

The efficacy of airway pressure release ventilation in acute respiratory distress syndrome adult patients: A meta-analysis of clinical trials

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Abstract:

BACKGROUND: To recruit poorly ventilated lung areas by providing active and adequate oxygenation is a core aspect of treating patients with acute respiratory distress syndrome (ARDS). The airway pressure release ventilation (APRV) mode is increasingly accepted as a means of supporting patients with ARDS. This study aimed to determine whether the APRV mode is effective in improving oxygenation, compared to conventional ventilation, in adult ARDS patients.

METHODS: We conducted the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched for clinical trials in PubMed, Embase, Web of Science, and the Cochrane Library until April 2019. We included all studies comparing APRV and other conventional mechanical ventilation modes for adult ARDS patients. Our primary outcome was oxygenation status (defined as the day 3 PaO₂/FiO₂ ratio). The secondary outcomes were the length of stay (LOS) in the intensive care unit (ICU) and mortality. Sensitivity analyses were performed including studies with conventional low-tidal volume ventilation as a comparator ventilation strategy.

RESULTS: We included six clinical trials enrolling a total of 375 patients. The day 3 PaO₂/FiO₂ was reported in all the studies, and it was significantly higher in patients receiving APRV (mean difference [MD] 51.9 mmHg, 95% confidence intervals (CI) 8.2–95.5, *P* = 0.02, *I*² = 92%). There was no significant difference in mortality between APRV and the other conventional ventilator modes (risk difference 0.07, 95% CI: –0.01–0.15, *P* = 0.08, *I*² = 0%). The point estimate for the effect of APRV on the LOS in ICU indicated a significant reduction in the ICU LOS for the APRV group compared to the counter group (MD 3.1 days, 95% CI 0.4–5.9, *P* = 0.02, *I*² = 53%).

CONCLUSION: In this study, using the APRV mode may improve oxygenation on day 3 and contribute to reducing the LOS in ICU. However, it is difficult to draw a clinical message about APRV, and well-designed clinical trials are required to investigate this issue.

Keywords:

Acute respiratory distress syndrome, airway pressure release ventilation, meta-analysis, oxygenation

Acute respiratory distress syndrome (ARDS) is a serious condition requiring admission to an intensive care unit (ICU), and it is associated with significant hospital mortality.^[1] In the clinical progression of ARDS, refractory hypoxemia is the most important pathophysiological

feature.^[2,3] A core aspect of treating ARDS is to recruit poorly ventilated lung areas by providing active and adequate oxygenation.^[4] The management plan of ARDS, therefore, involves invasive mechanical ventilation.^[5] Low tidal volume (LTV) ventilation and conventional positive end-expiratory pressure are the standard mechanical ventilation strategies

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for treating ARDS.^[5] However, invasive mechanical ventilatory management of ARDS patients is complicated and associated with ventilator-induced lung injuries due to the heterogeneity in the distribution of alveolar consolidation.^[4]

Ideally, invasive mechanical ventilatory modes used for managing ARDS patients should maintain the alveoli open throughout the ventilator cycle to reduce repetitive alveolar collapse and over distention, to minimize lung injuries.^[5] Airway pressure release ventilation (APRV) is a ventilation mode proposed as an advantage compared to conventional mechanical ventilation.^[6-10] The main feature of APRV is delivering a continuous positive airway pressure (CPAP) from a high pressure (P_{high}) to low pressure (P_{low}), with a brief intermittent release phase.^[7,11] This allows using an inversed inspiration to expiration (I: E; $T_{\text{high}} : T_{\text{low}}$) ratio, in which T_{high} is the period to use the CPAP to recapture the collapsed alveoli, and T_{low} allows both adequate ventilation and complete exhalation. The process advances alveolar recruitment and oxygenation while reducing physical damage to the alveoli.^[6,7]

Due to the possible physiologic advantages over other ventilatory modes, many animal and human observational studies explored the immediate hemodynamic and respiratory consequences of using APRV in treating ARDS.^[9,12-16] Many studies suggested that applying APRV protocols enhance alveolar recruitment and gas exchange in patients with ARDS.^[10] Based on the observational studies, a few clinical trials have been published to assess the efficacy of the early application of APRV in ARDS patients to improve oxygenation and reduce mortality. However, the efficacy of APRV in patients diagnosed with ARDS is still controversial, mainly due to the heterogeneity in APRV application and the initiation time.^[17] The aim of this study, therefore, was to assess the efficacy of APRV, compared with other modes of mechanical ventilation, to improve oxygenation and reduce mortality in critically ill adults with ARDS.

Methods

The current study is a meta-analysis conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.^[18] The protocol was approved by the King Abdullah International Medical Research Center (protocol number SP19/141/R). The main objective of this study was to assess the efficacy of APRV, compared with other modes of mechanical ventilation, to improve oxygenation in critically ill adults with ARDS.

Eligibility criteria and search strategy

Published clinical trials investigating APRV in the management of adult ARDS patients, admitted to ICU,

were retrieved from the following databases: MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials database, from inception to April 2019. All clinical trials in which APRV was compared with any alternative conventional mode have been included. We excluded observational studies, crossover studies, experimental animal studies, and review articles from the search. The following keywords were combined in defining the relevant articles: "Airway Pressure Release Ventilation," "APRV," "Continuous Positive Airway Pressure," "CPAP Ventilation," "Respiratory Distress Syndrome," "ARDS," "Acute Lung Injury," and "ALI." We searched for additional articles using the reference list and gray literature. We included only articles published in English.

Study selection and data extraction

Two investigators conducted the primary search independently and screened the titles and abstracts for potentially eligible articles. Subsequently, the full text of potentially relevant articles was assessed for inclusion, according to the documented oxygenation measured as the $\text{PaO}_2/\text{FiO}_2$ on day 3 after the initiation of the mechanical ventilation. The secondary data related to all-cause mortality, i.e., ICU or hospital mortality and ICU length of stay (LOS) were collected.

Data extraction forms were used to extract the data regarding the primary and secondary outcomes, in addition to information on the type of study, year of publication, type of conventional mode, number of patients in APRV group and conventional mode, the proportion of patients who died, and the baseline and day 3 $\text{PaO}_2/\text{FiO}_2$ ratio.

Assessment of the risk of bias in the included studies

The risk of bias was assessed using the Cochrane Collaboration's tool to determine the risk of bias in the clinical trials.^[19] The assessment tool has seven domains, assessing random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other sources of bias.^[19] Based on the assessment of each domain, the quality ranged from low, high risk, or with concern bias. The quality criteria of each article were reviewed by two independent reviewers (TI and FO), and the results compared. The third reviewer resolved any conflicts.

Statistical approach

The meta-analysis was performed using RevMan, version 5.3 (Cochrane Collaboration). For both improving in oxygenation, that measured as the day 3 $\text{PaO}_2/\text{FiO}_2$ ratio, and the LOS in ICU, the outcome

variables were continuous variables and expressed as mean differences (MDs). Most of the studies reported this outcome as mean and standard deviation (SD); however, we estimated the mean and SD using the proposed method for the studies that only reported medians.^[20] Mortality was managed as a dichotomous variable, expressed as risk differences (RD). The pooled estimate and their 95% confidence interval (CI) were used to summarize the weighted effect size for each study using random effect model, and $P < 0.05$ was set for statistical significance. Heterogeneity was assessed using the I^2 test, with an I^2 higher than 70% considered as substantial heterogeneity. We performed a sensitivity analysis by comparing the studies with conventional LVT strategy as the comparator group because it is considered the standard ventilatory strategy to manage ARDS patients.

This study has been registered in King Abdullah International Medical Research Center database reference number SP19.141.R.

Results

Study selection and study characteristics

In the initial search in the electronic databases, we identified 276 citations for review. After the removal of duplicates, we screened the titles and abstracts of 168 records and assessed the full text of six clinical trials, enrolling a total of 375 patients.^[21-26] The six clinical trials were included in the analysis [Figure 1].

Table 1 displays the main characteristics of the selected studies. The mean age of the APRV group was 48 years (range 40–57 years), and for the conventional mode group, 47 years (range 42–53 years). Four studies compared APRV versus conventional modes that use

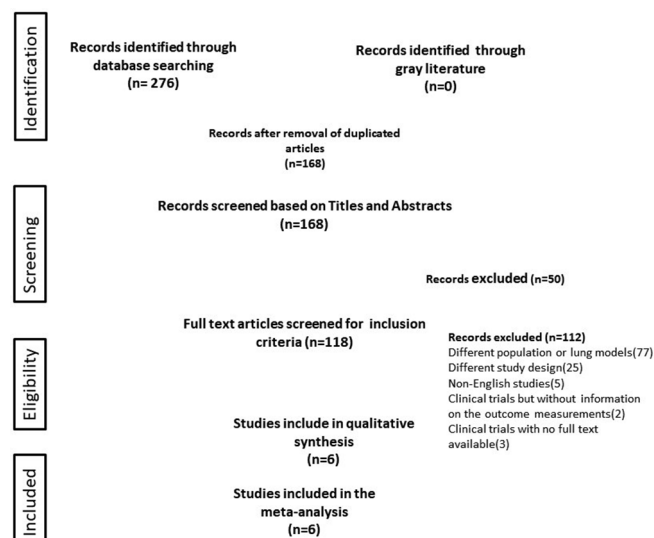


Figure 1: Flowchart of literature screening and study selection of the meta-analysis

LVT strategy in which tidal volume (Vt) set between 4 and 6 mL/kg,^[21,23,25,26] and two studies compared APRV versus synchronized intermittent mandatory ventilation in which they used Vt more than 6 mL/kg. For the main outcome, all studies reported the day 3 PaO₂/FiO₂, in the tables or figures of the articles. The mortality outcome was reported in all studies, but the LOS in ICU, in only five studies.^[21,23-26] The definition of ARDS varied between the studies, some studies defined ARDS according to the American–European Consensus Conference on ARDS, and others used the Berlin definition of ARDS.^[27,28]

Risk of bias and quality of evidence

The results of the quality assessment of the studies are provided in Table 2. Two studies had a low bias for the randomization process.^[25,26] All studies had a high risk of bias due to deviations from the intended intervention as the investigators were not blinded. The majority of the studies had a moderate risk of bias in terms of the measurement of the outcome, due to the same reason. Based on the direction of the bias for each domain, the overall bias was with concern.

Study outcomes

The day 3 PaO₂/FiO₂ was significantly higher in patients receiving APRV compared to other conventional ventilatory modes (MD 51.9 mmHg, 95% CI 8.2–95.5, $P = 0.02$, $I^2 = 92%$) [Figure 2]. This yield similar results when the analysis includes only conventional mode with LTV strategy as the comparator ventilation approach (MD 68.5 mmHg, 95% CI 6.84–130.1, $P = 0.03$, $I^2 = 94%$) [Figure 3].

The forest plot comparing the mortality is presented in Figure 4. There was no significant difference in mortality between APRV and the other conventional ventilator modes (RD 0.07, 95% CI: –0.01–0.15, $P = 0.08$, $I^2 = 0%$). With LTV as the comparator ventilation strategy, there was no significant reduction in mortality in the APRV group (RD 0.09, 95% CI: –0.01–0.21, $P = 0.16$, $I^2 = 40%$) [Figure 5]. The point estimate for the effect of APRV on the LOS in ICU indicated a significant reduction in the ICU LOS for the APRV group compared to the counter group (MD 3.1 days, 95% CI 0.4–5.9, $P = 0.02$, $I^2 = 53%$) [Figure 6]. The point estimate changed with the LTV as the comparator ventilation strategy (MD 3.7, 95% CI: –0.41–7.84, $P = 0.08$; $I^2 = 60%$) [Figure 7].

Discussion

Key finding

This study contributed new evidence to the growing body of literature related to the effectiveness of using APRV in managing ARDS patients. We demonstrated that APRV is associated with an improvement in the day 3 oxygenation and not associated with reduction in

Table 1: Characteristics of the clinical trials that included in the meta-analysis

Study	Years	Comparator mode and tidal volume strategy	Sample size	Age (years)	PaO ₂ /FiO ₂ at baseline (mmHg), mean (SD)	PaO ₂ /FiO ₂ at day 3 (mmHg), mean (SD)
Putensen <i>et al.</i> ^[21]	2001	AC-PC with LVT (Vt=6 ml/kg)	AC-PC: 15 APRV: 15	AC-PC: 42 (5) APRV: 40 (5)	AC-PC: 250 (14) APRV: 250 (14)	AC-PC: 175 (38) APRV: 320 (58)
Varpula <i>et al.</i> ^[22]	2004	SIMV + PS-PC (Vt=8-10 ml/kg)	SIMV-PC: 28 APRV:30	SIMV-PC: 44 (4) APRV: 49 (5)	SIMV-PC: 164 (6) APRV: 150 (7)	SIMV-PC: 165 (60) APRV: 195 (76)
Maxwell <i>et al.</i> ^[23]	2010	SIMV + PS-VC with LVT (Vt=6 ml/kg)	SIMV-VC: 32 APRV:31	SIMV-VC: 42.4 (16) APRV: 40 (14)	SIMV-VC: 363 (36) APRV: 320 (33)	SIMV-VC: 280 (32) APRV: 300 (45)
Li <i>et al.</i> ^[24]	2016	SIMV-VC (Vt=6-8 ml/kg)	SIMV-VC: 26 APRV: 26	SIMV-VC: 53 (9) APRV: 54 (8)	SIMV-VC: 118 (36) APRV: 119 (35)	SIMV-VC: 212 (55) APRV: 220 (46)
Zhou <i>et al.</i> ^[25]	2017	AC-VC with LVT (Vt=6 ml/kg)	AC-VC: 67 APRV: 71	AC-VC: 52 (15) APRV: 51 (15)	AC-VC: 138 (56) APRV: 121 (46)	AC-VC: 180 (68) APRV: 280 (83)
Hirshberg <i>et al.</i> ^[26]	2018	AC-VC with LVT (Vt=6 ml/kg)	AC-VC: 17 APRV: 17	AC-VC: 51 (14) APRV: 57 (15)	AC-VC: 121 (50) APRV: 109 (67)	AC-VC: 162 (34) APRV: 168 (98)

A/C=Assist control ventilation, AC-PC=Assisted control with pressure control ventilation, APRV=Airway pressure release ventilation, LTV=Low tidal volume, PC=Pressure control ventilation, SIMV=Synchronized intermittent mandatory ventilation

Table 2: Assessment of the risk of bias in the included studies

Reference	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Putensen <i>et al.</i> 2000	AC-PC versus APRV	Some concerns	High	Some concerns	Some concerns	Low	Some concerns
Varpula <i>et al.</i> 2004	SIMV-PC versus APRV	Some concerns	High	Some concerns	Some concerns	Some concerns	Some concerns
Maxwell <i>et al.</i> 2010	SIMV-VC versus APRV	Some concerns	High	Some concerns	High	Low	Some concerns
Li <i>et al.</i> 2016	SIMV-VC versus APRV	Some concerns	High	Some concerns	Some concerns	Some concerns	Some concerns
Zhou <i>et al.</i> 2017	AC-VC versus APRV	Low	High	Low	Some concerns	Low	Some concerns
Hirshberg <i>et al.</i> 2018	AC-VC versus APRV	Low	High	Low	Low	Low	Low

A/C=Assist control ventilation, AC-PC=Assisted control with pressure control ventilation, APRV=Airway pressure release ventilation, LTV=Low-tidal volume, PC=Pressure control ventilation, SIMV=Synchronized intermittent mandatory ventilation

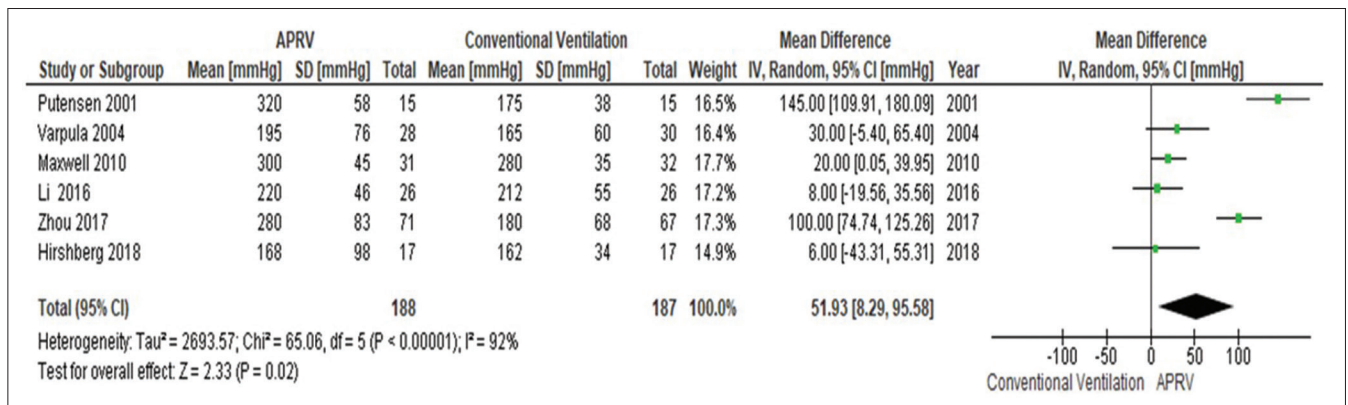


Figure 2: The forest plot comparing the ventilation PaO₂/FiO₂ at day 3 between airway pressure release ventilation and conventional ventilatory modes

mortality. APRV was also associated with a significant reduction in the LOS in ICU. However, the finding was inconsistent when limiting the analysis to the LTV ventilation strategy.

Comparison to the literature

The key concept for managing ARDS patients is to use protective ventilation strategies to avoid

over-distension or lung damage from the cyclical opening and closing of the alveoli. The APRV mode is able to optimize gas exchange while reducing the risk of lung injury. In addition, APRV allows for spontaneous breathing, which leads to alveolar recruitment, improve functional residual capacity, and a reduced elastic work of breathing, enhancing gas exchange.^[7]

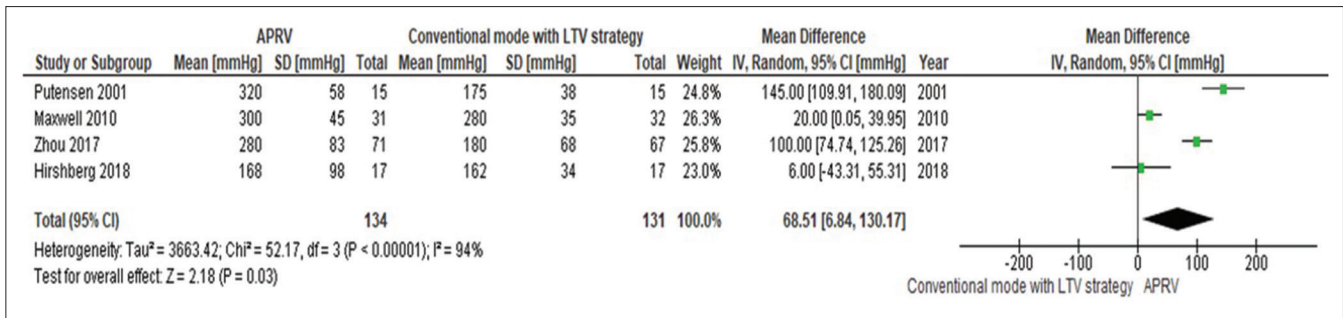


Figure 3: The forest plot comparing the ventilation PaO₂/FiO₂ at day 3 between airway pressure release ventilation and conventional mode with low-tidal volume strategy

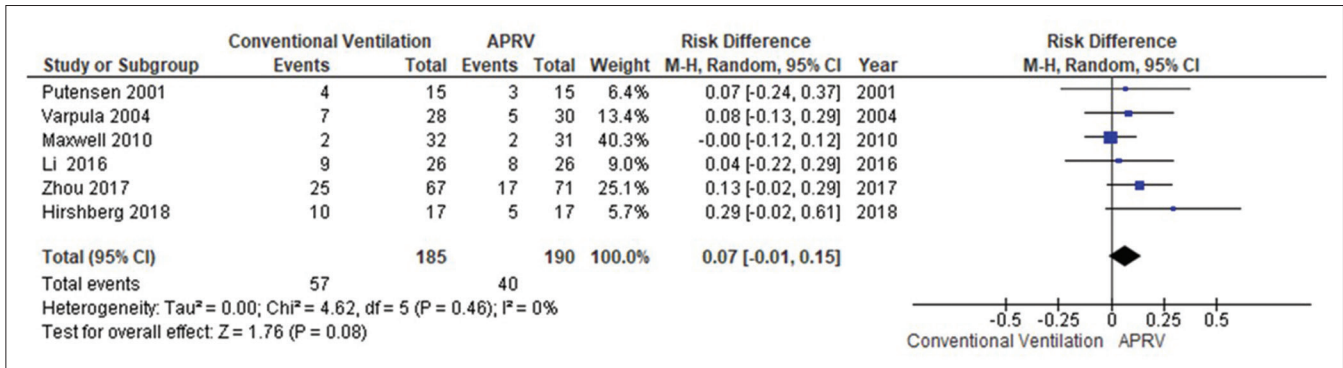


Figure 4: The forest plot comparing the mortality between airway pressure release ventilation and conventional ventilatory modes

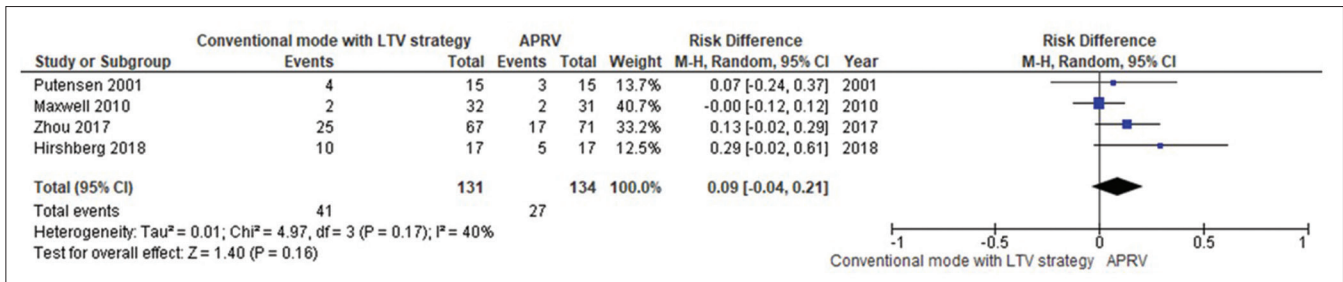


Figure 5: The forest plot comparing the mortality between airway pressure release ventilation and conventional mode with low-tidal volume strategy

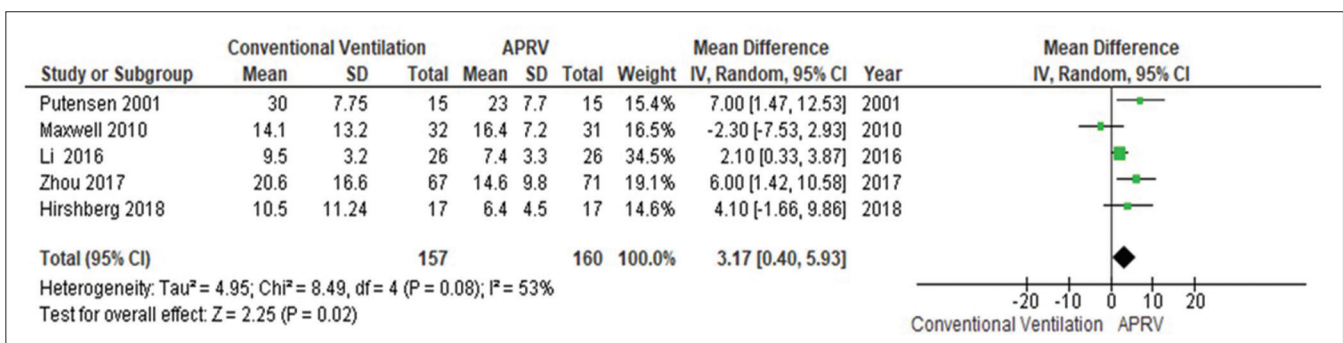


Figure 6: The forest plot comparing the length of stay in the intensive care unit between airway pressure release ventilation and conventional ventilatory modes

During the study period, three systematic review and meta-analysis studies comparing the efficacy of APRV to other ventilatory modes in managing ARDS patients were published in 1 year (2019–2020).^[17,29,30] This indicates the support for using the

APRV mode as a concept of open lung ventilation in the management of ARDS. In the first, in April 2019, Carsetti *et al.* compared the number of ventilator-free days in intubated ARDS patients, using the APRV mode compared with a conventional ventilation strategy.^[17]

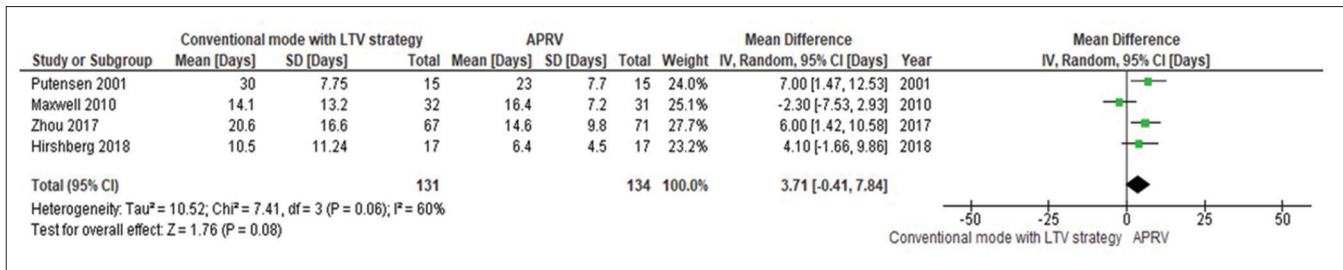


Figure 7: The forest plot comparing the length of stay in the intensive care unit between airway pressure release ventilation and conventional mode with low-tidal volume strategy

The authors included five clinical trials,^[21,22,24-26] and they reported a higher number of ventilator-free days at 28 days and lower hospital mortality in the ARDS patients treated with APRV compared to conventional ventilation. Furthermore, they reported no difference in PaO₂/FiO₂ on day 3 between the APRV group and the conventional ventilatory mode group, which was inconsistent with the result of the current study. This variation can be attributed to different clinical trials that had been included for the pooled estimate for the outcome measured. Thus, Carsetti *et al.* included only three out of five clinical trials in the analysis of PaO₂ / FiO₂ at day 3,^[17] and only two clinical trials for the mortality (defined as hospital mortality). In the current study, we included six clinical trials in the analysis of PaO₂/FiO₂ on day 3 and mortality. The mortality outcome was measured as all-cause mortality (hospital or ICU mortality), explaining the difference between the two studies' results.

The second meta-analysis study examined the efficacy of APRV in managing ARDS patients, focused primarily on reviewing the all-cause mortality rate.^[29] They reported a reduction in the ARDS adult patients' mortality, managed with APRV compared with conventional ventilation strategies. They included six clinical trials, including a study that was excluded from our meta-analysis because it published an abstract in which we could not obtain the full text to assess it in detail. In this second meta-analysis, the authors used relative risk to estimate the mortality where we expressed the mortality outcome as RDs. Although relative risk and RD provide two different assessments on the same outcome, the RD offers a straightforward interpretation of the absolute difference. Thus, RD describes the difference in the observed risk of mortality between APRV and comparator interventions; therefore, it provides more directly relevant information than relative measures.^[31] Although the point estimate for mortality outcome in this current study does not fall across the significant threshold, it still indicates a potential reduction in mortality. The consistency between the literature suggests evidence to support the efficacy of APRV to reduce mortality among ARDS from a clinical perspective.

The last study, in January 2020, including observational studies and clinical trials, demonstrated that using APRV in managing ARDS patients could increase the day 3 PaO₂/FiO₂.^[30] However, a major limitation of the third study was combining the results from observational studies and clinical trials, due to the heterogeneity in the methodology which would affect the validity of the results. In addition, the different characteristics of the pooled population from the observational studies and clinical trials would also affect the results.

Both Lim *et al.* and Xuri *et al.* reported an improvement in the day 3 oxygenation PaO₂/FiO₂ ratio in the APRV group, compared to the conventional ventilatory mode group. In our study, we found a significantly higher day 3 PaO₂/FiO₂ ratio in the APRV group, and this remained unchanged when we include studies that implement conventional mode with LTV strategy. A possible mechanism that could explain this finding is that APRV increases lung recruitment and oxygenation in addition to the preservation of spontaneous breathing. Those advantages may promote better ventilation/perfusion matching and less need for sedation, and subsequently, higher ventilation free days. Several studies indicated that higher ventilation free days show lower mechanical ventilation duration and decreased ICU LOS.^[32,33] This has been demonstrated in the first meta-analysis study that examined the efficacy of APRV in treating ARDS patients. Thus, patients with ARDS who are ventilated with APRV mode have higher number of ventilated free days than the conventional ventilation strategy.

Strength and limitation

Our study has several limitations. The studies included in this meta-analysis have some concerns related to quality as it is difficult to blind the assessor in terms of the intervention arm. Second, the variation of the baseline PaO₂/FiO₂ ratio due to the severity of the disease, may explain the heterogeneity in the primary outcome. Third, the mortality outcome measure in this study was not standardized in which it was defined either as ICU, hospital, or 28 days mortality. The consequence of this is that it may underestimate the effect of APRV on mortality, which explains the inconsistency of the

results in terms of the reduction in mortality. Fourth, the validity of our results could be affected by the publication bias as did not use the funnel plot as a statistical assessment for publication bias due to the low number of included studies.^[34] We used a nonstatistical approach. We reviewed the unpublished clinical trials on the clinical trial registries as failure to publish neutral or negative trials could influence the accuracy of reported outcomes.^[34] At the time of carrying this study, we found ten registered clinical trials; two were published,^[25,26] three have been withdraw due to slow requirement, and the remaining five in the recruiting process. For the selection bias due to restricting our research to the English language literature, we do not anticipate that it will cause deviation of the results as clinical trials tend to register and publish their study in the English language journals.

Since the first description of APRV, the definition of APRV was inconsistent. The terms biphasic and APRV are used interchangeably. In the current analysis, we used different combinations to capture studies with different terminology. The lack of an APRV protocol with standardized settings and parameters, implemented in the different trials, may affect the outcomes that were measured. Not only is there paucity in the number of high-quality trials in humans, but there is a lack of consistency in how APRV is applied. In the literature, there is no standardized protocol for starting APRV as there is a conflict data with regard to the potential risks of using APRV. Many reports demonstrated that barotrauma risk among APRV groups did not differ from the conventional ventilatory mode.^[25,26,29] On the other hand, some studies reported a potential safety profile of using APRV including improvement in cardiac function and cardiac index during spontaneous respiration and subsequently improved systematic blood flow.^[15,21,35] Other studies reported a potential reduction in the risk of ventilator-associated pneumonia using APRV mode.^[36] However, those potential benefits should be carefully reviewed as most of those studies were from lung simulation studies or different study populations.

Conclusion

In this study, using the APRV mode may have improved oxygenation on day 3 and contributed to a reduction of the LOS in ICU. Although the point estimate for mortality outcome does not across the significant threshold, it still indicates a potential reduction in mortality. In light of this study's limitations, it is crucial to consider the effect of the heterogeneity and the quality of the included studies in interpreting those findings. Nevertheless, the data regarding the use of APRV for ARDS appear promising, and further studies are required to validate those results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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