cirrhosis of liver, e) terminal cancer, f) refractory hypoxemia and hypercarbia at presentation, g) patients extubated or deceased before 72 hours, and h) failure of a modality of ventilation. Randomization was done by lottery method. Sample size was calculated on the basis of a previous similar study,[16] to detect a difference in mean PaO_2 of 20mmHg, assuming that the common standard deviation is 40mmHg, with a 0.05 two-sided significance level ($Z\alpha$ =1.96), and a power of 90% ($Z\beta$ = 1.282). Considering 20% drop out rate, the final number of participants in each group was 101 patients.

Written informed consent was taken after obtaining ethical approval from Institutional Review Committee of Institute of Medicine. Demographic data, PaO_2, and PaO_2/FiO_2 ratio at 0, 24 and 72 hours of mechanical ventilation were recorded. $PaCO_2$ at 0, 24 and 72 hours, sedation requirement, inotrope requirement, length of ICU stay, duration of mechanical ventilation and all cause in-hospital mortality and baseline APACHE II score were also recorded. Patients were randomized into two groups: Low Tidal Volume (LTV) group and Airway Pressure Release Ventilation (APRV) group.

ORICARE™ V8800 Ventilator was used for all patients. Initial tidal volume was set at 6 ml/kg of predicted body weight while on VCV (Volume Control Ventilation) mode. Ventilator management in either group was as follows:

In APRV group, the initial high-pressure setting (P_{High}) was adjusted to equal the plateau pressure from the original VCV settings. The low-pressure setting was set at zero by convention. Time spent at P_{High} (T_{High}) was set based on spontaneous respiratory rate starting at 5 seconds (range 4 to 10 seconds). Duration of low pressure (T_{Low}) setting was adjusted, so that pressure release terminated at 25% to 75% of peak expiratory flow (range 0.2 to 1.0 seconds). FiO_2 was initially set at 100% and then gradually titrated down to 40% with the target SpO_2 of ≥92%. For hypoxic conditions (PaO_2 <60 mmHg and/or arterial oxygen saturation (SpO_2) <92%), P_{High} was increased by 2 cm of H_2O, followed by an increase in T_{High} by 0.5 seconds and then an increase in FiO_2 by 10% (Maximum limits of P_{High}, T_{High}, and FiO_2 were 35 cm of H_2O, 10 seconds and 100% respectively). If this did not correct even after maximum limits of P_{High}, T_{High}, and FiO_2, the patient was excluded from the study and managed with other modes of mechanical ventilation. If CO_2 was >50 mmHg and arterial pH <7.35, the P_{High} was increased by 2 cm of H_2O and T_{High} was increased by 1 second at a time. This was repeated every 60 – 120 minutes. If this did not correct even after three consecutive modifications, the patient was excluded from the study and managed with other modes of mechanical ventilation. Weaning was initiated when PaO_2 >70 mmHg, SpO_2 >92%, and pH <7.35. The primary method used to wean APRV was an alternate decrease in P_{High} by 2 cm of H_2O followed by an increase in T_{High} of 0.5 seconds to 1.0 seconds. This "drop and stretch" method was used to achieve a P_{High} of less than 10 cm of H_2O on 40% FiO_2, at which time patients were evaluated for extubation.

After initial ventilator setup, patients in LTV group remained on VCV mode. Initial minute ventilation was set at 100 mL/kg and the ventilator rate was determined by dividing this amount by the set tidal volume. Positive end expiratory pressure was set at 6 cm of H_2O. FiO_2 was initially set at 100% and then titrated down to less than 50% at a gradual decrement of 10% every half an hour with the aim to maintain SpO_2 ≥ 92% or PaO_2 ≥ 70 mmHg. If spontaneous respirations were >25 breaths per minute, the ventilator rate was readjusted. For hypoxic conditions, PEEP was increased in 2 cm of H_2O increments, repeated twice as necessary, followed by an increase in FiO_2 of 10%. This cycle was repeated as necessary until PaO_2 ≥70 mmHg or SpO_2 ≥92%. At maximum, PEEP will be increased up to 24 cm of H_2O and FiO_2 up to 100%. Weaning

from LTV was conducted on a time-based protocol similar to the APRV group. The set ventilator rate was weaned as long as spontaneous respirations are <30 breaths per minute. When weaned off LTV, patients were placed on CPAP and pressure support. When CPAP was reduced to less than 10 cm of H_2O and pressure support to 8 cm of H_2O, patients were evaluated for extubation.

Arterial blood gas analysis was done within half an hour of presentation to ICU (time 0), and at 24 hours and 72 hours and at other time points as necessary. PaO_2 and PaO_2/FiO_2 ratio, pH and $PaCO_2$ were recorded.

Data were entered into Microsoft Excel 2010 and then imported to and analyzed by using Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Ltd, Chicago, IL, USA). Independent t test was used to compare age and height of patient, baseline APACHE II score, PaO_2 at 0, 24 and 72 hours, PaO_2/FiO_2 ratio at 0, 24, and 72 hours, $PaCO_2$ at 0, 24, and 72 hours, duration of mechanical ventilation, and the duration of ICU stay. Chi-square test was used to compare gender differences, in-hospital mortality and incidence of ventilator associated pneumonia. Oxygenation and ventilation were also compared within the group at 0 hour and 72 hours to look for the effectiveness of intervention using paired t test. Mann-Whitney U test was used to analyze the use of analgesia and sedative drug doses between the groups.

RESULTS

A total of 360 patients were assessed for eligibility, of which 202 patients were enrolled in the study and included for the final analysis. Graphic outline of our study design is presented in Figure 1(Figures in brackets are the number of patients).

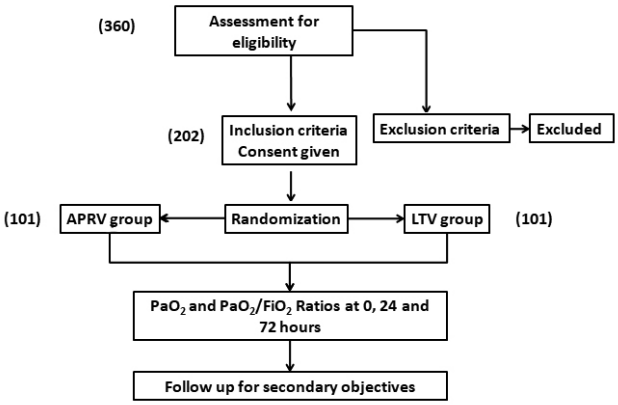

Figure 1: Graphic outline of the study design

Baseline demographic parameters were similar in both the APRV and LTV groups (Table 1). Hospital acquired pneumonia was the most common cause of acute respiratory failure requiring invasive mechanical ventilation (Table 2).

Table 1: Demographic and baseline characteristics of patients

Parameter	APRV group	LTV group	'p' value
Age (years ±SD)*	49.84 ± 18.62	52.08 ± 20.35	0.416
Gender (Female)	44.6%	41.6%	
Height (Inches ± SD)*	69.11 ± 2.17	69.32 ± 2.42	0.521
APACHE II Score	23.90 ± 4.12	24.69 ± 4.18	0.177
PaO_2 (mmHg ± SD)*	73.73 ± 22.23	75.13 ± 20.43	0.643
PaO_2/FiO_2 (mmHg ± SD)*	178.67 ± 55.51	186.09 ± 53.34	0.334

**Data are Mean ± Standard Deviation*

Table 2: Causes of Respiratory Failure at ICU Admission

Cause of Respiratory Failure	APRV [(Number of Patients (%)]	LTV [(Number of Patients (%)]	Total Number of Patients (%)
Hospital Acquired Pneumonia	49 (48.51)	37 (36.63)	86 (42.57)
Community Acquired Pneumonia	20 (19.80)	25 (24.75)	45 (22.27)
Sepsis	18 (17.82)	22 (21.78)	40 (19.80)
Trauma	2 (2)	6 (6)	8 (3.96)
Pulmonary Aspiration	6 (6)	4 (4)	10 (4.95)
Postoperative Respiratory Failure with Pneumonia	2 (2)	5 (5)	7 (3.46)
Disseminated TB	1 (1)	1 (1)	2 (0.9)
Severe Acute Pancreatitis	3 (3)	1 (1)	4 (1.9)

Oxygenation was similar and followed similar trend over time in both the groups (Table 3). Changes in oxygenation over time within the group are shown in Table 4 and 5.

Table 3: Comparison of PaO_2 and PaO_2/FiO_2 values (mmHg ± SD) at various time points

Time point	APRV group	LTV group	'p' value
PaO_2 at Admission (0 hour)	73.73 ± 22.23	75.13 ± 20.43	0.643
PaO_2 at 24 hours	176.21 ± 50.70	180.62 ± 53.19	0.547
PaO_2 at 72 hours	208.17 ± 61.20	211.36 ± 50.89	0.688
PaO_2/FiO_2 at Admission (0 hour)	178.67 ± 55.51	186.09 ± 53.34	0.334
PaO_2/FiO_2 at 24 hours	285.87 ± 69.08	290.95 ± 63.56	0.587
PaO_2/FiO_2 at 72 hours	288.95 ± 71.51	283.78 ± 59.13	0.576

Table 4: Change in oxygenation at 0 hour and 72 hour in APRV group

Parameter	Mean ± SD	p value
PaO_2 at 0 hour (mmHg)	73.73 ± 22.23	<0.001
PaO_2 at 72 hour (mmHg)	208.17 ± 61.20	
PaO_2/FiO_2 at 0 hour	178.67 ± 55.51	< 0.001
PaO_2/FiO_2 at 72 hour	288.95 ± 71.51	

Table 5: Change in oxygenation at 0 hour and 72 hour in LTV group

Parameter	Mean ± SD	p value
PaO_2 at 0 hour (mmHg)	75.13 ± 20.43	<0.001
PaO_2 at 72 hour (mmHg)	211.36 ± 50.89	
PaO_2/FiO_2 at 0 hour	186.09 ± 53.34	< 0.001
PaO_2/FiO_2 at 72 hour	283.78 ± 59.13	

Mean duration of mechanical ventilation in APRV and LTV groups was 9.24 ± 4.87 days and 8.64 ± 3.75 days respectively (p=0.332). Duration of ICU stay was 11.63 ± 5.71 days and 11.07 ± 4.16 days in APRV and LTV groups respectively.

The most common complication was ventilator-associated pneumonia (VAP) with an incidence of 19.8% in APRV and 21.8% in LTV group (p=0.729). One patient in APRV and two in LTV group had pneumothorax. Two patients in APRV group and 3 patients in LTV group had unplanned extubation. All-cause mortality during hospital stay was 25.7% in APRV group whereas it was 23.8% in LTV group. ICU mortality was 25 cases (24.5%) in APRV group and 21 (20.5%) in the LTV group. (p = 0.086).

DISCUSSION

The major findings in our study are consistent improvement in oxygenation status compared to baseline values in all patients in both the groups. But there was no statistical difference in the oxygenation indices when compared between the two groups at various specified time points of 0, 24 and 72 hours.

Use of both APRV and LTV ventilation improved oxygenation at 24 and 72 hours when compared to baseline values signifying effectiveness of both the strategies to optimize oxygenation status of patients. But neither of the two strategies was found to be superior over each other in improving oxygenation measured in terms of PaO_2 and PaO_2/FiO_2 at 24 and 72 hours. Similar findings were noted in various other studies.[9,10,11,17] Improvement in oxygenation in APRV mode is probably because of favorable increase in mean airway pressures at relatively lower peak and plateau pressures compared to conventional mechanical ventilation. This increased mean airway pressure then helps better aerate recruitable alveoli and improves oxygenation[12]. On the other hand some other studies have shown largely similar oxygenation between APRV and conventional mode of mechanical ventilation.[13] Another mechanism of improvement in oxygenation in APRV mode is that it allows spontaneous breathing at both high and low pressure levels that helps improve gas exchange through the optimization of ventilation/perfusion matching in dependent lung regions.[14]

Regarding adequacy of ventilation, mean $PaCO_2$ values were slightly higher in APRV group compared to LTV group at the time of admission but values did not reach the level of statistical significance. The $PaCO_2$ values were similar at 24 hours and at 72 hours. Maxwell et al.[16] also observed the $PaCO_2$ values for initial five days in trauma patients and found $PaCO_2$ values to be comparable.

Ventilator-Associated Pneumonia (VAP) was the major complication in both the groups. One study from India reported by Gadani et al. found the incidence of early onset VAP (within 96 hours) to be 27% and the late-onset type (>96 hours) to be 73% which is quite high as compared to our study. In other studies incidence of VAP is reported to be 9 – 27%.[15, 16] One patient in APRV group suffered pneumothorax as a complication of central venous catheterization. The other two cases of pneumothorax were in LTV group, one as a complication of central venous catheterization and the other had spontaneous pneumothorax, probably ventilator associated, secondary to high PEEP requirement. Incidence of pneumothorax is, reportedly, 14 – 87% depending on severity and duration of ARDS and mode of ventilator used.[17]

There are some limitations of this study. It was a single center study. Blinding was not feasible because of the nature of the study using two different modes of mechanical ventilation. The patient population was heterogeneous including patients with primary pulmonary disease as well as patients with pulmonary manifestations of other diseases like severe sepsis, burn, pancreatitis etc. Non-availability of esophageal manometer devices precluded measurement of transpulmonary pressures.

CONCLUSION

APRV and LTV ventilation strategies are equally effective to improve oxygenation in patients with ARF requiring endotracheal intubation and mechanical ventilation.

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