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ORIGINAL RESEARCH ARTICLE

An Investigation of Various Inspiratory Times and Inflation Pressures during Airway Pressure Release Ventilation

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Abstract

An Evaluation of Various Inspiratory Times and Inflation Pressures During Airway Pressure Release Ventilation.

Introduction: There are few recommendations how best to apply certain modes of mechanical ventilation, and the application of Airway Pressure Release Ventilation (APRV) requires strategic implementation of specific inspiratory (I-time) and expiratory times (E-time) and particular mean airway pressures (MAWP), neither of which is standardized. We sought to identify whether an ideal I-time or MAWP could be identified to favor more positive clinical outcomes.

Methods: A retrospective analysis of archived electronic health record data to evaluate the clinical outcomes of adult patients that had been placed on APRV for a target of at least 8 hours. 68 adult subjects were evaluated from a convenient sample.

Results: All outcomes of interest (surrogates) for short-term clinical outcomes to include the PaO_2/FiO_2 (P/F) ratio, Oxygen Index (OI), Oxygen Saturation Index (OSI), and Modified Sequential Organ Failure Assessment (MSOFA) scores showed improvement after at least approximately 8 hours on APRV. Most notably, there was significant improvement in P/F ratio ($p = 0.012$) and OSI ($p = 0.000$). Results of regression analysis showed MAWP as a significant positive predictor of post-APRV OSI and P high as a significant positive predictor of post-APRV MSOFA score.

Conclusion: In summary, it was found that settings for P high, Plow, and T low in addition to overall MAWP and Body Mass Index (BMI) had significant correlation to impact at least one of the short-term clinical outcomes measured with a lower setting for both P high and MAWP predictive of a better post-APRV OSI and MSOFA score.

Keywords

Airway pressure release ventilation (APRV), Ventilator settings, Inspiratory time, Inflation pressures

An Evaluation of Various Inspiratory Times and Inflation Pressures During Airway Pressure Release Ventilation

Introduction

Temporary positive pressure ventilation (PPV) is a common, potentially life-saving, modality, but it poses significant risks [1-3]. It has been established that PPV is anti-physiologic and contributes to morbidity and mortality under certain conditions [2], in part, to the development of ventilator-induced lung injury (VILI) [3,4]. Furthermore, there is a correlation between ventilation volume, airway pressure, and the development of VILI [5].

Contemporary animal studies have attempted to establish a type of strain threshold at which lung damage occurs, but there is lacking evidence as to which entity primarily contributes to principal lung injury [6,7]. It may be the avoidance of atelectrauma, however, caused from cyclic opening and closing of the lung, that is most effective in VILI prevention [8]. Some studies suggest an open lung approach is ideal because it prevents atelectrauma [8], and that the management of specific mean airway pressures (MAWP) is more protective by minimizing lung stretch compared to the traditional ap-

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proach of targeting conservative inspiratory volumes [9,10].

Although there is no consensus regarding how best to specifically apply pressure modes of PPV, Airway Pressure Release Ventilation (APRV), in particular, offers an alternative to conventional ventilation strategies. In several small-scale, observational studies, PPV with APRV has been shown to improve overall oxygenation and allow a shorter intensive care unit stay with fewer ventilator days [11]. Specifically, APRV allows for sustained lung inflation over a more prolonged period than other pressure modes of PPV [11], resulting in less cyclic opening and closing of lung units [6,11,12].

APRV

Downs and Stock introduced APRV to the healthcare market circa 1987 via a small animal study with results suggestive of APRV as a viable mode to treat ALI [13]. The following year, the same group conducted the first human trial of APRV with similar findings in that patients with ALI were able to be successfully ventilated at lower peak airway pressures compared to traditional PPV [14]. After two landmark APRV studies were published [14,15], scores of variable studies have followed, eventually establishing APRV as a means of protective lung strategy as well as a recommended early treatment for ALI or ARDS [12,16]. More recently, it has been suggested that early implementation of APRV is ideal [17,18]. There remains, however, a lack of specific recommendation on how best to apply this protective ventilation strategy [19].

Under a majority of circumstances, pressure-targeted modes of PPV are preferred over volume-targeted modes for lung protection [20]. And, although lower tidal volume ventilation compared to conventional tidal ventilation is associated with better clinical outcomes [21,22], pressure-targeted ventilation is more protective against VILI. Needhem, et al. compared the use of volume-limited ventilation to the use of pressure-limited ventilation in a large prospective cohort, noting that lung protective ventilation via pressure-limited modes was associated with a substantial long-term survival benefit in patients with ALI [23]. In 2016, the "LUNG SAFE" study by Laffey, et al. concluded that both lower plateau and lower driving pressures are associated with improved survival in ARDS [24].

Current recommendations of APRV use

To date, studies comparing APRV to conventional PPV have yet to demonstrate any significant difference in mortality outcomes [16,25,26]. Even though the oxygenation benefit of APRV use has been well established [11], there remains an overall lack of consensus concerning when to implement or how to manage this mode. Two of the more common published management strategies of APRV simply include generic recommendations for setting the four primary variables of: 1) Lung inflation pressure (P high); 2) Lung inflation time (T high); 3) Lung deflation pressure (P low) and 4) Lung deflation time (T low). Habashi and Modrykamien, et al. suggest target I-times of at least 4 seconds with a strategy of matching pre-APRV, conventional ventilator plateau pressure as a starting point for P high. Both published strategies suggest setting T low to target inducement of auto positive end-expiratory pressure (PEEP) with an initial P low setting of 0 cm H_2O [12,27]. To date, no single APRV recommendation is widely accepted in practice, and, over the last 30 years of APRV use, studies have rarely evaluated similar settings in order to assess the efficacy of a single APRV strategy [19].

Methods

This study was completed in partial fulfillment of a PhD program requirement at Nova Southeastern University. After Institutional Review Board approval, a retrospective analysis of electronic health record (EHR) data was conducted to evaluate adult subjects who were placed in APRV (*BiVent* - Maquet; Rastatt, Germany; *BiLevel* - GE Healthcare; Chicago, Illinois). Data was transferred into SPSS® for statistical analyses. Subject pre-APRV dosing and post-APRV dosing P/F ratio, OI, OSI, and MSOFA scores were calculated to represent validated predictors of clinical outcomes [28-32].

Subjects

Adults receiving APRV for a minimum of approximately 8 hours continuously were included. Subject that had been placed on APRV but found without documented settings for both I-time or ventilation pressures were excluded. Any subject lacking the information necessary to calculate neither the P/F ratio, OI, OSI or MSOFA score were excluded.

Specific procedures

A data collection tool (DCT) form (see Appendix) was created and thereafter, an electronic database was compiled utilizing File Maker Pro software. The database was converted to an Excel spreadsheet and into SPSS®. The pre-APRV and post-APRV P/F ratio, OI, OSI, and MSOFA scores were manually calculated utilizing an "if, then" formula in Excel. All other applicable metrics were analyzed via SPSS (See Table 1, Table 2 and Table 3).

Statistical analyses

Descriptive statistics were calculated with pertinent clinical data reported as a conglomerate. All change scores for clinical outcomes were calculated to identify statically significant results. Correlation matrixes were created, and a bivariate analysis was performed for all categorical variables. An additional correlational matrix was created linking potential predictor variables to change scores at pre-APRV and post-APRV dosing. A bivariate analysis of categorical variables and change

Table 1: Subject demographics.

(*n* = 68)	$\bar{x}$
Age, yr,	**($\bar{x}$; min-max, SD)**
Height, in	46.39 (18-84, 16.77)
Weight, lbs	68.10 (53-76, 4.87)
BMI	204.50 (66-356, 55.30)
	30.90 (13.32-59.23, 7.86)
(*n* = 67)	**n (%)**
Sex, male	49 (72.13)
Race	
White	44 (65.67)
Black	23 (34.32)
(*n* = 59)	**n (%)**
MICU	14 (23.72)
SICU	42 (71.18)
Neuro ICU	1 (1.69)
Other	2 (3.38)

SICU: Surgical Intensive Care Unit; MICU: Medical Intensive Care Unit; Neuro ICU: Neurosurgical Intensive Care Unit.

Table 2: Clinical data.

Pre-APRV Mode	**n (%)**
PRVC	30 (44.77)
PC	8 (11.94)
PS	23 (34.32)
Unknown	6 (8.95)
	n, $\bar{x}$ (SD)
MAWP	63, 15.03 (5.75)
FiO_2	65, 70.98 (22.08)
Pre-APRV Initiation:	$\bar{x}$ **n ($\bar{x}$; min-max, SD)**
SpO_2	67 (93.46; 78.00-100.00, 4.98)
P/F ratio[1]	44 (96.39; 26.00-222.50, 44.09)
Pre-APRV OI[2]	43 (27.34; 5.42-88.46, 14.55)
Pre-APRV OSI[3]	63 (18.99, 6.73-75.00, 9.67)
Pre-APRV MSOFA[4]	58 (8.96, 2.00-17.00, 3.20)
APRV Initial Parameters:	$\bar{x}$ **n ($\bar{x}$; min-max, SD)**
Thigh, sec	65 (6.30; 0.90-11.00, 2.65)
Tlow, sec	61 (1.21; 0.40-10.00, 1.41)
Phigh, cmH_2O	65 (24.2; 18.00-35.00, 3.33)
Plow, cmH_2O	68 (3.51; 0.00-15.00, 4.47)
MAWP, cmH_2O	66 (21.87; 4.00-31.00, 4.28)
Post-APRV Dosing	$\bar{x}$ **n ($\bar{x}$; min-max, SD)**
Total Time on APRV,hrs	68 (19.27; 6.80-24.96, 5.49)
SpO_2	68 (93.51; 70.00-100.00, 5.47)
P/F ratio[1]	21 (147.27; 33.75-300.00, 71.63)
Post-APRV OI[2]	21 (19.81; 4.19-56.29, 14.12)
Post-APRV OSI[3]	68 (12.27; 1.68-26.66, 5.75)
Post-APRV MSOFA[4]	58 (8.79; 2.00-17.00, 3.16)

[1]PaO_2/FiO_2; [2]Oxygen Index = (FiO_2*MAWP)/PaO_2*100; [3]Oxygen Saturation Index = (FiO_2*MAWP)/SpO_2*100; [4]Modified Sequential Organ Failure Assessment Score.

scores was also performed. Finally, a multiple regression analysis was conducted to identify significant predictors of P/F ratio, OI, OSI, and MSOFA scores.

Data analysis was performed via SPSS® version 24 by descriptive and inferential statistics, as applicable. A $p < 0.05$ was considered statistically significant. A stepwise regression analysis was performed to identify any bivariate between outcomes and predictors. A *p*-value < 0.2 to start was considered statistically significant for all covariates. The P/F ratio, OI, OSI, and MSOFA scores were calculated utilizing original versions of each applicable equation - listed in the "Metrics" section [28-32].

Metrics

A standard equation was used for calculating OI: (FiO_2 × MAWP)/PaO_2 × 100 [29]. Due to the intermittent unavailability of certain subject's PaO_2, pulsatile oxygen saturation (SpO_2) was used as a replacement as necessary, allowing the calculation of a modified OI (OSI): (FiO_2 × MAWP/SpO_2 × 100) [28]. The MSOFA score was calculated based on the original table by Grissom, et al. [32]. The serum bilirubin from the original SOFA was used to replace the jaundice and icterus account on the MSOFA, not affecting the overall calculation. BMI was also calculated for each subject: (mass (kg)/height^2 (m)) × 703 [33]. Pre-APRV and post-APRV change scores were calculated for P/F ratio, OI, OSI, and MSOFA.

Special considerations

Initial MSOFA scores were calculated utilizing variables available within a window of 2-hours or less, at pre-APRV or post-APRV dosing, as applicable. It was found that most labs were acquired on a 12 to 24-hour schedule depending on physician's order and unit-specific protocol. Values as close to the exact time of APRV cessation were used even if recorded from different panels.

When available, invasive arterial mean arterial blood pressure was preferred. For GCS scores, we attempted to utilize the most coincidental record to pre-APRV and post-APRV dosing timeframe; however, for post-APRV dosing, available GCS scores up to 6 hours later were used.

Results

Table 1 and Table 2 provide an overview of subject and clinical data. Subjects tended to be clinically obese and middle age with the majority, Caucasian male, most of whom received care in the SICU and were considered at greater than normal risk category. Most subjects had been placed in PRVC or PS prior to APRV initiation with a majority receiving 100% FiO_2 prior to APRV. Pre-APRV MAWP was variable but most commonly found at 12-13 cmH_2O. Pre-APRV SpO_2 was also variable but found most commonly to be 94-100%. On average, subjects received

Table 3: Outcomes.

Δ Score: Pre-Post APRV	n ($\bar{x}$, SD)	*p*-value
P/F Ratio	18 (-44.28, 66.42)	0.012
OI	18 (8.77, 20.44)	0.086
OSI	63 (6.34, 9.50)	< 0.001
MSOFA	52 (0.096, 2.45)	0.778

Paired t-test performed.

APRV consecutively for 19.27 hours with highly variable settings. Average I-time (T high) was 6.30 seconds with high range noted. MAWP was also highly variable. A paired *t*-test was performed to compare change scores (Table 3). There was noted improvement in all scores, on average, for all subjects with statistically significant improvement in P/F ratio and OSI scores. A Pearson correlation was performed for all pertinent variables. No post-APRV variables were found to have statistically significant correlation with clinical outcomes. It is worth noting that APRV duration, P high, and MAWP could be viewed as impactful based on the close proximity of each variable to statistical significance in correlation to one of the clinical outcomes.

It was determined via bivariate analysis that only the ICU in which subjects were managed during APRV was found significant with post-OSI (p = 0.022) and both pre-MSOFA (p = 0.014) and post MSOFA (p = 0.030) as well as in relation to Δ P/F ratio (p = 0.034). An investigation of individual impacts via regression analysis showed that only the MAWP ($t(50) = 5.02$, $p < 0.001$) was a significant predictor of post APRV OSI. Investigation of the unstandardized beta coefficient value (B = 0.69) showed that MAWP positively predicted post APRV OSI. A one score increase in MAWP will result to a 0.69 increase in the post APRV OSI. Further investigation of the individual impacts showed that only the APRV P high ($t(42) = 2.55$, $p = 0.02$) was a significant predictor of post APRV MSOFA score. This was the only independent variable included in the stepwise linear regression model because this was the only p-value less than the level of significance value. Investigation of the unstandardized beta coefficient value (B = 0.32) showed that P high positively predicted post APRV MSOFA score. A one score increase in P high will result to a 0.32 increase in the post APRV MSOFA score.

Discussion

It is well-known that I-time affects MAWP [34], and this study confirmed that I-time is a setting of great importance. Several covariates should be considered including comorbid conditions and/or differential diagnoses that may alter the course of care outside of the original respiratory failure as well as time delay to APRV, settings, primary and secondary diagnoses, unit of management (SICU, MICU, Neuro ICU, Other), and total continuous duration on APRV. The presence and progression of organ failure as it relates specifically to MSOFA score as well as the model of ventilator have potential to influence findings [30-32].

Clinical data

Several subjects placed on APRV mode selection did not meet the criteria to be classified APRV as originally purposed (e.g. I-time < 1 sec; I:E < 1:1). On average, subjects received higher MAWP during APRV compared to their prior PPV mode. Although average APRV I-time was 6.3 seconds, there was wide range for this setting.

Outcomes of interest

All change scores were desirable with significant improvement in P/F ratio and OSI. The P high, P low, and T low settings as well as the overall MAWP and subject's BMI each impacted at least one of clinical outcome. MAWP was identified as a significant predictor of post-APRV OSI, and P high was identified as a significant predictor of post-APRV MSOFA score. A lower setting for P high and overall lower target MAWP were associated with a better OSI, and MSOFA score. In consideration of MSOFA score as a validated indicator of acuity and predictor of mortality, subjects in this study tended to be at moderate risk overall.

APRV current considerations

There is highly variable opinion on APRV management among PPV practitioners [35]. In current literature, APRV is recommended as a protective mode of PPV, favored above a majority of traditional modes for ARDS management [36]. A recent review by Niemen, et al. suggests that APRV allows for personalization in generating intrinsic PEEP to stabilize the lung and avoid VILI [37].

APRV is thought to reduce overall lung stress and strain by diminishing dynamic alveolar heterogeneity [38]. A systematic review by Andrews, et al. suggests that, in high risk patients, the early application of APRV may prevent progression to ARDS [39]. One of the most well-known published studies of APRV cites that APRV has a similar safety profile to that of low tidal volume ventilation [26]. Evans, et al. recommends a "physiology driven" approach to ventilator setup, adopting a view that P high and T high should not necessarily be considered concurrent entities [40]. Although almost no studies have addressed specific initial settings, Madden, et al. recommends setting a P_{low} of 0 cmH_2O in order to optimize CO_2 clearance [41], but this does not address oxygenation.

Implications for practice

There is no consensus, specifically, on how PPV should be managed [35], and this study revealed a congruency with this ideal. Study results are not absolutely conclusive based upon a small, convenient sample. However, patients with comparable acuity and risk may benefit from specific APRV employment over longer pe-

riods of time as evidenced by the appreciable improvement seen in the study outcomes. It was evident there was no particular standard at our institution for ordering APRV or managing settings, although it seemed the ordering provider had the greatest bearing on initial settings implementation. It was noted that certain providers ordered similar APRV settings on all subjects, regardless.

The I-time did not render a statistically significant relationship with any of the dependent variables, although a lower P high and lower overall MAWP was attributed to better OSI and MSOFA score. Longer inflation times allow for maintenance of MAWP at lower peak pressures while decreasing cyclic opening and closing of lung units [11], but this study was not able to identify an ideal target I-time.

Further research is warranted to explore deeper concepts surrounding APRV implementation and prolonged application. Ideally, a randomized control trial in a larger cohort should be executed in which APRV is maintained for at least 24 hours consecutively. Data is still lacking as to what particular settings should be recommended as starting points in the general adult population.

Limitations and Delimitations

Arguably, the greatest limitation of this study is underpowerment given the yield of only 68 subjects from a retrospective search of the EHR within a 3-year period. The EHR system was only recently adopted, beginning circa October, 2013, limiting the timeframe of study. Certain ventilator flowsheets lacked data, and there was also difficulty to identify lab values exactly concurrent with onset and cessation of APRV.

Conclusion

Both MAWP and P high setting identified as predictors impacting clinical outcomes, but each should only be considered within the constraints of this study. In order to account for covariates, such as those associated with particular comorbidities as sepsis, organ failure, and genetic predisposition, a more in-depth evaluation is necessary.

This study gives insight into the potential of exploring preferred ways in which to apply APRV. It should be noted that the application of longer I-times should allow maintenance of MAWP at lower overall plateau pressures. The ordering provider ultimately influences initial APRV settings. Likewise, the managing medical team most directly impacts the patient's course of care and ultimately influences the manipulation of PPV.

This study confirms that the purposeful application of APRV influences short-term clinical outcomes. We agree, in alignment with the prior published recommendations of both Habashi and Modrykamien, et al. it is still a good strategy to set T low to target inducement of auto PEEP with an initial P low setting of 0 cmH_2O [14,29]. The results of this study would suggest that both MAWP and P high should be applied judiciously and maintained as low as possible.

Based upon the study results, we offer the following recommendations for APRV use: 1) Utilize the lowest possible P high to achieve acceptable oxygenation, 2) Closely attend to T low, titrating as necessary but maintaining IRV and adequate CO_2 clearance, and 3) Adjust for lowest possible MAWP while allowing for adequate inflation and acceptable oxygenation.

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Authors Contribution

1. Tim W Gilmore - Literature search, Data collection, Study design, Analysis of data, Manuscript preparation, Review of manuscript.
2. Robert E Walter - Study design, Review of manuscript.
3. Patrick C Hardigan - Analysis of data, Review of manuscript.
4. Clifton F Frilot II - Analysis of data.
5. Guy M Nehrenz - Review of manuscript.

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