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Current practice of using the airway pressure release ventilation mode in acute respiratory distress syndrome patients among respiratory therapists in Saudi Arabia

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Abstract

Background: There is a limited data examining the practice of using the airway pressure release ventilation mode for patients with acute respiratory distress syndrome among respiratory therapists.

Objectives: To evaluate the current practice and barriers when using airway pressure release ventilation mode in the management of patients with acute respiratory distress syndrome.

Methods: A cross-sectional online survey was disseminated between November 2022 and April 2023 to respiratory therapists in Saudi Arabia. Descriptive statistics were used to analyze the respondents' characteristics.

Results: Overall, 802 respiratory therapists (male: 59.60%) completed the survey. Five hundred nineteen (64.71%) did not receive training on airway pressure release ventilation mode. Moreover, 325 (40.52%) and 391 (48.75%) did not know if airway pressure release ventilation was used at their hospitals and if the mode was managed via protocol with acute respiratory distress syndrome patients. Of the participants, 276 (34.41%) reported that plateau pressure should be used as a target when setting P-high initially, while 427 (53.24%) believed that the initial P-low should be equal to 0 cmH_2O. Moreover, 468 (58.36%) believed that the initial T-high should be between 4 and 6 s, while 548 (68.33%) believed the initial T-low should be a set time (between 0.4 and 0.8) seconds. The most appropriate intervention to improve ventilation and oxygenation was to increase the P-high, which was reported by 370 (46.14%) and 326 (40.65%) respiratory therapists, respectively. Inadequate training was the most common barrier (678, 84.54%) to airway pressure release ventilation implementation.

Conclusion: Airway pressure release ventilation management varies between respiratory therapists which may be due to inadequate training and the absence of protocols.

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Introduction

Airway pressure release ventilation (APRV) is a technique of ventilation that falls under the category of intermittent mandatory ventilation, and it is known for its safety and effectiveness.[1,2] The APRV mode is a ventilation strategy that utilizes continuous positive airway pressure (CPAP) while using an inverse ratio of inspiratory to expiratory time. This mode enables patients to engage in spontaneous breathing, irrespective of the ventilator cycle, hence, enhancing their comfort.[3] It is aimed to enhance oxygenation and accomplish lung recruitment while simultaneously managing safe peak inspiratory pressure in patients with acute respiratory distress syndrome (ARDS) and acute lung injury.[4] Several studies have shown significant enhancements in gas exchange and arterial oxygenation while using the APRV mode in comparison to other ventilator modes among patients with ARDS.[5–7] Significantly, the use of the APRV mode has shown a resultant reduction in both hospitalization duration and ventilator dependency in adult patients with COVID-19 who need mechanical ventilation.[8]

Although the APRV mode is often used as a therapeutic intervention for patients with ARDS in several intensive care units (ICUs) globally, the specific parameters for this mode may vary in nomenclature; however, the underlying principles remain comparable to those of other traditional modes.[2,9] The settings for APRV include P-high, T-high, P-low, and T-low. It is crucial for healthcare providers using this mode to possess knowledge about the underlying justifications and distinctions associated with these various settings on mechanical ventilators. The term "P-high" refers to the elevated level of CPAP that is set for an extended duration, known as "T-high." This therapeutic approach aims to optimize lung capacity and facilitate the recruitment of alveoli. The term "P-low" refers to the setting of a low level of CPAP for a brief duration known as "T-low." More importantly, the predominant portion of carbon dioxide elimination occurs at this specific pressure level. The principal objective of this mode is to ensure sufficient oxygenation while facilitating lung recruitment without causing excessive lung expansion during the high-pressure phase (P-high). Additionally, it aims to provide adequate ventilation during the low-pressure phase (P-low) to prevent air from getting trapped in the lung.[2,9,10] In contrast, the time-controlled adaptive ventilation approach modifies traditional APRV settings by dynamically adjusting T-low and T-high according to the patient's lung physiology. This adaptation enhances lung protection by minimizing VILI, thereby reducing the morbidity and mortality associated with ARDS.[11,12]

We have previously assessed the current practice of using the APRV mode among physicians and nurses working the critical care units.[13] However, there is a limited data examining the practice of using the APRV mode for those with ARDS among respiratory therapists (RTs).[13,14] Hence, this research was aimed to evaluate the current practice of the APRV mode in the management of patients with ARDS from the prospective of RTs. Additionally, this study aimed to identify the obstacles preventing RTs from using this ventilatory mode with ARDS patients in the critical care units.

Materials and methods

Study design and instrument

In this cross-sectional study, the questionnaire was adapted from previous literature by experts in the fields of respiratory therapy, ICU medicine, and pulmonary medicine, all of whom possess prior experience with the APRV mode.[10,13,15,16] The questionnaire consisted of 23 items divided into 3 sections: demographics, knowledge, and the clinical practice of the APRV mode and barriers to its implementation. The choices in the second section of the questionnaire were derived from available references and strategies for using and operating the APRV mode.[10,15,16] A pilot test was conducted with a sample of 10 RTs to assess the clarity and relevance of the survey questions.

Data collection and sampling

The survey instrument was made accessible and disseminated on the SurveyMonkey platform between November 2022 and April 2023. Invitations to RTs were sent via professional organizations established on social media platforms, as well as the Saudi Society for Respiratory Care. This study used a convenience sample technique, with the primary focus being on RTs in Saudi Arabia. At the start of the questionnaire, the researchers provided a clear explanation of the need of obtaining the participants' agreement, along with pertinent details about the study itself. Additionally, contact information was made available to participants for any further inquiries or concerns. Prior to initiating the survey, informed consent was obtained through the following statement: "By answering the first question, you consent to participate in this research study and authorize the use of your anonymized data for research purposes." To minimize redundancy and recurrent feedback, participants could only complete the survey link once. The anticipated duration for completing the survey was 10 min.

Data analysis

We gathered and transferred the data to an Excel file. Next, the main author verified data initially, and then a second author was available for cross-verification to reduce the likelihood of errors during data entry. The Statistical Package for the Social Sciences (SPSS) version 29 was used to perform the statistical analysis. Descriptive statistics were used to analyze the respondents' characteristics which were presented as frequency and percentages. We used Chi-square to compare groups. $p \leqslant 0.05$ was considered statistically significant.

Ethical approval

Ethical approval was obtained from bioethical committee at Jazan University (44/04/364) prior to the start of the study.

Results

Demographic data of study participants

Overall, 802 RTs of whom 478 (59.60%) were males, completed the online survey. Most of the respondents came from the Central Region (308: 38.40%), followed by the Western Region (229: 28.55%). Of the participants, 716 (89.28%) held a bachelor's degree and 462 (57.61%) had 1–5 years of clinical experience. Almost all of the participants worked in critical care areas (764: 95.26%) and had a mean (standard deviation) of 3 ± 2 number of ARDS patients care per shift. Surprisingly, 446 (55.71%) had not used the APRV mode before and 519 (64.71%) had not received training on it. Moreover, 325 (40.52%) and 391 (48.75%) did not know if APRV was used at their hospitals and if the APRV mode was managed using a protocol with ARDS patients. The full details about the demographic data of the study participants are in Table 1.

The current practice of using APRV mode with ARDS patients

When APRV mode is initiated with ARDS patients, 276 (34.41%) of RTs observed that the P-high should be equal to the plateau pressure on a conventional ventilator, while 427 (53.24%) observed that the P-low should be equal to 0 cmH_2O. Moreover, 468 (58.36%) believed that the T-high should be between 4 and 6 s, while 548 (68.33%) believed the T-low should be a set time (between 0.4 and 0.8) seconds (see Table 2).

The majority of RTs (680: 84.79%) reported that the maximum tidal volume should be between 4 and 6 ml/kg, while 478 (59.60%) observed that the maximum P-high should be 35 cmH_2O (Table 2). The most appropriate intervention to improve ventilation and oxygenation in ARDS patients was to increase the P-high was reported by 370 (46.14%) and 326 (40.65%) RTs, respectively. Figures 1 and 2 have the full details of interventions ranked by RTs.

During weaning process of ARDS patients on APRV mode, 242 (30.17%) RTs stated that the P-high should gradually be decreased to a target of 15 cmH_2O. More than half of RTs (447, 55.74%) stated that T-high should gradually increase to a target of 10 s. Last, when the patient is stable, 628 (78.30%) reported that the criteria to switch the patient to CPAP would be: $FiO_2 \leqslant 0.4$, P-high $\leqslant 10$ cmH_2O, and T-high $\geqslant 10$ s (see Table 2).

Common barriers to not using APRV mode with ARDS patients

RTs reported several barriers. The majority of RTs reported that inadequate training (678: 84.54%), followed by the absence of protocols (369: 46.01%) and lack of scientific evidence (244: 30.42%) were the most common barriers. Other reported barriers included the existence of alternative respiratory management for ARDS patients and not being the preferred option by the managing physician (see Figure 3).

Discussion

To the best of our knowledge, only limited studies have evaluated the perception and prevalence of using the APRV mode among RTs in Saudi Arabia.[17–19] Therefore, this is the first study to assess the current practice of RTs in Saudi Arabia and the barriers to utilizing APRV in patients with ARDS. Overall, our findings revealed inconsistent responses regarding the initial settings and the criteria for weaning and discontinuation of the APRV. However, there was modest consensus concerning the management of APRV parameters to maximize ventilation and oxygenation.

Over the past three decades, the APRV mode has become a significant rescue strategy for ventilating patients with ARDS and hypoxemia who are refractory to conventional mechanical ventilation (CMV).[2,20] Since it contributes extensively to promoting spontaneous breathing, patient-ventilator synchrony, stabilizing hemodynamic status, and optimizing gas exchange.[2,21] Nevertheless, the assessment of APRVs clinical efficacy has been hampered in clinical trials due to inconsistency in the APRV settings.[22,23] Current evidence has identified the lack of a standardized approach that is widely used for setting the APRV mode in clinical practice.[24] Similarly, relevant studies of RTs in Saudi Arabia have revealed moderate levels of APRV knowledge, with significant variations in adopting and managing APRV parameters due to a lack of protocol and training programs, which are hindering proper initiation and manipulation of these settings.[17,18] Accordingly, our findings have revealed that utilization of the APRV mode is very limited in 28% of the respondents' hospitals and, as a result, only about 44% of the RTs have ever used the APRV mode because it is not available in their institutions. Additionally, almost 73% of the participants managed APRV settings based on their clinical experience without following an existing protocol. Furthermore, 65% of the participants had

Table 1. Demographic data of study participants ($n = 802$).

Demographics	Frequency (%) or $M \pm SD$
Gender, *n* (%)	
Male	478 (59.60)
Female	324 (40.40)
Geographical location, *n* (%)	
Central region	308 (38.40)
Western region	229 (28.55)
Southern region	219 (27.31)
Eastern region	34 (4.24)
Northern region	12 (1.50)
Academic qualification, *n* (%)	
Associate degree	24 (2.99)
Bachelor's degree	716 (89.28)
Postgraduate degree	62 (7.73)
Years of clinical experience, *n* (%)	
<1 year	160 (19.95)
1–5 years	462 (57.61)
6–10 years	142 (17.71)
>10 years	38 (4.74)
Usual clinical practice area, *n* (%)	
Critical care areas (ICU, CCU, SICU, etc.)	764 (95.26)
Noncritical areas (medical ward, surgical ward, etc.)	309 (38.53)
Emergency room (ER)	341 (42.52)
Number of ARDS patients care for per shift	3±2
Used APRV, *n* (%)	
Yes	356 (44.39)
No	446 (55.61)
Received training on APRV, *n* (%)	
Yes	283 (35.29)
No	519 (64.71)
Utilization of APRV in your hospital, *n* (%)	
Yes	226 (28.18)
No	251 (31.30)
I don't know	325 (40.52)
APRV managed via protocol, *n* (%)	
Yes	215 (26.81)
No	196 (24.44)
I don't know	391 (48.75)

ICU: intensive care unit; CCU: coronary care unit; SICU: surgical intensive care unit; ARDS: acute respiratory distress syndrome; APRV: airway pressure release ventilation; SD: standard deviation.

never received training on the application of the APRV mode. This can lead to significant differences in initiating and managing APRV parameters. Inappropriate settings of the four parameters (P-high, P-low, T-high, and T-low) may have adverse consequences for the patient's health. Therefore, healthcare practitioners must adhere to validated guidelines to optimize clinical outcomes and minimize health risks.[10,25]

According to our study analysis, it was found that 34% of the respondents thought that P-high should be equivalent to the P-plat on CMV. A subsequent study revealed analogous findings, with approximately 48% of their participants stating that the P-high should be set similarly to the P-plat on the CMV.[16] These results are supported by the APRV protocols, which indicated that a P-high setting should be equal to the P-plat, typically $\leqslant 30\,cmH_2O$.[10,25] Importantly, a greater P-high may be warranted in morbidly obese patients with poor lung compliance.[25]

Over half (53%) of our respondents pointed out that P-low should be initiated at $0\,cmH_2O$, which is aligned with the APRV guidelines.[10,25] Miller et al. showed identical outcomes, only with a higher proportion among their participants (78%).[16] This significant variation can be explained by the limited size of their study sample, which involved only 100 participants compared to the 802 RTs in our study. Previous literature has shown that P-low is set at $0\,cmH_2O$, which is compatible with lung dynamics since the T-low time will ensure that the lungs are not fully

Table 2. Current practice of using APRV mode with ARDS patients.

Initial APRV settings	Frequency (%)
Initial P-high setting, *n* (%)	
At 25 cmH_2O	194 (24.19)
Equal to the plateau pressure on a conventional ventilator	276 (34.41)
Equal to the mean airway pressure on a conventional ventilator	86 (10.72)
2–5 cmH_2O above mean airway pressure on conventional ventilator	183 (22.82)
To achieve a tidal volume of 6 ml/kg/pbw (predicted body weight)	63 (7.86)
Initial P-low setting, *n* (%)	
0 cmH_2O	427 (53.24)
2–5 cmH_2O	160 (19.95)
Match to PEEP from a conventional ventilator	117 (14.59)
Variable depending upon oxygenation	98 (12.22)
Initial T-high setting, *n* (%)	
2–3 s	189 (23.57)
4–6 s	468 (58.36)
Per desired minute ventilation and respiratory rate	96 (11.97)
Per I:E ratio	49 (6.11)
Initial T-low setting, *n* (%)	
Set time (i.e., 0.4–0.8 s)	548 (68.33)
Per desired I:E ratio	134 (16.71)
When expiratory flow equals 25%–49% peak expiratory flow	80 (9.98)
When expiratory flow equals 50%–75% peak expiratory flow	40 (4.99)
APRV management	
The maximum allowed Vt, *n* (%)	
4–6 ml/kg	680 (84.79)
7–8 ml/kg	59 (7.36)
9–10 ml/kg	24 (2.99)
>10 ml/kg	24 (2.99)
No limit	15 (1.87)
The maximum allowed P-high, *n* (%)	
30 cmH_2O	102 (12.72)
35 cmH_2O	478 (59.60)
40 cmH_2O	195 (24.31)
No maximum	27 (3.37)
Utilization of pressure support with APRV, *n* (%)	
Yes	646 (80.55)
No	156 (19.45)
Weaning and discontinuation	
Criteria to wean P-high, *n* (%)	
Reduce P-high gradually in attempt to reach a target of 20 cmH_2O	143 (17.83)
Reduce P-high gradually in attempt to reach a target of 15 cmH_2O	242 (30.17)
Reduce P-high gradually in attempt to reach a target of 10 cmH_2O	234 (29.18)
Reduce P-high gradually in attempt to reach a target of 5 cmH_2O	183 (22.82)
Criteria to wean T-high, *n* (%)	
Increase T-high gradually in attempt to reach a target of 7 s	150 (18.70)
Increase T-high gradually in attempt to reach a target of 10 s	447 (55.74)
Increase T-high gradually in attempt to reach a target of 15 s	170 (21.20)
Increase T-high gradually in attempt to reach a target of 20 s	35 (4.36)
Criteria to switch clinically stable ARDS patient to CPAP, *n* (%)	
FiO_2 ⩽40%	82 (10.22)
P-high ⩽10 cmH_2O	54 (6.73)
T-high ⩾10 s	38 (4.74)
All criteria mentioned (FiO_2 ⩽40%, P-high ⩽10 cmH_2O, and T-high ⩾10 s)	628 (78.30)

APRV: airway pressure release ventilation; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; Vt: tidal volume; CPAP: continuous positive airway pressure; I:E: inspiratory to expiratory.

deflated and thus generate "auto-positive end-expiratory pressure PEEP," preventing the intrathoracic pressure from being equal to atmospheric pressure.[21,26,27] Recent recommendations have pointed out that setting P-low at 5 cmH_2O may contribute to reduced driving pressure and the risk of atelectrauma, but this is still undecided.[28]

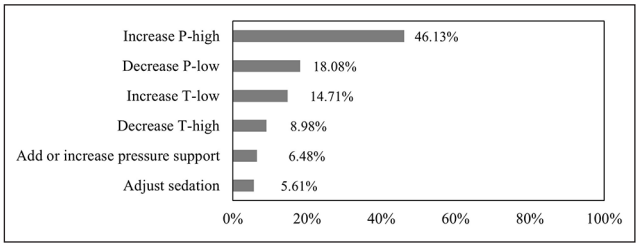

Figure 1. Percentage of the participants' most appropriate intervention to improve ventilation in ARDS patients while using APRV mode.
APRV: airway pressure release ventilation; ARDS: acute respiratory distress syndrome.

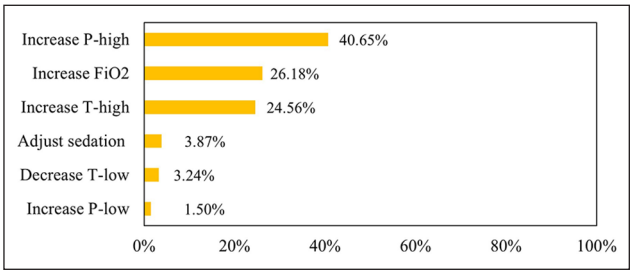

Figure 2. Percentage of the participants' most appropriate intervention to improve oxygenation in ARDS patients while using APRV mode.
APRV: airway pressure release ventilation; ARDS: acute respiratory distress syndrome.

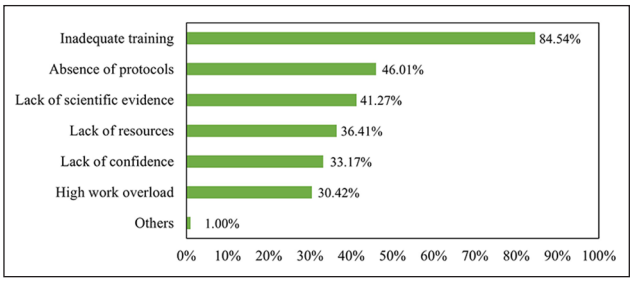

Figure 3. The most common barriers to not using the APRV mode reported by RTs.
APRV: airway pressure release ventilation; RT: respiratory therapist.

Published guidelines recommend the onset of T-high between 4 and 6 s.[10,25] These guidelines were followed by 58% of our study respondents, which is similar to the findings of Miller et al., where 65% of their participants were committed to the recommended time.[16] Conceptually, an extended T-high is thought to favorably promote alveolar recruitment since it offers adequate time for lung units to be inflated, thereby improving gas exchange.[2] Prolonged inflation periods of lung units during the T-high have been found to significantly promote spontaneous breathing, improve ventilation-perfusion matching, and reduce peak airway pressure.[29,30]

Interestingly, our study outcomes found that 68% of our respondents stated that T-low should be set between 0.4 and 0.8 s. The T-low setting can be the most challenging of the four basic variables as it must be adequate to avoid cyclic lung collapse and allow alveolar ventilation. Therefore, published APRV protocols recommend the use of expiratory flow analysis to determine the effective time of T-low.[10,25] In comparison, Miller et al. reported that only 37% of their participants adhered to the guidelines, while 39% used an arbitrary set time.[16] Indeed, Habashi pointed out that the T-low should be carefully adjusted to achieve expiratory flow termination at 75% of peak expiration.[15] As such, previous literature has demonstrated that an appropriate setting of the T-low maintains optimal end-expiratory volume, stabilizes alveoli and, hence, prevents lung derecruitment.[26,31] Therefore, APRV is considered a rescue mode and a life-saving approach in patients with ARDS.

Management and titration of the APRV mode are distinctive since its ventilation settings are very different from those of conventional modes. Nonetheless, a significant majority (85%) of our participants were highly experienced in manipulating APRV settings targeting 4–6 ml/kg of Vt during the release phase. In contrast, Miller et al. observed significant deviations in their study responses, with 38% claiming that Vt should be between 6 and 8 ml/kg and 36% claiming that there was no upper limit to maximum Vt during the release phase.[16] It is acknowledged that the resultant tidal volume can be extremely unpredictable and challenging to independently manage in a ventilated patient in the APRV mode as a result of the spontaneous inspiratory effort.[2] Nevertheless, the tidal volume should be consistent with a lung protection strategy targeting 4 and 6 ml/kg to reduce the risk of lung injury. It is indirectly processed by the T-low; when tidal volume is insufficient (<4 ml/kg), expiratory time is prolonged, and vice versa.[26] Additionally, almost 60% of our respondents indicated that the maximum P-high should be 35 cmH_2O, which is a higher proportion compared to the findings of relevant study, where only 45% reported similar results.[16] It is strongly suggested to limit the P-high within the range of 30–35 cmH_2O to reduce peak alveolar pressure, lung overdistension, and the risk of ventilator-induced lung injury (VILI).[2,32]

Several intervention techniques can be applied to enhance ventilation and oxygenation in patients with ARDS. Among these strategies, increasing the P-high was the most reported maneuver by 46% and 41% of RTs, respectively. Previous studies have demonstrated that prolonged P-high acts on an "open lung" approach as it positively contributes to alveolar recruitment and thus improves oxygenation status.[26] Likewise, it is evident that raising P-high, T-high, or both concomitantly could significantly treat hypoxemia and hypercapnia, given that it will increase the mean airway pressure, resulting in a greater oxygenation status, and will improve alveolar ventilation by optimizing release lung volumes.[25] In addition,

respiratory acidosis can be relieved by intermittent release periods at P-low, which enhances alveolar ventilation and facilitate CO_2 clearance.[21,26] Meanwhile, Modrykamien et al. have pointed out that the T-high should be reduced by 0.5–1 s in cases of severe hypercapnia.[10]

Regarding the weaning process of the APRV mode, our study results found that 30% of the RTs indicated that the P-high should be gradually decreased until it reaches 15 cmH_2O, and 56% of the RTs pointed out that the T-high should be gradually elevated to 10 s. In agreement with this, it is widely recommended to wean the P-high by 2 cmH_2O every 2–6 h until reaching 15 cmH_2O and increase the T-high by 1–2 s until it reaches 10 s.[10,26] Concerning the discontinuation criteria of the APRV mode, our findings demonstrated that 78% of the RTs observed that the criteria to switch the ARDS patient to CPAP would be having an FiO_2 $\leqslant$0.4, a P-high $\leqslant$10 cmH_2O, and a T-high $\geqslant$10 s. Our findings are in parallel with previously published ARDS protocols, which have indicated similar weaning parameters and suggested switching the stable patient to the CPAP mode with positive end-expiratory pressure (PEEP) equal to a P-high and pressure support of 5 cmH_2O to minimize lung tissue derecruitment.[25,26]

The clinical application of the APRV mode in a patient with ARDS can be hampered by certain barriers. Concerning this, our respondents claimed that inadequate training, the absence of protocols, and a lack of scientific evidence have been the most challenging obstacles to utilizing the APRV mode in the clinical setting. These findings have demonstrated that the APRV mode is not widely used as an initial mode, being classified as an alternative mode resorted to in refractory cases. In line with this, earlier studies have indicated that the main challenge of not applying APRV to patients with ARDS is the lack of clinical trials.[23] These barriers can be overcome through holding workshops and developing evidence-based guidelines to raise the knowledge and self-confidence of healthcare providers in adopting the APRV mode. In addition, clinical trials may be conducted to investigate the mechanism and benefits of this mode.

Strengths and limitations

This study is valuable since it is the first study to assess the current practice of RTs in Saudi Arabia and the barriers to utilizing APRV in patients with ARDS. Another strength of this study is the recruitment of a widely representative sample involving target populations from various regions in an attempt to generalize the results across the country. However, there are also certain limitations. The cross-sectional design of the study did not identify the cause and effect of inadequate APRV knowledge. Additionally, using a self-reported survey may provide subjective data, which can introduce recall bias. Furthermore, the inability to determine a precise response rate, as the survey was distributed through intermediaries, namely RT directors and the Saudi Society for Respiratory Care, and we did not have access to the total number of surveys disseminated. Therefore, additional studies are recommended to investigate the mechanism of the APRV mode and to develop guidelines that maximize the RTs' understanding of APRV in Saudi Arabia.

Conclusion

Only modest consensus for the management of APRV settings was detected among RTs, indicating a lack of comprehension of the APRV mechanism. Inadequate training, the absence of protocols, and a lack of scientific evidence have been the most challenging obstacles to utilizing the APRV mode in the clinical setting. Additional studies are strongly recommended to investigate the mechanism of the APRV mode and establish evidence-based guidelines that maximize Saudi Arabian RTs' understanding of APRV.

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None.

Author contributions

Conceptualization, AAA, AMA, JSA, HA, NYA, and MMA; methodology, RAS and JSA; software, RAS and SMA; validation, HA, MAA, NYA, and MSM; formal analysis, MAA and NYA; investigation, SMA and MMA.; resources, MSM and MMA; data curation, RAS and JSA; writing—original draft preparation, AHA, JSA, HA, MAA, NYA, and MMA; writing—review and editing, AAA, AMA, AHA, JSA, HA, MAA, NYA, and MMA; visualization, AAA and AMA; supervision, AAA and AMA; project administration, HA; funding acquisition, MMA. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical considerations

Ethical approval for this study was obtained from bioethical committee at Jazan University (44/04/364) prior to the start of the study.

Informed consent

Written informed consent was obtained from participants before completing the study questionnaire.

Trial registration

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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