Airway Pressure Release Ventilation in Adult Patients With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis

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Objectives: To evaluate the efficacy and safety of airway pressure release ventilation in critically ill adults with acute hypoxemic respiratory failure.

Data Sources: A systematic literature search of MEDLINE via PUBMED, EMBASE, the Cochrane Library, published conference proceedings and abstracts, reference lists of eligible studies and review articles, and hand searches of relevant journals and trial registers.

Study Selection: Eligible studies included randomized controlled trials published between years 2000 and 2018, comparing airway pressure release ventilation to any ventilation mode, in critically ill adults with acute hypoxemic respiratory failure and reporting at least one mortality outcome.

Data Extraction: Screened citations were reviewed and extracted independently by two investigators onto a prespecified proforma.

Data Synthesis: There were 412 patients from seven randomized controlled trials included in the qualitative and quantitative data synthesis. Airway pressure release ventilation was associated with a significant mortality benefit (relative risk, 0.67; 95% CI, 0.48–0.94; $I^2 < 0.1\%$; $p = 0.97$) and improvement in day 3 Pao_2/Fio_2 ratio (weighted mean difference, 60.4; 95% CI, 10.3–110.5). There was no significant difference in requirement to initiate rescue treatments including inhaled pulmonary vasodilators, prone positioning, or extracorporeal membrane oxygenation (relative risk, 0.51; 95% CI, 0.22–1.21; $I^2 = 64.7\%$; $p = 0.04$). The risk of barotrauma was only reported in three studies and did not differ between groups (relative risk, 0.39; 95% CI, 0.12–1.19; $I^2 < 0.1\%$; $p = 0.99$).

Conclusions: In adult patients requiring mechanical ventilation for acute hypoxic respiratory failure, airway pressure release ventilation is associated with a mortality benefit and improved oxygenation when compared with conventional ventilation strategies. Given the limited number of patients enrolled in the available studies, larger multicenter studies are required to validate these findings. (*Crit Care Med* 2019; XX:00–00)

Key Words: acute hypoxemic respiratory failure; acute respiratory distress syndrome; airway pressure release ventilation

Mortality associated with acute respiratory failure requiring mechanical ventilation remains high, with an occurrence of approximately 50% in critically ill patients with hypoxemic respiratory failure (1). A pivotal randomized controlled trial (RCT) demonstrated improved outcomes with low tidal volume (LTV) ventilation but is now nearly 20 years old (2). Most subsequent studies examining alternative ventilatory strategies have failed to demonstrate benefit and there remains an unmet need for effective interventions in severely hypoxic patients (3–6).

Airway pressure release ventilation (APRV) is a pressure-controlled mode of ventilation that allows continuous, unrestricted spontaneous respiration in addition to intermittent mandatory ventilation (7, 8). As conventionally described, the majority of the respiratory cycle occurs at the higher of two set pressures (P_{high}), with brief periods of lower pressure (P_{low}), often set as zero. Theoretical benefits of APRV include increased lung recruitment, reduced atelectrauma, improved ventilation/perfusion (V/Q) matching and lower sedation and neuromuscular blockade requirements and hemodynamic benefits (7, 9). Observational studies have demonstrated an association with improved oxygenation and lower requirement for the initiation of rescue therapies including extracorporeal membrane oxygenation (ECMO) (10).

Recent RCTs suggest that APRV may improve survival (11, 12). However, concerns remain about the safety of APRV, especially the risk of volutrauma and barotrauma (13, 14). To address this, we performed a systematic review and

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meta-analysis with the aim of evaluating whether APRV, compared with other modes of mechanical ventilation, decreased all-cause mortality in critically ill adults with acute hypoxemic respiratory failure.

MATERIALS AND METHODS

The systematic review was prospectively registered on the International prospective register of systematic reviews (PROSPERO) (CRD42018114916) (15).

Eligibility Criteria

We included RCTs of adult patients admitted to ICU with acute hypoxemic respiratory failure requiring mechanical ventilation, in which APRV was compared with an alternate mode of ventilation. Observational studies, crossover studies, and studies that did not report mortality were excluded. Studies published before the year 2000 were also excluded as this was before the publication of the landmark Acute Respiratory Distress Syndrome Network trial which established LTV ventilation strategies as the current gold standard strategy and thus reduced inter-study heterogeneity with regard to the control mode used as well as excluded modes of ventilation proven to be harmful (2).

Data Sources and Search Strategy

We performed a comprehensive search of MEDLINE via PUBMED, EMBASE, and the Cochrane Library from January 2000 to November 2018 without any language restrictions. Our search also included published conference proceedings and abstracts, reference lists of eligible studies and review articles, and hand searches of relevant journals and trial registers. The search was repeated prior to final analyses. The following key search terms (and their synonyms) were used as follows: APRV, hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), and critically ill.

Study Selection

Two reviewers (J.L., E.L.) independently conducted the primary search and screened the titles and abstracts of articles. The full text of potentially eligible studies were retrieved and independently assessed by both reviewers. The corresponding authors of relevant studies were contacted for further information if there was uncertainty over the eligibility of the study (16, 17). There were no major disagreements related to study eligibility criteria or outcomes. Minor disagreements between the authors were resolved through discussions without the requirement for a mediator.

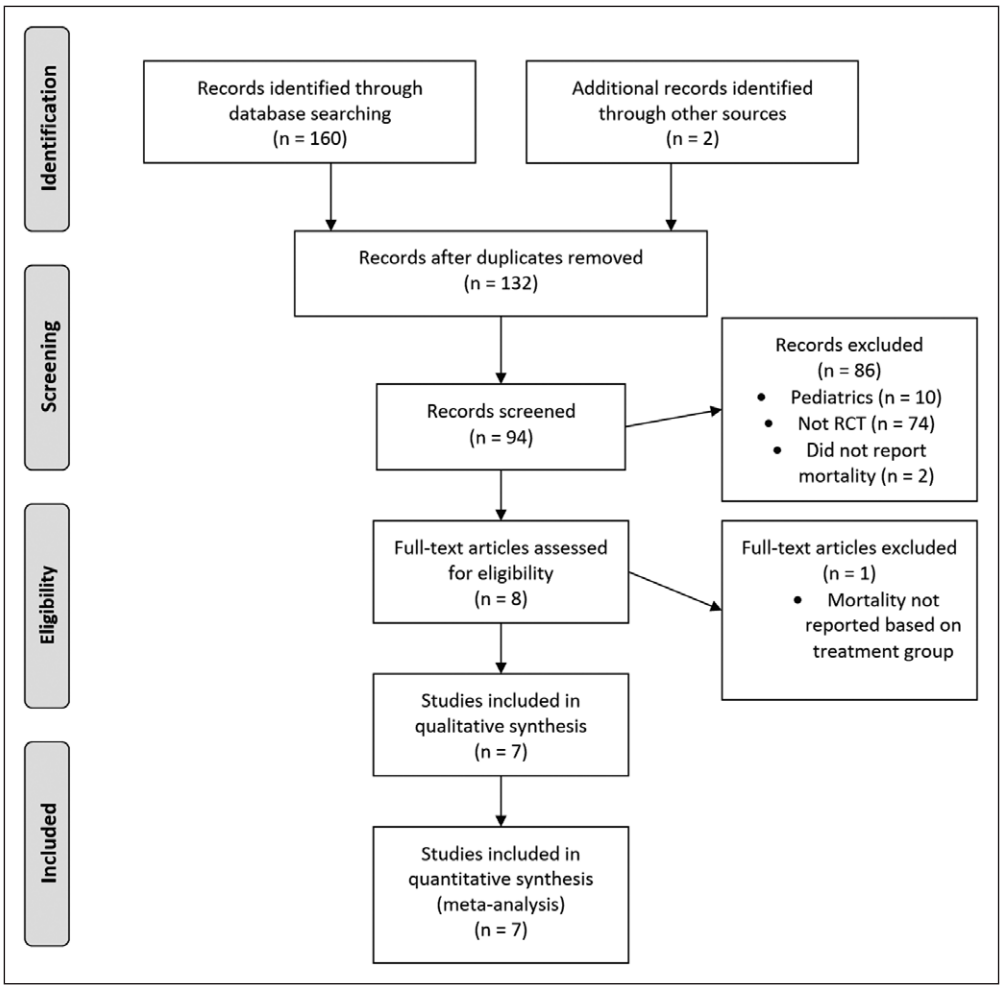

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram demonstrating study selection for inclusion in the quantitative meta-analysis. RCT = randomized controlled trial.

Data Extraction and Quality Assessment

A prespecified proforma was used to extract relevant data on the study design, patient demographics, intervention, control, and outcomes. Missing data were requested from the corresponding authors of the relevant studies. The risk of bias in individual studies was assessed using the Cochrane Risk of Bias tool (18).

Data Analyses

The primary outcome measure was the all-cause mortality at the longest reported time point. Secondary outcomes included risk of all-cause barotrauma defined as new pneumothorax, pneumomediastinum, or subcutaneous emphysema occurring after initiation of APRV or the comparator ventilation mode, occurrence of cardiac arrest, Pa_{O_2}/Fi_{O_2} on day 3, number of ventilator-free days to day 28, and requirement for rescue interventions defined as ECMO, proning, neuromuscular paralysis, recruitment

TABLE 1. Risk of Bias of Individual Studies

References	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Hirshberg et al (12)	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Li et al (21)	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk
Maxwell et al (22)	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Putensen et al (23)	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Unclear risk
Varpula et al (24)	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Zhou et al (11)	Low risk	Low risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Patel et al (17)	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

maneuvers, high-frequency oscillatory ventilation, inhaled nitric oxide, and/or inhaled epoprostenol.

Where there were three or more studies with an outcome of interest, a quantitative synthesis via meta-analysis was conducted. Standardized mean differences (SMDs) and weighted mean differences (WMDs) for continuous outcomes and risk ratios (RRs) for binary outcomes were calculated with 95% CIs and two-sided *p* values for each outcome. SD were derived from SEMs or 95% CIs based on formulae from the Cochrane Handbook if not directly reported (19). The results were pooled and analyzed primarily using the random-effects model due to anticipated significant inter-study heterogeneity. Fixed-effects model analysis were also conducted and reported if results were substantially different. Heterogeneity was assessed using the chi-square test and I^2 statistic. Sensitivity analyses excluding studies assessed to have a high risk of bias were performed.

We prespecified subgroup analyses comparing APRV with studies using LTV as the comparator mode versus alternative ventilation modes, and studies that exclusively enrolled patients with ARDS versus more heterogeneous pathologies. Risk of publication bias was assessed using Egger's test and a funnel plot. Trial sequential analysis (TSA) was also conducted to assess the risk of false inferences assuming a relative risk reduction in mortality of 33% from a baseline rate of 30%, double-sided $\alpha = 5\%$, $\beta = 20\%$ (power of 80%) and heterogeneity based on model variance (20). Stata 14 (StataCorp, College Station, TX) was used for all analysis except TSA which was conducted using TSA software (Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

RESULTS

There were 162 citations initially identified for review and seven studies with a total of 412 participants (11, 12, 17, 21–24) were included in the qualitative and quantitative data analysis (**Fig. 1**).

The causes of acute hypoxemic respiratory failure included both pulmonary and extrapulmonary pathology, with the majority related to pneumonia or trauma. The mean Acute Physiology and Chronic Health Evaluation II score was 20.26 (SD 5.4), and 308 patients (74.8%) were diagnosed with ARDS or acute lung injury (this was used in studies predating the Berlin definition [25]). The study and participant characteristics are provided in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/E886). The overall quality of the studies was moderate (**Table 1**).

OUTCOMES

Mortality

APRV was associated with a significant decrease in all-cause mortality (RR, 0.67; 95% CI, 0.48–0.94) without significant heterogeneity ($I^2 < 0.1\%$; $p = 0.97$) (**Fig. 2**). There was no evidence of publication bias based on the funnel plot (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886) or Egger's test (0.49; 95% CI, –0.17 to 1.15; $p = 0.11$).

The results were similar when analysis excluded four studies at high risk of bias (RR, 0.61; 95% CI, 0.41–0.91; $I^2 < 0.1\%$; $p = 0.87$) (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886).

On subgroup analysis, the point estimate for the effect of APRV on mortality was similar when including studies exclusively with LTV as a comparator ventilation strategy (RR, 0.67; 95% CI, 0.47–0.96; $I^2 < 0.1\%$; $p = 0.94$) compared with the single study in which APRV was compared with an alternative ventilation strategy (pressure-controlled synchronized intermittent mandatory ventilation aiming for tidal volume 8–10 mL/kg), (RR, 0.67; 95% CI, 0.24–1.86) (**Supplemental Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886) (24).

The point estimate for the effect of APRV on mortality was also similar for studies exclusively enrolling patients with ARDS versus more heterogeneous pathologies (RR, 0.70; 95% CI, 0.47–1.03; $I^2 < 0.1\%$; $p = 0.915$) versus (RR, 0.61; 95% CI, 0.31–1.17; $I^2 < 0.1\%$; $p = 0.74$), respectively (**Supplemental Figs. 4** and **5**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886).

The results were also similar on sensitivity analysis, limited to studies reporting short-term mortality (longest available of 28-d, 30-d, ICU, and in-hospital mortality), (RR, 0.69; 95% CI, 0.49–0.98; $I^2 < 0.1\%$, $p = 0.91$) (**Supplemental Fig. 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886).

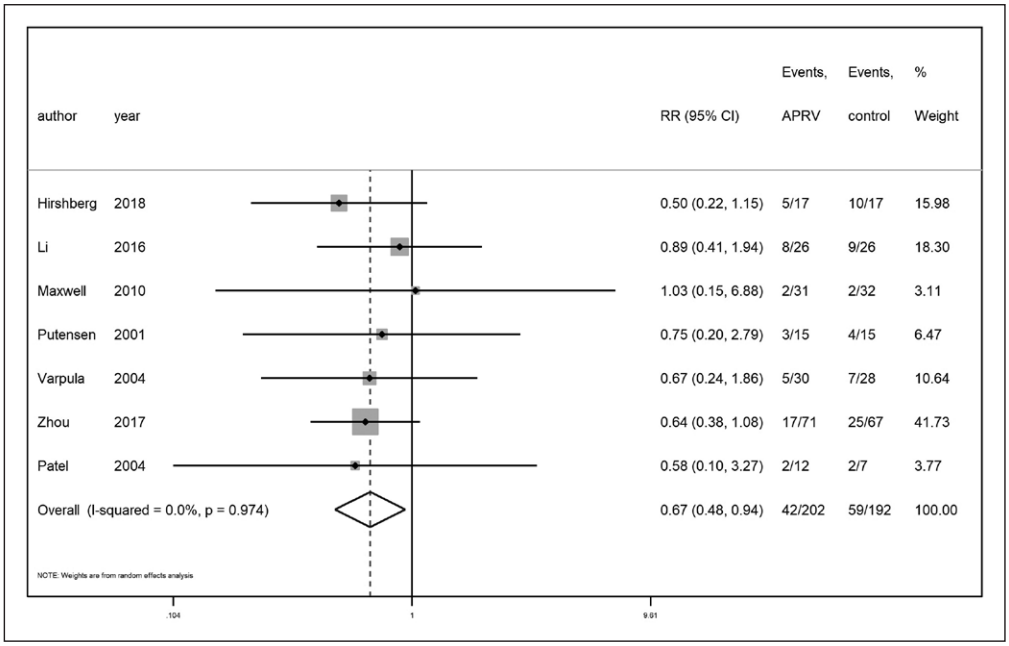

Figure 2. Forest plot of studies comparing airway pressure release ventilation (APRV) versus alternative modes of mechanical ventilation on mortality. RR = relative risk.

TSA demonstrated that although the cumulative Z-curve surpassed the conventional 95% confidence boundary favoring APRV, the trial sequential monitoring boundaries adjusting for sequential testing were not crossed and the required information size of 602 participants was also not achieved (**Supplemental Fig. 7**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886).

Oxygenation Rescue Strategies and Ventilation

Day 3 Pao_2/Fio_2 was reported by five studies and was significantly higher in patients receiving APRV although there was significant inter-study heterogeneity (WMD, 60.4; 95% CI, 10.3–110.5; I^2 = 93.4%; $p < 0.01$) (**Fig. 3**). The results were similar when assessing SMD in day 3 Pao_2/Fio_2 (SMD, 0.82; 95% CI, 0.60–1.05; I^2 = 87.8%; $p < 0.01$) (**Supplemental Fig. 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886). There was no significant difference in requirement to initiate rescue treatments which was reported by four studies (RR, 0.51; 95% CI, 0.22–1.21; I^2 = 64.7%; $p = 0.04$) (**Supplemental Fig. 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886).

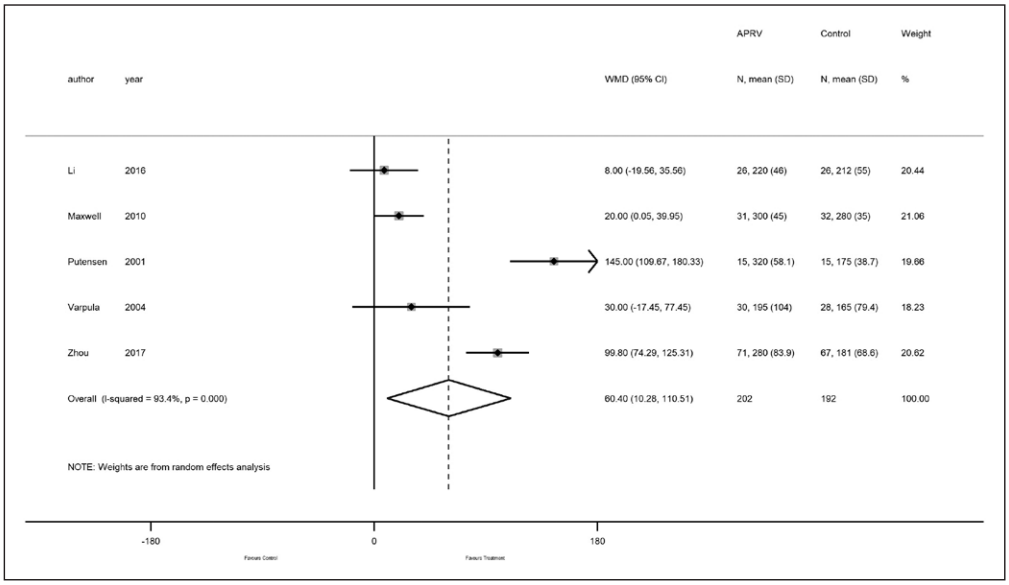

Figure 3. Forest plot of studies comparing airway pressure release ventilation (APRV) versus alternative modes of mechanical ventilation on Pao_2/Fio_2 ratio on day 3. WMD = weighted mean difference.

Safety

In total, three studies reported barotrauma with a total of 12 incidents, all of which were pneumothoraces (three in APRV group, nine in the control group) (11, 12, 22). The risk of barotrauma did not differ significantly between groups (RR, 0.39; 95% CI, 0.12–1.19; $I^2 < 0.1\%$; $p = 0.99$) (**Supplemental Fig. 10**, Supplemental Digital Content 1, http://links.lww.com/CCM/E886). None of the included studies reported the occurrence of cardiac arrest, volutrauma, or other serious adverse events.

DISCUSSION

In our systematic review of adult patients requiring mechanical ventilation for acute hypoxemic respiratory failure, APRV compared with other ventilator modalities was associated with lower mortality (RR, 0.67; 95% CI, 0.48–0.94). The findings were consistent when limiting the analysis to higher-quality studies, studies exclusively enrolling patients with ARDS, and studies exclusively comparing APRV to LTV ventilation strategies. APRV was also associated with a significant improvement in day 3 Pao_2/Fio_2 ratio (WMD, 60.4; 95% CI, 10.3–110.5). The number of barotrauma events was low and did not differ between treatment groups.

Several ventilation strategies have been used with the aim of improving oxygenation through the recruitment of atelectatic lung. However,

some have been demonstrated to cause harm (3, 6). In our analysis, day 3 oxygenation was improved among patients ventilated with APRV, but a signal of harm was not detected. Rather, mortality appears to be lower with APRV, suggesting that while APRV also increases lung recruitment and oxygenation (8, 13), it potentially does so without increasing the risk of barotrauma or other deleterious consequences.

In our analysis, patients receiving APRV had higher mean airway pressure despite receiving lower peak airway pressures than the comparator group. Although these measures are surrogates for the risk associated with high transpulmonary pressure and assume peak pressures correlate with plateau pressures, these results suggest that the lower peak pressures and higher mean airway pressures achieved with APRV may reduce the risk of secondary lung injury while still allowing progressively greater recruitment. Mean measured tidal volumes in the APRV group (7.47 mL/kg [SD 1.22]) were also very similar to the comparator group (7.45 mL/kg [SD 1.27]) where all but one trial used LTV strategies (although only three studies reported expired tidal volume among the APRV patients).

Other mechanisms may contribute to a decreased risk of death with APRV. APRV may result in greater ventilator synchrony when compared with LTV and thus lower sedation requirement (7). Excess sedation in the comparator groups in APRV RCTs may contribute to increased mortality risk. The risk of requiring rescue therapy was also lower in patients receiving APRV, although statistical significance was not reached. Several rescue therapies have substantial inherent risks, and it is plausible that avoidance of such treatments may protect against harm (26, 27). In contrast to equivocal evidence for ECMO, a strategy that requires substantial training and resourcing, APRV may be a more accessible and cost-effective strategy (28).

In contrast to our findings, a recent RCT conducted in 52 children between the ages of 1 month to 12 years receiving mechanical ventilation for ARDS was terminated early due to harm associated with APRV (29). Generalizability to an adult population remains uncertain, and possible explanations for the differences in findings include contamination of the APRV arm and baseline imbalance favoring LTV, with lower baseline Pao_2/Fio_2 ratio and younger children in the APRV arm. Furthermore, compared with adults, children have higher chest wall compliance (30), and pressure-based modes such as APRV may result in greater risk of excessively large tidal volumes and risk of volutrauma although the exhaled tidal volumes were similar in the two arms of the recent pediatric RCT.

Our study has several limitations. The TSA suggests that a false positive primary outcome cannot be excluded and that larger, multicenter studies are required to substantiate our findings. All included studies were conducted in single centers, and the generalizability of the findings is uncertain, although there was no heterogeneity in the primary outcome measure. There is a risk of study-level performance bias as blinding of the study intervention was not possible. Nonetheless, the use of mortality as an objective primary outcome measure reduces the risk of outcome assessment bias. Although APRV is conventionally defined with an end-expiratory pressure of zero, the use of positive end-expiratory pressure remains controversial. Indeed, a substantial number of the included studies used an end-expiratory pressure of greater than zero, and further exploration of the optimal delivery of APRV is required.

CONCLUSIONS

In adult patients requiring mechanical ventilation for acute hypoxic respiratory failure, APRV is associated with a mortality benefit and improved oxygenation when compared with conventional ventilation strategies. Given the limited number of patients enrolled in the available studies, larger multicenter studies are required to validate these findings.

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