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New developments in mechanical ventilation

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New developments in mechanical ventilation

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Editorial: New developments in mechanical ventilation

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KEYWORDS

non-invasive ventilation, acute respiratory failure, ARDS, respiratory monitoring, weaning, electrical activity of the diaphragm, neurally adjusted assist ventilation, weakness assessment

Editorial on the Research Topic
New developments in mechanical ventilation

This Research Topic collection entitled "*New developments in mechanical ventilation*", involving papers with different prospective, confirming that there is a continuous interest in understanding the pathophysiological mechanisms by advanced monitoring useful for preserving the functionality of the respiratory muscles and lungs (1). The effects of hypercapnia in ARDS patients are not completely understood. One of the things that may influence the effect of CO_2 on the lung is the way how hypercapnia is generated. Spinelli et al. compared the effect of different strategies to generate hypercapnia and their mechanisms of lung protection in an experimental model of unilateral pulmonary artery ligation. Interestingly, full bilateral lung protection (lower histological score, higher regional compliance, lower wet-to-dry ratio, and lower degree of inflammation). In contrast, when hypercapnia was generated by using low tidal volume ventilation or by adding an instrumental dead space, it does not protect the left ligated lung. Of note, inhaled CO_2 was associated with a lower degree of overdistension in the right lung and increased perfusion of the left lung. This study provides the rationale for testing the effect of CO2 inhalation in patients with ARDS and high dead space fraction to increase lung protection. In this issue, Lescroart et al. analyzed the hemodynamic effects of Time-controlled adaptative ventilation (TCAV) in a swine model of ARDS. One of the main concerns of using TCAV is that it may be associated with a significant hemodynamic impairment due to the high intrathoracic pressures during the prolonged inspiratory phase (CPAP - Phigh). Compared with low tidal volume ventilation, TCAV was not associated with any change in systemic arterial blood pressure, pulmonary blood pressure or cardiac output. Moreover, driving pressure and lung elastance was significantly lower with TCAV, suggesting that TCAV may be potentially useful in ARDS patients (Lescroart et al.). Tailoring protective mechanical ventilation approach based on lung and respiratory muscle physiology is crucial in the future of mechanical ventilation practice. In this issue, Palamim et al. verified the role of comorbidities (such as diabetes mellitus, systemic arterial hypertension, and older age) to determine the outcomes of patients undergone to mechanical ventilation in ICU. Furthermore, they showed that the use of PEEP level >8 cmH2O at admission could be a marker of potential severe hypoxia, associated with increased mortality (Palamim et al.).

Of particular interest, the paper proposed by Cammarota et al. that showed how the patient discomfort during Non-invasive ventilation (NIV) play a role to avoiding intubation and improving survival in patients with acute ARF. Indeed, several aspects should be considered to improve patient adaptation, i.e., the ventilator setting. The use of electrical activity of the diaphragm (EADi)-driven ventilation has been demonstrated to improve patient comfort. Another goal of MV is to guarantee an adequate coordination between the patient's respiratory activity and the assistance provided by the mechanical ventilator. The mismatch between the demand of patient and the level of assistance may produce a patient-ventilator asynchrony and leads to poor clinical outcomes. In this issue, Longhini et al. underline how is crucial to identify promptly the patient–ventilator asynchronies by advanced monitoring or automated software, in order to optimizing the strategies for improving the synchronization of patient-ventilator, using advanced mode of ventilation in adult and pediatric patients. Growing evidences suggest that the use of neurally adjusted ventilatory assist (NAVA) mode, guided by electrical activity of the diaphragm, optimizes patient-ventilator synchronization and avoids both over and under assistance, both conditions that can worsen diaphragmatic function, respectively, causing fatigue or atrophy (2). In a systematic review and meta-analysis conducted by Wu et al., they analyzed the beneficial and physiological effects of NAVA mode in adult patients compared to conventional mode of ventilation, offering a deep analysis of the potential physiologic benefits that may help to identify who can benefit of this strategy. The preservation of diaphragmatic function is a crucial during MV and in particular during the weaning from MV. In elegant pilot study, Bertoni et al. pointed out the role of limb intensive care unit-acquired weakness in ICU and how can play a relevant role in the weaning process. In the last research, Zheng et al. showed that the prophylactic combined use of NIV and high flow nasal cannulae (HFNC) after extubation could be an effective strategy to prevent reintubation in selected patients with high-risk of failure.

In conclusion, this Research Topic pays particular attention to recently progress made on use of innovative mode of ventilation, ventilation strategy and respiratory muscle monitoring, which is expected to provide new insights into research.

Author contributions

SS, OR, and SR conducted the manuscript. OR and SR the final amendments and approved the final version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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SYSTEMATIC REVIEW
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Neurally Adjusted Ventilatory Assist vs. Conventional Mechanical Ventilation in Adults and Children With Acute Respiratory Failure: A Systematic Review and Meta-Analysis

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Background: Patient-ventilator asynchrony is a common problem in mechanical ventilation (MV), resulting in increased complications of MV. Despite there being some pieces of evidence for the efficacy of improving the synchronization of neurally adjusted ventilatory assist (NAVA), controversy over its physiological and clinical outcomes remain. Herein, we conducted a systematic review and meta-analysis to determine the relative impact of NAVA or conventional mechanical ventilation (CMV) modes on the important outcomes of adults and children with acute respiratory failure (ARF).

Methods: Qualified studies were searched in PubMed, EMBASE, Medline, Web of Science, Cochrane Library, and additional quality evaluations up to October 5, 2021. The primary outcome was asynchrony index (AI); secondary outcomes contained the duration of MV, intensive care unit (ICU) mortality, the incidence rate of ventilator-associated pneumonia, pH, and Partial Pressure of Carbon Dioxide in Arterial Blood (PaCO2). A statistical heterogeneity for the outcomes was assessed using the I^2 test. A data analysis of outcomes using odds ratio (OR) for ICU mortality and ventilator-associated pneumonia incidence and mean difference (MD) for AI, duration of MV, pH, and PaCO2, with 95% confidence interval (CI), was expressed.

Results: Eighteen eligible studies ($n = 926$ patients) were eventually enrolled. For the primary outcome, NAVA may reduce the AI (MD = −18.31; 95% CI, −24.38 to −12.25; $p < 0.001$). For the secondary outcomes, the duration of MV in the NAVA mode was 2.64 days lower than other CMVs (MD = −2.64; 95% CI, −4.88 to −0.41; $P = 0.02$), and NAVA may decrease the ICU mortality (OR =0.60; 95% CI, 0.42 to 0.86; $P = 0.006$). There was no statistically significant difference in the incidence of ventilator-associated pneumonia, pH, and PaCO2 between NAVA and other MV modes.

Conclusions: Our study suggests that NAVA ameliorates the synchronization of patient-ventilator and improves the important clinical outcomes of patients with ARF compared with CMV modes.

Keywords: neurally adjusted ventilatory assist, acute respiratory failure, asynchrony index, patient-ventilator asynchrony, conventional mechanical ventilation

INTRODUCTION

Mechanical ventilation is regarded as an effective method and is widely used in the treatment of critically ill patients with acute respiratory failure (ARF) to maintain adequate gas exchanges (1). However, with traditional modes of mechanical ventilation (MV), the mismatching between the demand of patient and the level of assistance may produce a patient-ventilator asynchrony and leads to poor clinical outcomes, such as increased airway pressure, delayed triggering, and excessively loaded respiratory muscles, which can give rise to respiratory fatigue, asynchrony index (AI) increasing, and, eventually, extend the duration of MV (2–4). Consequently, optimizing the strategies for improving the synchronization of patient-ventilator has been a crucial goal to reduce adverse clinical complications and outcomes.

Neurally adjusted ventilatory assist (NAVA) is a ventilation mode, which controls the time and intensity of ventilation assistance through the electrical activity of the diaphragm (EAdi) (1). Different from the CMV mode, mechanical breath is triggered by the patient's inspiratory effort and enables the patient to influence the machine-cycling to a varying extent (5). In previous studies, NAVA is associated with a better patient-ventilator interaction, both in adult and in pediatric patients (6, 7). However, the controversy of the differential impacts of NAVA on physiologic and clinical outcomes remains. Furthermore, large randomized controlled trials (RCTs) are needed to clarify whether these potential physiologic benefits may improve the clinical prognosis (8).

This study aims to assess the effects of NAVA on the patient-ventilator interaction and clinical outcomes in patients with ARF compared with CMV modes.

METHODS

This systematic review and meta-analysis adhere to the applicable Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

We included all randomized controlled trials (RCTs) and randomized crossover trials. Studies were eligible if they (i) compared NAVA with the conventional mechanical ventilation mode in patients with ARF, (ii) included outcomes such as AI or secondary outcomes, (iii) were published in English. We did not include trials from neonates, especially premature infants, as this is completely another population and respiratory distress syndrome (RDS) in infants is a different pathology compared with acute respiratory distress syndrome (ARDS) in adults and children.

Asynchronies were classified into six types: (a) ineffective triggering (missed effort); (b) ineffective inspiratory triggering; (c) double-triggering; (d) auto-triggering; (e) a prolonged cycle; and (f) a short cycle (9). The AI, defined as the number of asynchrony events divided by the total respiratory cycles computed as the sum of the number of ventilator cycles (triggered or not) and of wasted efforts (2, 9), was the primary outcome. The secondary outcomes included the duration of MV, ICU mortality, and the incidence rate of ventilator-associated pneumonia.

Search Strategy

An ordinary database retrieval of PubMed, EMBASE, Web of Science, Medline, Cochrane Central Register of Controlled Trials, trial registers, and gray literature from 2008 to October 2021 was executed. The articles of those published were restricted to English. Sea terms included "NAVA," "neurally adjusted ventilatory assist," "ARF," and "acute respiratory failure. In PubMed, we used a neurally adjusted ventilated assist" or "NAVA," and "ARF" or "acute respiratory failure" for search strategy. Furthermore, the retrieved literature contained the bibliographies of all relevant studies and reviews to confirm the potentially qualified studies.

Selection of Studies

The search results were merged, and the duplicate records of the same report were removed. Two authors (MF and XY) have independently sifted all study titles and abstracts to determine the initial search strategy for potential eligibility and retrieved the potentially related studies for a full-text review.

Assessment of Risk of Bias

The risk of bias of the involved trials included in this meta-analysis was assessed according to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions in the following domains: selection bias (a random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) (http://handbook.cochrane.org). Jadad scale was used to calculate the quality of every enrolled study. The quality appraisal was mostly based on whether the authors added quality appraisal indicators (e.g., whether the article showed the concealment of randomization, whether it showed the randomization number occurring) in their articles.

Statistical Analysis

All statistical analyses were accomplished with Review Manager 5.3 [The Nordic Cochrane Centre, The Cochrane Collaboration (28)] and StataSE12.0. Data analysis of the continuous outcome was expressed as mean difference (MD) with 95% CI, while data analysis of the dichotomous outcome was expressed as odds ratio (OR) with 95% CI. To statistically aggregate the data from the included studies, we used the method proposed by Liu et al. (29) to convert the median along with the 25 and 75% percentiles to mean and standard deviation. Statistical heterogeneity for the outcomes was assessed using the I^2-test. We considered I^2 greater than or equal to 50% and a p-value of less than 0.1 as high heterogeneity (30). Funnel plots and Egger's test were used to evaluate the publication bias on the primary outcome (31). The choice of fixed-effect and random-effect models depended on statistical heterogeneity. If it is $p < 0.10$ or $I^2 > 50\%$, we used a random effect to combine data; otherwise, the fixed-effect model was chosen. Meta-regression was used to explore the source of heterogeneity. Meanwhile, we used a sensitivity analysis to evaluate the robustness and the reliability of the combined results. Forest plots were generated

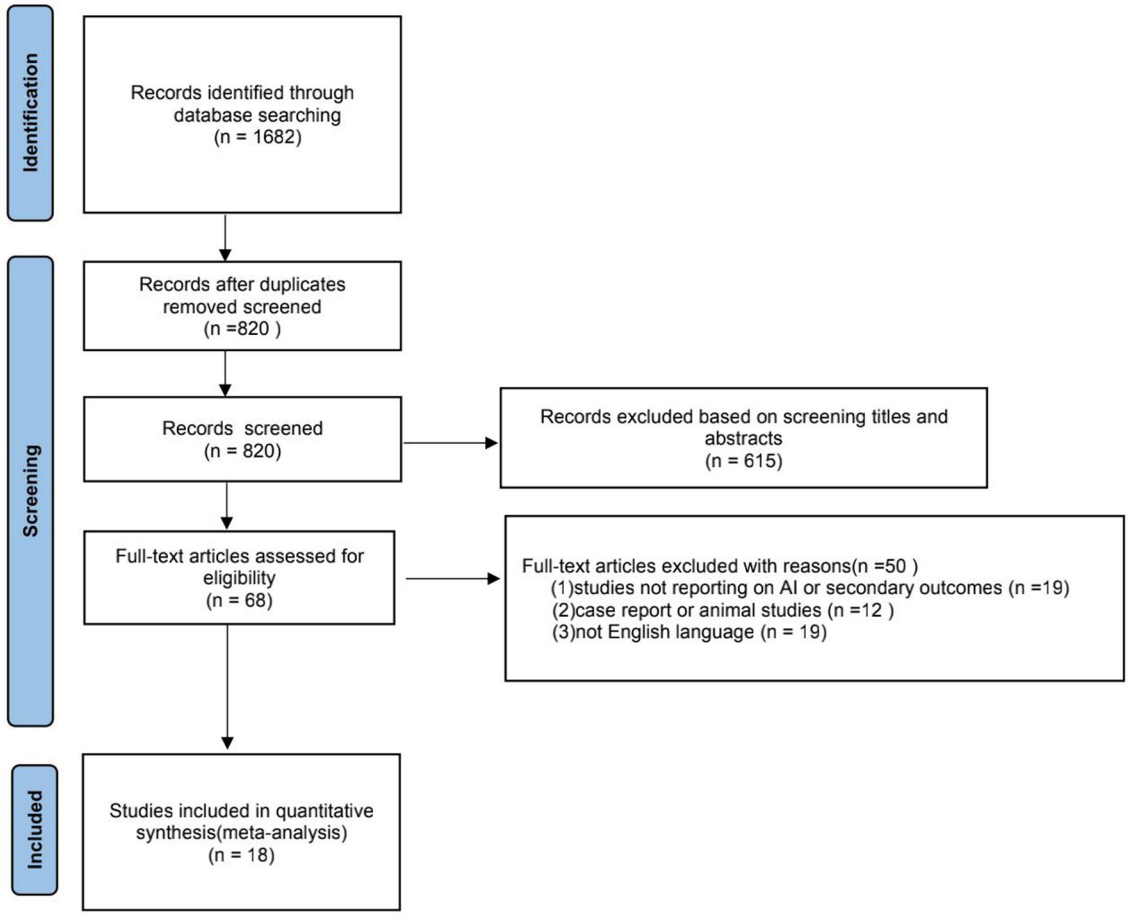

FIGURE 1 | A flow chart of the selection process for the included studies.

to demonstrate the individual study data, as well as the pooled data for each endpoint. For the primary outcome, subgroup analyses were performed to compare AI grouped by age (i.e., adult, pediatric), ventilation methods [i.e., invasive ventilation, non-invasive ventilation (NIV)], and the cause of ARF (i.e., COPD, others) because of the high heterogeneity.

RESULTS

Study Characteristics

We identified 1,682 records in accordance with the search strategy and assessed the full text of 68 studies for eligibility. A flow chart of the search process is presented in **Figure 1**. Of these 68 studies, 18 studies have satisfied all the inclusion criteria and were incorporated in the final data analysis (10–27). A total of 926 patients comprised 18 studies.

Table 1 presents the basic characteristics of the included trials and the number of participants. All the studies were published between 2008 and 2021. We identified 6 parallel-group RCTs (20, 22–25, 27) and 12 randomized crossover studies (10–19, 21, 26). The Jadad Scales of all the included studies ranged from 2 to 6, and the relatively low scores of the included studies resulted from the particularity of these studies that investigated the kinds of ventilation modes. The assessment of the risk of bias in the included studies is detailed in **Supplementary Figures 1, 2**. The overall quality of these studies was at a medium-to-low level. In these studies, the blind methods cannot be implemented because of the principle of study design, but it was applicable for outcomes evaluation. However, all the studies involved in our study were prospective, and RCTs are of higher quality in reducing selection bias.

Primary Outcome

Patient-Ventilator Asynchrony Index

For the AI, our study included 11 studies (12–19, 21, 24, 27), with 274 patients in total. The AI was significantly lower in the NAVA group the than PSV group) (MD = −18.31; 95% CI, −24.38 to −12.25; $p < 0.001$; **Figure 2**). Heterogeneity testing showed that $I^2 = 89\%$, indicating a high heterogeneity. So, we used the random-effects model and subgroup analysis to solve it.

Subgroup Analysis

Subgroup analysis grouped by age showed that the AI of NAVA was lower than the conventional MV modes in adults (MD,

−15.53; 95% CI: −22.62 to −8.44; $I^2 = 89\%$), and children (MD, −24.95; 95% CI: −36.52 to −13.37; $I^2 = 86\%$; **Figure 3**). The AI of NAVA was lower in NIV (MD, −19.13; 95% CI: −27.99 to −10.26; $I^2 = 90\%$), and in invasive ventilation (MD, −17.49; 95% CI: −26.88 to −8.11; $I^2 = 80\%$; **Figure 4**). According to different causes of ARF, we divided studies into the COPD group and the others group. The AI of NAVA was lower compared with conventional MV modes in the COPD group (MD, −12.78; 95% CI: −21.15 to −4.41; $I^2 = 69\%$) and in the others group (MD, −20.58; 95% CI: −28.78 to −12.38; $I^2 = 88\%$; **Figure 5**).

A funnel plot on AI was evaluated and did not imply evidence of publication bias (**Supplementary Figure 3**). Sensitivity analyses showed that these studies might result in a high heterogeneity (**Supplementary Figure 4**). Noteworthy, meta-regression suggested that the year of publication, Jadad scale, and ventilation methods did not contribute to the high heterogeneity (**Supplementary Figure 5**).

TABLE 1 | Baseline characteristics of these studies.

References	Type	Jadad scale	Participants	Treat	Control
Colombo et al. (10)	Randonmized, cross-over	1+2+0+1 = 4	14	NAVA	PSV
Schmidt et al. (11)	Randonmized, cross-over	1+1+0+0 = 2	12	NAVA	PSV
Piquilloud et al. (12)	Randonmized, cross-over	1+1+0+0 = 2	22	NAVA	PSV
Piquilloud et al. (13)	Randonmized, cross-over	1+1+0+0 = 2	13	NAVA	PSV
Bertrand et al. (14)	Randonmized, cross-over	1+1+2+0 = 4	13	NAVA	PSV
Vignaux et al. (15)	Randonmized, cross-over	1+1+0+0 = 2	19	NAVA	PSV
Doorduin et al. (16)	Randonmized, cross-over	2+1+1+1 = 5	12	NAVA	PSV
Baudin et al. (17)	Randonmized, cross-over	1+1+0+0 = 2	11	NAVA	PSV
Vignaux et al. (18)	Randonmized, cross-over	2+1+1+1 = 5	6	NAVA	PSV
Chidini et al. (19)	Randonmized, cross-over	2+1+1+1 = 5	18	NAVA	PSV
Demoule et al. (20)	RCT	1+2+0+1 = 4	128	NAVA	PSV
Ferreira et al. (21)	Randonmized, cross-over	2+2+1+0 = 5	20	NAVA	PSV
Kacmarek et al. (22)	RCT	2+2+1+1 = 6	306	NAVA	CMV
Hadfield et al. (23)	RCT	2+2+1+0 = 5	77	NAVA	PSV
Tajamul et al. (24)	RCT	2+1+1+1 = 5	40	NAVA	PSV
Liu et al. (25)	RCT	2+2+1+1 = 6	99	NAVA	PSV
Cammarota et al. (26)	Randonmized, cross-over	2+2+1+0 = 5	16	NAVA	PSV
Prasad et al. (27)	RCT	2+2+1+1 = 6	100	NAVA	PSV

NAVA, neurally adjusted ventilatory assist; RCT, randomized controlled trial; PSV, pressure support ventilation; and CMV, conventional mechanical ventilation.

Secondary Outcomes

Duration of MV

For the result of ventilation days, our study included 6 studies (20, 22–25, 27), about a total of 650 patients, and showed that NAVA was significantly lower than other MV modes in ventilation days (MD = 2.64; 95% CI, −4.88 to −0.41; $p = 0.02$; **Figure 6**). Heterogeneity testing showed that $I^2 = 75\%$, indicating a high heterogeneity, so a random-effects model and a sensitivity analysis shown in **Supplementary Figure 6** were used. The certainty of the evidence was moderate due to inconsistency.

ICU Mortality

For the result of ICU mortality, our study included 5 studies (22–25, 27) with 713 patients in total, and the result proved that the ICU mortality of patients ventilated with NAVA was significantly lower than those of patients ventilated with conventional MV (OR,0.60; 95% CI, 0.42 to 0.86, $p = 0.006$; **Figure 7**). Heterogeneity testing showed that $I^2 = 16\%$, indicating a low heterogeneity.

Ventilator-Associated Pneumonia

For the result of ventilator-associated pneumonia, our study included 4 studies (20, 22, 23, 25), with a total of 510 patients, and showed that there was no statistically significant difference in

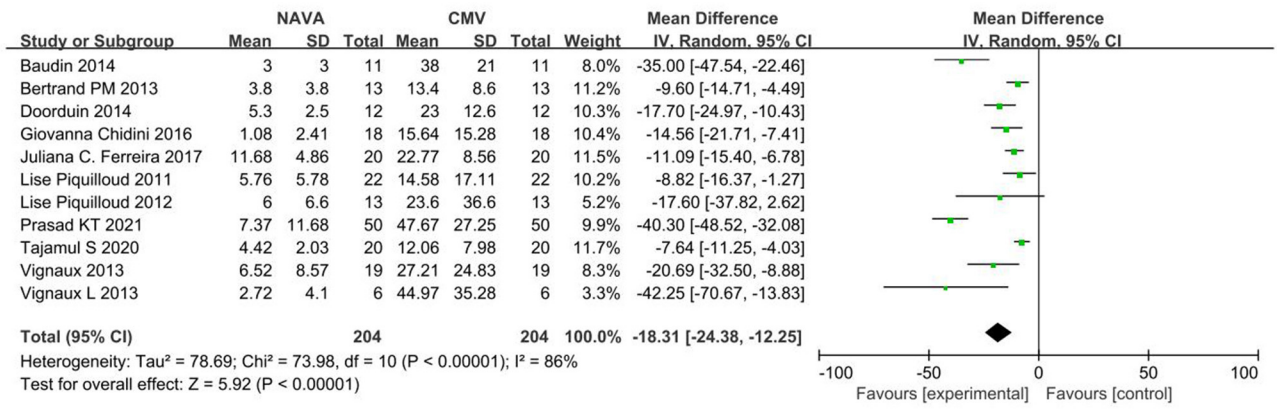

FIGURE 2 | A forest plot for AI.

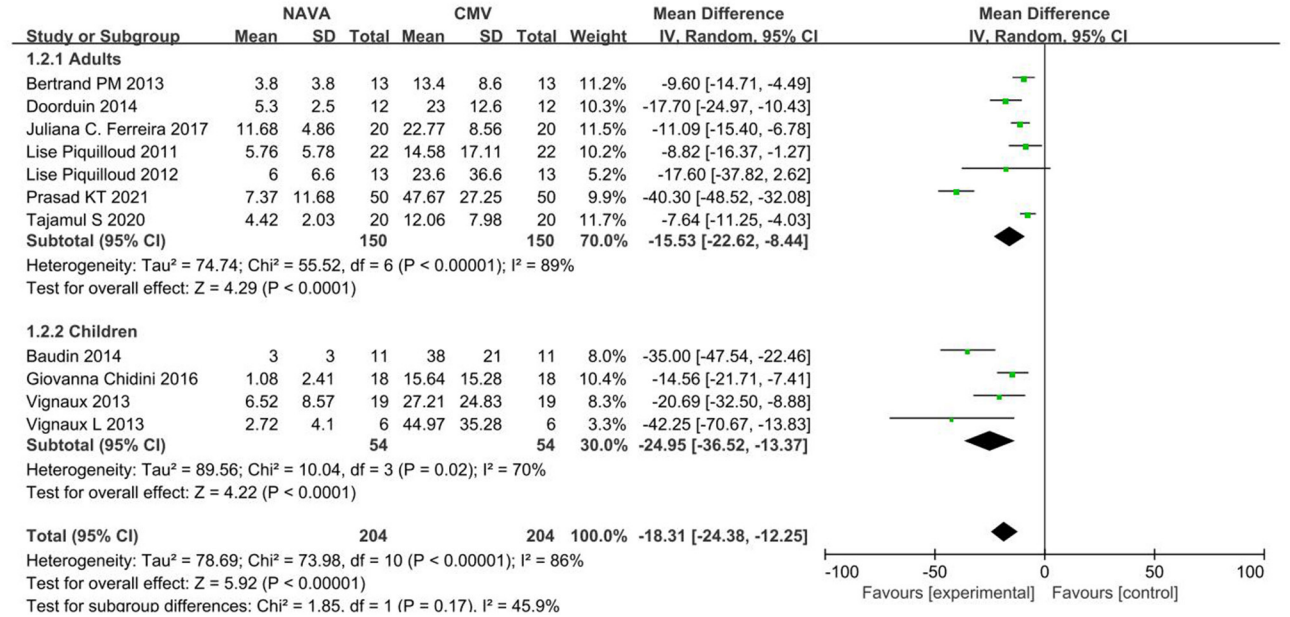

FIGURE 3 | A forest plot for AI in adults and children.

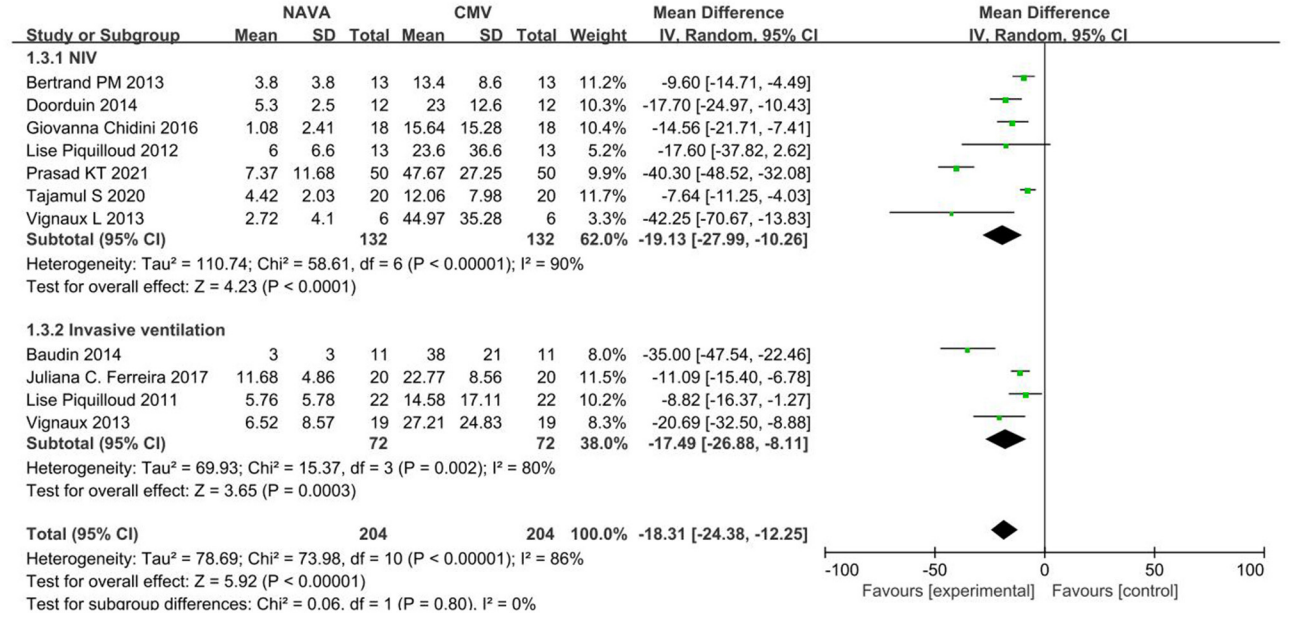

FIGURE 4 | A forest plot for AI in NIV and invasive ventilation.

ventilator-associated pneumonia (OR, 1.46; 95% CI, 0.73 to 2.91, $p = 0.006$; **Figure 8**). Heterogeneity testing showed that $I^2 = 0\%$, indicating a low heterogeneity.

pH

For the result of pH, our study included 5 studies (10, 11, 16, 21, 22), with 264 patients, and showed that there was no statistically significant difference between the NAVA group and the control group (MD = −0.00; 95% CI, −0.01 to 0.01; $p = 0.90$; **Figure 9**). Heterogeneity testing showed that $I^2 = 0\%$, indicating a low heterogeneity.

PaCO2

For the result of PaCO2, our study included 5 studies (10, 11, 16, 21, 22), with 264 patients, and showed that there was no statistically significant difference between the NAVA group and

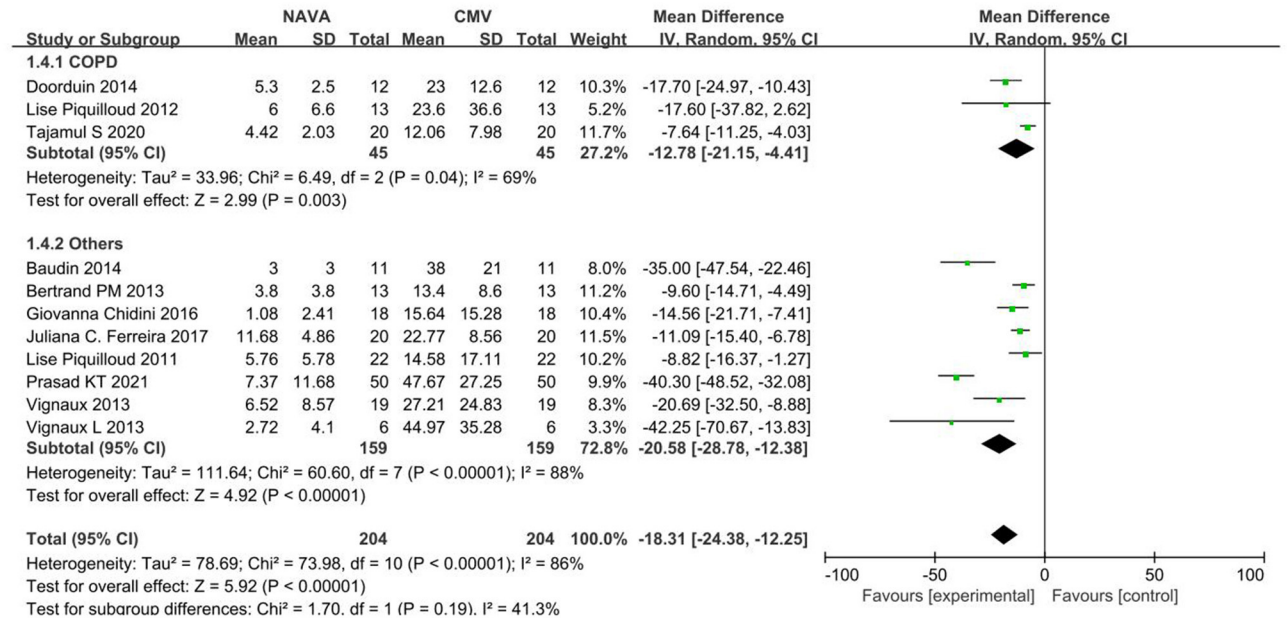

FIGURE 5 | A forest plot for AI in patients with COPD or other causes.

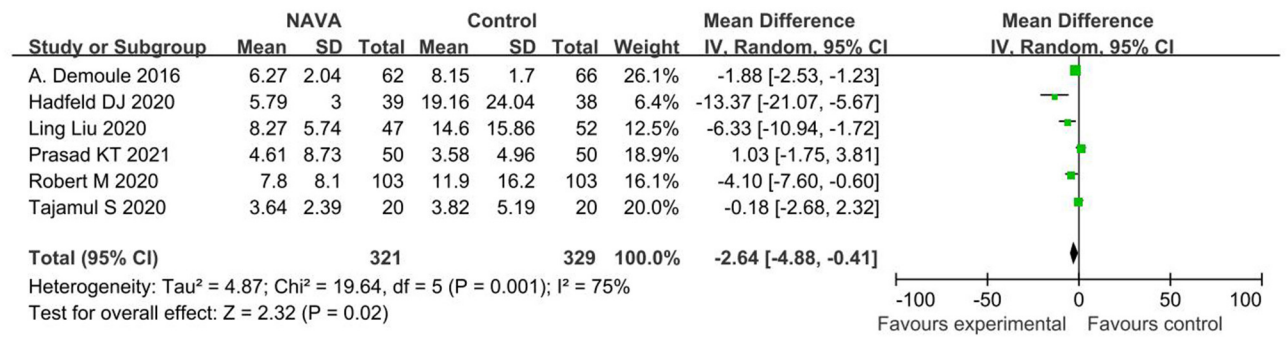

FIGURE 6 | A forest plot for duration of MV.

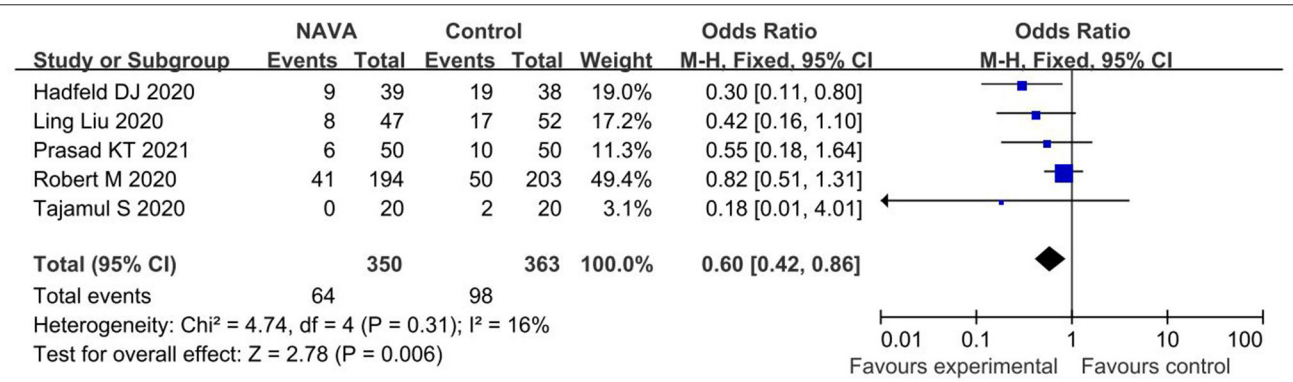

FIGURE 7 | A forest plot for ICU mortality.

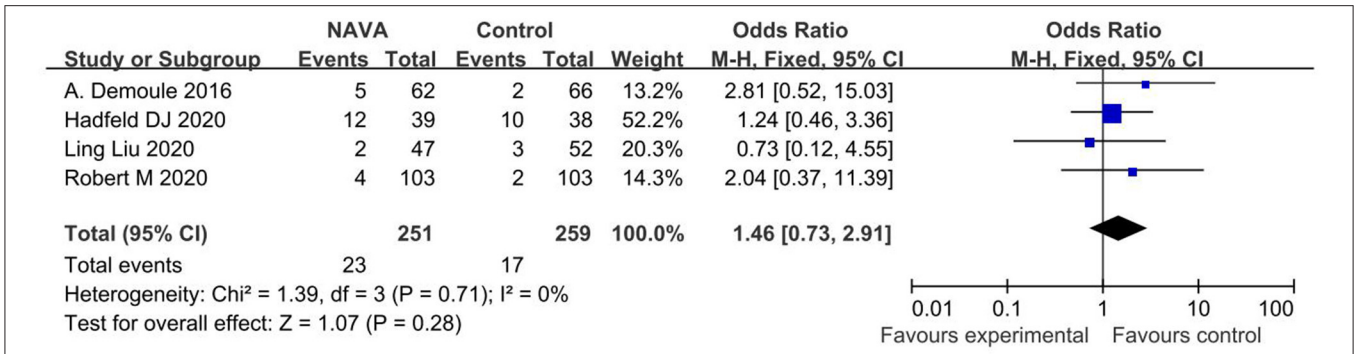

FIGURE 8 | A forest plot for ventilator-associated pneumonia.

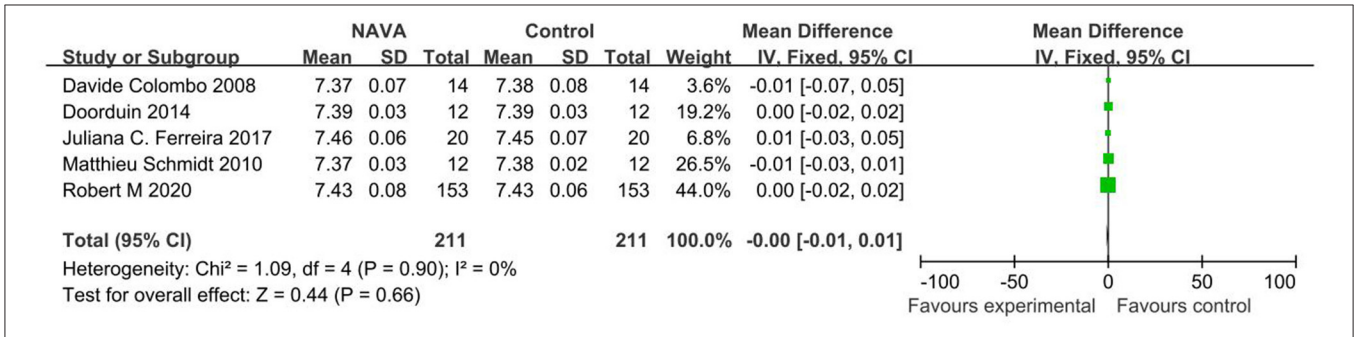

FIGURE 9 | A forest plot for pH.

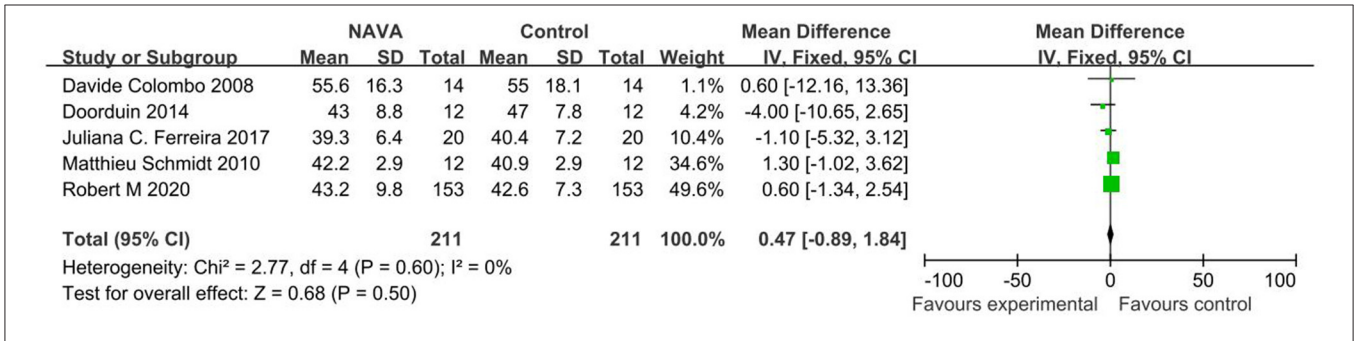

FIGURE 10 | A forest plot for $PaCO_2$.

the control group (MD =0.47; 95% CI, −0.89 to 1.84; p = 0.60; **Figure 10**). Heterogeneity testing showed that I^2 = 0%, indicating a low heterogeneity.

DISCUSSION

Our systematic review and meta-analysis have identified 18 studies of 919 patients that evaluated the effect of NAVA on patient-ventilator interaction and clinical outcomes in patients with ARF compared with conventional MV modes. The key findings were that, compared with traditional modes of MV, NAVA has obvious advantages: (a) improving the patient-ventilator interaction; and (b) decreasing the duration of MV and ICU mortality. Subgroup analysis suggested that whether in adult patients or patients with the pediatric condition, invasive ventilation or NIV, COPD, or other causes, NAVA had the benefits in better patient-ventilator interaction. There are many other factors over and above the ventilation modes influencing the patient-ventilator interactions during NIV, such as the compliance and tolerance of the patient to the interface, different kinds of interface, psychological factors of patients, and so on. So, it is necessary to clarify the influence of NAVA on patient-ventilator interaction among many factors in further study.

Synchronization of patient-ventilator with MV has been the objective of numerous ventilation strategies. In this study, the significant decrease in AI in patients with NAVA can easily be explained by the fact that the EAdi, the temporal sum of the electromyographic potentials of the crural diaphragm

recorded by means of a nasogastric tube, with multiple arrays of electrodes (5, 32), is used to trigger the ventilator rather than a pneumatic signal located at the airway opening or inside the ventilator (33, 34). The patients were ventilated with a ventilator equipped with the NAVA software that includes the "neuro-ventilatory tool" for EAdi measurement (35). After receiving these signals, the ventilator gives ventilation support according to the preset trigger range and the support level. The ventilation support pressure level (unit: cmH_2O) is determined by the product of the preset support level (unit: $cmH_2O/\mu V$) and EAdi (unit:μV). In theory, NAVA is in line with the physiological characteristics of respiration and can maximize the synchronization of patient-ventilator. If the EAdi signal is lost, this mode reverts to PSV. To a certain extent, NAVA avoids the situation of over-assistance under-assistance because the level of ventilation support is matched with the respiratory drive through feedback regulation of EAdi. Over-assistance would put the patient at risk of diaphragmatic atrophy, while, on the other hand, under-assistance would result in dyspnea, diaphragmatic fatigue, and patient self-inflicted lung injury. The Eadi, according to Bellani et al. (36), with adequate measurements, could be considered a surrogate of work of breathing. Optimizing the work of breathing may reduce the incidence and change the quality of asynchrony. It should be noted that double triggering was more frequent in NAVA than in CMV in our study, which followed the results of Piquilloud and colleagues (12). The reason for the prevalence of double-triggering during NAVA is the biphasic appearance of EAdi signals, which could be related to early cycling when the inspiratory time of the ventilator is less than the neural inspiratory time of the patient, and this causes two successive cycles. This may not increase the work of breathing, but it may participate in the discomfort felt by patients (12).

This study is the first to appraise the clinical prognosis in patients undergoing NAVA. A recent report of a review (37) has observed the association of NAVA with better patient-ventilator synchrony in comparison with PSV in mechanically-ventilated adults. However, its effects on clinical outcomes remain uncertain. Previous studies have shown that patient-ventilator asynchrony may lead to lung and vascular damage, resulting in adverse clinical outcomes, including a prolonged MV (38), increased mortality (39), intensive care unit and hospitalization (40), discomfort (41), and sleep disturbances (42). Our study found that NAVA was associated with a reduction in the duration of MV and ICU mortality. Some short-term physiologic crossover studies with small sample sizes (10, 12, 14) in our systematic review provided definite conclusions on the clinical effect of NAVA, but heterogeneous inclusion criteria, asynchrony detection methods, and NAVA titration strategies are still needed. Some studies (19, 30) reported that NAVA might further decrease the ICU mortality and the ventilator-associated pneumonia incidence when compared with PSV. Furthermore, it has been manifested that NAVA could improve the success rate of direct weaning from the ventilator (2, 42). These beneficial effects could be examined in multiple different clinical situations, such as the comfort degree of patients, depth of sedation, patients sustained with ECMO, and long-term respiratory rehabilitation. Considering that MV is related to complications, such as a ventilator-induced lung injury and a ventilator-induced diaphragmatic dysfunction, the physiologic benefits of NAVA are expected to improve the clinical outcomes (43).

Although this meta-analysis suggests that NAVA has advantages in improving physiological and important clinical outcomes in ARF patients with MV, notably, NAVA, still, has some potentially relevant boundedness such as the necessary condition for the application. The accurate positioning of the NAVA catheter is necessary (44). Nevertheless, the sensitivity of the electrode will be affected by many factors, such as the position and time of placement, depth of sedation, and muscle relaxants. Therefore, ventilation in reserve is required to ensure the safety of patients. The need for specific equipment and an intact neuromuscular transmission, the persistence of double triggering (16, 29, 45–47), and the occurrence of hypervariable respiratory patterns at high-assistance levels (34, 45) are also limitations.

Limitations of this study exist as well. First, the quantitative synthesis of some endpoints was only composed of four or five studies that were pooled so that there were not enough data to assess the incidence of ventilator-associated pneumonia or blood gas results (pH and PaCO2), which may explain why some of the experimental results are not consistent with the expected situation. On the other hand, no pediatric or neonatal study could, so far, show an impact on the outcome with the use of NAVA; thus, we can only focus on adults and children, and the results cannot be extended to the general population. Nonetheless, these were pooled to visually depict the pooled effect as well as to quantify the pooled effect. Second, some of the included studies are crossover trials, which is a theoretical risk that the efficacy of NAVA may be overestimated or underestimated compared with that of other CMV modes. Third, a relatively large number of studies on Europeans and Americans had been included. It may reduce the applicability of our results to different races. Another limitation is that they used the variable definitions of outcomes (e.g., duration of MV) in the included studies despite attempts to reduce the clinical heterogeneity. Finally, all studies in our analysis had a high risk of performance bias because of the inability to blind the investigators. So, it is possible that the decisions and actions of the investigators may be influenced, resulting in biased estimates of results.

In conclusion, NAVA ameliorates the patient-ventilator synchrony and improves the clinical outcomes of patients (especially in adults) with ARF compared with CMV modes. Although our research suggests that NAVA is beneficial in physiological and clinical outcomes, a large number of RCTs of neonates are still needed to verify its reliability.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MW and XY searched the scientific literature and collected the data. MW drafted the manuscript and performed statistical analyses. YY contributed to the conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. LL participated in data interpretation and revision of the manuscript. All authors have read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.814245/full#supplementary-material

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REVIEW
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Comfort During Non-invasive Ventilation

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Non-invasive ventilation (NIV) has been shown to be effective in avoiding intubation and improving survival in patients with acute hypoxemic respiratory failure (ARF) when compared to conventional oxygen therapy. However, NIV is associated with high failure rates due, in most cases, to patient discomfort. Therefore, increasing attention has been paid to all those interventions aimed at enhancing patient's tolerance to NIV. Several practical aspects have been considered to improve patient adaptation. In particular, the choice of the interface and the ventilatory setting adopted for NIV play a key role in the success of respiratory assistance. Among the different NIV interfaces, tolerance is poorest for the nasal and oronasal masks, while helmet appears to be better tolerated, resulting in longer use and lower NIV failure rates. The choice of fixing system also significantly affects patient comfort due to pain and possible pressure ulcers related to the device. The ventilatory setting adopted for NIV is associated with varying degrees of patient comfort: patients are more comfortable with pressure-support ventilation (PSV) than controlled ventilation. Furthermore, the use of electrical activity of the diaphragm (EADi)-driven ventilation has been demonstrated to improve patient comfort when compared to PSV, while reducing neural drive and effort. If non-pharmacological remedies fail, sedation can be employed to improve patient's tolerance to NIV. Sedation facilitates ventilation, reduces anxiety, promotes sleep, and modulates physiological responses to stress. Judicious use of sedation may be an option to increase the chances of success in some patients at risk for intubation because of NIV intolerance consequent to pain, discomfort, claustrophobia, or agitation. During the Coronavirus Disease-19 (COVID-19) pandemic, NIV has been extensively employed to face off the massive request for ventilatory assistance. Prone positioning in non-intubated awake COVID-19 patients may improve oxygenation, reduce work of breathing, and, possibly, prevent intubation. Despite these advantages, maintaining prone position can be particularly challenging because poor comfort has been described as the main cause of prone position discontinuation. In conclusion, comfort is one of the major determinants of NIV success. All the strategies aimed to increase comfort during NIV should be pursued.

Keywords: non-invasive ventilation (NIV), acute respiratory failure (ARF), continuous positive airway pressure (CPAP), comfort, respiration

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INTRODUCTION

In recent years, non-invasive ventilation (NIV), including non-invasive variable positive airway pressure ventilation and continuous positive airway pressure (CPAP) (1), has progressively gained a key role in the therapy of both hypoxemic and hypercapnic acute respiratory failure (ARF) (2–6).

This has been even more true during the massive spread of severe acute respiratory syndrome-related to the novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] pandemic, when NIV has extensively been used to cope with the massive demand for ventilatory assistance outside the intensive care unit (ICU) (7). In the management of ARF, NIV reduces the recourse to invasive mechanical ventilation (IMV), consequently avoiding the side effects related to endotracheal intubation, i.e., upper respiratory airways trauma and hemorrhage, and the use of muscle relaxants and sedatives drugs that have been demonstrated to negatively affect clinical outcomes (8).

Non-invasive ventilation has been shown to be effective in preventing intubation and improving survival of patients with ARF (9) when compared to conventional oxygen therapy (10, 11). Accordingly, NIV has been progressively employed outside the emergency department, in both clinical and surgical wards in the early treatment of ARF (12, 13).

However, this widespread diffusion of NIV has in turn allowed to find out the limits of its application. In this regard, NIV failure, defined as the need for endotracheal intubation, is the main issue while dealing with patients with NIV (14). Surprisingly, NIV is still burdened with a high failure rate (up to 40%) today, due, in most cases, to patient discomfort or rejection (15–17). During NIV, comfort is intended as the complex dynamic state based on the acceptance of non-invasive respiratory assistance in the absence of pain and emotional/physical distress (18). Accordingly, it is easy to understand why NIV is often described by patients as an extremely unpleasant experience. Patient comfort must therefore be monitored, along with vital parameters, during NIV sessions, using tools, such as the 11-point numeric rating scale (NRS) from 0 (no discomfort) to 10 (maximum discomfort) (19, 20). In keeping with a recent survey conducted in non-invasively assisted patients with the aim of assessing patients' perceptions (21), NIV is reported as a negative experience. Specifically, patients have claimed to suffer from difficult breathing, fear, and intolerance to the interface during NIV assistance. All of these factors, both combined or not, could lead to NIV failure (22). Unsuccess of NIV represents a relevant issue because it is associated to adverse clinical outcomes (23), such as mortality and prolongation of mechanical ventilation (24). Therefore, increasing attention has been progressively paid to understand all the possible factors that are responsible for poor tolerance to improve patient comfort during NIV.

In patients who underwent IMV, discomfort depends on many causes, such as pain, dyspnea, sleep deprivation, anxiety, thirst, inability to communicate, and lack of control. Among these, the management of pain and dyspnea has been demonstrated to improve clinical outcomes (25–27). A poor comfort, instead, might also be the consequence of a lack of response to NIV, suggesting the progression of the underlying disease. In keeping with previous findings (28), moderate-to-severe dyspnea after the first NIV session is associated with anxiety and is independently associated with NIV failure and subsequent intubation. In addition, the persistence of moderate-to-severe dyspnea after the first NIV session is associated with a prolonged hospital stay and mortality. Thus, the assessment of comfort overall plays a key role in the management of patients who underwent NIV. If on the one hand, discomfort depends on the NIV setting and all the strategies aimed to avoid/reduce discomfort must be pursued, on the other hand, a poor comfort is the sign of a lack of response to NIV and consequent switch to IMV is necessary.

TABLE 1 | Principal causes of discomfort in non-invasive ventilation (NIV).

Interface
Anchor system
Ventilatory setting
Humidification
Noise
Position of the patient
Psychological distress
Anxiety
Fear
Pain

A list of possible factors responsible for poor comfort is shown in **Table 1**. Here are presented and discussed several causes of comfort deterioration during NIV, along with a proposal for an interventional strategy to improve patient's comfort (**Figure 1**).

Interface

One of the most widely investigated aspects is related to the interface dedicated to NIV. NIV interface is a potential source of pain and claustrophobia that leads to NIV discontinuation and recourse to endotracheal intubation (29). When choosing an interface, it is mandatory to take into account the time of NIV application, especially if non-invasive assistance is delivered for many hours a day (30). Specifically, it is of pivotal importance to consider the type, i.e., mask or helmet, and the size of the interface that, as much as possible, must be adapted to the patient's face and neck profile, as well the fixing system. Particularly, interface sealing system and fixing equipment play a key role in the determinism of major mask-related side effects, such as air leaks, skin breakdown, and discomfort (31).

In recent years, device manufacturers have developed different types of interfaces with various technologies and materials. There are six main classes of interfaces commercially available: the oronasal mask, the nasal mask, the full-face mask, the nasal prongs, the mouthpieces, and the helmet (32). A comparison between the characteristics of the interfaces is reported in **Table 2**. Many studies (33–35) have followed over time to compare the different devices and evaluate both their efficacy and tolerability in delivering NIV. A poor tolerance has been mainly reported with NIV delivered *via* the nasal mask due to the vast air loss

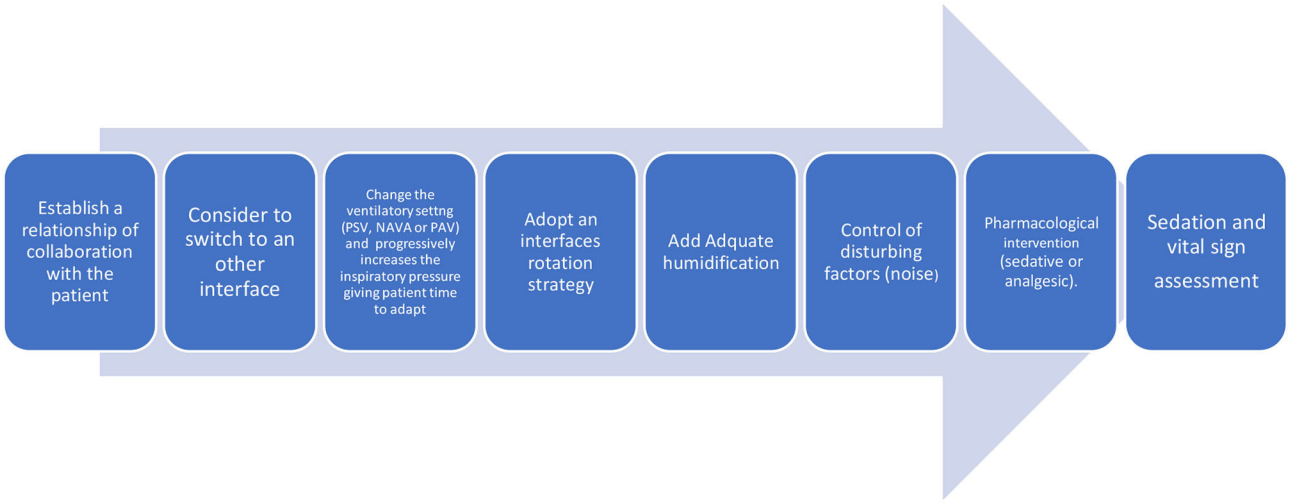

FIGURE 1 | Patient intolerance bundle of intervention.

through the mouth (36, 37); in these circumstances, the major air leaks can result in dry mouth and in less effective ventilation due to a precarious patient-ventilator interaction, in terms of wrong inspiratory triggering and cycle off (38). Nevertheless, it is worth to consider that in some cases, the nasal mask could be better tolerated than the face mask due to claustrophobia or a frequent cough (19).

The fixing system is necessary to maintain the interface in place during NIV. A proper closure of the fixing apparatus should also be pursued to prevent air leaks. A slack fixing system is the cause of both large and small air leaks that interfere with the effectiveness of the ventilatory assistance. Major leaks are accompanied by an increase in patient-ventilator asynchrony with a worsening in patient's workload (39). To compensate for leaks, the ventilator machine must deliver an increased inspiratory assistance that could result in a worse patient comfort (40). Small air leaks are accompanied by a reduced comfort also, as they can be responsible for eye irritation and produce noise (32). Conversely, an excessively tightened anchoring system can lead to pressure ulcers, with consequent NIV interruption (32). To reduce the risk of skin damage during NIV, a bundle of interventions has been proposed suggesting a rotation strategy of NIV interface application, a proper tightening of the fixing system, and the use of anti-ulcers devices, i.e., appropriate barrier tapes, cushioning, and adjustable pads between mask and face (38).

Rotating interfaces can be a useful strategy not only to avoid skin lesions but also to increase NIV tolerance, as supported by data showing a reduction in NIV failure rate when a rotational strategy of interface encompassing both mask and helmet application was adopted (41).

Problems related to air leaks and skin injuries have been partially resolved with the advent of the helmet (42). In fact, this device has been shown to have a greater tolerability over time and a lower rate of NIV interruptions when compared to masks (43, 44). In addition, the helmet allows the administration of oral nutrition and fluids along with therapy without interrupting NIV (45, 46).

In terms of effectiveness, unfortunately, the helmet is accompanied by less-efficient rates of pressurization and triggering performance when compared with the mask (47). In addition, the anchoring system is a well-recognized concern for traditional helmet (44). The armpit braces holding the helmet in place can cause discomfort and axillary skin lesions, leading to discontinuation of NIV (44). To overcome these side-effects, a new helmet equipped without armipt braces has been recently introduced (48). The new helmet also shows better performance of ventilatory assistance, particularly, in terms of ventilator machine triggering and pressurization rate (49). Due to all these advantages, a new generation of the helmet appears to be the most reasonable choice in patients who require NIV for prolonged periods, thanks to the better patient-ventilator interaction provided (50).

In selected patients and when clinical status allows, a rescue trial of high flow nasal cannula (HFNC) oxygen therapy can be tried as an alternative in case of intolerance to the various interfaces used for NIV (51). The HFNC is an open system of oxygenation therapy that can be employed to overcome the drawbacks related to the NIV interface (52, 53). According to recent findings (54) obtained in a cohort of sepsis critically ill patients weaned from IMV, the HFNC group showed a better comfort and a lower incidence of facial pressure ulcers and delirium when compared to NIV delivered *via* facial mask.

Ventilatory Setting

The ventilatory setting adopted for NIV is associated with varying degrees of patient comfort: patients are more comfortable with pressure-support ventilation (PSV) than volume-controlled ventilation (55). However, the volume-targeted mode may be beneficial in patients with acute and marked modifications of respiratory system mechanical properties or in the case of hypercapnic encephalopathy with modifications in respiratory

TABLE 2 | Comparison between interfaces*.

Types	Advantages	Disadvantages
Nasal mask	• Less claustrophobic • Easy to cough or expectorate • Easy to speak • Less risk of aspiration	• High incidence of leaks • Eye irritation • Higher resistance • Nasal irritation or damage
Nasal prongs	• Less claustrophobic • Easy to cough or expectorate • Easy to speak • Option for a rotating strategy	• High incidence of leaks • Nasal irritation
Mouth pieces	• Less claustrophobic • Little dead space • Option for a rotating strategy	• High incidence of leaks • Less effective for ARF
Oro-nasal mask	Good for ARF	• More claustrophobic • Possible air-leaks • Eye irritation
Total face mask	• Adequate for prominent facial anatomy • No pressure on nasal bridge • Low air-leaks	• More claustrophobic • Difficult to speak
Helmet	• Adequate for prominent facial anatomy • Low air-leaks • Easy to speak • No pressure on nasal bridge	• Can be claustrophobic • Noise • High gas flow required • Discomfort of axillae with armpit braces

*Data from references 6, 12, and 20.

drive (56, 57). Volume control continuous mandatory ventilation during NIV has been employed in patients with amyotrophic lateral sclerosis (58) and volume-targeted modes of ventilation are used in patients affected by chest wall disorders (59–61) and obesity associated with chronic respiratory failure (62). During PSV, the degree of comfort shows a U-shaped trend: pressure at the extreme levels of assistance, both low and high inspiratory supports, corresponds to a reduced comfort on NIV (63). In addition to the pressure setting, the extent of patient-ventilator interaction expressed in terms of asynchrony event occurrence is also important. Indeed, asynchrony is defined as a condition in which there is a mismatch between the patient's own breathing drive and the mechanical action of the ventilator (64). According to several studies (65, 66), a high incidence of asynchronies is associated to a poor NIV tolerance.

On this basis, new ventilatory modalities aimed at increasing the degree of synchrony between patient and ventilator machine have been demonstrated to improve patient's comfort during NIV. Compared to pneumatically triggered and cycled-off PSV, the use of the electrical activity of the diaphragm (EADi) to drive the "neural"-pressure ventilation (67–69) as well as the delivery of ventilatory assistance in proportion to patient's effort (70, 71) has demonstrated to ameliorate patient-ventilatory synchrony and comfort.

The ventilator machine is obviously important during NIV. In line with recent results (72), the asynchrony events are significantly reduced with a dedicated NIV ventilator machine than with ICU ventilators equipped with an NIV algorithm, probably thank to a more effective and specific compensation system for air leaks (37). Always in terms of patient-ventilator synchrony, air leaks by promoting the dispersion of the inspiratory gas flow are the major determinants of auto-triggering events that put the patients at risk for rebreathing of exhaled gas and volotrauma (39).

Asynchrony

Optimal patient-ventilator interaction may be of pivotal importance in NIV success. According to recent findings, high rates of asynchrony also occur during NIV. It has been demonstrated that the ability of ICU physicians to detect patient-ventilator asynchrony during NIV by inspection of flow and pressure waveforms is low. Moreover, the asynchrony detection is slightly higher with mask than with helmet and the rate of proper detection is inversely related to the prevalence of asynchrony. In patients who underwent NIV, ineffective efforts are more frequently observed with the helmet while double triggers are more recurrent with mask (73). Regarding autotriggers, no difference is reported between mask and helmet NIV. Moreover, pneumatic triggers are characterized by delays in the ventilator assistance onset and interruption, defined as inspiratory and expiratory triggers delays, respectively (49, 74).

Several strategies, such as the use of ventilators with algorithms for air-leak detection and compensation, application of leak-insensitive ventilatory modes, reduction of the applied pressure, and choice of the appropriate interface, may reduce the number of asynchronies during NIV. Moreover, the application of the neural trigger in delivering NIV has been reported to improve asynchronies, by reducing the delay from neural effort onset to inspiratory assistance initiation and reducing the incidence of ineffective efforts (49, 74).

Humidification

Inadequate humidification during NIV assistance may cause patient distress because it is associated with upper airway mucosa dryness and nasal congestion (75). Thus, an adequate humidification must be pursued to improve respiratory comfort and prevent drying of bronchial secretions (76). Humidification can be achieved with a passive heat-moisture exchanger (HME), or through actively heated humidification, two systems that overlap in terms of major clinical outcomes, i.e., ICU stay, intubation rates, or mortality (77). It must be considered that once installed in the ventilatory circuit, HME increases the dead space and the flow resistance of the circuit with detrimental effects on patient's respiratory load (78). Furthermore, the effectiveness of the HME is compromised in the presence of air leaks (79). Active humidification during NIV may be considered for those patients who suffer from the excessive dryness of inhaled gas (38). However, when NIV is delivered through a helmet and an active humidification system is installed, attention

must be paid to the increase in condensation on the inner surface of the interface, because the reduced visibility worsens the visual contact with the patient (77).

Noise

Surrounding noise may negatively affect patient's comfort during NIV. Recently, a "bundle of interventions" has been proposed to improve the comfort in patients undergoing NIV, such as noise reduction (80). Noise exposure during NIV can be a relevant concern especially in presence of air leaks, mainly when NIV is delivered through mask (31). Minimizing the gas loss by repositioning the mask, applying a linear sealing on the face to reduce the gap between interface cushion and skin, and changing the type of mask for NIV can help to reduce the noise associated to air leaks (24). Despite the lower incidence of leakages, noise is also a significant problem when helmet NIV/CPAP is adopted due to the high gas flow system employed (31). To face off this problem, the application of earplugs, sound traps, and circuit tubes with smooth inner surfaces, as well as trying to limit, when possible, unnecessarily high flows, has been suggested as conceivable solutions (81).

Position

The optimization of patient's position also plays a key role in assuring comfort during NIV (79). The sitting or semi-recumbent position is suggested during NIV to assure a high level of comfort to patients and a side-lying position can be obtained to remove pressure from a pendulous abdomen as in case of pregnancy or obesity (79). Recently, the use of the prone position has been introduced in patients with ARF, particularly those with Coronavirus Disease-19 (COVID-19) disease (82–84). The analysis of this rescue therapy is better explained in the last paragraph on the COVID-19 pandemic.

Other Factors

Patient's emotional state is a major determinant of NIV success. In the case of intolerant patients, it is suggested to try a strategic relational approach. To preserve and/or improve patient's comfort and tolerance to NIV, it is fundamental to establish a trust relationship with patients, by reassuring them during ventilatory assistance, providing information on expected benefits of NIV, and involving them in the process of care (85).

Sedation

When none of the non-pharmacological strategies listed above are successful, analgo-sedative medications schemes can be employed to manage agitation during NIV (86).

Agitation can be caused by several factors, such as fear, pain, anxiety, sleep deprivation, fever, and hypoxia (87). To face off pain affecting the musculoskeletal compartment with consequent stiffening of the chest wall and diaphragm, the administration of simple analgesics, such as acetaminophen, non-steroidal anti-inflammatory drugs, or opioid, should be considered (87).

In case of agitation due to anxiety or intolerance, the choice must fall on sedative drugs. It has been demonstrated that sedation strategy could reduce the rate of NIV failure (88). Sedation facilitates ventilation, calms anxiety, promotes sleep, and modulates the autonomic system responses to stress, such as tachycardia and hypertension, with a final improvement of patient's adaptation to NIV (89, 90). Several studies have demonstrated the efficacy and safety of sedation during NIV using dexmedetomidine, midazolam, propofol, and remifentanil (91, 92). According to the previous investigation (90), benzodiazepines (33%) and opiates (29%) are the most often selected sedative agents for NIV.

In choosing the drug, the intrinsic characteristics and clinical effects of the various pharmacological categories must be considered, mainly taking into account the effects exerted by the drug on patient's own respiratory drive. Benzodiazepines should preferentially be avoided in the elderly with agitation due to the risk of paradoxical the effect and of promoting a state of delirium (87). In addition, the benzodiazepines pharmacokinetics profile is prone to accumulation in the case of obese patients or in those subjects with renal injury or low albumin levels (93).

Propofol, thanks to its pharmacokinetic rapidity, is a particularly attractive sedative agent in NIV. However, in the choice of the propofol sedation regimen dose, it is of pivotal importance because propofol has shown to adversely affect the breathing pattern and the respiratory drive, as well as gas exchange, proportionally to the rate of its infusion (94); in this context, it has been effectively used even with a target-controlled infusion (95).

Dexmedetomidine, a selective α2 agonist with intrinsic properties of sedative and analgesic effects, may be useful for sedation of NIV patients, due to its limited effect on the respiratory pattern. According to previous findings (90) net of the sedation target, dexmedetomidine-based sedation is superior to midazolam in terms of pharmacokinetics manageability.

Remifentanil is a short-acting opioid proven to be safe and effective to achieve optimal sedation in case of intolerance to NIV (96). In keeping with a recent investigation (97), a remifentanil-based sedation plan has demonstrated the same efficacy in ameliorating moderate to severe NIV intolerance, as dexmedetomidine.

A separate description of the advantages and disadvantages of sedative drugs in NIV is summarized in **Table 3**.

Regardless of the sedation plan adopted, sedation assessment is of pivotal importance during NIV, through subjective scales (e.g., Richmond agitation-sedation scale) or tool, i.e., bi-spectral index, entropy. The sedation assessment, at regular time intervals, allows to provide the desired target of sedation and to avoid hypersedation (66).

Regarding the concern related to the respiratory drive depression by sedative medications, it is worth to remark that sedation assessment must be assured whatever the therapeutic scheme adopted. Therefore, sedative and anxiolytic drugs should be administered in the appropriate environment, staffed with well-trained personnel in the monitoring of vital signs and sedation depth and airway emergencies management (98).

Novel COVID-19 Pandemic

The massive spread of COVID-19 outbreak has put in crisis the surge capacity response of whole sanitary systems worldwide (99). In particular, ICU surge capacity response has been severely

TABLE 3 | Advantages and disadvantages of sedative drugs in NIV*.

Drugs	Advantages	Disadvantages
Midazolam	• Good efficacy • Hemodynamic stability	• Increased risk of delirium and paradoxical agitation • Accumulation in critically ill patients who are obese, have low albumin levels, or renal failure
Propofol	Advantageous pharmacokinetic profile	Can cause hypotension and apnea
Dexmedetomidine	• No respiratory depression • Providing sedation, anxiolysis and analgesia • Seems superior to midazolam in terms of maintaining sedation with fewer dose adjustments	• Bradycardia and hypotension • Cautiously in patients with hemodynamic instability
Remifentanil	• Metabolism not affected by hepatic or renal dysfunction • Easy to titrate to effect • No accumulation	• Chest wall rigidity • Nausea and Vomiting

*Data from references 75–76, 83.

stressed by enormous requests for ventilatory assistance due to hypoxemic acute respiratory distress syndrome (ARDS) COVID-19 (100). To stabilize the respiratory condition and avoid intubation, NIV has been used outside the ICU (101). In this context, all the strategies finalized to increase the success of NIV have been pursued. Thus, awake prone position (APP) has been introduced as a rescue therapy in patients who underwent NIV, to ameliorate oxygenation and possibly avoid intubation (82–84).

Despite these advantages, maintaining an APP for long-lasting sessions could be very challenging. In fact, the main cause of interruption of APP has been shown to be scarce comfort (101).

The prone position reduces the compliance of the chest wall, leading to an increase in the work of breathing, and generating discomfort (7). In addition, the patients are requested to lay in an obligated position for several hours a day. According to recent data (102), when APP is employed at the expense of a comfort reduction, the consequent rise in diaphragmatic activity puts the patients at risk for IMV. Thus, to increase the chance of success of NIV combined with APP, management strategies must be implemented to increase comfort and facilitate patient's adaptation (103).

However, during the current COVID-19 pandemic, the importance of close monitoring of the patient in NIV has clearly emerged, as despite its clear benefits, a delay in intubation turns out to be associated with worse outcomes (104–106).

Patients with delayed onset of invasive ventilation have increased mortality and more severe pulmonary sequelae in terms of lung carbon monoxide diffusion capacity (DLCO) and radiological imaging (105). One possible explanation may be that maintaining patients with NIV when not appropriate can trigger patient self-induced lung injury (P-SILI) due to increased inspiratory efforts (105). Therefore, in addition to NIV comfort, it is of pivotal importance to monitor predictors of failure of NIV, i.e., no change or worsen in pH, blood gases, respiratory rate, and agitation (19), to early intervene with intubation and not worsen patients' prognosis.

CONCLUSIONS

In conclusion, net of the underlying pathological disease, enhancing the patient comfort, seems the best strategy to improve the NIV rate of success, especially when NIV is administered for a prolonged period of time, also in combination with APP as rescue therapy. Accordingly, a strict comfort assessment with the "*ad hoc*" corrective measures is mandatory to prevent NIV discontinuation related to poor patient's tolerance.

AUTHOR CONTRIBUTIONS

GC and RS proposed the project and conducted the research. GC and RS wrote the manuscript while RS was responsible for tables and figure. ED revised the manuscript. All authors approved the final version of the manuscript.

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Corrigendum: Comfort during non-invasive ventilation

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Time-Controlled Adaptive Ventilation Does Not Induce Hemodynamic Impairment in a Swine ARDS Model

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Background: The current standard of care during severe acute respiratory distress syndrome (ARDS) is based on low tidal volume (VT) ventilation, at 6 mL/kg of predicted body weight. The time-controlled adaptive ventilation (TCAV) is an alternative strategy, based on specific settings of the airway pressure release ventilation (APRV) mode. Briefly, TCAV reduces lung injury, including: (1) an improvement in alveolar recruitment and homogeneity; (2) reduction in alveolar and alveolar duct micro-strain and stress-risers. TCAV can result in higher intra-thoracic pressures and thus impair hemodynamics resulting from heart-lung interactions. The objective of our study was to compare hemodynamics between TCAV and conventional protective ventilation in a porcine ARDS model.

Methods: In 10 pigs (63–73 kg), lung injury was induced by repeated bronchial saline lavages followed by 2 h of injurious ventilation. The animals were then randomized into two groups: (1) Conventional protective ventilation with a VT of 6 mL/kg and PEEP adjusted to a plateau pressure set between 28 and 30 cmH_2O; (2) TCAV group with P-high set between 27 and 29 cmH_2O, P-low at 0 cmH_2O, T-low adjusted to terminate at 75% of the expiratory flow peak, and T-high at 3–4 s, with I:E > 6:1.

Results: Both lung elastance and PaO_2:FiO_2 were consistent with severe ARDS after 2 h of injurious mechanical ventilation. There was no significant difference in systemic arterial blood pressure, pulmonary blood pressure or cardiac output between Conventional protective ventilation and TCAV. Levels of total PEEP were significantly higher in the TCAV group ($p < 0.05$). Driving pressure and lung elastance were significantly lower in the TCAV group ($p < 0.05$).

Conclusion: No hemodynamic adverse events were observed in the TCAV group compared as to the standard protective ventilation group in this swine ARDS model, and TCAV appeared to be beneficial to the respiratory system.

Keywords: mechanical ventilation, ARDS, TCAV, APRV, hemodynamic, heart-lung interactions

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening condition due to a lung injury that can result from numerous causes (e.g., infectious, toxic, or inflammatory). Its mortality raises up to 50% in the most severe cases (1).

ARDS treatment is based on protective mechanical ventilation, prone positioning, neuromuscular blockade or VV-ECMO (2). The current standard of care is based on the limitation of ventilator-induced lung injury (VILI) by reducing the insufflated tidal volume (V_T) to 6 mL/kg of predicted body weight (PBW) and by maintaining driving pressure (ΔP) below 15 cmH_2O (3, 4). As positive end expiratory pressure (PEEP) can provide both lung recruitment and overdistension, it can lead to an increase in pulmonary blood pressure (PBP) (5, 6). An alternative strategy is the time-controlled adaptive ventilation (TCAV), a specific combination of settings applied to set the airway pressure release ventilation (APRV) mode. Initially reported by Habashi et al., TCAV reduces lung injury in both experimental and clinical studies (7–9). TCAV is based on delivering a continuous inspiratory positive airway pressure (CPAP) phase (P_{high}), followed by a brief expiratory release phase (T_{low}) (10).

A significant concern is the hemodynamic effect of an increase in intrathoracic pressure leading to a decrease in cardiac output (6, 11). Our hypothesis is that TCAV, that results in higher intra-thoracic pressures due to the prolonged inspiratory phase, can lead to harmful heart-lung interactions. The main objective of our study was to compare hemodynamics during the first hour of TCAV or conventional protective ventilation in a porcine ARDS model.

METHODS

The present study was conducted in accordance with the ARRIVE consensus guideline for reporting animal experimental studies (12).

Abbreviations: APRV, Airway pressure release ventilation; ARDS, Acute respiratory distress syndrome; ATC, Automatic tube compensation; CO, Cardiac output; CPAP, Continuous positive airway pressure; C_{RS}, Compliance of respiratory system; E_L, Elastance of the lung; ER, Elastance ratio; E_{RS}, Elastance of respiratory system; $EtCO_2$, End-tidal carbon dioxide; EIT, Electrical Impedance Tomography; FIO_2, Fraction of oxygen inspired; HiFi, High-fidelity pressure catheter; I:E, inspiratory to expiratory time ratio; IVC, Inferior vena cava; LVV, Left ventricular volume; PAWP, Pulmonary artery wedge pressure; P_{aw}, Airway pressure; P_{es}, Esophageal pressure; PBW, Predicted body weight; PEEP, Positive end-expiratory pressure; PEFR, Peak expiration flow rate; P_{high}, High pressure; P_L, Transpulmonary pressure; P_LER, Transpulmonary pressure according to ratio of elastance method; P_{low}, Low pressure; PLV, Left ventricular pressure; P_{es}, Pleural pressure or esophageal pressure; PVR, Pulmonary vascular resistance; RAP, Right atrial pressure; RR, Respiratory rate; S/D/M ABP, Systolic, diastolic, mean aortic blood pressure; S/D/M CBF, Systolic, diastolic, mean carotid blood flow; S/D/M PBP, Systolic, diastolic, mean pulmonary blood pressure; SVO_2, Mixed venous oxygen saturation; TCAV, Time-controlled adaptive ventilation; T_{high}, Time high; T_{low}, Time low; VCV, Volume-controlled ventilation; VD, Dead volume; VILI, Ventilator-induced lung injury; LVV, Left ventricular volume; VT, Tidal volume; VV-ECMO, Veno-venous extracorporeal membrane oxygenation; ΔPaw, Driving pressure; ΔP_L, Inspiratory transpulmonary pressure—expiratory transpulmonary pressure; ROI, Region of interest; RC_{ROI}, Regional compliance.

Ethics

All experiments were reviewed and approved by the Nancy University Ethics Committee for Animal Experimentation (APAFIS Number 2020082407561244). The procedure for the care and sacrifice of the study animals was in accordance with the European Community Standards on the Care and Use of Laboratory Animals.

Animal Preparation

Animals were fasted overnight with free access to water. All the pigs were of male sex with a median weight of 67 kilograms. Intramuscular premedication was performed with ketamine (1.5 mg/kg, Warner Lambert, Nordic, AB Solna, Sweden) before transportation to the experiment facility. Sedation was deepened with propofol (2.5 mg/kg, B. Braun, Melsungen, Germany) *via* an ear vein cannula. After being placed in a supine position, animals were intubated with a 7.5-mm internal diameter endotracheal tube (ETT). Anesthesia was maintained with a continuous infusion of midazolam 5 mg/h and sufentanyl 20 μg/h. Depth of anesthesia was assessed regularly by checking on movements and hemodynamic response to a painful stimulus. Muscle paralysis was then maintained with a continuous infusion of cisatracurium (0.5 mg/kg/h) (GlaxoSmithKline, Marly-le-Roi, France) throughout the experiment. Pigs were connected to the ventilator (Dräger Evita Infinity V500, Lübeck, Germany), with the baseline settings adjusted to the following levels: V_T,7 mL/kg; respiratory rate (RR), 22 breaths/min; PEEP, 5 cmH_2O; fraction of inspired oxygen (FiO_2),100%. Automatic tube compensation (ATC) was adjusted to 100%. The ventilator settings were then adjusted to pH > 7.35 and $PaCO_2$ between 40 and 45 mmHg.

Hemodynamic Monitoring

Measurements were performed at the following successive periods: after intubation and catheters placement at basal state (T_B), after ARDS induction with saline lavages and injurious mechanical ventilation (T_0), and at 15 min (T_{15}) and 60 min (T_{60}) following randomization to either conventional protective ventilation or TCAV (**Supplementary Figure 1**). A pulmonary artery catheter (Swan-Ganz, Edwards Lifesciences, Irvine, USA) was inserted *via* the left internal jugular vein for measuring PBP, pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP) and mixed venous oxygen saturation (SVO_2). The pressure transducer was positioned at the level of the right atrium. A conductance catheter (Transonic Systems Inc., Ithaca, USA) was inserted into the left ventricle *via* the left carotid artery for simultaneous registration of both instantaneous high-fidelity left ventricular pressure (PLV) and instantaneous left ventricular volume. Central aortic pressure (ABP) was assessed by a high-fidelity pressure catheter (HIFI) (Transonic Systems Inc., Ithaca, USA) percutaneously inserted *via* the femoral artery into the descending thoracic aorta. The catheters were inserted under fluoroscopy. The right carotid artery was dissected, and a Transit Time Flow probe (Transonic Systems Inc., Ithaca, USA) was secured around it. Data were computed using a designated analysis program (IOX 2.4.2.6®, EMKA Technologies, France). The signals were recorded continuously at a sampling rate of 2,000 Hz. A period of 2 h was required for the calibration and

the correct positioning of the probes, assessed by fluoroscopy and chest X Ray. The core body temperature was measured *via* a rectal probe and maintained between 37 and 38° by a warming blanket system.

Respiratory Monitoring

Airway pressure (P_{aw}) was continuously registered by a probe set on the ventilator Y-piece. The esophageal pressure (P_{es}) was assessed by an esophageal balloon (BA-A-008 probe, MBMed, Argentina) positioned with fluoroscopy and inflated up to 4 mL. The correct positioning of the devices was checked by using the Baydur manoeuver (13). Transpulmonary pressure ($P_{L)}$ was calculated in absolute value, as follows: $P_L = P_{aw} - P_{es}$. ΔP_L is defined as the difference between $P_{Lend-insp}$ and $P_{Lend-exp}$. The absolute value of P_L reflects the local pressure in the dependent lung regions, adjacent to the esophageal balloon, independently of the mediastinal structures (14). Elastance of the respiratory system (El_{RS}) was assessed by: $El_{RS} = \Delta P_{aw}/V_T$. The elastance ratio (ER) was calculated as follows: $ER = El_L/El_{RS}$, i.e., the lung elastance (El_L) to total respiratory system elastance ratio (15). Inspiratory transpulmonary pressure based on elastance ratio (P_LEr) reflects the local pressure in the non-dependent lung regions (16). It was calculated as follows: $P_LEr = P_{aw}$ x ER. End inspiratory and end expiratory P_L were measured after a 5-s airway occlusion of the ventilator circuitry. Data were computed using a designated analysis program with sampling rate of 2,000 Hz (IOX 2.4.2.6®, EMKA Technologies, France). In TCAV, total PEEP was measured during a 5-s occlusion period at the end of expiration.

End-tidal carbon dioxide ($EtCO_2$) was monitored for assessing the $PaCO_2$-$EtCO_2$ gradient and estimate the physiologic dead space as described by Enghoff's modification of the Bohr equation: $\frac{VD}{VT} = \frac{PaCO2 - EtCO2}{PaCO2}$ where VD is the dead space volume (mL), V_T is tidal volume (mL), $EtCO_2$ is the end tidal expiratory CO_2 (mmHg), and $PaCO_2$ (mmHg) is the systemic arterial CO_2 pressure (17).

Electrical Impedance Tomography

An electrical impedance tomography (EIT) electrode belt, which carries 16 electrodes with an inter-electrode distance of 40 mm, was placed around the thorax in the fifth intercostal space, and one reference electrode was placed on the animal's abdomen (PulmoVista 500, Dräger Medical, Lübeck, Germany). The measures of EIT were averaged over five respiratory cycles and the images were divided into four regions of interest (ROI): ROI 1 being the most ventral, to ROI 4, being the most dorsal. Results are expressed as the percentage of total tidal volume ventilation in the four ROIs (18, 19). The regional compliance was calculated in the four ROIs as follows: $RC_{ROI} = \frac{VT\ x\ ROI}{\Delta Paw}$ expressed in mL/cmH_2O.

ARDS Induction

Induction of a double hit lung injury was performed by 4 repeated lung lavages for a total of 30 mL/kg warm 0.9% saline solution intratracheally at 38.5°C. The lung was filled up to the endotracheal tube and fluid was drawn from the airways after 2 min *via* a tracheal aspiration. During the bronchoalveolar lavage, all the animals developed a profound desaturation with $SpO_2 < 60\%$ without any bradycardia or life-threatening hemodynamic alteration. This was followed by 2 h of injurious ventilation with PEEP 0 cmH_2O and inspiratory pressure of 40 cmH_2O, RR 10/min, inspiratory to expiratory time ratio (I:E) of 1:1 (20). The FiO_2 was set at 1.0, providing an additional mechanism of lung injury (21). Of note, mechanical power of mechanical ventilation transferred to the respiratory system was estimated at 41 J/min, by applying the equation proposed by Louis et al. (22). The animals received a continuous intravenous infusion of normal saline at 10 mL/Kg/h during lung injury induction, and 2 mL/Kg/h during the study period.

Interventions and Study Groups

After the induction of ARDS, animals were randomly allocated to one of the following two groups:

- *Conventional protective group (n = 5):* with V_T 6 mL/kg, PEEP adjusted to reach a plateau pressure of 28 to 30 cmH_2O, RR 25 bpm, I:E 1:2.
- *TCAV group (n = 5):* P_{high} set between 27 and 29 cmH_2O, P_{low} at 0 cmH_2O, T_{low} set to terminate at 75% of the expiratory flow peak, T_{high} at 3–4 s, and I:E > 6:1.

STATISTICAL ANALYSES

Given the small sample size, all results are expressed as median and interquartile range (IQR). Baseline and T_0 measurements were compared by using the non-parametric Friedman test for analysis of variance by ranks. Respiratory and hemodynamics values between the two groups at T_0, T_{15}, and T_{60} were compared by using mixed effects regression models for evaluating the association of variables of interest (fixed effects) with the dependent variable, using the animal number as random effect to account for the repetition of regional measurements in each animal, and the lung level as a random slope. Multicollinearity and interactions were systematically evaluated in multivariate models; in the case of a significant interaction, a *post-hoc* analysis using pairwise comparison adjusted for the repetition of statistical tests was performed using the Tukey method. In the case of *post-hoc* multiple comparisons to a single reference level, we used the Dunnett adjustment method. All statistical analyses were with a significance level of 0.05 and performed using R version 4.0.1 for MacOS® (https://www.r-project.org/, accessed March 2020).

RESULTS

Effect of Experimental ARDS on Respiratory Mechanics and Hemodynamics

Thirteen pigs were involved in the experiment. Ten pigs were included into the final analyses. Two pigs developed an early hemorrhagic shock, and one pig developed a refractory ventricular fibrillation at the time of the left ventricular catheter insertion before randomization.

TABLE 1 | Hemodynamic characteristics.

	TCAV ($n = 5$)	Conventional protective ventilation ($n = 5$)	Effect of group	Effect of time	Group × time
Heart rate (bpm)			$p = 0.3$	$p = 0.2$	$p = 0.4$
T0	122 (121 to 134)	136 (135 to 137)			
T15	135 (134 to 136)	132 (129 to 141)			
T60	133 (130 to 139)	135 (134 to 138)			
Mean aortic blood pressure (mmHg)			$p = 0.9$	$p = 0.7$	$p = 0.7$
T0	104 (92 to 104)	85 (83 to 102)			
T15	100 (95 to 105)	90 (85 to 110)			
T60	104 (90 to 109)	90 (76 to 95)			
Mean pulmonary blood pressure (mmHg)			$p = 0.4$	$p = 0.3$	$p = 0.3$
T0	39 (35 to 40)	40 (34 to 42)			
T15	38 (33 to 40)	32 (27 to 42)			
T60	37 (36 to 38)	40 (30 to 46)			
Pulmonary vascular resistance (U Woods)			$p = 0.3$	$p = 0.1$	$p = 0.3$
T0	2.6 (2.3 to 3.5)	2.8 (2.4 to 3.0)			
T15	2.7 (2.8 to 3.1)	2.5 (2.3 to 3.2)			
T60	3.1 (3.0 to 3.5)	2.6 (2.2 to 3.8)			
Right atrial pressure (mmHg)			$p = 0.4$	$p = 0.7$	$p = 0.3$
T0	9 (9 to 10)	10 (9 to 11)			
T15	11(10 to 11)	11 (10 to 13)			
T60	9 (9 to 10)	9 (8 to 11)			
PAWP (mmHg)			$p = 0.3$	$p = 0.1$	$p = 0.08$
T0	13 (13 to 14)	14 (13 to 17)			
T15	14 (13 to 16)	13 (12 to 14)			
T60	12 (10 to 14)	11 (10 to 12)			
Cardiac output (L.min^{-1})			$p = 0.3$	$p = 0.1$	$p = 0.06$
T0	8.7 (6.8 to 9.9)	6.5 (6.0 to 9.3)			
T15	8.1 (8.0 to 9.7)	8.7 (8.0 to 9.7)			
T60	7.6 (5.5 to 8.6)	7.6 (6.9 to 11.5)			
LV Tau 1/e (ms)			$p < 0.05$	$p = 0.1$	$p = 0.3$
T0	20.6 (18.0 to 22.0)	13.5 (10.1 to 15.8)			
T15	16.0 (15.8 to 21.3)	13.6 (9.7 to 15.4)			
T60	20.1(16.0 to 20.9)	15.6 (14.1 to 17.9)			
LV –dP/dtmax (mmHg.s-1)			$p = 0.3$	$p = 0.5$	$p = 0.8$
T0	−1,719 (−2,397 to −1,545)	−2,987 (−3,000 to −1,984)			
T15	−1,972 (−2,060 to −1,785)	−2,100 (−2,527 to −1,115)			
T60	−2,048 (−2,150 to −1,695)	−2,489 (−2,878 to −1,855)			
LV +dP/dtmax (mmHg.s^{-1})			$p < 0.05$	$p = 0.4$	$p = 0.3$
T0	1,738 (1,661 to 4,772)	3,969 (3,460 to 4,179)			
T15	1,609 (1,494 to 4,737)	3,746 (1,848 to 6,044)			
T60	1,604 (1,483 to 5,038)	4,404 (4,334 to 6,816)			
LV +/–dP ratio			$p = 0.4$	$p = 0.1$	$p = 0.2$
T0	1.32 (0.65 to 2.74)	1.91 (1.35 to 2.08)			
T15	1.19 (0.75 to 2.65)	2.79 (2.39 to 2.80)			
T60	2.13 (0.87 to 2.45)	2.65 (1.32 to 3.26)			
Total fluid loading (mL)			$p = 0.3$	$p = 0.1$	$p = 0.3$
T0	1,675 (1,650 to 1,825)	1,660 (1,570 to 1,830)			
T15	1,710 (1,680 to 1,860)	1,700 (1,610 to 1,860)			
T60	1,820 (1,780 to 1,970)	1,810 (1,780 to 1,960)			

The analysis used all data collected in both groups at the 3 study time points, using a mixed effects linear regression with study group and study time point as independent variables, and animal identification number as the random effect. Interaction of time with study group was systematically checked for. If no interaction was identified, the p-value of the effect of Group and Time are given, respectively. In case of a significant interaction, a pairwise post-hoc multiple comparison was performed to compare groups at each time points on the one side, and compare T15 and T30 to T0 in each group, on the other. TCAV, Time controlled adaptative ventilation; PAWP, Pulmonary artery wedge pressure; LV +dP/dtmax and LV -dP/dtmax, minimum and maximum rate of pressure change in the left ventricle; LV dP ratio, represent catecholaminergic impregnation and was calculated as the ratio of -dP/dtmax and +dP/dtmax; LV Tau, Isovolumic relaxation constant. T0: After ARDS induction; T15: 15 min after start of study; T60: 60 min after start of study; Data are presented as median (25th−75th percentile).

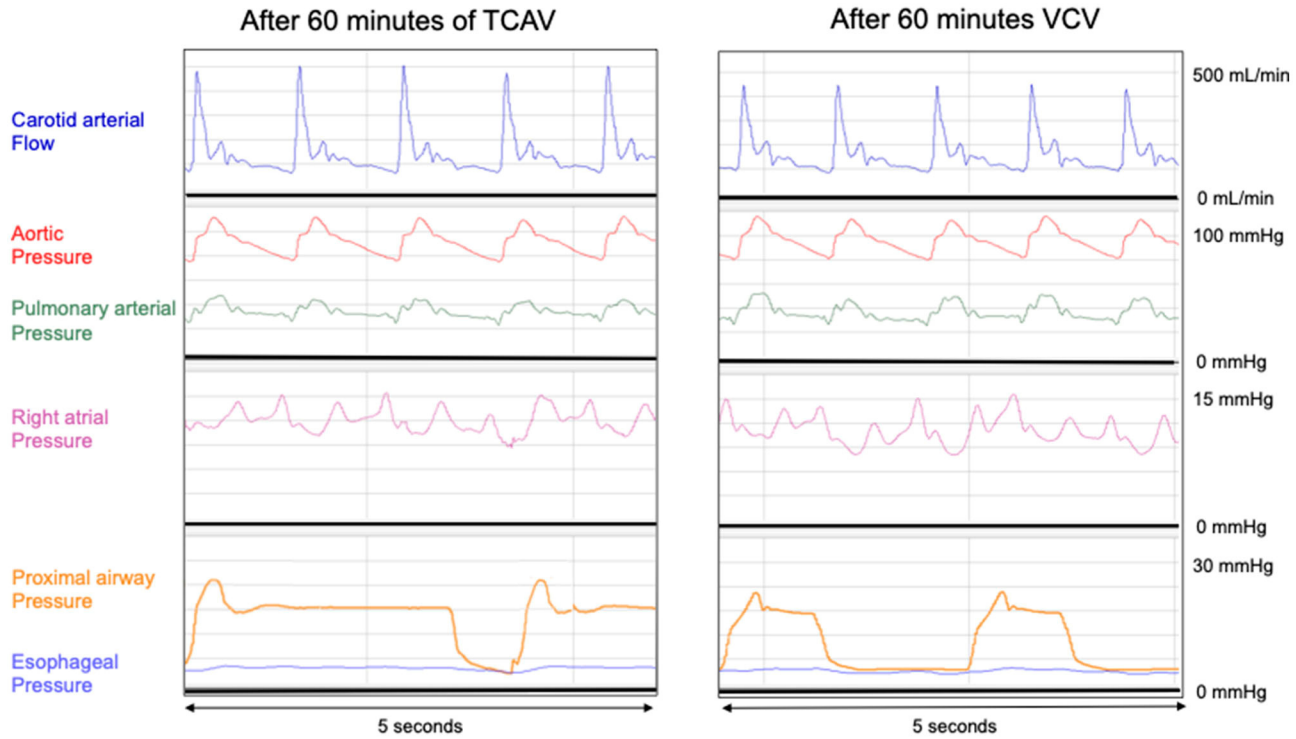

FIGURE 1 | Polygraphic recordings between two groups at T_{60} of the main hemodynamic and respiratory outcomes. VCV: Conventional protective group with VT 6 ml.kg^{-1}, PEEP 10 cmH_2O, RR 25 bpm, I:E 1:2. TCAV: Phigh 27 cmH_2O, Plow at 0 cmH_2O, Tlow 0.4 s, Thigh 4.

Respiratory and hemodynamic parameters at baseline and after ARDS induction are summarized in **Supplementary Table 1**. At T_0 (after ARDS induction) both El_L [32 cmH_2O/L (29–33)] and PaO_2/FiO_2 ratio [99 (88–115)] were consistent with a severe ARDS.

Effect of Ventilation Strategies on Hemodynamics

All the results related to hemodynamics are presented in **Table 1** and **Supplementary Table 2**. There were no significant between group differences at T_0 for the main hemodynamic parameters: heart rate (HR), cardiac output (CO), ABP, PBP, RAP, and pulmonary vascular resistance (PVR). The only significant difference was observed for the left ventricle (LV) isovolumic relaxation time constant (Tau) and LV maximal rate of pressure rise (LV + dP/dtmax) values, which reached higher levels in the conventional protective ventilation population at T_0 but also at T_{15} and T_{60} ($p < 0.05$, no interaction was detected in multivariate analysis). There was no between-group difference at T_{60} for HR, CO, ABP, PBP, RAP and PVR. There was no between group difference in lactate values at T_{60} between the TCAV group [1.1 mmol/L (1.0–2.1)] vs. 1.5 (1.5–1.7) in the conventional protective group ($p = 0.06$).

Polygraphic recordings between two groups at T_{60} of the main hemodynamic and respiratory outcomes are presented in **Figure 1**.

Effects of the Ventilation Strategies on Respiratory Mechanics

All the results related to respiratory parameters are presented in **Table 2** and **Supplementary Table 3**. There were no significant differences in the respiratory parameters between the TCAV and conventional protective groups at T_0 except for pH ($p < 0.05$).

Respiratory rate was significantly lower at T_{60} in the TCAV group compared to the conventional protective group ($p < 0.05$). Levels of total PEEP were significantly higher in the TCAV group at T_{60} ($p < 0.05$). Mean airway pressure was significantly higher in the TCAV group at T_{15} and T_{60} ($p < 0.05$). The ΔP_{aw} was significantly lower in the TCAV group at T_{15} and T_{60} ($p < 0.05$). V_T in the TCAV group significantly differed from conventional protective group at T_{60}: 7.4 mL/kg (6.4–7.8) in the TCAV group vs. 6.1 mL/kg (5.8–6.2) in the conventional protective group ($p < 0.05$). Elastance of the lung at T_{15} and T_{60} was significantly lower in the TCAV group ($p < 0.05$). PaO_2/FiO_2 increased in both groups at T_{60} without significant differences between the two groups. During the study period $PaCO_2$ did not differ significantly. The regional compliance in the mid-ventral and mid-dorsal regions (RC_{ROI} 2 and RC_{ROI} 3) was significantly higher at T_{60} in the TCAV group ($p < 0.05$) (**Supplementary Table 4**).

Fluid Loading and Vasopressors

The total fluid loading was of 1,675 mL (1,650–1,825) in the TCAV group and of 1,660 ml (1,570–1,830) in the VCV group

TABLE 2 | Respiratory characteristics.

	TCAV ($n = 5$)	Conventional protective ventilation ($n = 5$)	Effect of group	Effect of time	Group × time
VT (mL/kg)			-	-	$p < 0.05$
T0	5.9 (5.5–6.0)	5.9 (5.9–6.0)			
T15	6.9 (6.2–7.2)	5.9 (5.7–6.1)			
T60	7.4 (6.4–7.8)[a]	6.1 (5.8–6.2)[bc]			
RR (.min^{-1})			-	-	
T0	24 (23–26)	25 (24–26)			$p < 0.05$
T15	20 (18–20)[a]	27 (26–28)[bc]			
T60	20 (18–20)[a]	27 (26–28)[bc]			
PEEPt (cmH_2O)			-	-	$p < 0.05$
T0	5 (5–6)	5 (5–6)			
T15	11 (10–13)[a]	11 (11–11) [b]			
T60	14 (14–15)[a]	11 (11–11)[bc]			
ΔP_{AW} (cmH_2O)			-	-	$p < 0.05$
T0	19 (18–21)	20 (19–21)			
T15	14 (13–15)[a]	18 (18–19)[bc]			
T60	13 (11–14)[a]	18 (18–19)[bc]			
ΔP_L (cmH_2O)			-	-	$p < 0.05$
T0	15 (14–16)	17 (15–18)			
T15	11 (8–11)[a]	16 (15–19)[c]			
T60	10 (7–11)[a]	15 (12–16)[c]			
El_L ($cmH_2O.L^{-1}$)			-	-	$p < 0.05$
T0	41 (40–41)	40 (37–41)			
T15	25 (19–26)[a]	42 (41–45)[c]			
T60	22 (15–23)[a]	40 (39–42)[c]			
$PaCO_2$ (mmHg)			$p = 0.3$	$p = 0.5$	$p = 0.4$
T0	43 (35–44)	48 (44–49)			
T15	44 (38–45)	43 (41–49)			
T60	39 (37–45)	46 (38–54)			
PaO_2/FIO_2 (mmHg)			$p = 0.5$	$p < 0.05$	$p = 0.3$
T0	88 (44–99)	100 (98–115)			
T15	140 (95–200)	101 (80–117)			
T60	135 (100–219)	117 (75–180)		#	

The analysis used all data collected in both groups at the 3 study time points, using a mixed effects linear regression with study group and study time point as independent variables, and animal identification number as the random effect. Interaction of time with study group was systematically checked for. If no interaction was identified, the p-value of the effect of Group and Time are given, respectively. In case of a significant interaction, a pairwise post-hoc multiple comparison was performed to compare groups at each time points on the one side, and compare T15 and T30 to T0 in each group, on the other.

[#]$p < 0.05$ compared to T0 at the time point (no interaction with study group).

[a]$p < 0.05$ compared to T0 in the TCAV group in multiple comparison.

[b]$p < 0.05$ compared to T0 in the conventional protective ventilation group in multiple comparison.

[c]$p < 0.05$ compared to the TCAV group at this time point in multiple comparison.

TCAV, Time controlled adaptative ventilation; VT, Tidal volume; RR, Respiratory rate; PEEPtot, Positive End Expiratory Pressure total; ΔP_{AW}, driving pressure, difference in airway pressure at end-inspiration (plateau pressure) and end-expiration (total PEEP); ΔP_L, difference in transpulmonary inspiratory pressure at end-inspiration and end-expiration; El_L, lung elastance; T0, After ARDS induction; T15, 15 min after start of study; T60, 60 min after start of study; Data are presented as median (25th−75th percentile).

($p = 0.3$) and no norepinephrine was infused during the study period (**Table 2**).

DISCUSSION

The main result of the present study is that TCAV did not significantly impact hemodynamics, despite the increase in intrathoracic pressures. Additionally, TCAV improved the lung elastance after only 1 h of ventilation.

ARDS Model

Saline lavages followed by 2 h of injurious mechanical ventilation is a well-established model for inducing ARDS. It provides a highly reproducible and significant homogenous alteration of the PaO_2/FiO_2, El_L, and the dead space volume. ER was

0.8 after ARDS induction, indicating specific lung involvement for El_{RS} alteration without chest wall participation (16). This method provided a triple-hit lung injury: saline lavages leads to surfactant depletion, 100% oxygen delivery can lead to denitrogenation and injurious ventilation provides both barotrauma and volotrauma (23).

Hemodynamic Assessment of TCAV

In our work, TCAV was not associated with a hemodynamic impairment compared to standard ventilation. Regarding the right ventricular function, there were no elements suggestive of right ventricle failure, as right atrial pressure values remained low in both groups and the cardiac output was stable during the study period. Even if higher intrathoracic pressures can impair hemodynamics, changes in lung physiology can have beneficial consequences on the right ventricle and thus on hemodynamics. As pulmonary vascular resistance relates to lung volume, higher intrathoracic pressures could be in fact associated with an increase in FRC and thus a reduction in PVR (24). Sharpey-Shafer et al. reported in 1965 that a "square wave" response of the arterial pressure to the Valsalva maneuver was observed in the case of inferior vena cava (IVC) maximal repletion (25). Conversely, under hypovolemic conditions, increased mean thoracic pressure could induce the compressive occlusion of the IVC at its distal portion, at the junction with the right atrium, and lead to an acute cardiovascular collapse (26). Sympatho-vagal tone drives tolerance for acute intra thoracic pressure variation as it provides immediate inotropic, lusitropic and chronotropic adaptation (27).

Regarding the LV function, LV + dP/dtmax and shortened LV relaxation duration were observed in the conventional protective group, which can be explained by both higher ΔP_L in relation to probable overdistention and more marked sympathetic stress in this group. In line with the above-mentioned literature, our results suggest that TCAV might be safe assuming the IVC repletion. Further studies are needed to assess hemodynamic safety underlying increased mean thoracic pressures during prolonged periods of ventilation.

These results are in line with data from an existing animal sepsis model, with a less robust cardiac assessment, in which TCAV was safe compared with low tidal volume ventilation, in terms of CO and MAP. Further studies are needed to evaluate TCAV in other injury models (28).

Respiratory Assessment of TCAV

The higher mean airway pressure and the lower respiratory rate observed in the TCAV group compared to the conventional protective group are explained by a longer I/E ratio, which is one of the fundamental characteristics of TCAV. Total PEEP was also higher, in relation with the decrease in ΔP_{aw} and improvement in El_L. Tidal volume delivered in the TCAV group was closely monitored and averaged 7 mL/kg as T_{low} was adjusted to terminate at 75% of PEFR, in order to prevent alveolar collapse (7). $P_L Er$ provides indirect information about overdistension in the non-dependent lung areas and was lower at T_{60} in the TCAV group. TCAV significantly improved ΔP_{aw} and EIT regional compliance at T_{60}. This can be explained by a gain in aerated lung tissue volume. There were no differences between the two groups regarding both $PaCO_2$ and pH values. Our results are in line with the literature, suggesting benefits of TCAV in terms of lung protective ventilation (12, 29).

Study Limitations

One of the limitations of our study lies in the small sample size of each study group. The study might have been underpowered in its attempt to assess a clinically relevant effect of TCAV on hemodynamics. It is worth mentioning that dorsal decubitus is poorly tolerated in pigs and involves important modifications in both "West physiology" and hemodynamics that could mitigate external validation of the present results. Improvement in pulmonary elastance in the TCAV group can be in relation with higher levels of total PEEP and mean airway pressure. Furthermore, it could be suggestive of alveolar recruitment, but we did not perform any CT scan in order to verify this hypothesis, especially with the use of an recruitable ARDS (29, 30). In our work, the right ventricular function was assessed only with measures obtained with a pulmonary arterial catheter, as placement of the conductance catheter in the right ventricle and transthoracic echocardiography in pigs was not feasible in our study setting. The addition of paralysis may not fully encompass the hemodynamics associated with either ventilator mode as it does not incorporate the hemodynamic and respiratory effects of spontaneous breathing (28). To finish, this study was designed with only a 1-h ventilation period to observe the safety of initiation of TCAV on heart-lung interactions, limiting the evaluation of a longer period of TCAV on lung mechanics (31).

CONCLUSION

In conclusion, no hemodynamic adverse events were observed with TCAV compared to standard protective ventilation in this swine ARDS model, as TCAV appeared to be beneficial for the respiratory system.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The animal study protocol was approved by Nancy University Ethics Committee for Animal Experimentation (APAFIS Number 2020082407561244).

AUTHOR CONTRIBUTIONS

ML, BP, BL, MK, HP, and N'GT contributed to conception and design of the study. N'GT organized the study. BP and ML wrote the first draft of the manuscript. LB, J-LH, J-CR and MK wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.883950/full#supplementary-material

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Inhaled CO_2 vs. Hypercapnia Obtained by Low Tidal Volume or Instrumental Dead Space in Unilateral Pulmonary Artery Ligation: Any Difference for Lung Protection?

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Background: Unilateral ligation of the pulmonary artery (UPAL) induces bilateral lung injury in pigs undergoing controlled mechanical ventilation. Possible mechanisms include redistribution of ventilation toward the non-ligated lung and hypoperfusion of the ligated lung. The addition of 5% CO_2 to the inspiratory gas ($FiCO_2$) prevents the injury, but it is not clear whether lung protection is a direct effect of CO_2 inhalation or it is mediated by plasmatic hypercapnia. This study aims to compare the effects and mechanisms of $FiCO_2$ *vs.* hypercapnia induced by low tidal volume ventilation or instrumental dead space.

Methods: Healthy pigs underwent left UPAL and were allocated for 48 h to the following: Volume-controlled ventilation (VCV) with V_T 10 ml/kg (injury, $n = 6$); VCV plus 5% $FiCO_2$ ($FiCO_2$, $n = 7$); VCV with V_T 6 ml/kg (low V_T, $n = 6$); VCV plus additional circuit dead space (instrumental V_D, $n = 6$). Histological score, regional compliance, wet-to-dry ratio, and inflammatory infiltrate were assessed to evaluate lung injury at the end of the study. To investigate the mechanisms of protection, we quantified the redistribution of ventilation to the non-ligated lung, as the ratio between the percentage of tidal volume to the right and to the left lung ($V_{TRIGHT/LEFT}$), and the hypoperfusion of the ligated lung as the percentage of blood flow reaching the left lung ($Perfusion_{LEFT}$).

Results: In the left ligated lung, injury was prevented only in the $FiCO_2$ group, as indicated by lower histological score, higher regional compliance, lower wet-to-dry ratio and lower density of inflammatory cells compared to other groups. For the right lung,

the histological score was lower both in the $FiCO_2$ and in the low V_T groups, but the other measures of injury showed lower intensity only in the $FiCO_2$ group. $V_{TRIGHT/LEFT}$ was lower and $Perfusion_{LEFT}$ was higher in the $FiCO_2$ group compared to other groups.

Conclusion: In a model of UPAL, inhaled CO_2 but not hypercapnia grants bilateral lung protection. Mechanisms of protection include reduced overdistension of the non-ligated and increased perfusion of the ligated lung.

Keywords: ventilator-induced lung injury, pulmonary perfusion, inhaled CO_2, therapeutic hypercapnia, mechanical ventilation

INTRODUCTION

Pathologic changes in lung perfusion in acute respiratory failure include a spectrum of functional and anatomical alterations ranging from impaired regional vaso-regulation to perfusion micro-thrombotic defects to pulmonary embolism (1, 2). These changes might contribute to ventilation-induced lung injury (VILI) through several mechanisms, including alveolar hypocapnia (3, 4), inhomogeneous distribution of ventilation (5–7), and regional hypoperfusion (8, 9). Notably, these mechanisms may be at play even when ventilation is delivered within protective limits. In the current clinical practice, prevention of VILI is based on the minimization of the injurious effects of tidal volume and pressure (10), the cornerstone of protective ventilation (11). On the contrary, prevention of VILI through correction of pathological alterations due to ventilation and perfusion inhomogeneity has received little attention.

A previous study conducted by our group showed that the addition of 5% CO_2 to inspiratory gas prevents bilateral VILI in an experimental model of ligation of the left pulmonary artery (12). Mechanisms of protection included decreased inflammation in both lungs and more homogeneous distribution of ventilation, with reduced overdistension of the right lung.

Inhalation of 5% CO_2 corrects alveolar hypocapnia in the ligated lung but also induces plasmatic hypercapnia. A few studies showed that plasmatic hypercapnia *per se* exerts anti-inflammatory actions and could prevent lung injury (13–15). Inhaled CO_2 limits the deleterious consequences of alveolar hypocapnia in the ligated lung dampening pneumoconstriction (16) and surfactant depletion (4, 17). Thus, the question of the mechanism by which CO_2 protects the lung (through a specific effect of the inhalation route or by plasmatic hypercapnia) still remains unanswered. Moreover, while the addition of CO_2 to inspiratory gas has the unique potential of correcting alveolar hypocapnia, plasmatic hypercapnia can be obtained by clinically easier methods, such as low tidal volume ventilation or the addition of instrumental dead space.

We designed this experimental study to compare the lung-protective effects of inhalation of 5% CO_2 *vs.* hypercapnia obtained either by low tidal volume or instrumental dead space in our model of unilateral pulmonary artery ligation. Our hypothesis was that the effects of inhaled CO_2 might be more comprehensive in the presence of unilateral perfusion block, possibly leading to more effective protection of the lungs. We also explored the mechanisms of protection for each lung by monitoring regional ventilation and perfusion by electrical impedance tomography (EIT).

MATERIALS AND METHODS

Figure 1 summarizes the study design. The study was approved by the Italian Ministry of Health (protocol No. 543/2018-PR) and conducted according to the European Directive 2010/63/EU on the protection of animals used for scientific purposes and Italian legislative decree 26/2014. Approval by the Institutional Animal Care Committee was obtained before starting the experiments.

Animal Preparation

Twenty-five healthy female pigs (36 ± 5 Kg) were anesthetized, intubated through surgical tracheostomy, and ventilated in the prone position using volume-controlled ventilation with tidal volume (V_T) 10 ml/kg, respiratory rate (RR) 25 bpm, inspiratory/expiratory time ratio (I/E) 1:2, positive end-expiratory pressure (PEEP) 5-cm H_2O, and FIO_2 0.5 (baseline settings).

General anesthesia and neuromuscular blockade were maintained by IV propofol 5–10 mg/kg/h, medetomidine 2.5–10.0 μg/kg/h, and pancuronium bromide 0.3–0.5 mg/kg/h for the whole study period.

After baseline measurements, surgical ligation of the left pulmonary artery was performed as previously described (12). Briefly, a left mini-thoracotomy was performed with the animal in the right lateral position and the main left pulmonary artery was isolated and progressively (5 minutes) occluded and then ligated.

Study Groups

Right after the ligation procedure, animals were turned prone and allocated to one of four study groups:

Left pulmonary artery ligation (injury, $n = 6$) with the following standard ventilation settings: V_T 10 ml/kg, RR 25 bpm, I:E 1:2, PEEP 5 cmH_2O, FiO_2 0.5.

Left pulmonary artery ligation + inhaled CO_2 ($FiCO_2$, $n = 7$) with standard ventilation settings except for inspired gases switched to a mixture of 50% O_2, 5% CO_2, and 45% N_2.

Left pulmonary artery ligation with low tidal volume (low V_T, $n = 6$) with standard ventilation settings except for V_T 6 ml/kg, as recommended by the American Thoracic Society's guidelines of protective ventilation in Acute Respiratory Distress Syndrome (ARDS) patients (18).

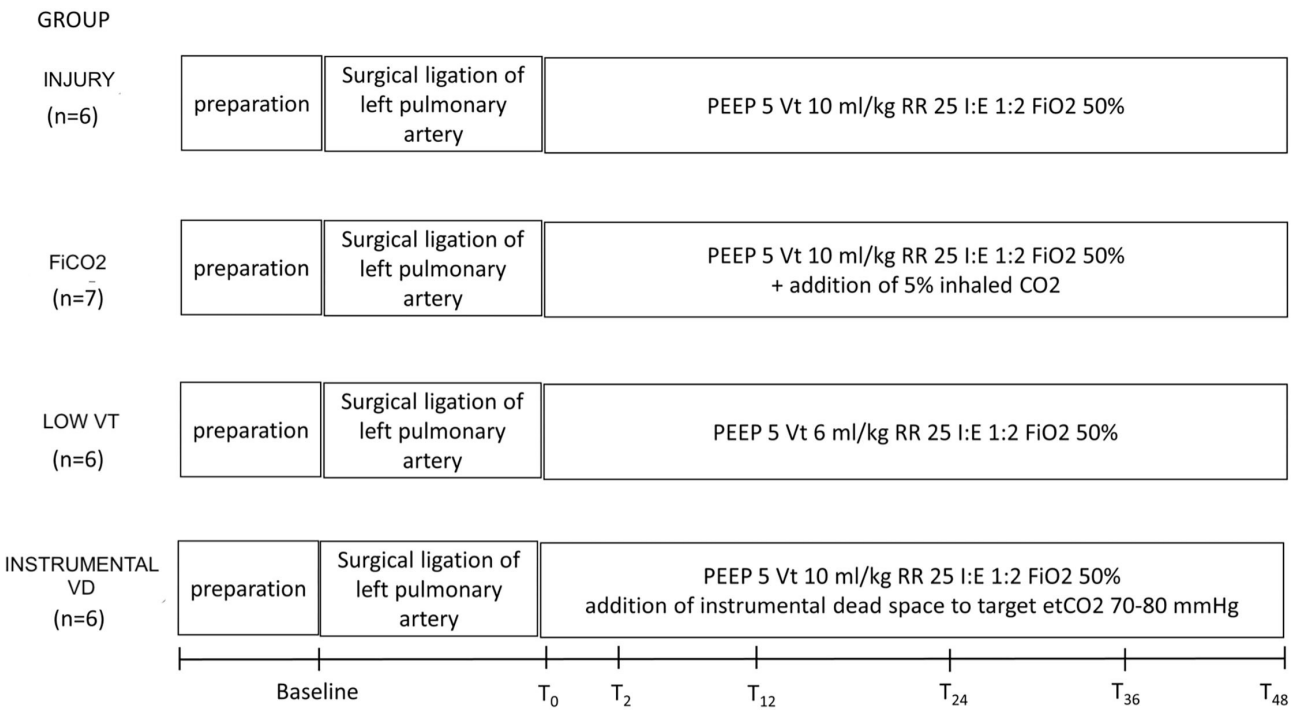

FIGURE 1 | Study design and timeline. Preparation corresponds to anesthesia and invasive monitoring, which took about 1 h. After baseline measurements, animals underwent surgical ligation of the left pulmonary artery. T0 to 48 corresponds to the study period, during which each group received a specific treatment, according to the study group. VT, tidal volume; PEEP, positive end-expiratory pressure in cm H_2O; RR, respiratory rate in breaths/min.

Left pulmonary artery ligation with increased instrumental dead space (instrumental V_D, $n = 6$) with standard ventilation settings plus additional tubing positioned after the circuit Y-targeted to end-tidal CO_2 of 70–80 mmHg (similar to end-tidal CO_2 levels obtained in the low V_T group).

All animals were ventilated for 48 h.

Study Measurements

Data from respiratory mechanics, hemodynamics, blood gas analysis, and EIT were collected at baseline and after 2, 12, 24, 36, and 48 h from end of the ligation procedure (T2, T12, T24, T36, T48). The EIT data were recorded and stored for offline analysis by dedicated software (Dräger EIT Data Analysis Tool 6.3, Lübeck, Germany). From EIT ventilation maps we measured regional V_T distribution for the right lung (V_{TRIGHT}) and left lung (V_{TLEFT}), the ratio between the two lungs ($V_{TRIGHT/LEFT}$) and regional respiratory system compliance of each lung as the ratio between regional V_T and driving pressure. The EIT perfusion maps were derived from offline analysis of the time–impedance curve obtained during the first pass of a 10-ml bolus of 5% saline solution during end-inspiratory occlusion, as previously described (19), and used to measure the percentage of perfusion to the left lung ($Perfusion_{LEFT}$).

End of the Experiment

At T48, animals were euthanized, and lung tissue samples were collected for the following:

- Histology: the severity of regional lung injury in each lung was quantified by using a composite histological score, ranging from 0 (no injury) to 30 (severe), as previously described (12).
- Wet-to-dry calculation (12).
- Quantitative immunohistochemical analysis for measuring the percentage of cells positive for myeloperoxidase (MPO, i.e., neutrophils) and allograft inflammatory factor 1 (AIF-1, i.e., macrophages) (20).
- the Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay (ApopTag Plus Peroxidase *In Situ* Apoptosis Kit from Merck-Millipore) was employed to evaluate apoptosis on tissue samples of the left lungs from two representative animals for each study group as previously described (21).

Sample Size

The difference in histological scoring of the lungs of the four study groups was the primary endpoint of the study. The sample size was similar to the previous animal studies on the same topic (6, 13). However, we performed an exploratory power analysis and we hypothesized, based on our previous study (12), an effect size of 0.75; to obtain the power of 0.8 with alpha 0.05, the minimum sample size resulted in $n = 6$ per group.

Statistical Analysis

The data are shown as mean ± standard deviation or median [quartiles], as appropriate. The data measured at the end of

the experiment were compared using one-way ANOVA or Kruskal–Wallis test, followed by Dunnett or Dunn's test for multiple comparisons. Longitudinal data (physiological and EIT variables along the study time points) was analyzed using repeated measures two-way ANOVA or mixed-effect analysis, as appropriate, with time and group as a covariate. Statistical significance was defined by $p < 0.05$. Analyses were performed using GraphPad Prism 9.

Additional details are available in the online **supplement**.

RESULTS

Alterations of Gas Exchange and Respiratory Mechanics

At T48, animals in the $FiCO_2$ group had significantly higher respiratory system and lung compliance and PaO_2/FiO_2 ratio in comparison to all the other study groups. Indeed, the low V_T and instrumental V_D groups showed global signs of lung injury in terms of decreased compliance of the respiratory system due to decreased lung compliance and decreased PaO_2/FiO_2 ratio (**Figures 2A–C**).

Complete data on respiratory mechanics, blood gases, and hemodynamics at T48 in the four study groups are reported in **Supplementary Table S1**.

Protection of the Left Ligated Lung

The signs of lung injury for the left ligated lung, including left-side respiratory system compliance measured by EIT, histological score, and wet-to dry ratio, were significantly different between the four study groups ($p = 0.005$, $p = 0.0015$, $p = 0.026$, respectively) (**Figures 3A–C**). The most efficient lung protection was found in the $FiCO_2$ group, which showed higher regional compliance [14 (12 – 16) *vs.* 9 (7 – 11), $p = 0.02$] and lower histological score [3 (2 – 4) *vs.* 9 (8 – 11), $p = 0.01$] compared to the injury group.

The left lungs of animals in the $FiCO_2$ group showed nearly normal histologic appearance, while injury was evident in all the other study groups. Hemorrhagic areas and inflammatory infiltrate composed mainly of macrophages characterized the injury group; vascular congestion, edema, and inflammatory infiltrate composed of macrophages and lymphocytes were prevalent in the low V_T group; extensive consolidation by inflammatory infiltrate composed of macrophages, granulocytes, and lymphocytes described the instrumental V_D group (**Figure 3D**).

Immunohistochemical analyses showed significantly different densities of MPO-positive neutrophils in the left lungs of the four groups ($p = 0.002$). Interestingly, lungs from the $FiCO_2$ showed the lowest values, while the low V_T and instrumental V_D groups had very high values (**Table 1** and **Supplementary Figure S1**).

Left lungs from the $FiCO_2$ group also showed the lowest presence of apoptotic cells as detected by the TUNEL assay (**Supplementary Figure S2**). Conversely, the lungs from the injury, low V_T, and instrumental V_D showed a high prevalence of apoptotic cells within the lung parenchyma (**Supplementary Figure S2**).

Protection of the Right Lung

The signs of injury in the right lung differed between groups ($p = 0.021$ for right-side compliance, $p = 0.005$ for histological score, $p = 0.001$ for wet-to-dry ratio). The right-side compliance was higher in the $FiCO_2$ [25 (22 – 28)], while the other two hypercapnic groups did not differ from the injury group [17 (14 – 19) in low V_T *vs.* 16 (14 – 23) in instrumental V_D *vs.* 16 (10 – 16) in the injury] (**Figure 4A**). However, the histological score was lower both in the $FiCO_2$ (3 ± 1) and in the low V_T groups (4 ± 2) as compared to the injury (10 ± 2) (**Figure 4B**). Like the right-side compliance, the wet-to-dry ratio was lower only in the $FiCO_2$ group [4.4 (4.3–4.5) vs 4.8 (4.5–6.6) in the low V_T, 4.8 (4.7–5.0) in the instrumental V_D, 5.2 (5.1–6.2) in the injury] (**Figure 4C**).

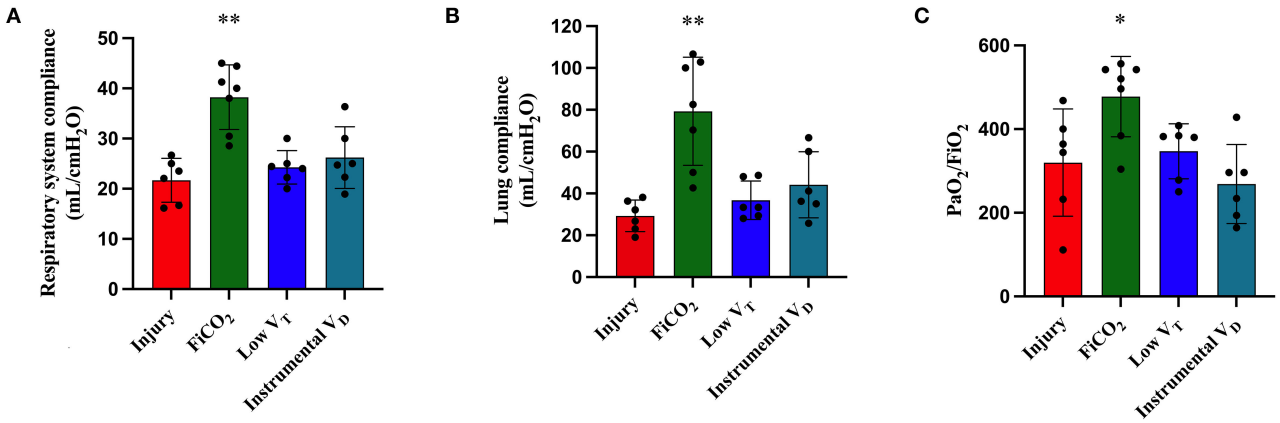

FIGURE 2 | Respiratory mechanics and gas exchanges at the end of the experiment. Respiratory system compliance **(A)**, lung compliance **(B)**, and PaO_2/FiO_2 ratio **(C)** were higher in the $FiCO_2$ group compared to the other groups. Data are expressed as mean ± SEM. Comparisons are obtained with ordinary one-way ANOVA or Kruskal–Wallis test for normally and non-normally distributed values, respectively, followed by Dunnett or Dunn's multiple comparison test. $^*p < 0.05$, $^{**}p < 0.01$ vs. Injury group.

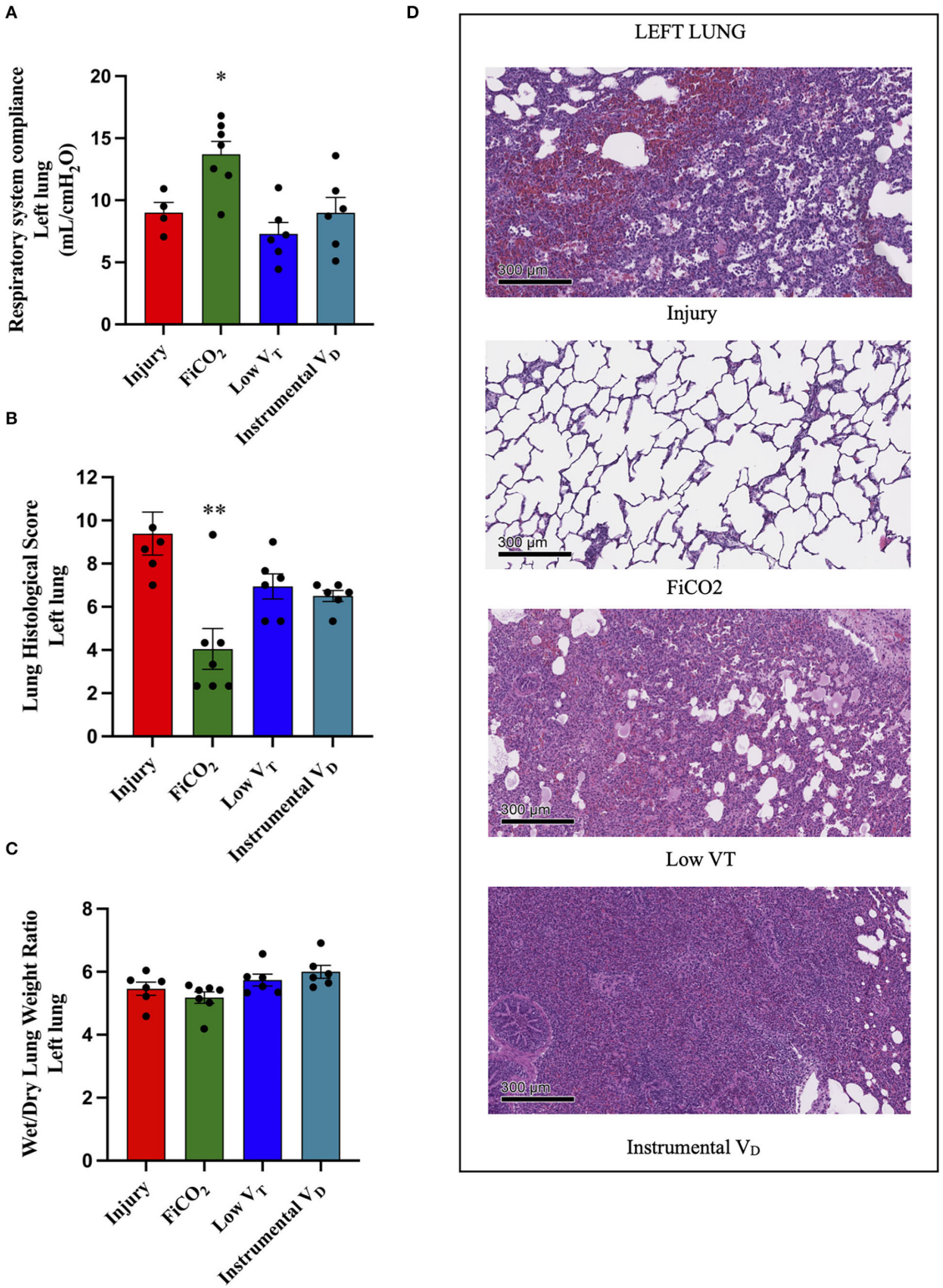

FIGURE 3 | Left lung injury. Left-side respiratory system compliance at the end of the experiment **(A)**. Histological score of left lungs from each study group **(B)**. Wet-to-dry of left lungs **(C)**. Microscopic appearance of the lungs at the end of the experiment **(D)**. Representative microphotographs of the left ligated lungs from the four study groups (H&E, original magnification 100×). Data are expressed as scatter dot plots with mean ± SEM. Comparisons are obtained with ordinary one-way ANOVA or Kruskal–Wallis test for normally and non-normally distributed values, respectively, followed by Dunnett or Dunn's multiple comparison test. $^{*}p < 0.05$, $^{**}p < 0.01$ vs. Injury group.

TABLE 1 | Characterization by immunohistochemistry of the lung immune cell infiltrates in the different groups.

	Injury ($n = 6$)	$FiCO_2$ ($n = 7$)	Low V_T ($n = 6$)	Instrumental V_D ($n = 6$)	*p* value
Left lung					
MPO positive cells, %	0.8 [0.5–1.9]	0.4 [0.3–0.5]	11.5 [2.4–33.5]	10.8 [3.4–16.9]	**0.002**
AIF-1 positive cells, %	54 [34–62]	26 [24–38]	45 [32–56]	47 [36–55]	0.096
Right lung					
MPO positive cells, %	2.2 [1.2–9.2]	0.1 [0.1–0.1]**	0.4 [0.2–8.9]	8.0 [0.8–13.2]	**0.001**
AIF-1 positive cells, %	59 [39–86]	24 [24–37]*	41 [32–77]	59 [48–65]	**0.045**

Data are expressed as median (quartiles).
*Comparisons are obtained with Kruskal–Wallis followed by Dunn's multiple comparison test. *$p < 0.05$, **$p < 0.01$ vs. Injury group.*
MPO, Myeloperoxidase; AIF-1, Allograft inflammatory factor 1.
Bold values highlight significant differences.

Again, except for the right lung of the $FiCO_2$ group – which showed nearly normal histologic appearance – various patterns of injury were observed in all the study groups at histological microscopic analysis. The right lungs of the injury group presented almost complete consolidation with a dense inflammatory infiltrate, composed of granulocytes, histiocytes, and lymphocytes, while right lung injury in the low V_T and instrumental V_D consisted in a mild macrophagic infiltrate with focal areas of emphysema (**Figure 4D**).

Inflammation in the right lung measured by immunohistochemistry was decreased only in the $FiCO_2$ group, in which MPO-positive neutrophils were almost absent, while the low V_T and instrumental V_D groups showed similar or even higher levels of neutrophils compared to the injury group (**Table 1** and **Supplementary Figure S1**).

Distribution of Ventilation and Perfusion by EIT

The EIT analysis performed 2 h after pulmonary artery ligation (i.e., a time-point at which mechanisms of injury were already at play but lungs were not injured yet) showed that the ratio between the percentage of tidal volume to the right and the percentage of tidal volume to the left lung was significantly lower in the $FiCO_2$ group as compared to all the other study groups (**Figure 5A**).

Regional perfusion measured by EIT throughout the study showed that the percentage of blood flow reaching the left ligated lung was higher in the group $FiCO_2$ compared to the other groups (**Figure 5B**).

Representative EIT images showing the distribution of ventilation and perfusion in the four study groups are displayed in **Figure 5C**.

Baseline

Before the start of the experiment (i.e., at baseline, measured before the ligation procedure with standard ventilation settings), there were no differences between the animals allocated to the four groups in terms of respiratory mechanics, gas exchange, and hemodynamics (**Supplementary Table S2**).

Trends of Physiological Variables Over Time

The course of arterial CO_2 and arterial pH throughout the study are shown in **Figures 6A,B**. The evolution of injury through changes in respiratory system compliance and PaO_2/FiO_2 is shown in **Figures 7A,B**. The data collected for each variable at all time-points in the four study groups can be found in **Supplementary Table S3** and confirm that the most differences appeared after 24 h.

DISCUSSION

The main findings of this study can be summarized as follows: The addition of 5% CO_2 to inhaled gas confers full bilateral lung protection in experimental unilateral pulmonary artery ligation; hypercapnia is obtained by lowering the tidal volume and by increasing the instrumental dead space, instead, offers limited lung protection, if any, to the right perfused lung and fails to protect the left ligated lung. Mechanisms of lung protection by inhaled CO_2 were confirmed in terms of reduced overdistension of the right lung and dampened bilateral lung inflammation. In this context, this study provides novel evidence of the additional role of increased regional perfusion reaching the left ligated lung (probably through the bronchial circulation) in preventing left lung injury.

This experimental study assessed the protection from VILI conferred by inhaled CO_2 compared to hypercapnia induced by the low tidal volume and by the increased instrumental dead space in a model of unilateral pulmonary artery ligation. We confirmed that the protection of the left ligated lung is effectively achieved by addition of 5% CO_2 to the inspired gas while the alternative methods used to induce hypercapnia were not effective. Our results confirm the mechanisms of injury for the left lung previously described as follows: Inflammation (12) and apoptosis triggered by alveolar hypocapnia (4), which could be effectively prevented by inhaled CO_2. Interestingly, our results also showed that, in the left lung, plasmatic hypercapnia induced by the decreased tidal volume or the increased instrumental dead space did not prevent infiltration and activation of immune cells and did not prevent apoptosis. In contrast to adding inspired

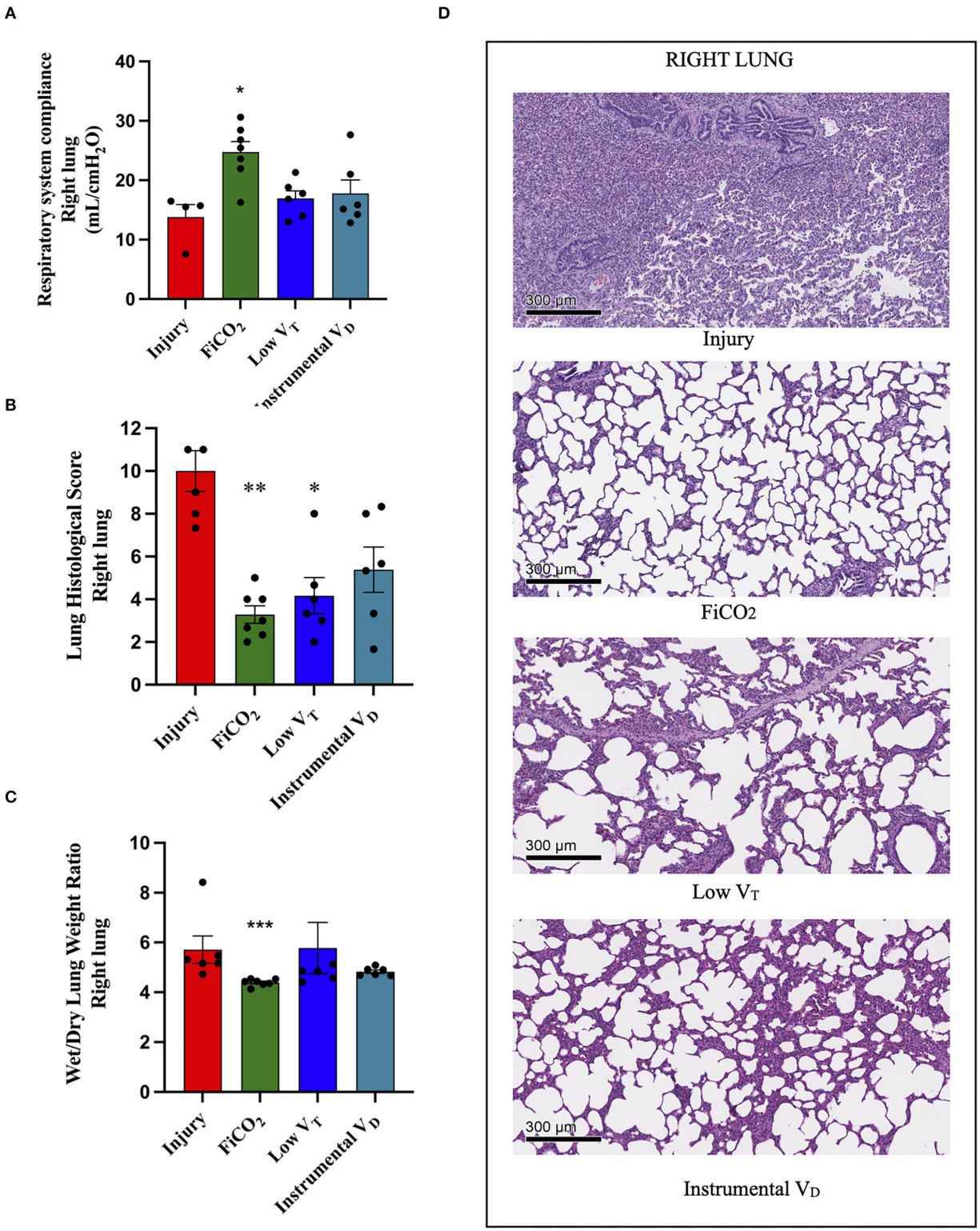

FIGURE 4 | Right lung injury. Right-side respiratory system compliance at the end of the experiment **(A)**. Histological score of right lungs from each study group **(B)**. Wet-to-dry of right lungs **(C)**. Microscopic appearance of the lungs at the end of the experiment **(D)**. representative microphotographs of the right lungs from the four study groups (H&E, original magnification 100×). Data are expressed as scatter dot plots with mean ± SEM. Comparisons are obtained with ordinary one-way ANOVA or Kruskal–Wallis test for normally and non-normally distributed values, respectively, followed by Dunnett or Dunn's multiple comparison test. *$p < 0.05$, **$p < 0.01$ vs. Injury group, and *** $p < 0.001$ vs. Injury group.

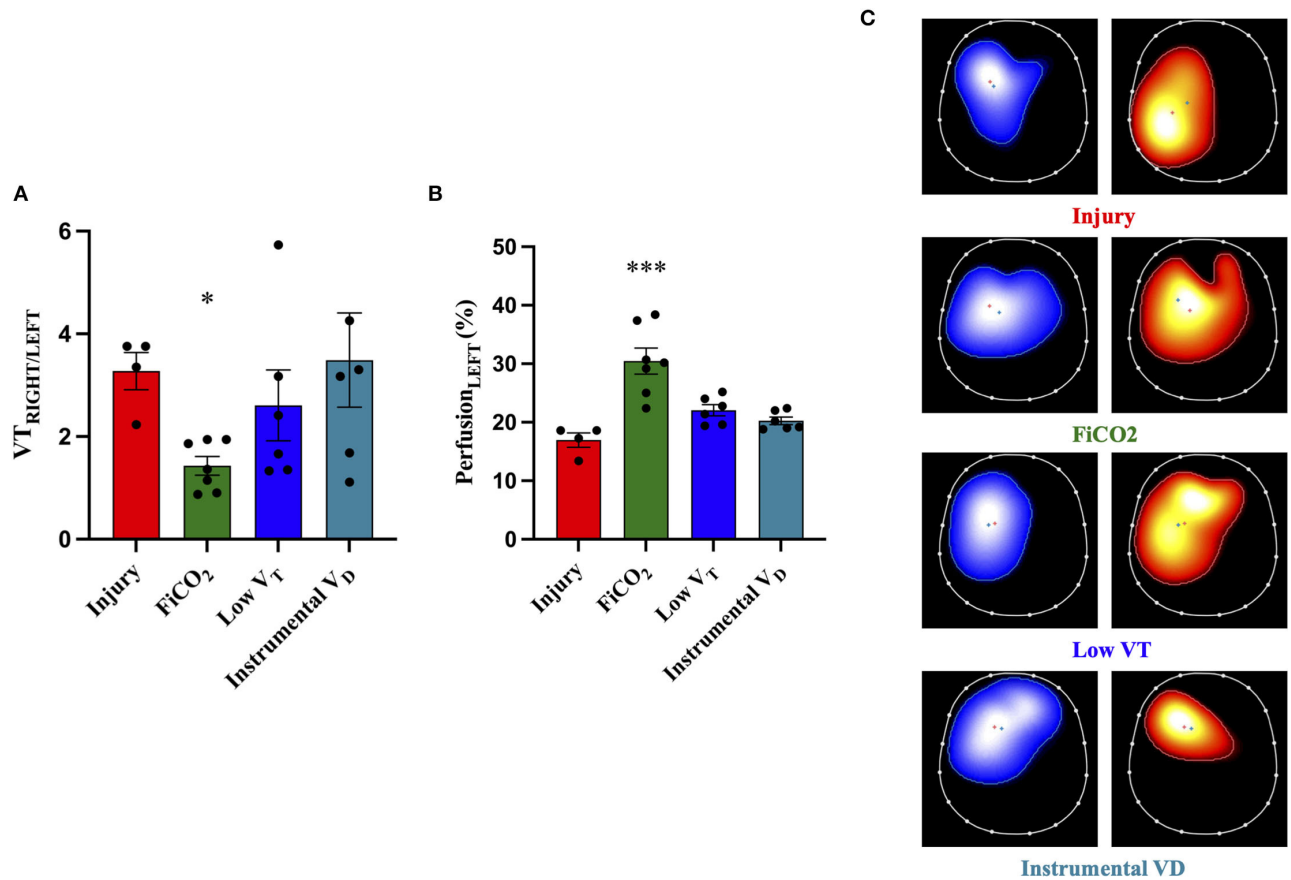

FIGURE 5 | Distribution of ventilation and perfusion by EIT. The ratio between tidal volume distending the right and the left lung [$V_{TRIGHT/LEFT}$, **(A)**] at 2 h after ligation of the left pulmonary artery shows significant imbalance in all the study groups, which was decreased only by $FiCO_2$. The percentage of blood flow to the left lung [$Perfusion_{LEFT}$, **(B)**] throughout the experiment (average between T2 and T48) was higher in the $FiCO_2$ group compared to the other groups. Representative EIT images for ventilation (blue maps), perfusion (red maps), and distribution **(C)** showed increased ventilation and perfusion of the left lung in the $FiCO_2$ group. Data are expressed as mean ± SEM. Comparisons are obtained with ordinary one-way ANOVA or Kruskal–Wallis test for normally and non-normally distributed values, respectively, followed by Dunnett or Dunn's multiple comparison test. *$p < 0.05$, ***$p < 0.001$ vs. Injury group.

CO_2, alveolar hypoventilation due to instrumental dead space might result in an uneven distribution of CO_2 within the lungs, with a limited increase of CO_2 content in the left lung due to the dilution with external gases and pulmonary artery perfusion block. A new finding is that inhalation of CO_2, but not plasmatic hypercapnia obtained by the other two methods, increases blood flow to the left ligated lung. Our methods do not provide evidence for the source of this higher regional blood flow, but it is likely to derive from bronchial circulation (22). Indeed, bronchial perfusion increases in the presence of higher alveolar O_2 and CO_2 (23); both might have been obtained by inhaled CO_2 through direct effect (for CO_2) and higher regional ventilation of the left lung (for O_2). Our observation suggests that the reduction of tissue hypoperfusion might be a novel mechanism underlying the protective effect of inhaled CO_2 (8, 9, 24).

Concerning the right lung, protection was granted by addition of inhaled 5% CO_2 – confirming the previous data (12) – but also by ventilation with low tidal volume. Plasmatic hypercapnia induced by the increased instrumental dead space, instead, was not effective. We have previously reported that hyperventilation and activation of inflammation are the key injurious mechanisms for the right non-ligated lung, which can be effectively prevented by inhaled CO_2 (12). In the low V_T group, reduced over-distension and plasmatic hypercapnia seemed to protect the right non-ligated lung. However, in our model, right lung protection by low VT was inferior to inhaled CO_2, as suggested. However, in our model, lung protection conferred by the low tidal volume was inferior compared to the inhaled CO_2, as suggested by higher regional markers of inflammation, lower right-side respiratory system compliance, and higher wet-to-dry ratio. A reason for partial right lung protection by reduced V_T might be a lack of prevention of left ligated lung injury yielding organs cross-talk (25).

When we consider the global physiological consequences of lung injury in terms of impairment of oxygenation and respiratory mechanics, they once again confirm that only inhaled CO_2 appears to confer effective protection from VILI in this model.

Experimental studies have demonstrated that therapeutic hypercapnia induced by inhaled CO_2 is effective in attenuating

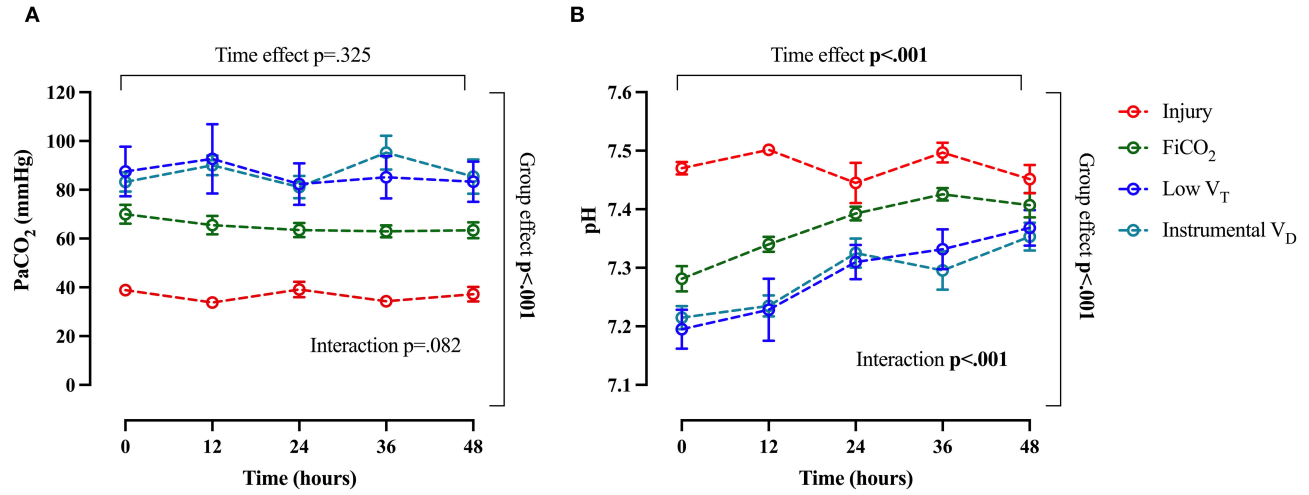

FIGURE 6 | Trend of arterial CO_2 and arterial pH throughout the study. Arterial pCO_2 **(A)** and pH **(B)**. Data are expressed as mean ± SEM. Comparisons are obtained with a two-way ANOVA test for normally distributed values followed by Dunnett's multiple comparisons test.

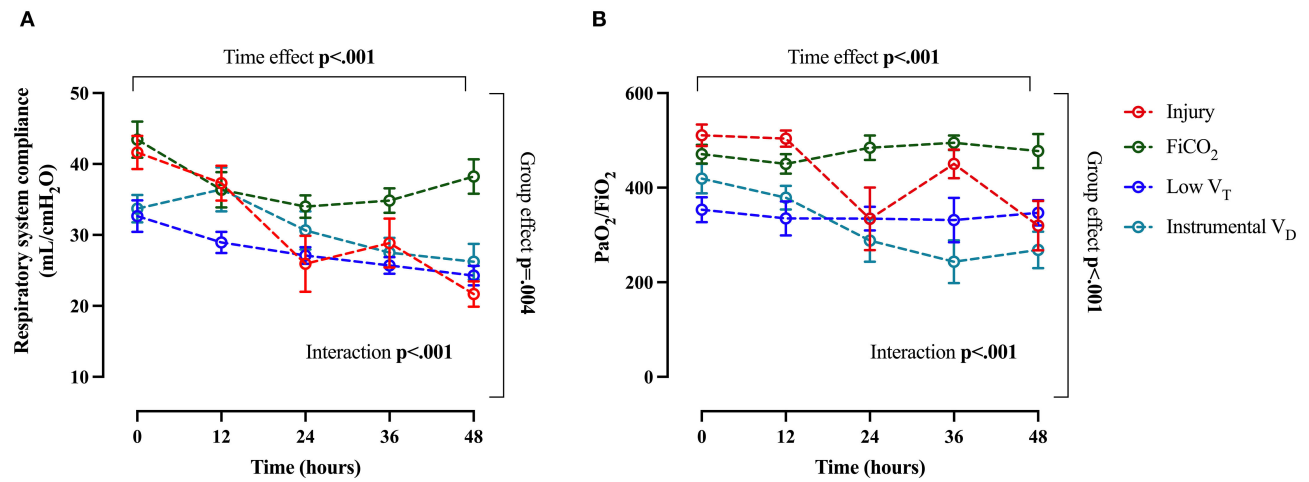

FIGURE 7 | Main global markers of injury. Trend of respiratory system compliance **(A)** and PaO_2/FiO_2 **(B)** throughout the study. Data are expressed as mean ± SEM. Comparisons are obtained with two-way ANOVA test for normally distributed values followed by Dunnett's multiple comparisons test.

lung injury in ARDS (15) and in protecting from VILI induced by high tidal volume ventilation (13, 14, 26). Regarding the role of hypercapnia induced by reduction of tidal volume ("permissive hypercapnia"), it has been difficult to separate the protective effect of hypercapnia *per se* from the established benefit due to the reduction of lung stress and strain (27). Clinical studies indicate that the permissive hypercapnia could improve clinical outcomes (28), but, at the same time, ARDS patients ventilated by a protective strategy developing severe hypercapnia are at higher risk of mortality (29). Experimental studies aimed at dissecting the protective effects of hypercapnia *vs.* those of low tidal volume have been scarce and led to conflicting results. Hypercapnia induced by reduced tidal volume and the respiratory rate has been shown to amplify inflammatory lung injury in experimental lipopolysaccharide-induced ARDS (30). On the contrary, ventilation with low tidal volumes and associated hypercapnia was proved protective in a model of surfactant depletion (31), although the protective effect seemed to depend mainly upon lower tidal volume (32). In contrast to adding inspired CO_2, alveolar hypoventilation by low tidal volumes might result in an uneven distribution of CO_2 within the lungs (33), and this could lead to failure to correct areas of alveolar hypocapnia. In conclusion, the reduced tidal volume ventilation with or without the permissive hypercapnia remains a cornerstone of ARDS treatment, but the evidence is growing on the potential role of inhaled CO_2 as a complementary strategy leading to full lung protection.

This study has limitations. First, the results partially overlap with our previous work (12); however, we present alternative methods to obtain hypercapnia, as well as new data on

regional lung perfusion and apoptosis, which increased our understanding of pathophysiological mechanisms. Second, we applied pragmatic methods to obtain plasmatic hypercapnia using a fixed value for low tidal volume and adding instrumental dead space targeted to a target CO_2 level. Other methods might have led to different results; however, our methods reflected values normally used in clinical practice and increase potential clinical translation. Third, alveolar hypocapnia, which is a key mechanism of injury in our model, was not measured, so we can only hypothesize its role to explain the differences between groups. Finally, EIT is a technique with limitations, including imaging limited to a portion of the lung and the relative nature of the measures of regional ventilation and perfusion.

CONCLUSION

This study shows that inhaled CO_2 allows more effective bilateral lung protection compared to plasmatic hypercapnia induced by low tidal volume and additional instrumental dead space in a model of left pulmonary artery ligation. Further studies are needed to understand whether a protective strategy combining low tidal volume and inhaled CO_2 might be beneficial in patients with large perfusion defects (e.g., ARDS with high dead space fraction).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Italian Ministry of Health (protocol n. 543/2018-PR).

AUTHOR CONTRIBUTIONS

ES, AP, and TM conceived, planned, carried out the experiments, interpreted the results, and wrote the manuscript. GL, AD, FD, EG, GD, AC, GG, VF, OB, MB, and CL carried out the experiments and collected the results. VV processed experimental data. OB and MB helped in the implementation of the experiments. GL, VV, and SF collected and processed biological samples and analyzed the results. LR, SF, and SG provided critical feedback, helped shape the research, analysis, and manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.901809/full#supplementary-material

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ORIGINAL RESEARCH
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Occurrence and Effects on Weaning From Mechanical Ventilation of Intensive Care Unit Acquired and Diaphragm Weakness: A Pilot Study

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Purpose: Limb intensive care unit (ICU)-acquired weakness (ICUAW) and ICU acquired diaphragm weakness (DW) occur frequently in mechanically ventilated (MV) patients; their coexistence in cooperative and uncooperative patients is unknown. This study was designed to (1) describe the co-occurrence of the two conditions (2) evaluate the impact of ICUAW and DW on the ventilator-free days (VFDs) at 28 days and weaning success, and (3) assess the correlation between maximal inspiratory pressure (MIP) and thickening fraction (TFdi) in patients with DW.

Methods: This prospective pilot study was conducted in a single-center on 73 critically ill MV patients. Muscle weakness was defined as a Medical Research Council score < 48 in cooperative patients or a bilateral mean simplified peroneal nerve test < 5.26 mV in uncooperative patients. Diaphragm dysfunction was defined as MIP < 30 cm H_2O or as a TFdi $< 29\%$. Weaning success was defined according to weaning according to a new definition (WIND).

Results: Fifty-seven patients (78%) had ICUAW and 59 (81%) had DW. The coexistence of the two conditions occurred in 48 patients (65%), without association ($\chi^2 = 1.06$, $p = 0.304$). In the adjusted analysis, ICUAW was independently related to VFDs at 28-days (estimate difference 6 days, $p = 0.016$), and WIND (OR of 3.62 for having WIND different than short weaning), whereas DW was not. The linear mixed model showed a significant but weak correlation between MIP and TFdi ($p < 0.001$).

Conclusion: This pilot study is the first to explore the coexistence of ICUAW and DW in both cooperative and uncooperative patients; a lack of association was found between DW and ICUAW when considering both cooperative and uncooperative patients. We

found a strong correlation between ICUAW but not DW with the VFDs at 28 days and weaning success. A future larger study is warranted in order to confirm our results, and should also investigate the use of transdiaphragmatic twitch pressure measurement during bilateral anterior magnetic phrenic nerve stimulation for the diagnosis of DW.

Keywords: intensive care unit-acquired weakness, diaphragmatic weakness, simplified peroneal nerve test, thickening fraction of the diaphragm, maximum inspiratory pressure, coexistence, weaning from mechanical ventilation

INTRODUCTION

Limb intensive care unit-acquired weakness (ICUAW), a common consequence of critical illness, is defined as a clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness (1). ICUAW can persist for months after ICU discharge, increasing the incidence of physical and psychological sequelae and resulting in poor long-term functional status and quality of life. Muscle weakness might be present in up to 80% of critically ill mechanically ventilated (MV) patients (2). When the weakness involves the diaphragm, the term used is ICU Acquired Diaphragmatic Weakness (DW). DW is associated with difficult respiratory weaning, and increased morbidity and mortality; its prevalence can be as high as 63–80% during the ICU stay (3).

There is some debate as to whether ICUAW and DW represent two different epiphenomena of the same pathological condition or different diseases (4–6). Studies on this topic are controversial, mainly because the coexistence of these two conditions has been assessed using different diagnostic approaches (7). The diagnosis of ICUAW relies on the Medical Research Council (MRCss) scale, a clinical scale that requires full patient cooperation (4). In uncooperative patients, the function of peripheral nerves and muscles can be assessed using appropriate electrophysiological investigations of peripheral nerves and muscles, which require specialized personnel and are time-consuming (8, 9). The gold standard of DW diagnosis is based on the measurement of transdiaphragmatic twitch pressure (PdiTw) generated in response to bilateral anterior magnetic phrenic nerve stimulation (BAMPS). Alternative methods are the thickening fraction of the diaphragm (TFdi) obtained with ultrasound, or maximum inspiratory pressure (MIP) generated during a prolonged expiratory occlusion maneuver (10–12). To date, there are no studies assessing the coexistence of ICUAW and DW using electrophysiological tests for ICUAW and MIP and/or TFdi for DW, in both cooperative and uncooperative critically ill MV patients. The two largest studies on this topic included only cooperative patients and used MRCss to diagnose ICUAW (4, 13).

Therefore, the primary objective of this pilot study was to measure the coexistence of ICUAW and DW using objective techniques in both cooperative and uncooperative patients. In addition, we also investigated the association between ICUAW and DW with ventilator-free days (VFDs) at 28 days and weaning success. Finally, we assessed the correlation between MIP and TFdi.

Abbreviations: ICUAW, intensive care unit-acquired weakness; DW, diaphragmatic weakness; MV, mechanical ventilation; MRCss, medical research council scale; BAMPS, bilateral magnetic phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; MIP, maximum inspiratory pressure; PENT, simplified peroneal nerve test; FRC, functional residual capacity; WIND, weaning according to a new definition; AMV, assisted mechanical ventilation; PSV, pressure support ventilation; SBT, spontaneous breathing trial; VFDs, ventilator-free days.

MATERIALS AND METHODS

Patient Selection

This prospective pilot study was conducted between May 2019 and January 2021 at the Spedali Civili University affiliated Hospital of Brescia, Italy. The study was approved by the local Ethical Committee and informed consent was obtained for all patients. The STROBE guidelines for reporting observational studies were followed (14).

All consecutive patients admitted to the ICU for at least 72 h and who were MV on assisted mechanical ventilation for at least 48 h, were assessed for enrolment. Exclusion criteria were: age < 18 years old; pre-existing neuromuscular disorders that may have affected the diagnosis of ICUAW and DW; impossibility to assess the presence of ICUAW neither with MRCss nor with simplified peroneal nerve test (PENT). We recorded demographic data, ICU admission severity scores (SAPS II and admission SOFA), comorbidities, the reason for ICU admission, ICU and hospital length of stay (LOS), VFDs at 28 days, weaning success, and hospital mortality. Weaning success was assessed using the Weaning according to a New Definition (WIND) classification. Briefly, patients were categorized into four groups according to the time of weaning: patients in whom no separation attempt was made (Group: NW); patients who terminated the weaning process within 1 day from the first attempt (Group 1: short weaning); patients who completed the weaning process after 1 day but within 1 week from the first Spontaneous breathing trials (SBT; Group 2: difficult weaning); patients who required more than 7 days to be separated from the ventilator with success (Group 3a: prolonged weaning); patients who required more than 7 days to be separated from the ventilator without success (Group 3b: weaning failure; 15). Successful weaning was defined as separation from the MV for at least 7 days.

Study Protocol

Data collection started on the first day of *assisted mechanical ventilation*. The presence of ICUAW was monitored every 48 h until an ICUAW diagnosis was made or until the patient was discharged from ICU. Data on DW were collected every 48 h until SBT success or ICU discharge. All patients were ventilated

in pressure support ventilation (PSV). MIP measurements were performed only when P0.1 (airway occlusion pressure at 100 ms) ranged between 1.5 and 3 cm H_2O, to avoid over-or under-estimation (12). Measurements were repeated until the day of separation from the MV. SBT were performed in PSV using an inspiratory pressure of 6 cm H_2O and a PEEP level of 6 cm H_2O (16). The study protocol is represented in **Figure 1**.

Muscles Assessment

The presence of ICUAW was monitored every 48 h either with MRCss (cooperative patients) or with bilateral PENT performed at the bedside (uncooperative patients). We validated PENT as a screening tool for ICUAW in two previous studies (8, 9), and we found a threshold value of 5.26 mV with a sensitivity of 100% and specificity of 85%. In the case of pathological MRCss, PENT was performed to confirm the diagnosis; when ICUAW was excluded by MRCss, PENT was not performed.

Diaphragm Assessment

Maximum inspiratory pressure values were obtained by averaging the results of three expiratory occlusion maneuvers. In cooperative patients, the MIP was obtained by asking the patient to voluntarily perform a maximal inspiratory effort starting from the functional residual capacity (10). In uncooperative patients, the maximal pressure generated against a prolonged expiratory occlusion maneuver was considered MIP. The respiratory drive was intensified by inducing an airway occlusion for a 25 to 30 s period, in this manner eliciting a maximal inspiratory effort (10, 12). To minimize bias resulting from sedation and low respiratory drive, we performed MIP only when P0.1 ranged between 1.5 and 3 cm H_2O during the breath just before the occlusion. As previously reported, the respiratory drive should not affect MIP estimation at these P 0.1 values (12, 17). MIP was always directly measured from the ventilator's airway pressure waveforms using either Maquet Servo U (Getinge, Göteborg, Sweden) or Bellavista, 1000e (Imtmedical ag, Buchs, Switzerland) ventilators.

Right hemidiaphragm TFdi was obtained as described elsewhere (18). Briefly, the thickening fraction was computed as the percentage change in thickness between End-Expiration (i.e., minimum muscle thickness, TEE) and Peak Inspiration (i.e., maximal muscle thickness, TPI) visualized in M-mode (TFdi: TPI- TEE/TEE). TFdi was measured while the patients were ventilated in pressure support set to provide an adequate tidal volume and respiratory drive. According to previous studies DW was defined as a MIP less than –30 cm H_2O or a TFdi < 29% (19).

Statistical Analysis

Variables are reported as means (SDs), medians (IQRs), or numbers (percentages) as appropriate. The Shapiro–Wilk test

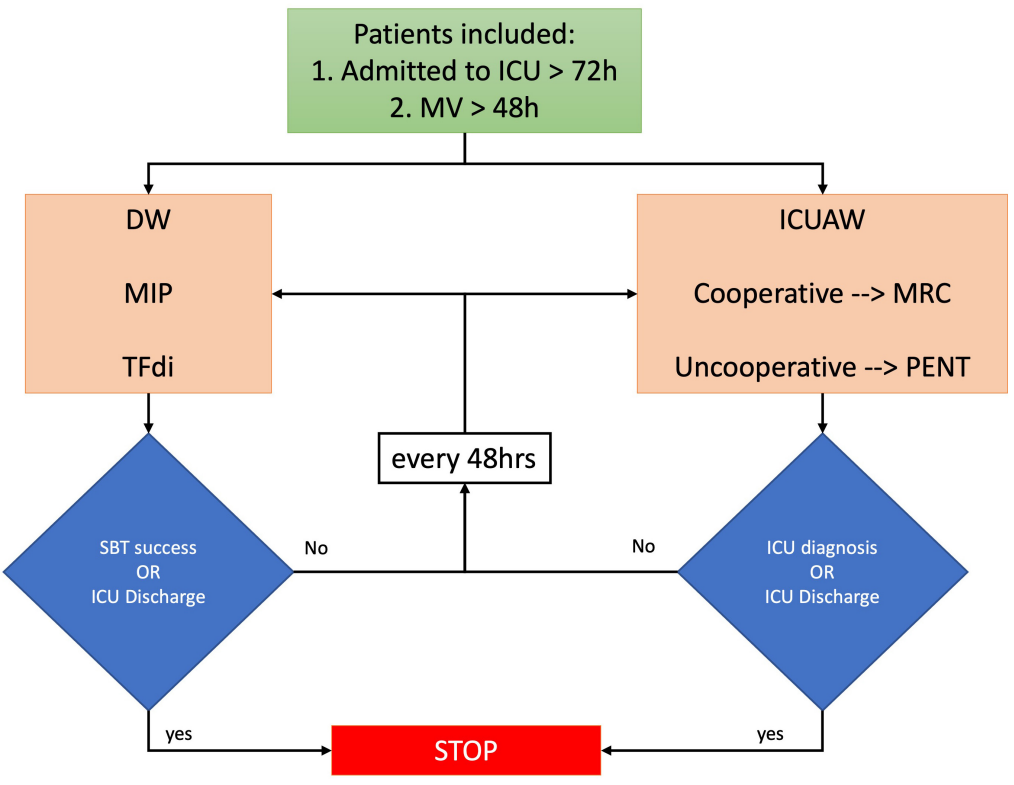

FIGURE 1 | Study protocol. Patients admitted to intensive care medicine (ICU) for >72 h and mechanically ventilated for >48 h were screened. ICUAW was evaluated using MRC and PENT, and DW was diagnosed with MIP and TFdi. MV, mechanical ventilation; TFdi, diaphragm thickening fraction; MIP, maximal inspiratory pressure; MRC, medical research council scale; PENT, simplified peroneal nerve test; SBT, spontaneous breathing trial (PSV 6/6 cmH2O).

was used to assess whether continuous data were normally distributed. The association between DW and ICUAW was evaluated using the χ^2 test. We coded VFDs at 28 days = 0 if either the subject died within 28 days of mechanical ventilation or if MV for more than 28 days; in all the other cases VFDs at 28 days were defined as 28-days of mechanical ventilation (20).

Logistic regression was used to compare ICU admission baseline characteristics between patients with and without ICUAW or DW. An unadjusted multivariate linear regression or ordered logistic regression was used to determine the association between VFDs at 28 days and weaning success (using WIND as ordered dependent variable), respectively, including the presence of ICUAW and DW as an independent variable, adjusting for the following confounders: age, sex, BMI, and SAPS II. Adjusted logistic regression was then performed keeping all the variables in the model after the selection of confounders by using direct acyclic graphs, **Supplementary Figure 1**. We did not include SOFA at ICU admission since is strongly correlated to SAPS II. Finally, a linear mixed model was used to correlate MIP and TFdi, using the subject as a random effect, to overcome the issue of the repeated measures. Since this is a pilot study sample size was not calculated. All tests were two-sided, and a *p*-value less than 0.05 was considered statistically significant. No data imputation was performed for these data. All analyses were conducted using R (version 4.1.1).

RESULTS

During the study period, 73 patients were enrolled. The Median [IQR] age was 65 [16.5] years; 45 (62%) patients had COVID-19 related Acute Respiratory Distress Syndrome (CARDS). Median [IQR] SAPS II was 32 [18], and the median [IQR] admission ICU SOFA score was 4 [3]. The Median [IQR] duration of MV was 10 [10] days; 4 (6%) patients never received any separation attempt (WIND = NW), 11 (15%) patients failed weaning from mechanical ventilation despite separation attempts (WIND 3b), and 58 (79%) patients were weaned (WIND 1–3a), **Table 1**.

Fifty-seven patients (78%) had ICUAW and 59 (81%) had DW. The coexistence of the two conditions occurred in 48 patients (65%), **Figure 2**. There was no association between the two conditions (χ^2 = 1.06, p = 0.304). Patients with ICUAW had (1) higher SOFA score (median [IQR] 5 [5] vs 4 [1.25], p = 0.032), (2) higher SAPS II (24 [10] vs 33 [19], p = 0.021),

TABLE 1 | Demographics and outcomes characteristics.

Presence of DW, N°(%)	**No ICUAW (*N* = 16; 21%)**		**ICUAW (*N* = 57; 78%)**		**Total *N* = 73**
	No DW *N* = 5 (6%)	**DW *N* = 11 (15%)**	**No DW *N* = 9 (12%)**	**DW *N* = 48 (65%)**	
Age (years), Median [IQR]	71 [16]	68 [8]	71 [20]	62 [15]	65 [16]
Gender (Female), N° (%)	0 (0%)	5 (46%)	4 (44%)	17 (35%)	26 (36%)
Body mass index (kg/m^2), Median [IQR]	28.6 [7.8]	24.1 [4.6]	23.1 [8.0]	27.8 [7.6]	27.8 [8.1]
Admission diagnosis, N° (%)					
Polytrauma	0 (0%)	1 (9%)	1 (11%)	2 (4%)	4 (5%)
Respiratory failure (NON-COVID)	1 (20%)	0 (0%)	2 (22%)	5 (10%)	8 (11%)
Sepsis	0 (0%)	0 (0%)	0 (0%)	7 (14%)	7 (9%)
Neurological disease	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)
CARDS	4 (80%)	9 (81%)	3 (33%)	29 (60%)	45 (61%)
Cardiac disease	0 (0%)	0 (0%)	0 (0%)	2 (4%)	2 (2%)
Other	0 (0%)	1 (9%)	1 (11%)	0 (0%)	2 (2%)
Comorbidities, N° (%)					
0	2 (40%)	3 (27%)	2 (22%)	3 (6.3%)	10 (13%)
1	1 (20%)	3 (27%)	1 (11%)	15 (31%)	20 (27%)
2	2 (40%)	2 (18%)	1 (11%)	12 (25%)	17 (23%)
≥3	0 (0%)	3 (27%)	5 (55%)	18 (37%)	26 (35%)
SAPS II, Median [IQR]	32 [9]	23 [4]	34 [10]	32 [21]	32 [18]
SOFA Score, Median [IQR]	4 [1]	4 [1]	5 [3]	4 [5]	4 [3]
MV duration (days), Median [IQR]	4 [6]	7 [3]	17 [10]	12 [11]	10 [10]
WIND, N° (%)					
Group NW: no separation attempt	0 (0%)	1 (9%)	1 (11%)	2 (4%)	4 (5%)
Group 1: short weaning	2 (40%)	8 (72%)	2 (22%)	12 (25%)	24 (32%)
Group 2: difficult weaning	2 (40%)	2 (18%)	3 (33%)	12 (25%)	19 (26%)
Group 3a: prolonged weaning	0 (0%)	0 (0%)	2 (22%)	13 (27%)	15 (20%)
Group 3b: weaning failure	1 (20%)	0 (0%)	1 (11%)	9 (18%)	11 (15%)
ICU LOS (days), Median [IQR]	6 [6]	10 [5]	18 [6]	15 [12]	13 [11]
Hospital LOS (days), Median [IQR]	20 [20]	27 [11]	21 [17]	27 [13]	27.0 [15]
Alive (at Hospital discharge), N° (%)	4 (80%)	9 (81%)	7 (77%)	42 (87%)	62 (84%)

MV duration, duration of mechanical ventilation; CARDS, COVID-19 ARDS; WIND, Weaning according to a New Definition; ICU LOS, ICU lenght of stay; and Hospital LOS, Hospital lenght of stay.

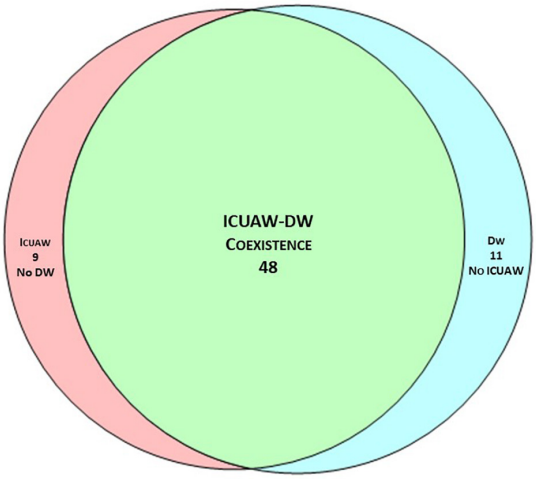

FIGURE 2 | Venn diagram of ICUAW and DW coexistence. The coexistence of the two conditions occurred in 48 patients (65%); there was no association between ICUAW and DW ($\chi^2 = 1.06$, $p = 0.304$).

(3) longer duration of MV (median [IQR] 12 [12] vs 6.5 [3.25], $p = 0.002$), (4) more frequently a prolonged weaning (WIND 3a) or a higher percentage of weaning failure despite weaning attempt (WIND 3b), and (5) longer ICU LOS (median [IQR] 15 [11] vs 8 [5], $p = 0.002$), **Supplementary Table 1**. Conversely, in our cohort, we did not observe an association between DW and ICU admission severity scores, VFDs at 28 days or weaning success (**Supplementary Table 2**).

In the unadjusted analysis, the presence of ICUAW, SAPS II and SOFA were related to VFDs at 28 days and WIND (using short weaning as reference), **Supplementary Tables 3, 4**. In the adjusted analysis, patients with ICUAW had fewer VFDs at 28 days (estimate difference 7 days, $p = 0.016$), and had an OR of 3.62 ($p = 0.050$) for WIND different than short weaning (difficult weaning, prolonged weaning or no weaning) compared to patients without ICUAW, **Table 2**. The presence of DW was not related to either VFD at 28 days or weaning success, **Table 2**.

The linear mixed model showed a significant but weak correlation between MIP and TFdi ($p < 0.001$, $R^2 = 0.43$), **Figure 3**.

DISCUSSION

To our knowledge, this is the first study to address the coexistence of ICUAW and DW by using objective measurements in both cooperative and uncooperative patients. In our cohort, we found that these two entities do not always coexist and that ICUAW, but not DW, is independently related to both VFDs at 28 days and weaning success. Moreover, we found a significant but weak correlation between MIP and TFdi.

The occurrence of ICUAW was 80%, representing one of the highest percentages reported in the literature (21). However, we believe that the inclusion of uncooperative critically ill patients, the use of PENT (i.e., a screening tool for ICUAW) and the significant proportion of severely ill patients in our cohort of exclusively MV patients, may have contributed to the high occurrence of ICUAW. The occurrence of DW in our population was also found to be 80%, similar to what has been previously reported in the literature (22, 23).

The coexistence of ICUAW and DW was 65%, much higher than the 21% reported by Dres et al. (4). However, in their study, Dres et al. evaluated ICUAW only at the time of SBT and by using the MRCss; therefore, uncooperative patients with DW would not have been tested for ICUAW, potentially underestimating its real incidence. Interestingly, in a cohort of patients with established ICUAW, Jung et al. reported the coexistence of ICUAW and DW in 80% of the subjects; these results are similar to our findings when considering only the patients with ICUAW (74%; **Table 2**). Despite a higher coexistence in our cohort, we confirmed the lack of association between the ICUAW and DW ($\chi^2 = 1.06$, $p = 0.304$). Whether DW and ICUAW are manifestations of the same pathological process is currently a source of debate in the literature. Indeed, ICUAW and DW share similar risk factors and common pathophysiological mechanisms. However, from a histopathological point of view, limb muscle and diaphragm have different features, and limb muscle affected by ICUAW shows muscle necrosis more frequently than the diaphragm affected by DW (24). Our results seem to support the hypothesis that *ICUAW and DW are not necessarily expressions of the same biological phenomena* and that different factors may be involved in this disjunct development of weakness in critically ill patients.

In our cohort, patients without ICUAW had approximately 7 more FVDs (calculated at 28 days) than patients with ICUAW.

TABLE 2 | Adjusted analysis for mechanical ventilation duration and weaning success as measured by WIND.

Predictors	VFDs at 28-days			Wind		
	Estimates	*CI*	*p*	*OR*	*CI*	*p**
Presence of ICUAW	−6.83	−12.34 – −1.31	0.016	3.62	1.06–13.84	0.050
Presence of DW	4.76	–0.82–10.35	0.093	0.87	0.29–2.68	0.814
SAPS II	−0.27	–0.52 – −0.02	0.034	1.10	1.04–1.16	0.001
Age (years)	−0.14	–0.31–0.04	0.133	1.03	0.99–1.07	0.115
Gender, Male	−0.43	–5.32–4.47	0.862	2.39	0.86–7.01	0.106
Body mass index	−0.22	–0.63–0.20	0.296	1.01	0.92–1.11	0.804

MV duration, duration of mechanical ventilation; WIND, Weaning according to a New Definition; and CI, 95% Confidence Interval.
**p is calculated using WIND = Group 1: short weaning is used as reference class.*

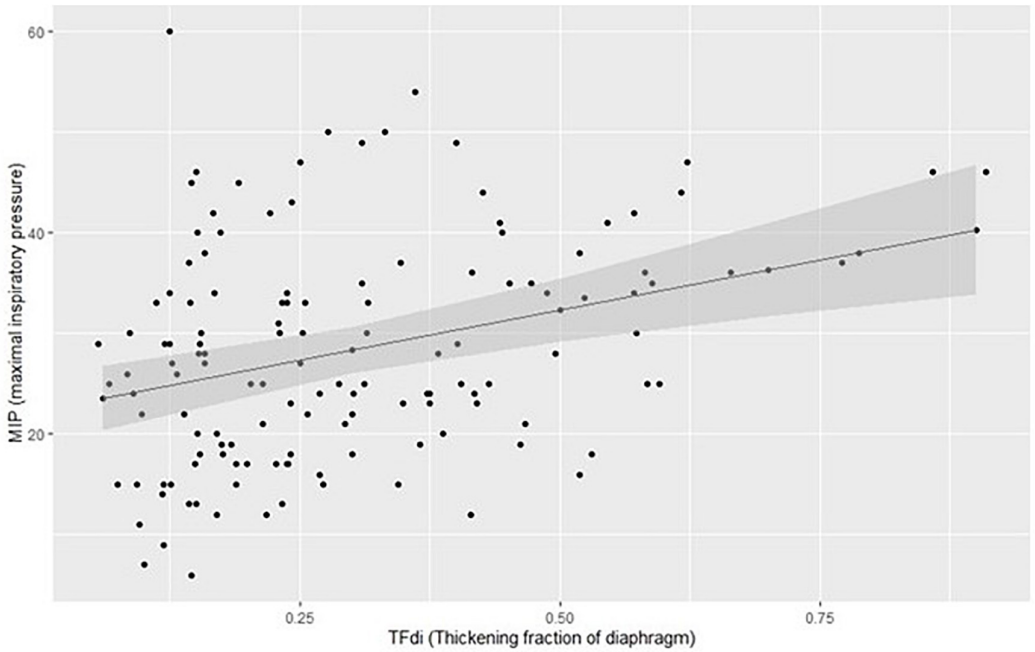

FIGURE 3 | Plotting of model estimates of the correlation between MIP (maximal inspiratory pressure) and TFdi (thickening fraction of diaphragm).

Moreover, the development of ICUAW was associated with a significantly higher probability (OR 3.62) of a more challenging weaning process (i.e., difficult weaning, prolonged weaning, or no weaning vs short weaning). Although the relation between mechanical ventilation and diaphragm dysfunction (ventilator-induced diaphragmatic dysfunction) is well known (25), we found that DW was not related to either weaning success or the VFDs at 28 days. Different studies have reported the association between ICUAW and the duration of mechanical ventilation (6) and weaning failure (26, 27), but none of them has tested the DW coexistence.

When comparing our results with the largest published study on the coexistence of ICUAW and DW (5), we observed similar duration of mechanical ventilation in (1) patients ICUAW−/DW− (4 days), patients ICUAW+/DW+ (12 days), and patients ICUAW−/DW+ (7 days), **Supplementary Table 1**. Our data diverge from Dres et al. (5) for a higher duration of mechanical ventilation in patients ICUAW+/DW− (17 vs 7 days). Furthermore, and contrary to our results, Dres reported a higher impact of DW on weaning failure than did ICUAW. The important differences between the two studies could be explained by the fact that (1) we assessed the presence of DW and ICUAW throughout the entire ICU admission and not only at the time of liberation from MV; (2) by including uncooperative patients, we identified a large number of patients with ICUAW. Finally, we can't exclude that in both DW− and DW+ the presence of an inappropriate diaphragm activity might have contributed to prolonging MV duration (28).

Despite the interesting findings, some limitations must be pointed out; firstly, we classified patients as suffering from ICUAW by using average bilateral PENT in uncooperative patients. PENT has been validated in ICU to diagnose critical illness myopathy and polyneuropathy (CIP) but it does not necessarily prove the presence of ICUAW. Notwithstanding, Hermans et al. demonstrated that an abnormal PENT, even in the absence of weakness, is independently associated with worse outcomes (29), including increased 5 years mortality (30). Secondly, concerning the diagnosis of DW, although MIP and TFdi have been both validated to diagnose respiratory muscle weakness, we did not use an objective maximal stimulation with BAMPS and we did not measure PdiTw to assess diaphragmatic strength (10). While TFdi describes the diaphragmatic function, MIP is a marker of global inspiratory strength (19, 22). Although the two techniques may not seem completely interchangeable, we found a strong correlation between MIP and TFdi with an increased dispersion for non-pathological values, **Figure 2**. In patients with pathological conditions (i.e., presence of DW) TFdi and MIP could be both useful as bedside screening tools for DW presence. To note, although MIP is easier to perform and has higher inter-rater reliability, it has not been tested against the gold standard (measures of PdiTw during BAMPS stimulations). Finally, the baseline characteristics of our population (a high SAPS II and prolonged mechanical ventilation) highly increased the chance of developing DW and/or ICUAW, explaining the low number of patients without weakness. Moreover, 62% of our patients suffered from CARDS, a risk factor for peripheral muscle weakness (31, 32), limiting the generalization of our results in classical ARDS.

In conclusion, this pilot study is the first to explore the coexistence of ICUAW and DW in both cooperative and uncooperative patients; a lack of association was found between DW and ICUAW when considering both cooperative and

uncooperative patients. We found a strong correlation between ICUAW but not DW with the VFDs at 28 days and weaning success. A future larger study is warranted in order to confirm our results, and should also investigate the use of PdiTw measurement during BAMPS for the diagnosis of DW.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico di Brescia, Brescia, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MiB, SP, and NL conceptualized the study. MiB, AB, RC, and FB collected the data. SP conducted the statistical analysis. MiB and SP drafted the manuscript. All authors critically revised the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.930262/full#supplementary-material

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Efficacy of preventive use of oxygen therapy after planned extubation in high-risk patients with extubation failure: A network meta-analysis of randomized controlled trials

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Background: Extubation failure is common in critically ill patients, especially those with high-risk factors, and is associated with poor prognosis. Prophylactic use of oxygen therapy after extubation has been gradually introduced. However, the best respiratory support method is still unclear.

Purpose: This study aimed to evaluate the efficacy of four post-extubation respiratory support approaches in reducing reintubation and respiratory failure in patients at high-risk of extubation failure.

Methods: A comprehensive search was performed in Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and Web of Science from inception to June 2022. Randomized controlled trials (RCTs) comparing post-extubation preventive use of respiratory management strategies, including conventional oxygen therapy (COT), non-invasive ventilation (NIV), and high-flow nasal catheter (HFNC) in high-risk patients with extubation failure were reviewed. Primary outcomes were reintubation rate and respiratory failure. Secondary outcomes included intensive care unit (ICU) mortality, ICU stay and length of hospital stay (LOS).

Results: Seventeen RCTs comprising 2813 participants were enrolled. Compared with COT, the three respiratory support methods (NIV, HFNC, NIV + HFNC) were all effective in preventing reintubation [odds ratio (OR) 0.46, 95% confidence interval (CI) 0.32–0.67; OR 0.26, 95% CI 0.14–0.48; OR 0.62, 95% CI 0.39–0.97, respectively] and respiratory failure (OR 0.23, 95% CI 0.10–0.52; OR 0.15, 95% CI 0.04–0.60; OR 0.26, 95% CI 0.10–0.72, respectively). NIV and NIV + HFNC also reduced ICU mortality (OR 0.40, 95% CI 0.22–0.74; OR 0.32, 95% CI 0.12–0.85). NIV + HFNC ranked best in terms of reintubation

rate, respiratory failure and ICU mortality based on the surface under the cumulative ranking curve (SUCRA) (99.3, 87.1, 88.2, respectively). Although there was no significant difference in shortening ICU stay and LOS among the four methods, HFNC ranked first based on the SUCRA.

Conclusion: Preventive use of NIV + HFNC after scheduled extubation is probably the most effective respiratory support method for preventing reintubation, respiratory failure and ICU death in high-risk patients with extubation failure. HFNC alone seems to be the best method to shorten ICU stay and LOS.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/], identifier [CRD42022340623].

KEYWORDS

high-flow nasal catheter, extubation failure, reintubation, respiratory failure, non-invasive ventilation, high-risk patients, network meta-analysis

Introduction

Extubation failure still occurs in 10–20% of patients who pass a spontaneous breathing trial (SBT) and undergo planned extubation, and is associated with poor outcomes such as reintubation, prolonged duration of intensive care unit (ICU) stay and hospital stay, and increased mortality (1, 2). For patients at high-risk of extubation failure, such as those older than 65 years and those with underlying cardiopulmonary disease, the rate of reintubation can be as high as 48% (3). And the need to reintubation is related to an increased ICU mortality of 26–50% (4). In addition to the personal challenges on patients and their families, the intensive care related resources these patients receive place a significant burden on the public health system (5). Therefore, it is essential to receive prophylactic respiratory support for post-extubated patients, especially those with high risk factors.

Various respiratory management strategies have been proposed to alleviate extubation failure and reintubation. Conventional oxygen therapy (COT) is the most frequently administered respiratory support method to improve post-extubation hypoxemia. However, the delivered fraction of inspired oxygen (FiO_2) of COT such as nasal cannulas and facemasks with reservoirs is unstable (6). And for Venturi masks, one of the COT, oxygen is passively heated and humidified (7). NIV has been recommended for patients at high-risk of reintubation, particularly those with hypercapnia (8). Nevertheless, NIV is prone to aspiration pneumonia, interface intolerance, and patient discomfort (9). High-flow nasal cannula (HFNC) is a novel device that delivers high-concentration humidified oxygen through nasal cannulas, and generates a low level of positive end-expiratory pressure (PEEP) in the upper airways, facilitating alveolar recruitment (10, 11). Moreover, HFNC improves respiratory secretions management and decreases the anatomical dead space ventilation and therefore the CO_2 rebreathing (12). But its ability to unload respiratory muscles in high-risk patients with extubation failure may be lower than that provided by NIV (13–15).

Previous meta-analyses have shown that HFNC was superior to COT but non-inferior to NIV in reducing reintubation rates in patients with acute respiratory failure (16, 17). However, the comprehensive effectiveness of these three oxygen therapies for high-risk patients with extubation failure, such as those over 65 years old and those with underlying cardiopulmonary disease, remains unclear. In addition, the use of HFNC during NIV breaks has been introduced recently, and this sequential alternate protocols (NIV + HFNC) could prevent reintubation compared with HFNC alone (18). While the efficacy on reducing mortality in patients at high-risk of extubation failure is controversial (18, 19). Therefore, we performed this network meta-analysis (NMA) to evaluate the comprehensive efficacy of prophylactic use of various oxygen therapies (COT, NIV, HFNC, and

Abbreviations: AECOPD, chronic obstructive pulmonary disease with acute exacerbation; APACHE, acute physiology and chronic health evaluation; CIs, confidence intervals; COT, conventional oxygen therapy; FiO_2, fraction of inspired oxygen; GRADE, grading of recommendation, assessment, development and evaluation; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; MDs, mean differences; NIV, non-invasive mechanical ventilation; NMA, network meta-analysis; ORs, odds ratios; $PaCO_2$, atrial partial pressure of carbon dioxide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SBT, spontaneous breathing trial; SUCRA, surface under the cumulative ranking curve; WOB, work of breathing.

NIV + HFNC) on reducing reintubation rate and respiratory failure after planned extubation in patients at high-risk of extubation failure.

Methods

This NMA was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statements for reviews incorporating network meta-analyses (**Supplementary Table 1**) (20). The study protocol was registered on PROSPERO (CRD42022340623).

Search strategy

The search strategy included controlled vocabulary (i.e., Medical Subject Headings) and free-text words for three basic concepts: (1) extubation, (2) high-risk patients with extubation failure, and (3) oxygen therapy, non-invasive ventilation, and high-flow therapy. Two researchers (XZ and RW) independently searched relevant literature in PubMed, Cochrane Central Register of Controlled Trials, Web of Science, and Embase from inception to June 2022, with no language restrictions. The detailed search strategy is presented in **Supplementary Table 2**. In addition, reference lists of included articles were reviewed. We also tried to contact authors of conference proceedings to obtain unpublished data.

Eligibility criteria

The inclusion criteria showed as following: (1) participants: adult patients (age $\geq$ 18 years) admitted to the ICU who received invasive mechanical ventilation (IMV) > 12 h, successfully passed the SBT and were ready for extubation, while were at high-risk of extubation failure (4, 13, 21); (2) interventions and comparisons: compared two of the four available devices: COT, NIV, HFNC, and NIV + HFNC. All of these methods were used for preventive purposes; (3) outcomes: the primary outcomes were reintubation rate and respiratory failure, and the second outcomes included ICU mortality, ICU stay and length of hospital stay (LOS). Studies reporting on at least one of the above outcomes were included; and (4) study design: prospective randomized controlled trials (RCTs).

The exclusion criteria included the following: (1) non-RCTs, including reviews, retrospective studies, cohort studies, and crossover studies; (2) more than half of the subjects were post-operative patients; (3) language not in English; (4) studies in which respiratory support was used for therapeutic purpose; (5) abstracts without full-text manuscripts.

According to the previous studies (4, 13, 21), "high risk" of extubation failure was defined as the presence of at least one of the following factors: (1) age > 65 years; (2) underlying cardiopulmonary disease; (3) APACHE II score > 12 at extubation; (4) body mass index > 30 kg/m^2; (5) upper airway obstruction with stridor; (6) weak cough; (7) more than one comorbidity; (8) more than one SBT failure; (9) $PaCO_2$ > 45 mmHg after extubation; and (10) duration of IMV > 7 days.

Study selection

After filtering duplicate records, two researchers (XZ and RW) independently selected and evaluated the titles and abstracts of the retrieved literature, and then the shortlisted studies were screened again to assess their adherence to the eligibility criteria. A third reviewer (JD) participated in the discussion to adjudicate disagreements. Language was limited to English during selection.

Data extraction

Data from eligible studies were extracted by two researchers (MM and MG) independently and combined to form a specific data collection sheet. The abstracted data included the name of the first author, publication year, number and locations of study centers, sample size, interventions and comparators, definition of high-risk patients, study outcomes, complications, main reason for intubation, and duration of mechanical ventilation before inclusion. Moreover, age, sex, acute physiology and chronic health evaluation (APACHE) II score on admission, atrial partial pressure of carbon dioxide ($PaCO_2$) at the end of SBT, and oxygenation index at the end of SBT were also recorded. The disagreement was resolved by a joint review of the full text to reach consensus.

Quality assessment

Two researchers (JD and MG) independently assessed the risk of bias for primary outcomes in eligible studies using the Cochrane Risk of Bias tool (22). Each trial was judged as low, unclear, or high risk with respect to adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We resolved disagreements by a discussion with a third reviewer (SG) to reach consensus.

Statistical analysis

Direct comparison meta-analysis

A conventional pairwise meta-analysis was performed using RevMan 5.3 (RevMan 2014). Effect sizes from the forest plots

were expressed as odds ratios (ORs) and mean differences (MDs), both with 95% confidence intervals (CIs), for categorical and continuous data, respectively. Outcome measures were pooled using a random effect model. A two-sided p-value < 0.05 was considered significant. To evaluate heterogeneity across studies within each direct comparison, we visually inspected the forest plots and quantified using the Q test and the I^2 statistic. When heterogeneity was identified ($I^2 > 50\%$), we quantified it using the Chi-square test (p value). We planned to use a funnel plot for the possibility of publication bias, if ≥ 10 studies were available.

Geometry of the network

Network plots were constructed to determine the number of studies included in this NMA. We demonstrated the network geometry that presented the nodes as interventions and each head-to-head direct comparison as lines connecting these nodes. The size of the node was proportional to the number of trials that included in each method. The thickness of the connecting line was proportional to the number of direct comparisons.

Network comparison meta-analysis

A random effect NMA was performed using a frequentist framework to calculate ORs for categorical outcomes and MDs for continuous outcomes, with corresponding 95% CIs. The statistical analysis was performed using the Netmeta package in Stata/SE 16.0 (Stata-Corp, College Station, TX, USA). A two-sided p-value < 0.05 was considered statistically significant.

Assessment of the risk of bias across studies followed considerations on pairwise meta-analysis. The indirectness of each study included in the NMA was evaluated according to the relevance to study population, interventions, outcomes, and study setting. The approach to imprecision comprised a comparison of the range of treatment effects included in the 95% CI with the range of equivalence. We assessed the imprecision of treatment effects for a clinically important ORs of <0.8 or >1.25 in the CIs. To evaluate the heterogeneity, we compared the posterior distribution of the estimated heterogeneity variance with its predictive distribution. The concordance between assessments based on CI and prediction intervals, which do and do not capture heterogeneity, respectively, was used to assess the importance of heterogeneity. Inconsistency between direct and indirect estimates in the entire network for each outcome was assessed locally with a loop-specific approach and globally with design-by treatment interaction model (23). And publication bias was assessed visually using a funnel plot (24).

We also ranked the preventive effectiveness of each strategy according to the probability of achieving the best results through the surface under the cumulative ranking curve (SUCRA) (25). The higher the SUCRA value, which ranges from 0 to 100%, the more likely this respiratory support method is to be ranked as best.

Grading the quality of evidence

We evaluated the quality of evidence for each outcome using the modified Grading of Recommendation, Assessment, Development and Evaluation (GRADE) tool for NMA (26). The weight contribution matrix was constructed to assess the information contribution of direct evidence to entire NMA estimates (27). The quality of evidence in NMA would be degraded because of the risk of bias, indirectness, imprecision, publication bias, and incoherence (27).

Sensitive analysis

Given that small sample size and hypercapnia ($PaCO_2 > 45$ mmHg) at the end of SBT might affect the relative effectiveness of respiratory support methods, two sensitivity analyses were performed to assess the robustness of NMA results to the primary outcomes by excluding studies with sample size < 50 or those involving patients with hypercapnia at the end of SBT.

Results

Study selection

The comprehensive database search yielded 5257 records. After excluding 1319 duplicates and 3844 irrelevant citations, we reviewed the full text of the remaining 94 records. Finally, a total of 17 eligible RCTs (3, 13, 15, 18, 19, 28–39), representing 2813 patients, were included in this NMA. A flowchart describing the detailed retrieval strategy is presented in **Figure 1**.

Study characteristics

The characteristics of each study included in this NMA are summarized in **Table 1** and **Supplementary Table 3**. All the selected studies were published between 2005 and 2022, and the sample size ranged from 29 to 641. Of the 17 included RCTs, 8 (47%) were multicenter (3, 13, 18, 19, 28–30, 33) and 9 (53%) were single-center (15, 31, 32, 34–39). Four trials (23.5%) recruited patients from Spain (3, 13, 28, 29), 4 (23.5%) from China (17, 34, 35, 38), and 3 (17.6%) from France (18, 19, 33). The definition of high-risk factors varied from study to study. Respiratory disease was the most common complication in these high-risk patients. The main reasons for intubation were chronic obstructive pulmonary disease with acute exacerbation (AECOPD) and pulmonary infection. Most patients among the trials were older than 65, with a higher mean proportion of male than female. The APACHE II score on admission was greater than 12 in 9 of 10 (90%) trials (3, 13, 28, 29, 32, 34, 37–39). The $PaCO_2$ at the end of SBT was greater than 45 mmHg in 2 of 12 (16.7%) trials (3, 35). Oxygenation index at the end of SBT was mostly greater than 200 mmHg among the included studies.

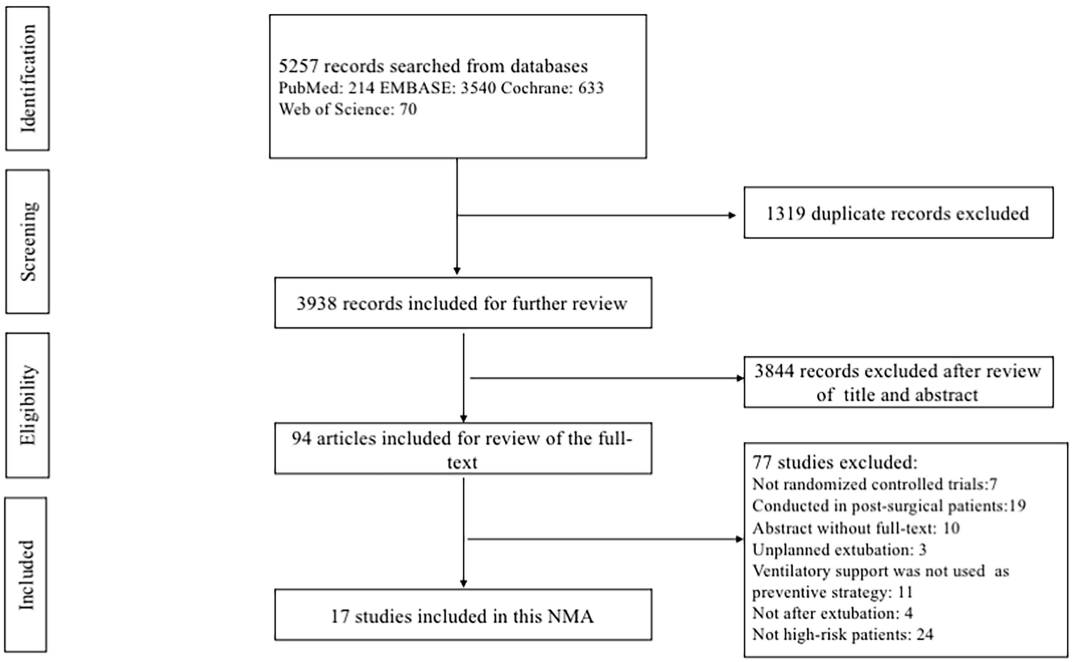

FIGURE 1
PRISMA flowchart for the study selection process. NMA, network meta-analysis.

Quality assessment

The risk of bias within eligible studies is shown in **Figure 2**. All trials were assessed as low or unclear risk of bias with respect to random sequence generation and allocation concealment, except for one (39) in which participants were grouped by the admission number. All studies were judged as having a high risk of performance bias because of the inability to blind caregivers to ventilation device. There were seven unclear detection bias due to the unknown definition of reintubation (3, 28, 30, 31, 33, 35, 37). Additionally, one trial (15) had a high risk of other bias associated with the imbalanced baseline.

Pairwise meta-analysis

Compared with COT, NIV was more effective in preventing reintubation, respiratory failure, and ICU mortality. NIV + HFNC reduced the rate of reintubation and respiratory failure compared with HFNC alone. HFNC shortened the ICU stay compared with NIV (**Supplementary Figures 1–5**).

Network meta-analysis

The included trials evaluated four interventions, including five head-to-head comparisons for reintubation and four head-to-head comparisons for respiratory failure (**Supplementary Figure 6**). There were two loops in the reintubation network plot (COT-NIV-HFNC; COT-HFNC- NIV + HFNC) (**Supplementary Figure 6A**). **Supplementary Figure 6B** showed only one loop in the network plot of respiratory failure (COT-NIV-HFNC). The weight contribution matrix and league table are shown in **Supplementary Figures 7–11** and **Supplementary Table 4**.

Reintubation

Sixteen studies were included in the analysis of reintubation (3, 13, 15, 18, 19, 28–37, 39). All the three methods (NIV, HFNC, NIV + HFNC) were superior to COT in reintubation (OR 0.46, 95% CI 0.32–0.67; OR 0.62, 95% CI 0.39–0.97; OR 0.26, 95% CI 0.14–0.48, respectively) (**Figure 3A**). HFNC was comparable to NIV in reducing reintubation rate (OR 1.33, 95% CI 0.94–1.90). Compared to NIV and HFNC, NIV + HFNC prevented reintubation with significant differences (OR 0.57, 95% CI 0.33–0.98; OR 0.43, 95% CI 0.28–0.65, respectively). **Figure 4A** showed the treatment rankings, which revealed that the hierarchy for efficacy in reducing reintubation was NIV + HFNC (SUCRA 99.3) > NIV (SUCRA 65.5) > HFNC (SUCRA 34.6) > COT (SUCRA 0.6).

The quality of evidence for reintubation estimated by NMA was rated as low to moderate (**Table 2A**). The study limitation was detected for all the comparisons because of a high risk of performance bias (**Figure 2**). The funnel plot

TABLE 1 Characteristics of the studies included in the network meta-analysis.

References	Design	Contrary	Sample size	C	I	Outcome	High-risk definition	Complication	Main reason for intubation	MV before inclusion (d)
Ferrer et al. (28)	Multi-center	Spain	162	COT	NIV	1, 2, 3, 4, 5, 6	Age > 65 year, cardiac failure as the cause of intubation, or increased severity, assessed by an APACHE II score >12 on the day of extubation.	Chronic respiratory disorders (49%; 52%)	AECOPD (30.1%; 30.4%)	C:7 ± 5 I:6 ± 4
Fernandez et al. (29)	Multi-center	Spain	155	COT	HFNC	1, 2, 3, 4, 5, 6	>65 years, heart failure as cause of intubation, non-hypercapnic moderate-to-severe COPD, APACHE II score >12 points at extubation, body mass index>30 kg/m^2, weak cough and copious secretions, more than one SBT failure, or MV>7 days.	Na	Na	C:7.4 ± 3.6 I:8.2 ± 5.9
Hernández et al., (13)	Multi-center	Spain	604	NIV	HFNC	1, 2, 3, 4, 5, 6	Age > 65 years; heart failure; moderate to severe chronic obstructive pulmonary disease; an APACHE II score > 12 on extubation day; body mass index of more than 30; airway patency problems; inability to deal with respiratory secretions; difficult or prolonged weaning; 2 or more comorbidities; and mechanical ventilation for > 7 days.	Respiratory primary failure (38.5%; 33.8%)	Na	C:4 (2–8) I:4 (2–9)
Cho et al. (15)	Single-center	Korea	60	COT	HFNC	1, 3, 4, 5, 6	Age > 65 years, APACHE II score > 12 points on extubation day, obesity, poor expectoration, airway patency problems, difficult or prolonged weaning, and more than one comorbidity.	Chronic lung disease (44.8%; 38.7%)	Pulmonary infection (80.6%; 51.7%)	C:5.7 ± 5.2 I:7.1 ± 4.7
Thille et al. (18)	Multi-center	France	641	HFNC	NIV + HFNC	1, 2, 3, 4, 5, 6	>65 years or had any underlying chronic cardiac or lung disease. Underlying chronic cardiac diseases; history of cardiogenic pulmonary edema; documented ischemic heart disease; or permanent atrial fibrillation. Underlying chronic lung diseases.	Na	Acute respiratory failure (52%; 49%)	C:5 (3–9) I:6 (3–11)

(Continued)

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TABLE 1 (Continued)

References	Design	Contrary	Sample size	C	I	Outcome	High-risk definition	Complication	Main reason for intubation	MV before inclusion (d)
Nava et al. (30)	Multi-center	Italy	97	COT	NIV	1, 3, 4, 5, 6	More than one consecutive failure of weaning trial, Chronic heart failure, PaCO2 > 45 mm Hg after extubation, More than one comorbidity (excluding chronic heart failure), Weak cough defined as Airway Care Score values > 8 and >12, Upper airways stridor at extubation not requiring immediate reintubation	Na	AECOPD (31%; 36%)	C:7.46 ± 6 I:6.14 ± 7
Ferrer et al. (3)	Multi-center	Spain	106	COT	NIV	1, 2, 3, 4, 5, 6	At high-risk of extubation failure	COPD or chronic bronchitis (69%; 70%)	AECOPD (48%; 52%)	C:4 ± 2 I:5 ± 3
Khilnani et al. (31)	Single-center	India	40	COT	NIV	1, 6	Acute exacerbation of COPD with type-2 respiratory failure	Chronic cor pulmonale (25%; 15%)	Na	C:11 ± 4.5 I:10 ± 4.7
Ornico et al. (32)	Single-center	Brazil	38	COT	NIV	1, 4, 5	Acute respiratory failure	Na	Pneumonia (88.9%; 80%)	C:9.5 ± 6.1 I:9.9 ± 8.1
Vargas et al. (33)	Multi-center	France	143	COT	NIV	1, 2, 3, 4, 5	Patients with known or suspected chronic respiratory disorders, or those who tolerated a spontaneous breathing trial with hypercapnia defined by a $PaCO_2$ > 45 mmHg.	Diabetes mellitus (33.3%; 26.7%)	AECOPD (55.5%; 56.3%)	C:6 (4–11) I:7 (5–11)
Song et al. (34)	Single-center	China	60	COT	HFNC	1	Acute respiratory failure	Na	Pneumonia (40%; 43.3%)	C:5.4 ± 2.8 I:5.5 ± 3.4
Jing et al. (35)	Single-center	China	42	NIV	HFNC	1, 2, 4, 5	AECOPD, with hypercapnia (PaCO2 >45 mmHg) at the time of extubation	Chronic cor pulmonale (90%; 86.4%)	AECOPD	C:3.4 ± 1.6 I:3.3 ± 1.6
Xu et al. (36)	Single-center	China	29	COT	NIV + HFNC	1	Patients with an LUS score ≥ 14 points	Na	Na	Na
Thille et al. (19)	Multi-center	France	410	HFNC	NIV + HFNC	1, 2, 3, 4, 5, 6	At high-risk of extubation failure	Underlying chronic cardiac disease (47%; 50%)	Acute respiratory failure (48%; 45%)	C:5 (3–10) I:7 (3–12)
Mohamed and Abdalla (37)	Single-center	Egypt	120	COT	NIV	1, 3, 5	Acute respiratory failure	COPD (31.6%; 26.6%)	Na	C:7.1 ± 1.8 I:6.2 ± 1.6

(Continued)

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TABLE 1 (Continued)

References	Design	Contrary	Sample size	C	I	Outcome	High-risk definition	Complication	Main reason for intubation	MV before inclusion (d)
Adıyeke et al. (39)	Single-center	Turkey	50	COT	NIV	1, 2	Acute respiratory failure	Na	Na	Na
Hu et al. (38)	Single-center	China	56	COT	HFNC	2, 4, 5	Age > 65 years, congestive heart failure, COPD, bronchiectasis or old pulmonary tuberculosis with lung destruction, idiopathic pulmonary fibrosis, ESRD under maintenance dialysis, respiratory muscle weakness related to neuromuscular disease, inadequate respiratory tract secretion management ability, body mass index > 30, adult respiratory distress syndrome, or invasive MV use of > 7 days.	Hypertension (63%; 58.6%)	Respiratory tract infection (33.3%; 44.8%)	C:7 (5–11) I:9 (6–12)

C, control setting; I, intervention setting; AECOPD, chronic obstructive pulmonary disease with acute exacerbation; 1, reintubation; 2, post-extubation respiratory failure; 3, ICU mortality; 4, ICU stay; 5, length of hospital stay; COT, conventional oxygen therapy; NIV, non-invasive ventilation; HFNC, high-flow nasal catheter; MV, mechanical ventilation. The data on MV before inclusion presented as mean ± SD or median (IQR).

suggested no publication bias (Supplementary Figure 12). The imprecision of two direct comparisons (HFNC vs. COT and NIV + HFNC vs. COT) resulted in "some concern" because 95% CIs included values favoring either treatment. Quality of evidence for indirect estimates downgraded by one level for serious heterogeneity due to I^2 in three comparisons (NIV vs. COT, HFNC vs. COT, and NIV + HFNC vs. COT). And heterogeneity was observed in one network comparison due to the predictive interval (HFNC vs. COT) (Figure 3A). There was no significant difference between direct and indirect comparisons (Supplementary Figures 13, 14), indicating the consistency of different studies.

Respiratory failure

Respiratory failure was reported in 10 trials (3, 13, 18, 19, 28, 29, 33, 35, 38, 39). The network estimates suggested that NIV, HFNC and NIV + HFNC were associated with a lower risk of respiratory failure compared with COT (OR 0.23, 95% CI 0.10–0.52; OR 0.26, 95% CI 0.10–0.72; OR 0.15, 95% CI 0.04–0.60, respectively) (Figure 3B). We found no significant difference in respiratory failure among NIV, HFNC, and NIV + HFNC (OR 1.13, 95% CI 0.42–3.03; OR 0.63, 95% CI 0.16–2.53; OR 0.56, 95% CI 0.21–1.48, respectively). Figure 4B showed that NIV + HFNC ranked first in reducing respiratory failure (SUCRA 87.1).

The quality of evidence for respiratory failure assessed by NMA was rated as low (Table 2B). There was still a high risk of performance bias in studies involving respiratory failure (Figure 2). Supplementary Figure 15 indicated no significant publication bias. Two network comparisons were heterogeneous due to the predictive interval (NIV vs. COT, and HFNC vs. COT) and the other two were imprecise due to the 95% CIs (HFNC vs. NIV, and NIV + HFNC vs. HFNC). The inconsistency test at the global and local levels showed no significant difference between direct and indirect comparisons (Supplementary Figures 16, 17).

Intensive care unit mortality

Ten trials reported ICU mortality (3, 13, 15, 18, 19, 28–30, 33, 37). Compared with COT, NIV and NIV + HFNC reduced ICU mortality, with significant differences (OR 0.40, 95% CI 0.22–0.74; OR 0.32, 95% CI 0.12–0.85, respectively) (Figure 3C). HFNC was comparable to COT in reducing ICU mortality (OR 0.63, 95% CI 0.30–1.33). There were no significant differences in ICU mortality among NIV, HFNC, and NIV + HFNC. Figure 4C showed the treatment rankings, revealing that NIV + HFNC (SUCRA 88.2) was the best to alleviate ICU death. Radar map indicated that NIV + HFNC was the most effective method to

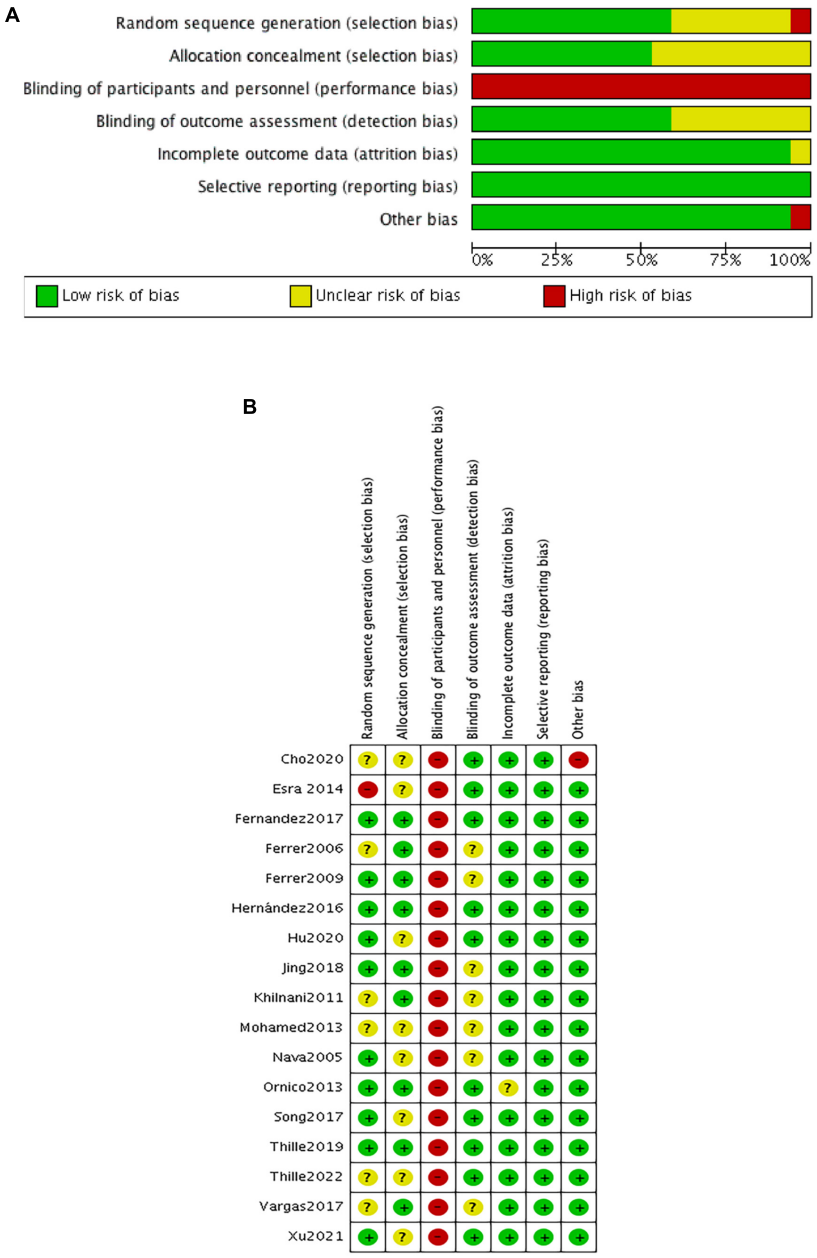


FIGURE 2
Risk of bias for each comparison. **(A)** Risk of bias summary; **(B)** risk of bias graph.

prevent reintubation, respiratory failure, and ICU death (Supplementary Figure 18). No significant publication bias was detected (Supplementary Figure 19). The imprecision of two network comparisons (HFNC vs. COT and HFNC vs. NIV) resulted in "some concern" (Table 2C). And heterogeneity was observed in one comparison of NMA estimates (NIV vs. COT) (Figure 3C). There was no significant inconsistency in the global and local levels tests (Supplementary Figures 20, 21). The network geometry for ICU mortality is shown in Supplementary Figure 22.

Intensive care unit stay

Thirteen trials reported the length of ICU stay (3, 13, 15, 18, 19, 28–30, 32, 33, 35, 37, 38). The network plot is shown in Supplementary Figure 23. There was no evidence for the superiority of one particular respiratory support method because all the CIs contained the null value (Figure 3D). HFNC ranked best among the four methods (SUCRA 69.7) (Figure 4D). The quality of evidence for ICU stay assessed by NMA was low (Table 2D). There was no significant difference

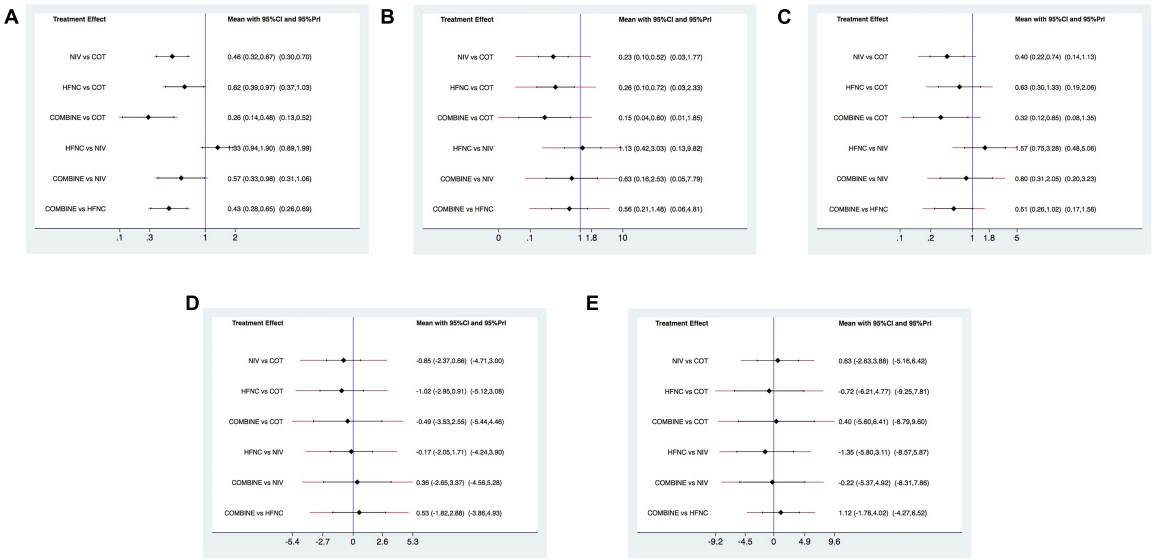
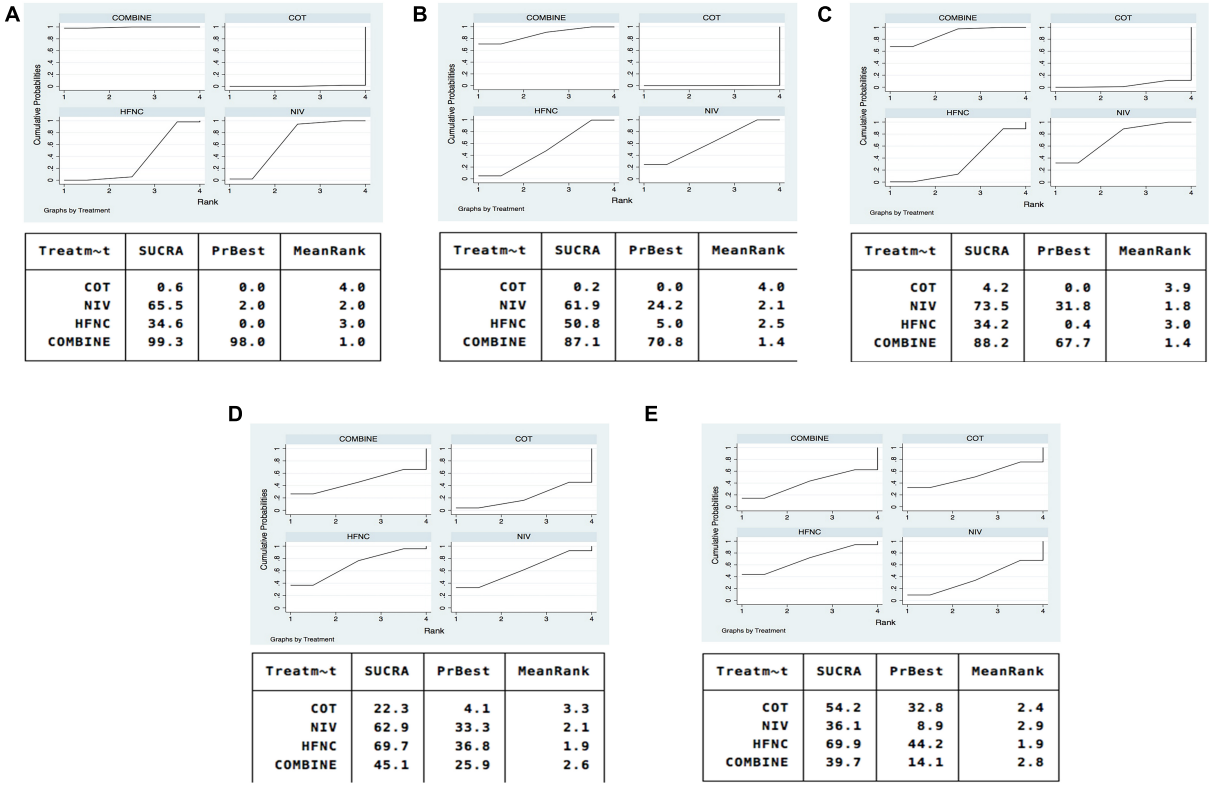


FIGURE 3
Forest plots for reintubation rate, respiratory failure, ICU mortality, ICU stay, and LOS. **(A)** Reintubation rate; **(B)** respiratory failure; **(C)** ICU mortality; **(D)** ICU stay; **(E)** LOS. ICU, intensive care unit; LOS, length of stay; NIV, non-invasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; CI, confidence interval; PrI, prediction interval.



Treatm~t	SUCRA	PrBest	MeanRank
COT	0.6	0.0	4.0
NIV	65.5	2.0	2.0
HFNC	34.6	0.0	3.0
COMBINE	99.3	98.0	1.0

Treatm~t	SUCRA	PrBest	MeanRank
COT	0.2	0.0	4.0
NIV	61.9	24.2	2.1
HFNC	50.8	5.0	2.5
COMBINE	87.1	70.8	1.4

Treatm~t	SUCRA	PrBest	MeanRank
COT	4.2	0.0	3.9
NIV	73.5	31.8	1.8
HFNC	34.2	0.4	3.0
COMBINE	88.2	67.7	1.4

Treatm~t	SUCRA	PrBest	MeanRank
COT	22.3	4.1	3.3
NIV	62.9	33.3	2.1
HFNC	69.7	36.8	1.9
COMBINE	45.1	25.9	2.6

Treatm~t	SUCRA	PrBest	MeanRank
COT	54.2	32.8	2.4
NIV	36.1	8.9	2.9
HFNC	69.9	44.2	1.9
COMBINE	39.7	14.1	2.8

FIGURE 4
SUCRA of oxygen therapies for reintubation rate, respiratory failure, ICU mortality, ICU stay, and LOS. **(A)** Reintubation; **(B)** respiratory failure; **(C)** ICU mortality; **(D)** ICU stay; **(E)** LOS. NIV, non-invasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; SUCRA, surface under cumulative ranking curve.

TABLE 2 Estimate and certainly of the evidence of direct, indirect, and network comparisons.

Comparisons	No. of RCTs	Estimate of direct comparison (95% CI)	Certainly of the evidence of direct comparison	Estimate of indirect comparison (95% CI)	Certainly of the evidence of indirect comparison	Estimate of network comparison (95% CI)	Certainly of the evidence in network comparison
(A) Reintubation							
NIV vs. COT	8	0.43 (0.29, 0.65)	⊕⊕⊕◯ Moderate[1]	0.62 (0.34, 1.15)	⊕⊕◯◯ Low [4,5]	0.46 (0.32, 0.67)	⊕⊕⊕◯ Moderate[8]
HFNC vs. COT	3	0.76 (0.34, 1.71)	⊕⊕◯◯ Low[1,2]	0.48 (0.32, 0.73)	⊕⊕◯◯ Low [4,5]	0.62 (0.39, 0.97)	⊕⊕◯◯ Low [8,9]
NIV + HFNC vs. COT	1	0.32 (0.05, 2.13)	⊕⊕◯◯ Low[1,2]	0.53 (0.36, 0.77)	⊕⊕◯◯ Low [4,5]	0.26 (0.14, 0.48)	⊕⊕⊕◯ Moderate[8]
HFNC vs. NIV	2	1.26 (0.85, 1.86)	⊕⊕⊕◯ Moderate [1]	0.46 (0.35, 0.60)	⊕⊕⊕◯ Moderate[4]	1.33 (0.94, 1.90)	⊕⊕⊕◯ Moderate[8]
NIV + HFNC vs. HFNC	2	0.33 (0.11, 0.97)	⊕⊕⊕◯ Moderate[1]	0.59 (0.40, 0.87)	⊕⊕⊕◯ Moderate[4]	0.43 (0.28, 0.65)	⊕⊕⊕◯ Moderate[8]
(B) Respiratory failure							
NIV vs. COT	4	0.20 (0.09, 0.43)	⊕⊕⊕◯ Moderate[1]	0.60 (0.32, 1.12)	⊕⊕⊕◯ Moderate[4]	0.23 (0.10, 0.52)	⊕⊕◯◯ Low [8,9]
HFNC vs. COT	2	0.26 (0.02, 3.60)	⊕⊕◯◯ Low[1,2]	0.31 (0.15, 0.62)	⊕⊕◯◯ Low [4,5]	0.26 (0.10, 0.72)	⊕⊕◯◯ Low [8,9]
HFNC vs. NIV	2	0.85 (0.20, 3.58)	⊕⊕◯◯ Low[1,2]	0.24 (0.11, 0.50)	⊕⊕◯◯ Low [4,5]	1.13 (0.42, 3.03)	⊕⊕◯◯ Low [8,10]
NIV + HFNC vs. HFNC	2	0.57 (0.43, 0.76)	⊕⊕⊕◯ Moderate[1]	NE[6]		0.56 (0.21, 1.48)	⊕⊕◯◯ Low [8,10]
(C) ICU mortality							
NIV vs. COT	5	0.33 (0.17, 0.62)	⊕⊕⊕◯ Moderate[1]	1.09 (0.63, 1.86)	⊕⊕◯◯ Low [4,5]	0.40 (0.22, 0.74)	⊕⊕◯◯ Low [8,9]
HFNC vs. COT	2	0.96 (0.38, 2.44)	⊕⊕◯◯ Low[1,2]	0.47 (0.23, 0.93)	⊕⊕⊕◯ Moderate[4]	0.63 (0.30, 1.33)	⊕⊕◯◯ Low [8,10]
HFNC vs. NIV	1	1.15 (0.59, 2.24)	⊕⊕◯◯ Low[1,2]	0.46 (0.27, 0.79)	⊕⊕⊕◯ Moderate[4]	1.57 (0.75, 3.28)	⊕⊕◯◯ Low [8,10]
NIV + HFNC vs. HFNC	2	0.47 (0.18, 1.21)	⊕⊕⊕◯ Moderate[1]	NE[6]		0.51 (0.26, 1.02)	⊕⊕⊕◯ Moderate[8]
(D) ICU stays							
NIV vs. COT	6	−1.25 (−3.63, 1.13)	⊕◯◯◯ Very low[1,2,3]	−0.83 (−1.47, −0.19)	⊕⊕⊕◯ Moderate[4]	−0.85 (−2.37, 0.66)	⊕⊕◯◯ Low [8,10]
HFNC vs. COT	3	0.02 (−2.00, 2.04)	⊕⊕◯◯ Low[1,2]	−1.16 (−2.57, 0.26)	⊕◯◯◯ Very low[4,5,7]	−1.02 (−2.95, 0.91)	⊕⊕◯◯ Low [8,10]
HFNC vs. NIV	2	−0.99 (−1.69, −0.30)	⊕⊕⊕◯ Moderate[1]	−0.89 (−2.70, 0.91)	⊕◯◯◯ Very low[4,5,7]	−0.17 (−2.05, 1.71)	⊕⊕◯◯ Low [8,10]
NIV + HFNC vs. HFNC	2	0.64 (−0.48, 1.75)	⊕⊕◯◯ Low[1,2]	NE[6]		0.53 (−1.82, 2.88)	⊕⊕◯◯ Low [8,10]
(E) Length of in-hospital stay							
NIV vs. COT	4	−0.66 (−3.76, 2.43)	⊕⊕◯◯ Low[1,2]	1.13 (−5.93, 8.20)	⊕⊕◯◯ Low [4,7]	0.63 (−2.63, 3.88)	⊕⊕◯◯ Low [8,10]
HFNC vs. COT	2	5.11 (−6.52, 16.73)	⊕⊕◯◯ Low[1,2]	−1.76 (-4.02, 0.49)	⊕⊕◯◯ Low [4,7]	−0.72 (−6.21, 4.77)	⊕⊕◯◯ Low [8,10]

(Continued)

TABLE 2 (Continued)

Comparisons	No. of RCTs	Estimate of direct comparison (95% CI)	Certainly of the evidence of direct comparison	Estimate of indirect comparison (95% CI)	Certainly of the evidence of indirect comparison	Estimate of network comparison (95% CI)	Certainly of the evidence in network comparison
HFNC vs. NIV	1	−3 (−6.28, 0.28)	⊕⊕◯◯ Low[1,2]	0.53 (−2.77, 3.83)	⊕⊕◯◯ Low [4,7]	−1.35 (−5.80, 3.11)	⊕⊕◯◯ Low [8,10]
NIV + HFNC vs. HFNC	2	1.19 (−1.08, 3.47)	⊕⊕◯◯ Low[1,2]	NE[6]		1.12 (−1.78, 4.02)	⊕⊕◯◯ Low [8,10]

CI, confidence interval; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; NO, number; RCT, random controlled trial; ICU, intensive care unit; NE, not estimable.
[1]Quality of evidence for direct estimate rated down by one level for serious risk of bias because of the high risk of unblinding of participants and personnel in all included trials. [2]Quality of evidence for direct estimate rated down by one level for serious imprecision because 95% CI include values favoring either treatment. [3]Quality of evidence for direct estimate rated down by one level for serious incoherence. [4]Quality of evidence for indirect estimate rated down by one level for serious risk of bias. [5]Quality of evidence for indirect estimate rated down by one level for serious incoherence. [6]Not estimable because no loop can be constructed for the two treatments in the evidence network. [7]Quality of evidence for indirect estimate rated down by one level for serious imprecision because 95% CI include values favoring either treatment. [8]Quality of evidence for network estimate rated down by one level for serious risk of bias. [9]Quality of evidence for network estimate rated down by one level for serious incoherence. [10]Quality of evidence for network estimate rated down by one level for serious imprecision because 95% CI include values favoring either treatment.

in publication bias (**Supplementary Figure 24**). All the network comparisons were imprecise (**Figure 3D**). The inconsistency test at the global and local levels indicated no significant difference (**Supplementary Figures 25, 26**).

Length of hospital stay

Length of hospital stay was reported in nine trials (3, 13, 15, 18, 19, 28–31). The network geometry is shown in **Supplementary Figure 27**. The network estimates provided low-quality evidence of no difference in LOS among the four methods (**Figure 3E**). **Figure 4E** suggested that HFNC was the most effective method to shorten LOS (SUCRA 69.9). No significant publication bias was detected (**Supplementary Figure 28**). All the network comparisons were subject to imprecision (**Table 2E**). There was no significant inconsistency in the test at global and local levels (**Supplementary Figures 29, 30**).

Sensitivity analysis

Two sensitivity analyses were performed for the primary outcomes, exclusively including 13 trials with sample size ≥ 50 and 15 trails with $PaCO_2 \leq 45$ mmHg at the end of SBT. The results revealed that the relative effectiveness of various therapies remained similar (**Supplementary Table 5**), and the SUCRA rankings were comparable to those of the preliminary analysis (**Supplementary Figures 31, 32**).

Discussion

In this study, NIV as well as HFNC, and NIV + HFNC significantly reduced reintubation rate and respiratory failure compared to COT. NIV and NIV + HFNC also lowered the risk of ICU death. Treatment rankings showed that NIV + HFNC scored highest in alleviating reintubation, respiratory failure, and ICU mortality. While HFNC ranked best in shortening ICU stay and LOS.

A multicenter RCT demonstrated that NIV + HFNC was effective in preventing reintubation compared with HFNC alone (18). NIV interspaced with HFNC breaks between NIV sessions is a strategy that combines the benefits of both methods: NIV for sustainable pressure support effect (32) and HFNC for increased comfort and easier clearance of secretions (13). As a result, NIV + HFNC can further improve gas exchange and decrease the work of breathing (WOB) (40). In this study, NIV + HFNC was found to be the best strategy for reducing reintubation rate, respiratory failure, and ICU mortality, which was consistent with the recommendation from the latest guidelines (41). In the ERS clinical practice guidelines, HFNC was recommended during NIV breaks in patients with acute hypoxemic respiratory failure to limit the need for prolonged NIV by maintaining adequate oxygenation and to increase patient comfort (41). However, a relevant NMA indicated that NIV + HFNC exhibited the potential to increase short-term mortality (42). The different conclusion may be related to the inclusion criteria. In the study by Zhou et al. (42), only part of the studies recruited patients at risk of extubation failure, and substantial heterogeneity was identified across the eligible trials. In addition, only one RCT (18) directly compared NIV + HFNC with HFNC in Zhou's study, and the insufficient sample size may lead to the inconsistency between direct and indirect estimation.

In this study, NIV was superior to COT in terms of reintubation and respiratory failure. The high success rate may be attributed to the early application of NIV, immediately after programmed extubation, which kept the upper airway open and improved ventilation and oxygenation, thus preventing overload of respiratory muscles, the development of atelectasis, and respiratory distress (32). However, a recent meta-analysis

concluded that NIV had no effect on reducing reintubation rate (43). In the above study (43), NIV was used as a treatment strategy for unplanned extubation patients in addition to a preventive strategy after scheduled extubation. And different from conventional pairwise meta-analyses that only include head-to-head comparisons, NMA can compare multiple treatments simultaneously by combining direct and indirect evidence and inform the relative effect of indirect comparison treatments, within a higher quality (44).

According to the latest ERS guidelines (41), NIV was recommended over HFNC after extubation for patients at high risk of extubation failure unless relative or absolute contraindications to NIV. In the current NMA, although HFNC was non-inferior to NIV in terms of reintubation and respiratory failure, NIV was beneficial to lower the risk of ICU death. It may be explained by the following: first, even though both methods can generate PEEP, the flow of HFNC only produces about 5–6 cmH_2O PEEP throughout the respiratory cycle (45, 46). While NIV can offer different levels of PEEP according to patient's needs. Therefore, the support effect of NIV is greater than that of HFNC. In addition, we focused on high-risk patients in the current study, such as those with underlying cardiopulmonary disease. NIV has been reported to have the greatest benefits in patients with hypercapnic respiratory failure caused by chronic obstructive pulmonary disease (COPD) (6), followed by congestive heart failure (CHF) (47). Positive pressure during inspiration reduces the WOB, and compensates for increased airway resistance. Positive pressure during expiration relieves venous return and prevents respiratory failure in patients with CHF (48). All of these effects may translate into a lower mortality among patients receiving NIV protocol. This may be another reason for the difference in mortality between the two methods.

In the current NMA, HFNC ranked first in shortening ICU stay and LOS among these oxygen treatments. This may be benefit from the fact that HFNC is more comfortable and better tolerated than oronasal mask (9). In a recent multicenter RCT by Maggiore et al., HFNC reduced the incidence of tachypnea and respiratory fatigue compared with Venturi mask, improving patient comfort (11). Although the ICU stay and LOS were comparable between the two groups in that study (11), this may be due to the use of therapeutic NIV rather than reintubation in patients with respiratory distress. In addition, patients with HFNC are not restricted by respiratory support in eating, drinking, and communication. And HFNC has a smaller contact area and well-humidified oxygen delivery, which is conducive to easy clearance of secretions and low risk of adverse effects (45). The high flow also irrigates the nasopharyngeal dead space, thus alleviating CO_2 re-breathing. However, NMA estimates suggested that the 95% CI contained the null effect and these findings should be interpreted with caution.

Although early weaning from IMV after a successful SBT improves prognosis, reintubation is inevitable and significantly increases mortality (3). Therefore, it is important to choose an appropriate strategy to prevent reintubation, especially for high-risk patients. In clinical practice, NIV + HFNC could be used prophylactically after planned extubation to reduce the risk of reintubation and respiratory failure in high-risk patients. Once the patient's vital signs are stable, HFNC alone should be applied as early as possible to shorten ICU stay and LOS.

The results of this study are useful for selecting an appropriate non-invasive oxygen therapy for post-extubation patients. There are still several limitations. First, the definition of high-risk patients lacks consistency. And the severity of the participants in each study is unknown, which may affect the certainty of NMA results. Second, we performed two sensitivity analyses to assess the robustness of NMA results. However, there were other effect modifiers, including the cause of intubation and duration of IMV. Unfortunately, no other sensitivity analyses were conducted given the limited information in the included studies. Third, only two RCTs directly compared HFNC to NIV, and the NMA effect size was mainly estimated by indirect evidence, which may lead to inaccurate evaluation of treatment effect. More studies are needed to provide a higher certainty of evidence. Finally, due to limited data, we didn't consider the safety and economic benefits of each methods.

Conclusion

In conclusion, prophylactic use of NIV + HFNC after scheduled extubation is probably the most effective respiratory support method to prevent reintubation, respiratory failure and ICU death in high-risk patients with extubation failure. Among these strategies, HFNC performed a beneficial effect on shortening ICU stay and LOS. Considering few direct comparison studies, more relevant high-quality RCTs are needed in the future.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

XZ participated in designing the study, performing statistical analyses, and drafting the manuscript. RW participated in designing the study, study search, and study selection. MG contributed to data extraction and quality assessment. JD participated in quality assessment and the interpretation of data. MM contributed to data extraction. SG contributed to conception, design, manuscript revision for

critical intellectual content, and supervision of the study. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1026234/full#supplementary-material

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Supraglottic jet oxygenation and ventilation *via* nasopharyngeal airway for a patient with iatrogenic tracheoesophageal fistula: A case report

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Background: Iatrogenic tracheoesophageal fistula (TEF) is a rare but life-threatening condition. No consensus has been reached regarding TEF treatment, though, stenting has been gaining popularity for less invasiveness than thoracic surgery. The airway management during stent placement for TEF could be challenging.

Case presentations: We report a patient who suffered from TEF after cardiac surgery with symptoms of persistent coughing and aspiration. He who was admitted for stent placement but ended up in failure and referred to our institution for further treatment. We successfully took advantage of the supraglottic jet oxygenation and ventilation (SJOV) during stent placement.

Conclusion: This is the first case so far describing SJOV in complicated stenting treatment. This demonstrates that SJOV can be applied for stent placement in TEF patients with restricted airways.

KEYWORDS

tracheoesophageal fistula, supraglottic jet oxygenation and ventilation, stent, nasopharyngeal airway, jet ventilation, rigid bronchoscope, flexible bronchoscope

Introduction

Tracheoesophageal fistula (TEF) is a rare iatrogenic late complication of tracheostomy in adults, with a prevalence of less than 1% (1). The main presentations include persistent cough, excessive secretions, recurrent aspiration, and gastric distention. Untreated TEF can deteriorate into acute respiratory distress syndrome and death (2). The treatment for this complication varies from stent deployment to thoracic surgical reconstruction. Ventilation management for iatrogenic TEF mainly relies on endotracheal tube (ET) and its modifications intubation (3, 4). However, the lack of high-level evidence has already prompted alternate measures (5). Herein,

Abbreviations: TEF, tracheoesophageal fistula; ET, endotracheal tube; SJOV, supraglottic jet oxygenation and ventilation; HFJV, high-frequency jet ventilation; RB, rigid bronchoscope; FB, flexible bronchoscope; NPA, nasopharyngeal airway; $ETCO_2$, end-tidal carbon dioxide; LMA, laryngeal mask airway; NIV, non-invasive ventilation.

we present a rare case of successful supraglottic jet oxygenation and ventilation (SJOV)-assisted stent placement. Written informed consent and approval from the patient and research Ethics Committee of our hospital were obtained for medical education and publication.

Case description

The patient was a 45-year-old man with a history of tracheostomy after surgery for hypertrophic cardiomyopathy, with a tracheostomy tube for 3 months. He was re-admitted to the same hospital because of coughing during the course of his diet and due to signs of pulmonary infection. The patient was diagnosed with TEF in the upper level after bronchoscopy examination and was scheduled to undergo tracheal stent placement after fasting and nasogastric tube insertion. However, the procedure failed because the stent was placed beneath the fistula and refractory to be adjusted appropriately or retracted, demanding transference. Additionally, his left upper limb experienced post-stroke paralysis. One day later, the patient was referred to our institution for further treatment.

The plan was to adjust the implanted stent or replace it with a new one by the most experienced endoscopist in our institution. After standard monitoring and pre-oxygenation, rapid sequence induction was initiated, at his weight of 54 kg, with 2 mg midazolam, 20 μg sufentanil, 80 mg propofol, and 50 mg rocuronium, followed by a pumping infusion rate of 20 μg/h remifentanil and 220 mg/h propofol, as well as intermittent injections of 10 mg/30 min rocuronium. A rigid bronchoscope (RB) was inserted to examine the tracheal status, including the fistula and the stent, confirming that the fistula was in the upper membranous tracheal wall (**Figure 1**). The metal stent beneath the fistula had undergone deformity, and the trachea beneath the fistula was constricted (**Figure 1**). The endoscopist attempted to adjust the stent but failed, considering that the deformed stent might not be large enough to secure the fistula and expand the constricted part. Replacement with a larger covered self-expanding metal stent was justified.

High-flow oxygen (20 L/min) *via* the side port of the RB was used to counteract the leak; however, in less than 5 min, SpO_2 deteriorated to 85%. Thus, RB was removed, and mask oxygenation was implemented to regain satisfactory oxygenation repeatedly until the entire stent was retracted by gentle extraction and twisting with biopsy forceps. As shown in the RB examination, the fistula lesion located in the upper membranous tracheal wall (approximately 2 cm beneath the glottis) precluded ET ventilation-assisted stent placement. Thus, we developed the idea of tubeless ventilation that we called SJOV (**Figure 2**). A nasopharyngeal airway (NPA) was inserted into the right nostril, with one of its catheters connected to a manual jet ventilator for oxygenation and ventilation, and the other was connected to an anesthesia machine for monitoring end-tidal carbon dioxide ($ETCO_2$). The inserted length was the alae of the nose and the earlobe on the same side that was comparable to the length of the nostril to the retropharyngeal space. To ensure that the NPA was above the glottis, we used a video laryngoscope for adjustment. Ventilation was performed manually by an assistant anesthesiologist. Effective ventilation manifested as symmetrical chest rises and falls, clear breath sounds and no gurgling from the stomach. Oxygenation was well-maintained throughout the procedure with stable vital signs, and sufficient space was created for stent deployment guided by flexible bronchoscope (FB). A covered metal stent (18 × 60 mm) was successfully placed to mend the tracheal fistula and expand the constricted trachea (**Figure 3**). At the end of the procedure, arterial blood gas analysis showed acceptable ventilation efficacy (pH, 7.35; $PaCO_2$: 47.9 mmHg). The patient was transferred to the post-anesthesia care unit after recovery of consciousness and regular spontaneous breathing.

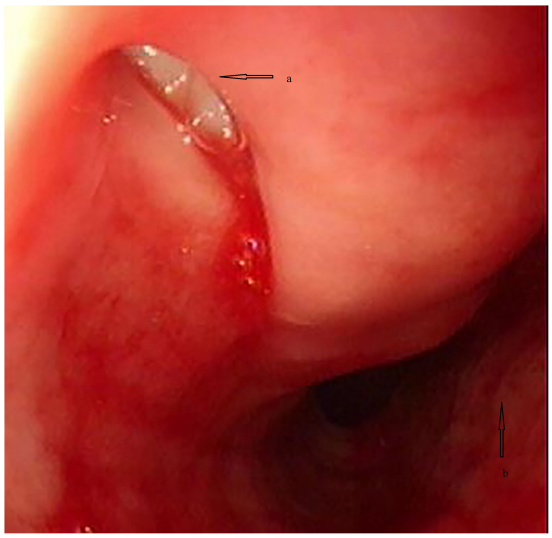

FIGURE 1
The pathological anatomy view of the trachea under bronchoscopy. **(a)** Fistula in the upper membranous wall; **(b)** the constricted trachea.

Discussion

This case describes a complicated ventilation strategy for stent treatment in a patient with iatrogenic TEF. Although stenting has been gaining popularity because it is less invasive, no consensus has been reached regarding TEF treatment. Considering the failed stent deployment and the medical history of the patient, the team placed it in high priority.

Aside from the constricted trachea, the previously stranded stent could have been incorporated into the mucosa and the granulation tissue originated from the tracheostomy (1), making it refractory to adjustment. During RB examination and stent retraction, desaturation occurred due to insufficient ventilation through the side port. High-flow oxygen ventilation could have been less compromised if no fistula in the trachea or oropharynx had been packed with gauze (6); or if the oxygen flow rate could be even higher (70 L/min) *via* a special ventilator like Optiflow® (7), we might not have to do mask ventilation repeatedly. However, the dilemma lies in further injury due to the fistula with a less open airway system. Alternatively, if a much shorter time was needed by the endoscopist, we would have been able to tolerate the temporary hypoxia, but this was challenging, considering the cardiac surgery and stroke history of the patient. We thought that spontaneous breathing could have been maintained during RB examination, but with or without muscle relaxants in therapeutic RB showed no difference in safety parameters (including hypoxemia, respiratory failure, mortality et al.) (8); besides, a motionless state and still operating fields were more

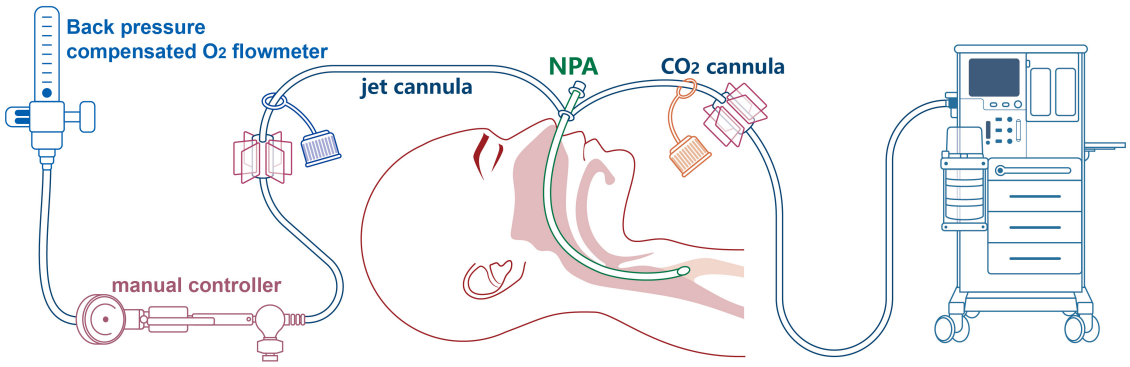

FIGURE 2
Pattern diagram of supraglottic jet oxygenation and ventilation (SJOV) *via* nasopharyngeal airway (NPA).

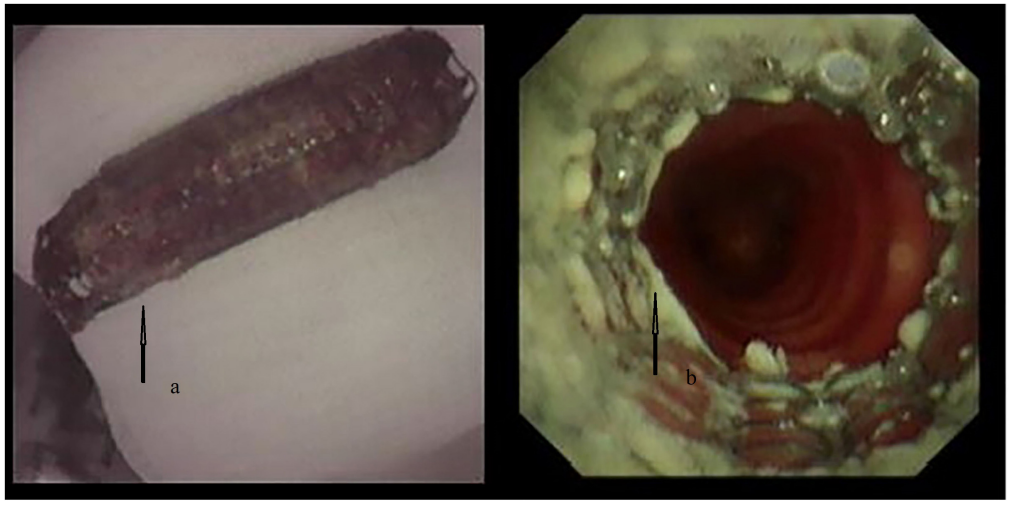

FIGURE 3
The deformed stent **(a)** and the covered metal stent mended the fistula and expanded the constricted trachea **(b)**.

favorable to the endoscopist, which could be achieved with muscle relaxant; further, ventilation asynchrony could be saved with muscle relaxants. Total intravenous anesthesia was preferable in this case, as it had no leak compared to inhalation anesthesia.

Other ventilation strategies could have been applied during stent placement, including a de-cuffed modified ET, i-gel laryngeal mask airway (i-gel LMA), or classic laryngeal mask airway (LMA) ventilation with FB guidance (9, 10). ET was not suitable for this complicated stent deployment as was stated before. I-gel LMA could be an option with enough space left for stent placement, though, we were not equipped with. We could have achieved a successful ventilation with classic LMA along with FB with a working channel that allows the guidewire insertion. However, the working channel of FB will not allow passage of self-expanded metal stent. Sufficient space would likely to be created if a smaller tube passed through the glottis, which had been introduced in FB-assisted stenting by high-frequency jet ventilation (HFJV) with a 14F nylon insufflation catheter placed in the trachea (11). However, HFJV would be a hindrance to the endoscopist because the airway would be shared, and the procedure could misplace the ventilation tube. It could also be a risk factor for barotrauma in narrowing airway systems (12). With limited resources, therapeutic demands, and our concerns regarding the operational convenience, the hypoxia intolerance and airway protection, we believe that SJOV should be the most suitable.

Oxygenation was well-maintained throughout the manual SJOV without interfering with the procedure. However, this was not the case for $ETCO_2$, although the CO_2 monitoring catheter is valuable in fast procedures with fewer secretions (13), which was quite the opposite in our case. We were supposed to have transcutaneous capnography ready for this demanding non-invasive ventilation (NIV), which has been proven to be the best way to monitor NIV efficacy (14). Instead, we collaborated with the endoscopist by manual ventilation during SJOV, in which we could adjust from a larger tidal volume and higher frequency to asphyxia ventilation and cleared the secretions if necessary.

When SJOV was used in emergent situations with full stomach, the potential risks of aspiration increase significantly due to gastric distension resulted from possible air influx into the stomach and insufficient fasting time; on the other hand, however, the open airway system during SJOV also allows continuous forceful air outflows from the lungs which can be served as an aspiration preventive valve (15). Measures should be taken to prevent aspiration from happening: preoperative gastric tube insertion is still recommended; rapid sequence induction and proper Sellick's maneuver with the

patient in a 40° head-up position would be favorable (16); limited data (15, 17) showed that lowering the head position and setting mechanical ventilation frequency of over 80 per min or manual ventilation frequency of 20 per min with I:E ratio of 1:2 may prevent aspiration.

This is the first case report of SJOV in stent placement so far. It was less traumatic compared to conventional ET ventilation. Although, there are some limitations. First, $ETCO_2$ monitoring was not applicable during the procedure, because CO_2 sampling tube was easily clogged. Respiratory monitoring relied more on the observation of the chest movement and SpO_2. Second, SJOV would have put the patient at the risk of aspiration if no gastric tube had been inserted.

Our strategy in this case was successful, proving that SJOV as an alternate ventilation strategy in stent placement is feasible and that communication with endoscopists is essential, especially when routine measures are inappropriate.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

YG and XZ contributed equally to the drafting and revision of the manuscript. KM, JW, and QZ revised the manuscript. RD and XL analyzed and interpreted the patient data, reviewed the literature, and revised the manuscript. All authors have approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Monitoring the patient–ventilator asynchrony during non-invasive ventilation

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Patient–ventilator asynchrony is a major issue during non-invasive ventilation and may lead to discomfort and treatment failure. Therefore, the identification and prompt management of asynchronies are of paramount importance during non-invasive ventilation (NIV), in both pediatric and adult populations. In this review, we first define the different forms of asynchronies, their classification, and the method of quantification. We, therefore, describe the technique to properly detect patient–ventilator asynchronies during NIV in pediatric and adult patients with acute respiratory failure, separately. Then, we describe the actions that can be implemented in an attempt to reduce the occurrence of asynchronies, including the use of non-conventional modes of ventilation. In the end, we analyzed what the literature reports on the impact of asynchronies on the clinical outcomes of infants, children, and adults.

KEYWORDS

non-invasive ventilation, patient–ventilator asynchrony, ventilator waveforms, diaphragm electrical activity, pressure support ventilation (PSV), neurally adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV)

Introduction

Patients with Acute Respiratory Failure (ARF) may benefit from different oxygenation or ventilation supports (1, 2). In patients affected with moderate to severe forms of ARF, including cardiogenic pulmonary edema and acute-on-chronic respiratory failure, non-invasive ventilation (NIV) plays a major role (1). However, NIV is affected by a certain percentage of treatment failure, requiring mostly orotracheal intubation and institution of invasive mechanical ventilation (3).

Behind the type and severity of ARF, worsening of gas change, respiratory distress, hemodynamic instability, or neurological deterioration, NIV may also fail because of the patient's intolerance to the treatment (3, 4). Among the reasons for treatment intolerance, there is a type of interface applied to the patient, the presence of massive air leaks, and the occurrence of patient–ventilator asynchronies (5).

Patient–ventilator asynchrony is still a major issue during NIV in neonatal, pediatric, and adult patients. In particular, patient–ventilator asynchrony significantly contributes to increasing the work of breathing (6, 7), as well as generating discomfort (8, 9). Although mechanisms behind these phenomena are well described (10–13), the impact of patient–ventilator asynchronies on clinical outcomes is still debated.

After defining the varying types of asynchronies, we aim to review the literature of the last 30 years about patient–ventilator asynchronies occurring during NIV in neonatal, pediatric, and adult patients with ARF. We aim to focus on the quantification, detection, management, and impact of asynchronies on the clinical outcomes of patients undergoing NIV.

Materials and methods

Search strategy for studies selection

The following search strategy was launched in PubMed on 10th November: ((“1992”[Date – Publication]: “2022”[Date – Publication]) AND (“patient–ventilator asynchrony” OR “patient–ventilator interaction” OR “ineffective effort” OR “wasted effort” OR “autotriggering” OR “auto-triggering” OR “double triggering” OR “premature cycling” OR “delayed cycling”)).

After retrieving all references in the published reviews to identify other studies of interest missed during the primary search, two authors independently checked all the articles and selected those enrolling neonatal, pediatric, and adult patients with ARF undergoing NIV, published between 1 January 1992 and 1 November 2022 in the English language. In case of disagreement, the expert opinion of a third examiner was requested for a conclusive decision. Case reports, review articles, editorials, and studies available only in abstract forms were excluded (**Figure 1**). Of the 585 searched records, 45 studies were included in the manuscript and their references were retrieved for further titles.

Definitions

Asynchronous events are the lack of coordination between the respiratory activity of the patient and the mechanical assistance of the ventilator. During NIV, patient–ventilator asynchronies have been classified as (1) major (ineffective triggering, auto-triggering, and double-triggering) and (2) minor (premature or anticipated cycling, prolonged or delayed cycling, and triggering delay), depending on the extent of the disturbance of coordination (14). An example of each type of asynchrony is depicted in **Figure 2**.

Ineffective triggering, also known as ineffective or wasted efforts, is defined by a patient’s inspiratory effort not assisted by the ventilator. This asynchrony may appear during both the expiratory phase of the ventilator and the inspiratory ventilatory assistance. The possible underlying mechanisms are recognized to be weak respiratory drive and/or effort, a high intrinsic positive end-expiratory pressure (PEEPi), and an excessively low ventilator trigger sensitivity (13, 15–18).

Auto-triggering consists of a mechanical insufflation not triggered by any inspiratory effort of the patient. This type of asynchrony is commonly triggered by disturbances in airway pressure and/or flow or by air leaks, which are wrongly sensed as triggering efforts (15, 19). Therefore, their occurrence depends primarily on trigger type, sensitivity, and the ability of the ventilator to compensate for air leaks (20).

Double-triggering is characterized by one single patient inspiration supported by two mechanical cycles separated by a very short expiratory time (<30% of the mean inspiratory time) (15). The interruption of the mechanical insufflation before the completion of the patient’s effort generates a second triggered mechanical insufflation, after a brief exhalation phase (8, 15).

Premature cycling is a form of patient–ventilator asynchrony characterized by an interruption of the ventilator insufflation anticipating the patient’s effort termination; whereas, in the case of delayed cycling, the mechanical assistance is longer than the patient’s effort and it extends into the patient’s own (neural) expiration. Premature cycling is more frequent in patients with Acute Respiratory Distress Syndrome (ARDS) (21, 22) and it may result in double triggering (23), whereas delayed cycling occurs more frequently in obstructive conditions (16). During NIV, delayed cycling is most commonly induced by air leaks which prevent the achievement of the expiratory trigger threshold and insufflation cycling-off (24).

Detection of asynchronies

The rate of asynchrony is commonly measured by the Asynchrony Index (AI%), defined by the ratio between asynchronous breaths and the overall breath count, that is, the sum of ventilator cycles and non-triggered breaths expressed as a percentage (25). In patients undergoing invasive mechanical ventilation, an AI% of ≥10 is associated with worsened clinical outcomes (15, 25, 26). On the opposite, AI% values of ≥10 in patients undergoing NIV are associated with poorer comfort reported by the patients, but not with intubation rate, length of stay in ICU, or mortality (8). Therefore, whenever the AI% value is ≥10, the physician should implement actions to reduce the rate of asynchronous events (refer to the following text).

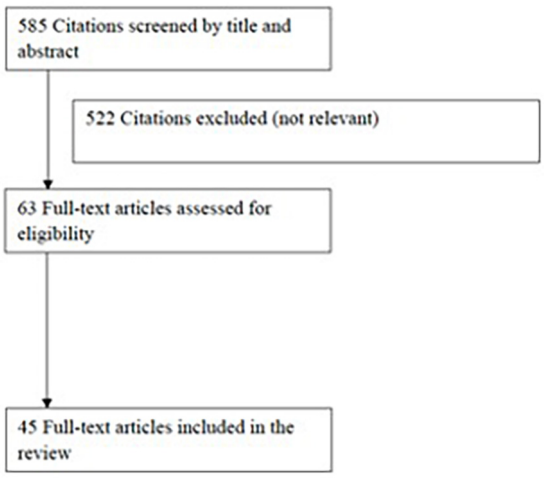

FIGURE 1
Study flow diagram according to the preferred reporting items for systematic review and meta-analysis protocols recommendations.

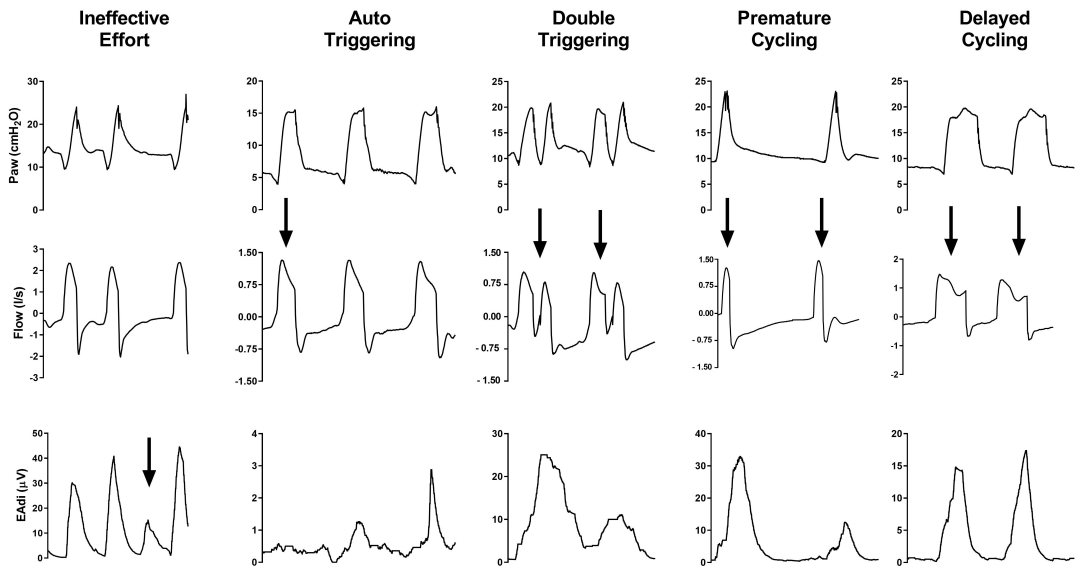

FIGURE 2
From top to bottom, waveforms of airway pressure (Paw), flow, and electrical activity of the diaphragm (EAdi) are depicted for each type of patient–ventilator asynchronies. Arrows highlight the asynchronous events.

Sinderby et al. also proposed an automated and standardized method to quantify asynchronies, the so-called NeuroSync Index (27). This index is based on the assessment and monitoring of the Electrical Activity of the Diaphragm (EAdi), which requires a dedicated catheter connected to a specific ventilator to acquire the diaphragmatic signal, and an off-line analysis of the ventilator waveforms to address the rate of asynchronies. The NeuroSync Index was shown to be reproducible and correlated with a manual analysis by experts (27).

Neonatal and pediatric patients

When high-flow oxygen therapy fails, NIV is considered the gold standard treatment in newborns, infants, and pediatric patients affected by ARF (28–30). Patient–ventilator asynchrony is a major challenge in non-adult patients and it is commonly evaluated with the adjunctive EAdi signal, to monitor the diaphragmatic signal and respiratory effort (10, 11, 31). In 35 newborns and children undergoing NIV in Pressure Support Ventilation (PSV) mode, Vignaux et al. reported that the median AI% was 65 (32). Ineffective efforts, auto-triggering, and premature cycling were the most common types of asynchrony. The authors also reported that, after adjusting and optimizing the ventilator settings, the median AI% significantly decreased to 40 (32). Extremely premature infants undergoing conventional modes of NIV can be characterized by even higher median AI% up to 86%, as recently reported (33). In the pediatric population, it has been demonstrated that the use of adjunctive signals, such as the EAdi, improves the ability of pediatric intensivists to detect ineffective efforts and auto-triggering (34).

Adult patients

In adult patients, patient–ventilator asynchronies have been evaluated with several methods, such as the observation of waveforms on the ventilator screen (14), dedicated algorithms (35), or additional signals (i.e., EAdi, esophageal, or transdiaphragmatic pressure) (36, 37).

Visual inspection of ventilator waveforms is the most common method adopted in routine clinical practice. In fact, this method does not need any placement of additional catheters, which can be considered difficult to be positioned and a source of further discomfort for the patient and air leaks. However, a multicenter study showed a very low sensitivity by expert and non-expert physicians in detecting asynchronies during NIV through a helmet or face mask by the sole ventilator waveform inspection (14). Worth remarking, the rate of correct detection was inversely related to the prevalence of asynchronies (14).

Mulqueeny et al. developed an automated algorithm to detect ineffective efforts, such as expiratory flow perturbation without any ventilatory support, and double-triggering, as two mechanical ventilatory inspiratory cycles separated by less than 500 ms (35). In 10 patients undergoing NIV in PSV mode, this algorithm showed a specificity of 95.1% in the detection of asynchronies. However, this algorithm has the inner limitation to detect only ineffective efforts during expiration and double triggerings (35).

The NeuroSync Index, proposed by Sinderby et al. (27), is another automated algorithm tested during NIV in 12 patients with acute-on-chronic respiratory failure (38). NeuroSync Index ensured a proper detection of wasted efforts, triggered delays, and cycling-off errors during PSV delivered by a dedicated NIV ventilator or an ICU ventilator equipped with software for air-leaks compensation, and by non-invasive Neurally Adjusted Ventilatory Assist (NAVA) (38).

As mentioned earlier, this algorithm requires the positioning of an EAdi catheter, which somehow increases costs and the use of a dedicated ventilator equipped for EAdi monitoring and NAVA ventilation. Therefore, this system has inner limitations which restrict its application in all centers.

More recently, the application of diaphragmatic ultrasonography has been proposed to recognize patient–ventilator asynchronies during invasive mechanical ventilation (39). This technique has

also been tested in healthy volunteers undergoing NIV with induced asynchronies (40). This method comprises monitoring the diaphragm dome excursion or its thickening in the apposition zone, to define the presence of the patient's respiratory effort (40). Diaphragm ultrasonographic imaging was then in real-time coupled with the ventilator waveforms to recognize and accurately identify asynchronies (40). To note, despite diaphragm ultrasonography could be considered an "easy to learn technique" (41), the need to visualize the airway pressure curve on the ultrasound machine screen limits its use in daily clinical practice (40). That said, whenever the ventilator waveforms will be screened on the ultrasound machines, this technique may potentially have a major role in the future to assess patient–ventilator synchrony.

Finally, Electrical Impedance Tomography, a tool for bedside functional imaging of the lung, has been applied in ARDS porcine model to study the "pendelluft" phenomenon in case of asynchronies with the ventilator (42). Besides this recent and experimental use, no studies have so far evaluated the aeration or lung ventilation distribution in patients undergoing invasive mechanical ventilation or NIV with severe patient–ventilator asynchronies.

Management of asynchronies

Neonatal and pediatric patients

In neonatal and pediatric patients, the management of patient–ventilator asynchrony is of paramount importance. Since non-adult patients have a respiratory rate of up to 50 breaths/min, an optimal patient–ventilator synchronization could better unload the diaphragm (32, 43, 44).

In the case of patient–ventilator asynchronies, the physician should first assess the ventilator settings and the applied interface. In fact, by adjusting the expiratory trigger settings during PSV, patient–ventilator synchrony improves (32). In addition, the presence of considerable unintentional air leaks also affects patient–ventilator synchrony. Therefore, a change in the type of interface or adjustment of its position should be considered (45). However, if these actions fail to reduce asynchronies, non-conventional modes of ventilation can be considered. NAVA is a non-conventional mode of ventilation driven by the EAdi signal that delivers inspiratory assistance proportionally to EAdi, which is the closest recordable signal of the patient's central respiratory drive (31). In particular, non-invasive NAVA was shown to guarantee optimal synchronization despite large air leaks or weak respiratory efforts (32, 46, 47).

Adult patients

Unintentional air leaks are the most important source of asynchrony during NIV in adults (8, 24). The presence of massive air leaks may generate a particular condition called "flow asynchrony". In fact, flow asynchrony is defined as a ventilator flow output not coinciding with the patient's inspiratory flow demand (48). In intubated patients, flow asynchrony increases the work of breathing (49) and dyspnea (50). To contain the occurrence of flow asynchrony, it is essential to optimize the flow delivery by adjusting the rise time, to apply NIV with a dedicated ventilator equipped with air leaks compensating software, and to reduce intentional and un-intentional leaks (3, 51, 52).

Therefore, the choice of a proper interface, the adjustment of ventilator mode and settings, and the use of ventilators with air-leaks compensating software can reduce the occurrence of patient–ventilator asynchronies, including flow asynchrony (10, 11).

The choice of the NIV interface and assessment of its positioning should be one of the first actions to implement in the case of patient–ventilator asynchrony (3). When NIV is delivered through masks or mouthpieces, the amount of air leaks is substantially different, and the higher the leaks, the higher the rate of asynchronies (53). As compared to invasive mechanical ventilation, both the mask and helmet as NIV interfaces increase the occurrence of asynchronies (54). Several studies have reported that the helmet generates a higher rate of asynchrony, compared to the mask (54, 55). Since the helmet has inner drawbacks related to the high inner volume and upward displacement during ventilator insufflation, a new generation of the helmet has been developed to improve the pressurization and patient–ventilator interaction (56, 57). As compared to the conventional helmet, the new one reduces the inspiratory trigger delay, increases the time of synchrony between diaphragm activity and ventilator assistance, and overall improves comfort (58). However, the recorded asynchronous events are similar between interfaces (58). Physicians should also minimize the number of air leaks because these events caused discomfort by themselves and are associated with asynchronous events (8).

The adjustment of ventilator settings and mode is another variable that could be corrected in case of patient–ventilator asynchrony during NIV. Among settings to be checked, a too-high inspiratory pressure is associated with AI% $>10\%$ (8). Furthermore, the cycling-off criterion should also be addressed and set with an individualized approach, to optimize synchronization with the ventilator and to avoid the "hung-up" phenomenon (24, 59).

In addition, the use of proportional modes of ventilation should also be considered, such as Proportional Assist Ventilation (PAV) or NAVA. PAV was shown to be comfortable and tolerated in patients with moderate ARF (60, 61), which may be in part attributable to synchrony. Another study has recently compared PAV with PSV in 15 patients with exacerbated COPD (62). PAV did not improve patient–ventilator interaction; in addition, the use of PAV+, a development of PAV, induced the runaway phenomenon (62), which may contribute to asynchrony (63). Indeed, PAV + requires a closed system without air leaks, making this mode no longer used during NIV (63).

In particular, while PAV requires that the physician set the assistance parameters (i.e., flow and volume assist) based on the respiratory mechanics of the patient, PAV+ has implemented software that continuously monitors the patient demand by measuring flow and volume every 5 msec during and by implementing short end-inspiratory occlusions. The physicians are asked to set only load-adjustable gain factors, and the ventilator would proportionally deliver inspiratory support based on the equation of motion of the respiratory system (64). Therefore, while air leaks would not impair the functioning of the former PAV mode, PAV+ requires a closed system to assess the flow and volume and to perform end-inspiratory occlusions (64).

On the contrary, several studies have investigated and proved that NAVA can efficiently optimize patient–ventilator synchrony during NIV delivered either by helmet (36) or by mask (65–67). More recently, a specific setting of NAVA (defined as Neurally Controlled Pressure Support) has been described during NIV through helmet

(68, 69) and mask (70). Neurally Controlled Pressure Support significantly improved patient–ventilator interaction and synchrony, compared to PSV.

Third, the use of ventilators equipped with software capable to detect and compensate for air leaks significantly improves patient–ventilator interaction and synchrony (51, 71). Of note, Carteaux et al. did not confirm that the presence of NIV software reduced the occurrence of asynchronous events in ICU ventilators; however, the use of dedicated NIV machines significantly improved patient–ventilator synchrony (72).

Impact of asynchronies on the patients' outcomes

Neonatal and pediatric patients

In an attempt to mitigate the possible effects of patient–ventilator asynchronies on clinical outcomes in neonatal and pediatric patients, several studies have compared NAVA with conventional modes of ventilation during NIV.

In a randomized crossover trial, Lee et al. randomized 15 preterm infants to receive NIV in NAVA and PSV modes (73). The authors reported that NAVA reduced the work of breathing and improved patient–ventilator synchrony, as compared to the conventional mode of NIV, even in the presence of large air leaks (73). In keeping with Lee et al. (73), Gibu et al. included eight preterm infants to receive NIV in NAVA or PSV modes (74). Infants appeared to be more comfortable during NAVA, as compared to conventional modes. However, no other clinical outcomes have been reported by both studies (73, 74). A recent systematic review with meta-analysis showed that NAVA and conventional modes of ventilation are characterized by similar NIV failure rates, but it could not determine if NAVA would prevent the worsening of respiratory failure (75). One recent randomized controlled trial has reported that NAVA ameliorated patient–ventilator synchrony; however, no differences were recorded with respect to vital parameters (i.e., heart rate and respiratory rate), comfort, apneic events or desaturations, and bradycardias (33). Another recent randomized controlled trial showed that NIV in NAVA modes reduced the occurrence of post-extubation respiratory failure in preterm infants, as compared to Continuous Positive Airway Pressure (CPAP) (76). It should be noted that CPAP does not require interaction with inspiratory pressurization of a ventilator, and this result cannot be associated with a reduction of asynchronies rate.

A physiologic crossover study demonstrated that NAVA reduces the asynchronies rate with the ventilator, and also in infants, it is a feasible and safe mode for NIV and well-tolerated by the patients (77).

In a randomized crossover study, 18 children with mild ARF received NIV in NAVA or PSV modality. The study demonstrated that NAVA is a feasible and safe mode of NIV and it reduces the occurrence of asynchronies; however, given the study design, no data are available on major clinical outcomes (78).

In addition to the large amount of data suggesting that NAVA improves patient–ventilator interaction and some minor physiological outcomes, no randomized controlled trials have so far investigated the impact of patient–ventilator asynchronies on major clinical outcomes, such as the duration of mechanical ventilation, ICU, or hospital lengths of stays and mortalities in the pediatric patients.

Adult patients

As mentioned earlier, the presence of patient–ventilator asynchronies may impair the tolerance and comfort of the patient to NIV, leading to treatment failure (3, 4, 8, 9).

AI% values of $\geq$ 10% significantly reduce the comfort and NIV tolerance in 60 patients who are critically ill (8) and another population including 69 acute patients undergoing NIV through oral-nasal masks (79). Proportional modes of ventilation such as NAVA have been also investigated in this regard and shown to reduce the occurrence of asynchronies (80). In a study by Schmidt et al., NAVA and PSV were compared with a cross-over design, also combining the presence or not of software for air-leaks compensation. Although NAVA improved patient–ventilator interaction and synchrony, comfort was not different between modes of ventilation (66). On the contrary, Neurally Controlled Pressure Support was demonstrated to enhance the pressurization and triggering performance, while guarantying optimal patient–ventilator synchrony during NIV through helmet (68, 69) and mask (70). In these settings, Neurally Controlled Pressure Support improved patients' comfort with NIV (68–70).

Behind comfort improvement, no differences in mortality rate or ICU length of stay were detected between patients with or without an AI% value of $\geq$10% by Vignaux et al. (8). Another observational study has recently compared a cohort of 91 patients undergoing NIV in NAVA mode, with a historically and concurrently matched cohort of (134 and 202) patients undergoing NIV in PSV (81). After adjustment for confounders, NAVA did not improve the intubation rate, duration of NIV, and 90-day mortality, as compared to PSV (81). In the NAVA-NICE trial, 40 patients with acute exacerbated chronic obstructive pulmonary disease (COPD) were randomized to receive NIV through a mask in NAVA or PSV modes (82). Although reducing asynchronies, NAVA did not reduce the NIV failure rate, duration of NIV, or hospital mortality (82). Very recently, a large randomized controlled trial compared PSV and NAVA during NIV in a population of 100 patients with *de novo* ARF (83). In the overall population, this study did not demonstrate any difference in terms of NIV failure rates (30% vs. 32%, $p = 0.83$) and 28-day mortality rate (18% vs. 34%, $p = 0.07$) between NAVA and PSV, respectively (83). However, in the subpopulation of patients with exacerbated COPD, NAVA improved the 28-day survival rate, as compared to PSV (83). Worth mentioning, in patients with mild-to-moderate exacerbated COPD, if NIV is no more tolerated, a high-flow nasal cannula could be applied to avoid intubation, in the absence of further gas exchange worsening or respiratory distress (2, 84, 85).

It should be finally mentioned that NAVA can assure optimal patient–ventilator interaction and synchrony since the respiratory effort of the patient directly and proportionally triggers and leads the ventilator inspiratory support. Of note, NAVA requires an adjunctive cost for the dedicated catheter and proper training of physicians (31). To date, the extensive use of NAVA in all patients is not supported by the actual evidence of literature; however, well-defined patients may benefit from NIV through NAVA.

Conclusion

Patient–ventilator asynchronies are common in both pediatric and adult patients during NIV. The detection of asynchronous events

(even with adjunctive signals or automated software) is fundamental to implementing changes in ventilator settings and reducing their occurrence. Although high rates of asynchrony may affect the comfort of the patient and the success of the treatment, it remains to be demonstrated if patient–ventilator asynchronies may determine a worsened clinical outcome in patients undergoing NIV.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FL, AB, EG, PN, ED, and GC provided substantial contributions to the conception and design of the work. AB, EG, ST, and LV participated in the acquisition, analysis, or interpretation of data for the work. All authors participated in drafting the work, whereas FL and GC further revised it critically for important intellectual content. All authors provided approval for publication of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Epidemiological profile and risk factors associated with death in patients receiving invasive mechanical ventilation in an adult intensive care unit from Brazil: a retrospective study

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Introduction: Understanding the epidemiological profile and risk factors associated with invasive mechanical ventilation (IMV) is essential to manage the patients better and to improve health services. Therefore, our objective was to describe the epidemiological profile of adult patients in intensive care that required IMV in-hospital treatment. Also, to evaluate the risks associated with death and the influence of positive end-expiratory pressure (PEEP) and arterial oxygen pressure (PaO_2) at admission in the clinical outcome.

Methods: We conducted an epidemiological study analyzing medical records of inpatients who received IMV from January 2016 to December 2019 prior to the Coronavirus Disease (COVID)-19 pandemic in Brazil. We considered the following characteristics in the statistical analysis: demographic data, diagnostic hypothesis, hospitalization data, and PEEP and PaO_2 during IMV. We associated the patients' features with the risk of death using a multivariate binary logistic regression analysis. We adopted an alpha error of 0.05.

Results: We analyzed 1,443 medical records; out of those, 570 (39.5%) recorded the patients' deaths. The binary logistic regression was significant in predicting the patients' risk of death [$X^2_{(9)}$=288.335; p<0.001]. Among predictors, the most significant in relation to death risk were: age [elderly ≥65years old; OR=2.226 (95%CI=1.728–2.867)]; male sex (OR=0.754; 95%CI=0.593–0.959); sepsis diagnosis (OR=1.961; 95%CI=1.481–2.595); need for elective surgery (OR=0.469; 95%CI=0.362–0.608); the presence of cerebrovascular accident (OR=2.304; 95%CI=1.502–3.534); time of hospital care (OR=0.946; 95%CI=0.935–0.956); hypoxemia at admission (OR=1.635; 95%CI=1.024–2.611), and PEEP >8 cmH_2O at admission (OR=2.153; 95%CI=1.426–3.250).

Conclusion: The death rate of the studied intensive care unit was equivalent to that of other similar units. Regarding risk predictors, several demographic and clinical characteristics were associated with enhanced mortality in intensive care unit patients under mechanical ventilation, such as diabetes mellitus, systemic arterial hypertension, and older age. The PEEP >8 cmH_2O at admission was also associated with increased mortality since this value is a marker of initially severe hypoxia.

KEYWORDS

epidemiological profile, intensive care unit, mechanical ventilation, positive end-expiratory pressure, SARS-CoV-2

1. Introduction

The intensive care unit (ICU) provides advanced life support to critical patients presenting different severity levels (1). It is, therefore, a specialized facility to monitor and stabilize the patients' clinical aspects (2). In such a context, critical patients admitted to an ICU might require the use of invasive mechanical ventilation (IMV) to maintain patent airways, improve oxygenation, and prevent aspiration (3, 4). IMV is a complex resource, and the team's expertise in managing it might generate better results. However, around 38% of the patients that require IMV still die (5). For this reason, knowing the factors that lead to the outcomes of patients under IMV in the ICU is vital to inform the professionals' conduct better and advise their families (6). Understanding the profile of patients under IMV might lead to decisions such as getting access to technologies, training human resources, and reevaluating care processes, which could allow the structural adjustment of the unit according to the demographic and morbidity characteristics of the population-assisted (7).

Since the appearance of the ICU in 1952, due to the devasting polio epidemic in Copenhagen, the mortality of patients that required care in such units has decreased (8, 9). However, we can consider some factors as death risks, such as male sex, age (elderly), presence of comorbidities (e.g., systemic arterial hypertension, diabetes mellitus, and obesity), and admission diagnosis (e.g., traumatic brain lesion, sepsis, and neurological disorders). Also, it is essential to evaluate the ventilatory parameters at admission, including the positive end-expiratory pressure (PEEP) value, which influences the dissolved oxygen partial pressure in arterial blood (PaO_2) (10–15).

Regarding ventilatory parameters at admission, the health professionals employed different strategies. However, the literature recommends using protective parameters (low current volumes along with driving pressure and mechanical power limitation) (3, 16, 17). The health professionals used the PEEP to improve oxygenation and stabilize alveolar units when considering ventilatory parameters. Besides that, the PEEP ideal value is still controversial in the scientific literature (18, 19). However, some reports suggest that PEEP ideal values might prevent pulmonary lesions due to the cyclic opening and closing of alveoli. Also, higher values can cause lesions due to alveolar hyperdistention (20).

Some studies considered using 8 cmH_2O initial PEEP as prophylactic PEEP as a preventive and compensatory value of the functional residual capacity resulting from orotracheal intubation (21). However, when health professionals applied this value to normal lungs, there was no description of improvement in the outcome or time of hospital stay in the scientific literature yet (20, 22). Therefore, according to individual ventilatory mechanics, we must make the best PEEP choice (23). At the same time, PaO_2 characterizes the degree of hypoxemia and hyperoxemia (24). Both might influence the clinical outcome and length of hospital stay since hypoxemia reduces oxygen supply to tissues. Its cause might have different origins: unbalance in the ventilation/perfusion rate, pulmonary shunt, and hypoventilation. Hyperoxemia, in turn, might cause non-cardiogenic pulmonary edema, formation of hyaline membrane, neutrophilic infiltration, type I pneumocyte damage, type II pneumocyte hyperplasia, alveolar hemorrhage, and an increase in the alveolar sept thickness (25, 26).

This study aimed to describe the epidemiological profile of adult patients admitted to the ICU and receiving IMV at a University Hospital and evaluate the characteristics of the population investigated as risk factors for death and the influence of PEEP and PaO_2 at admission on the clinical outcome.

2. Methods

We carried out an epidemiological study of electronic medical records described in the Philips Tasy® system (Philips Healthcare™), Barueri, São Paulo, Brazil, which records the diagnosis, laboratory data, monitoring of ventilatory support, and clinical evolution of inpatients who required IMV. The patients were included from January 2016 to December 2019. They were assisted at the University Hospital São Francisco de Assis na Providência de Deus ICU, located in Bragança Paulista, São Paulo, Brazil. The ICU has 20 beds for treating critical patients from 15 years old (yo) onwards. The time-period was selected to avoid the Coronavirus Disease (COVID)-19 impact on our data because our University Hospital was a referral center to treat severe cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

The patients' characteristics considered in our epidemiological study were: (i) age [years and grouped as adult (18–64 yo) or elderly (>65 yo)], (ii) sex (male and female), (iii) body mass index (BMI) [Kg/m^2; underweight (<18.5 Kg/m^2), normal weight (18.5–24.9 Kg/m^2), overweight (25–29.9 Kg/m^2), grade I obesity (30–34.9 Kg/m^2), grade II obesity (35–39.9 Kg/m^2), and grade III obesity (>40 Kg/m^2)], (iv) diagnostic (traumatic brain injury, polytraumas, sepsis, elective surgery, acute myocardial infarction, stroke, dyslipidemia, subarachnoid hemorrhage, neuromuscular disease, smoking habits, and others); (v) patient origin from clinics or surgery; (vi) previous history of comorbidities (smoking, alcoholism, cardiopathy, pneumopathy, neurologic sequelae, use of drugs, systemic arterial hypertension, diabetes mellitus, dyslipidemia, and others); (vii) PEEP values at admission in the ICU and during IMV (absolute value and the categorization using the 8 cmH_2O points as parameter); (viii) PaO_2 values at admission in the ICU and during IMV [absolute value and the categorization using the following distribution: hypoxia (<80 mmHg), normal (between 80 and 100 mmHg), and hyperoxia (>100 mmHg)]; (ix) length of hospital stay; (x) length of IMV; (xi) presence of ventilation-associated pneumonia; (xii) presence of tracheostomy during hospital stay; and (xiii) outcome (discharge–clinical recovery and death).

Importantly, the protocol used in the admission of patients under mechanical ventilation in the ICU of this study indicates the use of PEEP at levels described in the literature as safe (from 5 to 8 cmH_2O).

Given the need to use higher values, PEEP is titrated according to respiratory mechanics, hemodynamics, and oxygenation indexes. The main purpose of PEEP titration is to maintain alveolar stability and oxygenation at normal levels, that is, to maintain PaO_2 between 80 and 100 mmHg and peripheral capillary oxygen saturation between 92 and 96%. The tidal volume adopted at the admission of patients was 6 mL/Kg of predicted weight, following the literature recommendations (27).

We performed the descriptive analysis using two approaches. (i) categorical markers–N (%): sample size (percentage); and (ii) numeric markers – mean (standard deviation) and a 95% confidence interval (95%CI) of the mean or median, according to the data distribution, parametric or non-parametric, respectively. We evaluated the normality of the numeric data employing the following three methods: (i) analysis of descriptive measures for central tendency; (ii) plot methods (normal Q-Q plot, trendless Q-Q plot, and boxplot); and (iii) statistical tests (normality tests): Kolmorov-Smirnov test and Shapiro–Wilk test.

The presence of death (categorical data) was associated with the values of the markers with numerical distribution by using the T-test or the Mann–Whitney test. Concomitantly, we associated the death to features with categorical distribution using Fisher's Exact test or Qui-square test; also, we calculated the relative risk (RR) and the 95%CI for the categorical data. We evaluated Pearson's correlation coefficient between PaO_2 and PEEP levels to denote the mutual response. In the Spearman correlations, we considered the following cut-off points: (i) ±0.90–1.00, very strong positive–negative correlation index; (ii) ±0.70–0.89, strong positive–negative correlation index; (iii) ±0.40–0.69, moderate positive–negative correlation index; (iv) ±0.10–0.39, weak positive–negative correlation index; and (v) 0.00–0.09, insignificant (negligible) positive–negative correlation index.

We did the survival curve of patients who received IMV according to PEEP at admission and the classification of PaO_2 as normal, hypoxia, and hyperoxia at admission. We performed the statistical analysis using the Log-Rank (Mantel-Cose) test. We calculated the Hazard ratio using the PEEP $\leq$8 cmH_2O as the numerator.

The binary logistic regression by the stepwise forward method (likelihood ratio) included the patients' characteristics that presented $p \leq 0.05$ in the bivariate analysis. However, we excluded the patients' features with the multicollinearity effect. Also, we excluded BMI and the time when ventilation-associated pneumonia was diagnosed due to a high number of missing data. We considered death a dependent variable, whereas we allocated the other patients' characteristics as predictors of the risk of death.

We used an alpha error of 0.05, and we did not apply techniques to stipulate the missing data values. We carried out the statistical analysis using the Statistical Package for the Social Sciences version 24.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM Corp) software and in the MedCalc software version 15.0 (MedCalc for Windows, version 15.0; MedCalc Software, Ostend, Belgium). Concomitantly, we used the GraphPad Prism software version 8.0 (San Diego, California, United States of America) for figures.

The Ethics Committee of São Francisco University approved the research [CAAE no 29718820.9.0000.5514]. We obtained the waiver of the Informed Consent Term since only the data from the patient's medical records were obtained without the individual description of the patient.

3. Results

3.1. Epidemiological profile of patients receiving IMV

We evaluated 3,213 medical records from patients admitted to the ICU. We excluded 1,681 patients since they did not require IMV and 68 since the clinical data was missing. In the initial analysis, we included 1,464 patients who had received IMV. However, we excluded 21 patients later due to the transfer to a different ICU. Thus, we included 1,442 patients in our statistical analysis (Supplementary Figure S1).

We observed a higher frequency of male patients ($n = 901$; 62.4%), adults ($n = 914$; 63.3%), with normal BMI ($n = 423$; 29.3%), or overweight ($n = 372$; 25.8%; Table 1). Among the previous history of comorbidities, the most prevalent were systemic arterial hypertension ($n = 653$; 45.3%), smoking ($n = 388$; 26.9%), diabetes mellitus ($n = 325$; 22.5%), cardiopathy ($n = 310$; 21.5%), neurologic sequel ($n = 171$; 11.9%), alcoholism ($n = 221$; 15.3%), and pneumopathy ($n = 131$; 9.1%; Table 1; Supplementary Table S1).

A total of 923 (64%) patients were referred to the ICU by the surgery department and the main reason for the admissions were the need for elective surgery ($n = 616$; 42.7%), sepsis ($n = 375$; 26%), cardiopathy ($n = 222$; 15.4%), polytrauma ($n = 210$; 14.6%), and traumatic brain injury ($n = 197$; 13.7%; Table 1; Supplementary Table S2). Ventilation-associated pneumonia occurred in 410 (28.4%) patients, and the need for tracheostomy in 332 (23%) patients; the death of 570 (39.5%) patients was recorded.

3.2. Risk factors associated with death in patients receiving IMV

Several patients' characteristics were associated with enhanced lethality, such as older age [RR = 1.512 (95%CI = 1.334–1.713)], enhanced BMI, grades II and III obesity [RR = 1.426 (95%CI = 1.029–1.977)] and grade I obesity [RR = 1.354 (95%CI = 1.085–1.357)], which presented a higher risk of death (Figure 1). Individuals with a previous history of comorbidities of kidney disease [RR = 1.554 (95%CI = 1.251–1.931)], systemic arterial hypertension [RR = 1.271 (95%CI = 1.119–1.443)], and diabetes mellitus [RR = 1.262 (95%CI = 1.099–1.449)] were also at higher risk of death (Supplementary Table S3; Figure 1). The male sex was associated with decreased risk of death when compared to the female sex [RR = 0.776 (95%CI = 0.683–0.880)] (Supplementary Table S3; Figure 1).

We observed older age and higher BMI in the patients who died. Also, these patients were hospitalized for more days and diagnosed with ventilation-associated pneumonia earlier than patients who did not die (Figure 2). On the other hand, we related the lowest risk of death to the use of drugs and alcoholism, and the younger age of the patients might explain this finding in this group (data not shown). The presence of pneumonia caused by mechanical ventilation was associated with more extended hospital stays (Figure 3).

Several diagnoses were associated with enhanced lethality such as those from kidney disease [RR = 1.485 (95%CI = 1.094–2.017)], stroke [RR = 1.480 (95%CI = 1.246–1.757)], sepsis [RR = 1.391 (95%CI = 1.222–1.583)], and the clinical origin for the patients [RR = 1.387 (95%CI = 1.223–1.573)] (Supplementary Table S4; Figure 1).

TABLE 1 Characteristics of the patients in the intensive care unit on invasive mechanical ventilation support during the study period (2016–2019).

Patients' characteristics	Patients–*N*/1,443 (%)
Age (years)	56.71 ± 17.55; 59 (46–79)
Age group	
Adult (18 to 64 yo)	914 (63.3)
Elderly (>65 yo)	529 (36.7)
Sex	
Female	542 (37.6)
Male	901 (62.4)
Body Mass Index (Kg/m^2)	25.92 ± 5.36; 25.60 (22.6–28.8)
Underweight	55 (3.8)
Normal weight	423 (29.3)
Overweight	372 (25.8)
Grade I obesity	139 (9.6)
Grade II obesity	27 (1.9)
Grade III obesity	19 (1.3)
Not informed	408 (28.3)
Origin	
Surgery	923 (64.0)
Clinic	520 (36.0)
Previous history of comorbidities	
Systemic arterial hypertension	653 (45.3)
Smoking	388 (26.9)
Diabetes mellitus	325 (22.5)
Cardiopathy	310 (21.5)
Alcoholism	221 (15.3)
Neurological sequel	171 (11.9)
Pneumopathy	131 (9.1)
Dyslipidemia	108 (7.5)
Neoplasia	70 (4.9)
Thyroidopathy	70 (4.9)
Kidney disorder	60 (4.2)
Immunodepression	25 (1.7)
Hepatopathy	18 (1.2)
Gastrointestinal disorder	16 (1.1)
Other drugs	49 (3.4)
Other personal backgrounds*	45 (3.1)
Diagnostic	
Elective surgery	616 (42.7)
Sepsis	375 (26.0)
Cardiopathy	222 (15.4)
Polytrauma	210 (14.6)
Traumatic brain injury	197 (13.7)
Stroke	121 (8.4)
Subarachnoid hemorrhage	104 (7.2)
Acute myocardial infarction	89 (6.2)
Neurologic and psychiatry disorders	69 (4.8)
Nephropathy	31 (2.1)
Neoplasia	23 (1.6)
Other**	49 (3.4)
Days of hypoxia	2.57 ± 2.09; 2 (1–3)
Normal days	2.74 ± 2.0; 2 (1–4)
Days of hyperoxia	5.23 ± 4.32; 4 (2–8)
Ventilation-associated pneumonia	410 (28.4)
Tracheostomy	332 (23.0)
Deaths	570 (39.5)

We presented the data as the number of individuals (percentage) and using mean ± standard deviation; median (95% confidence interval).
*Supplementary Table S1; **Supplementary Table S2.

However, patients with traumatic brain injury [RR = 0.744 (95%CI = 0.596–0.928)], polytrauma [RR = 0.665 (95%CI = 0.290–0.836)], or those who needed elective surgery [RR = 0.677 (95%CI = 0.589–0.778)] and those who needed tracheostomy [RR = 0.644 (95%CI = 0.535–0.776)] presented a decreased risk of death (Supplementary Table S4; Figure 1); nevertheless, patients who suffered a traumatic brain injury or polytrauma were also younger (data not shown).

3.3. Risk of death associated with PEEP and PaO_2

We associated the PEEP >8 cmH_2O at admission with a higher risk of death [RR = 1.621 (95%CI = 1.393–1.887)]. In addition, a higher risk of death also occurred in patients with hypoxemia at admission [RR = 1.365 (95%CI = 1.126–1.655)]. In contrast, a lower risk of death occurred in those with hyperoxia [RR = 0.813 (95%CI = 0.693–0.954)] at admission (Supplementary Table S4; Figure 1).

In the analysis of the first 20 days of intubation, the patients who died required more extended ventilatory support and presented higher PEEP values throughout the first 20 days than those who were discharged, except on the 15th day of hospitalization (Figure 4). Curiously, the PaO_2 presented lower values in the patients who died between the day of intubation and the 5th day of follow-up and between the 7th and 10th day of intubation (Figure 5). We presented the patients according to the PEEP and the outcome for the 20 days of intubation in Figure 6. It seems relevant to point out that patients who died had more time on PEEP >8 cmH_2O.

In the Pearson correlation between numeric markers (PEEP at admission, PaO_2 at admission, IMV duration, length of hospital stay, time until the pneumonia diagnosis, BMI, and age), no statistically significant correlation was observed, except for the correlation between the IMV duration and length of hospital stay (CC = 0.70; $p < 0.001$–strong correlation index), as well as the time until the ventilation-associated pneumonia diagnosis (CC = 0.41; $p < 0.001$–moderate correlation index) and hospital stay (CC = 0.35; $p < 0.001$–weak correlation index) (Supplementary Figure S2).

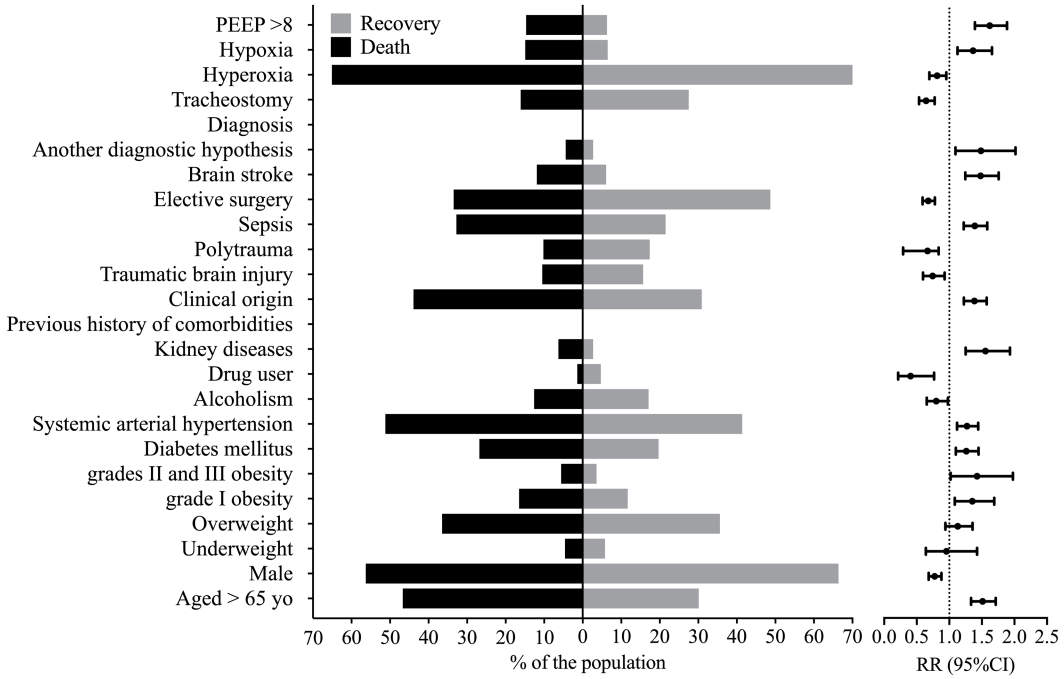

FIGURE 1
Markers that presented statistical significance in the association between patients that died and those that were discharged from the hospital. This figure shows the percentage of individuals that presented a marker according to the outcome and the relative risk, whose reference was the percentage of individuals discharged from the hospital against the group of patients that died. PEEP, positive end-expiratory pressure; RR, relative risk; yo, years old; 95%CI, 95% confidence interval. We carried out the statistical analysis using the Fisher Exact test or the Chi-square test and a 0.05 alpha error.

3.4. Survival analysis

In the survival analysis, we demonstrated that PEEP >8 cmH_2O at admission is associated with a survival of 26 days. In contrast, we observed in patients with PEEP ≤8 cmH_2O the survival of 41 days ($p < 0.001$) and a Hazard ratio of 1.713 (95%CI = 1.340–2.345). Regarding the PaO_2 classification, we found survival values of 40, 27, and 22, respectively, for hyperoxia, normal, and hypoxemia ($p < 0.001$; Figure 7).

3.5. Multivariate binary logistic regression analysis

We excluded the BMI and the day of the ventilation-associated pneumonia diagnosis due to a high number of missing data. We also excluded the following markers: previous diagnosis of kidney disease, kidney disease at admission, and use of drugs.

The multivariate analysis by the binary logistic regression performed by the stepwise forward method (likelihood ratio) was significant in determining whether the patients' characteristics evaluated were likely to predict death [$X^2_{(9)} = 288.335$; $p < 0.001$; Nagelkerke $R^2 = 0.245$]. Predictors that were significant in predicting the risk of death included older age [elderly ≥65 yo; OR = 2.226 (95%CI = 1.728–2.867)]; male sex (OR = 0.754; 95%CI = 0.593–0.959); sepsis (OR = 1.961; 95%CI = 1.481–2.595); need for elective surgery (OR = 0.469; 95%CI = 0.362–0.608); stroke (OR = 2.304; 95%CI = 1.502–3.534); length of hospital stay (OR = 0.946; 95%CI = 0.935–0.956); hypoxemia (OR = 1.635; 95%CI = 1.024–2.611), and PEEP >8 cmH_2O at admission (OR = 2.153; 95%CI = 1.426–3.250). In contrast, hyperoxia could not predict the risk of death (Table 2).

4. Discussion

This study described the death of 570 patients (39.5%) during ICU stay on IMV at a University Hospital. A higher risk of this outcome occurred in patients that presented older age, sepsis diagnosis, presence of cerebrovascular accident, hypoxemia at admission, and the use of PEEP >8 cmH_2O at admission. The epidemiological profile of patients admitted to the adult ICU of the University Hospital shows mainly adult male patients with a previous history of diabetes mellitus, systemic arterial hypertension, alcoholism, and smoking habits. Those patients were usually referred to the ICU by the surgical team, including those undergoing elective surgeries (42.7%). The leading causes of admission to the ICU included traumatic brain injury, polytrauma, and sepsis. During the follow-up period, 410 (28.4%) patients presented ventilation-associated pneumonia.

4.1. Epidemiological profile of patients receiving IMV and death risk

This study found a 39.5% death rate, which is only associated with patients receiving IMV. In the literature, a multicenter study that analyzed data from 361 ICUs located in the United States of America,

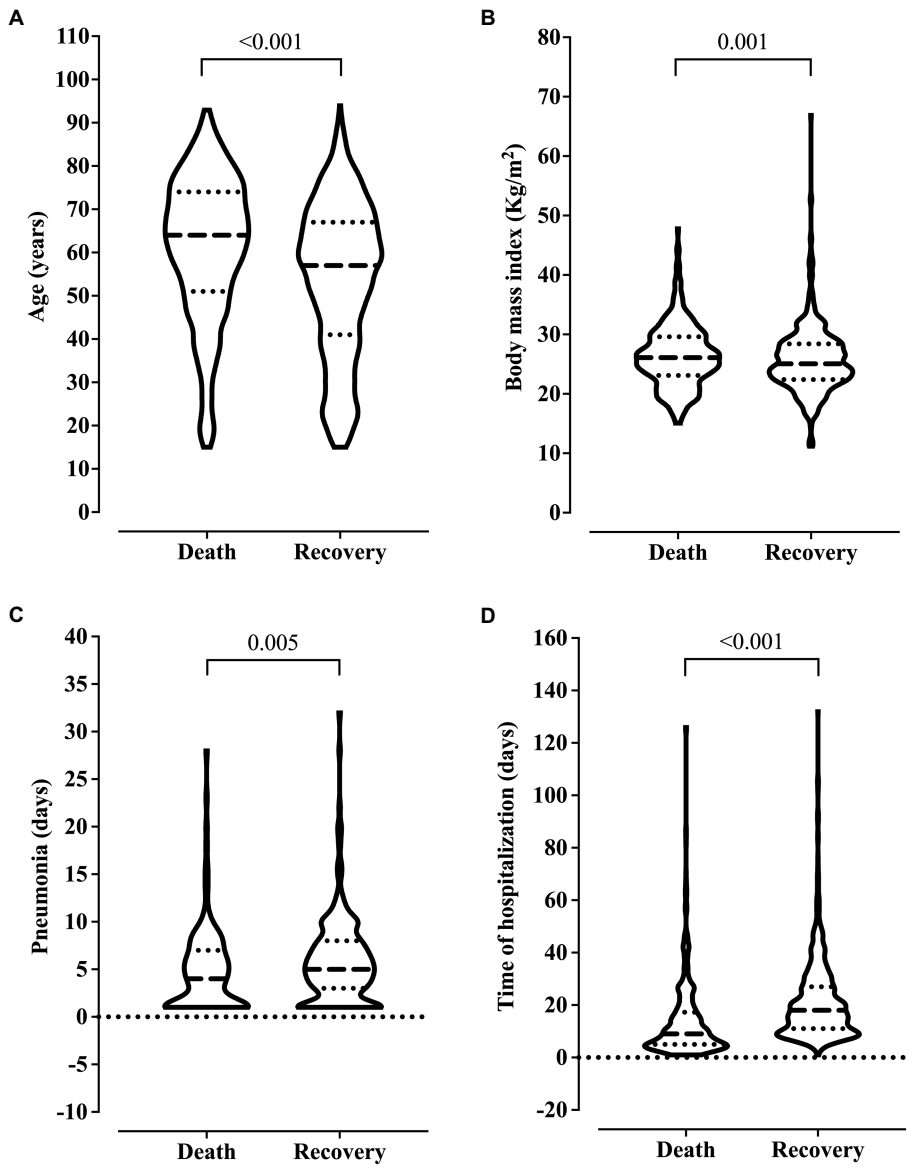

FIGURE 2
Association between clinical outcome and age **(A)**, body mass index **(B)**, ventilation-associated pneumonia **(C)**, and length of hospital stay **(D)**. We carried out the statistical analysis using the Mann–Whitney test and a 0.05 alpha error.

Europe, and Latin America and included 5,183 individuals receiving mechanical ventilation reported a 52% death rate in patients that required mechanical ventilation due to respiratory insufficiency (7). Another two studies performed in Brazil and Chile also reported a high prevalence of death in ICU patients who required mechanical ventilation, with 34 and 33.9%, respectively (28, 29). Interestingly, the overall in-hospital mortality in the Brazilian study was higher than in ICU (42% vs. 34%). Our study presented a similar demographic profile to those found in the literature, which showed the prevalence of male patients, and older individuals to be higher in ICU patients with mechanical ventilation; in contrast, our study showed the main causes of mechanical ventilation to be surgery followed by pneumonia, cardiopathy, sepsis, and trauma. Those authors also reported that the factor that leads to the need for mechanical ventilation might influence the outcome. In Brazil, most patients in ICU are male (50.78%) (30), which is similar to the ones found in the United States of America (51.5%) and the United Kingdom (57.2%) (30, 31). As for the age range, adult individuals prevail in Brazil and the United States of America (30, 31).

In this study, we associated the presence of older age, obesity, systemic arterial hypertension, diabetes mellitus, and kidney insufficiency with a higher likelihood of death. This data follows the literature (7, 28, 29). Curiously, these markers seem to be part of the profile of the patients assisted in Brazil since, according to the Brazilian Intensive Medicine Association, the most frequent comorbidities found in patients admitted to ICU in the country include systemic arterial hypertension (66.40%), diabetes mellitus (32.82%), and kidney disorders (11.63%). The prevalence of male patients was also reported (51.30%) by that institution (30). Such comorbidities might lead to the risk of ICU admission, in which diabetes mellitus, for example, is associated with an increased risk of infection in several sites (skin, nervous system, bones, and

articulations) (32). Systemic arterial hypertension, in turn, is the most critical morbidity and mortality risk factor in the world and is associated with an increased risk of cardiovascular diseases (33). Finally, kidney insufficiency presents a 57% increase in the mortality risk of critical patients due to its consequences, namely, metabolic acidosis, electrolytic unbalance, and uremic toxicity (34).

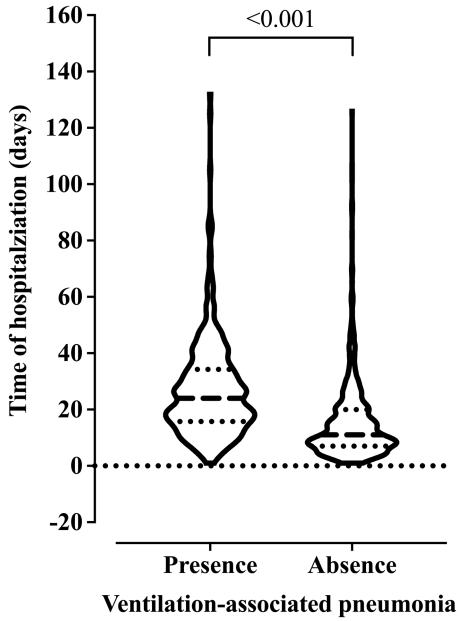

FIGURE 3
Association between the risk of developing ventilation-associated pneumonia according to the length of invasive mechanical ventilation. We carried out the statistical analysis using the Mann–Whitney test and a 0.05 alpha error.

Obesity is also a predictor of extended hospital stay since it might affect several organs, mainly the lungs and heart. In addition, it requires differentiated mechanical ventilation management and higher ventilatory weaning expertise (34). The literature reports a relevant study carried out in the United Kingdom, including over 3.6 million individuals, which pointed out higher death incidence in patients with BMI over the band considered healthy [BMI >30 Kg/m^2 (obesity)]. However, that study identified the influence of age and BMI and reported that low BMI increases death risk in young individuals. At the same time, a higher BMI might have a protective effect in older people (which might be associated with higher nutritional reserve) (35). However, several meta-analyses and other studies have reported that obesity mainly influences the length of hospital stay rather than death risk (36–40). Maybe the obesity variable is part of a Simpson paradox, that is, in which a certain tendency disappears or even reverses when groups are combined, which is perhaps related to the difficulty in asses the severity of patients with obesity in ICU since the most used scores (APACHE II or III, Sequential Organ Failure Assessment and Simplified Acute Physiology Score II) do not take into account patients weight (41–43). Additionally, APACHE II score in individuals with obesity might be over or underestimate since the patients tend to have a low alveolar gradient, mainly due to a higher prevalence of hypoventilation and apnea syndrome, and also have low urine output, leading to an illusory increased kidney dysfunction (41, 44). The obesity role in the outcome of patients admitted to the ICU, mainly those requiring IMV, still needs further studies since a new "pandemic" of individuals with obesity has been observed worldwide (45). Studies also need to assess the Simpson paradox, which could bias the analysis.

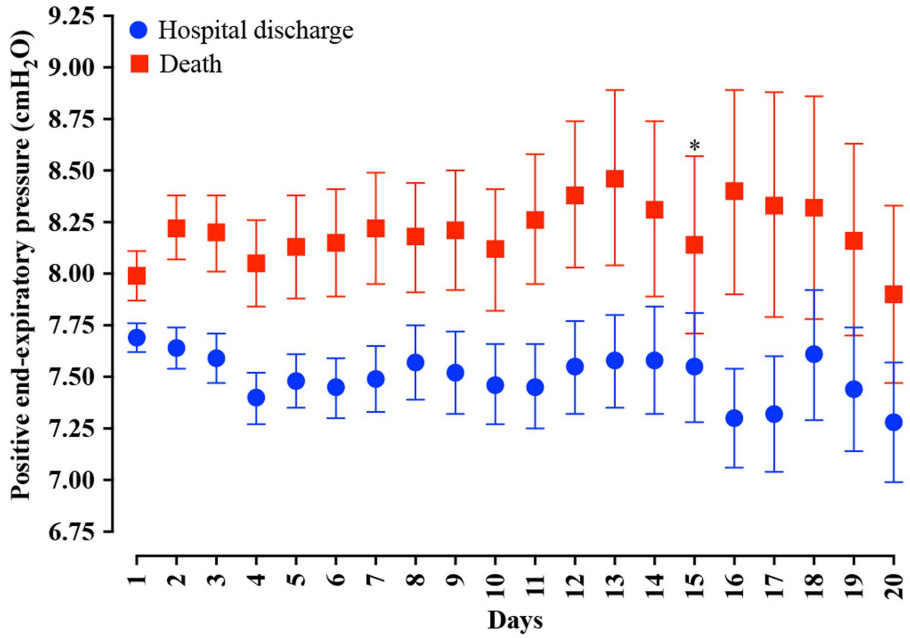

FIGURE 4
Distribution of the positive end-expiratory pressure (PEEP) values according to the days of invasive mechanical ventilation. Blue represents the individuals that were discharged. Red represents the individuals that died. We carried out the statistical analysis using the Mann–Whitney test and a 0.05 alpha error. The data is presented as mean [95% confidence interval, 95%CI]. *p>0.05.

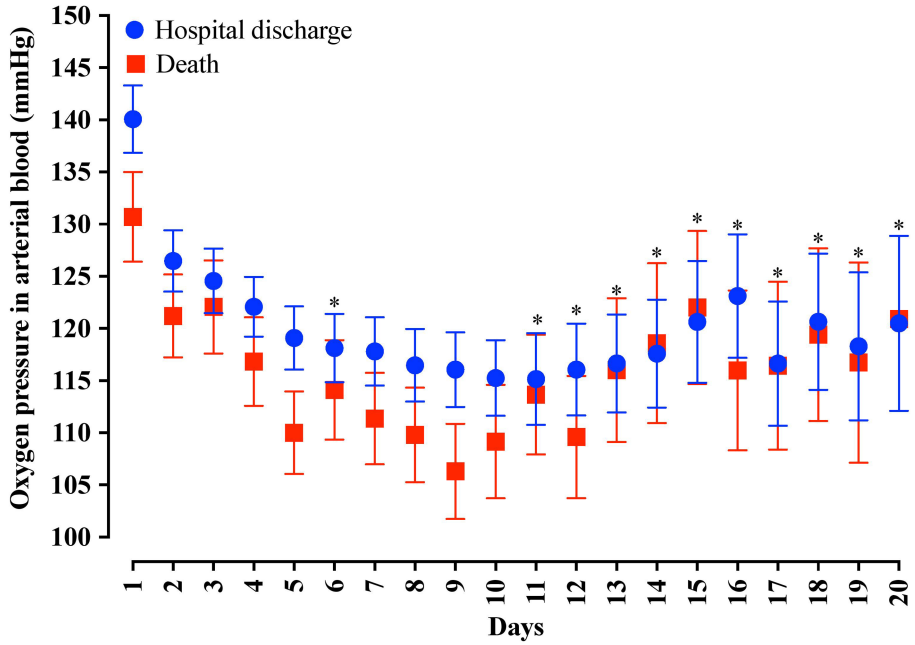

FIGURE 5
Distribution of the arterial oxygen pressure (PaO_2) values according to the days of invasive mechanical ventilation. Blue represents the individuals that were discharged. Red represents the individuals that died. We carried out the statistical analysis using the Mann–Whitney test and a 0.05 alpha error. The data is presented as mean [95% confidence interval, 95%CI]. *p>0.05.

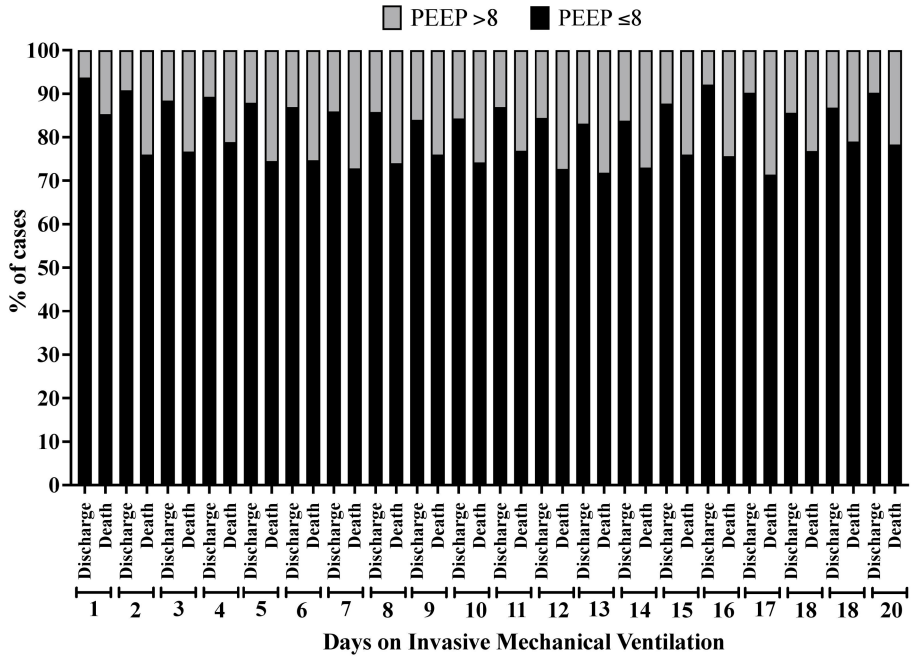

FIGURE 6
Percentage of patients according to the clinical outcome distributed by the positive end-expiratory pressure (PEEP) value (≤8 cmH_2O or >8 cmH_2O) and according to the time of invasive mechanical ventilation (days 1 to 20).

It seems relevant to emphasize that comorbidities do not always develop individually; therefore, when considered together, they might increase the likelihood of adverse outcomes even more. It is essential to highlight that the risk factors can be modifiable and reduced by public health policies, awareness-raising, and better access to health services. Implementing campaigns incentivizing healthy eating habits, regular physical exercises, adherence to disease control measures, and stopping smoking and consuming alcohol help manage those diseases.

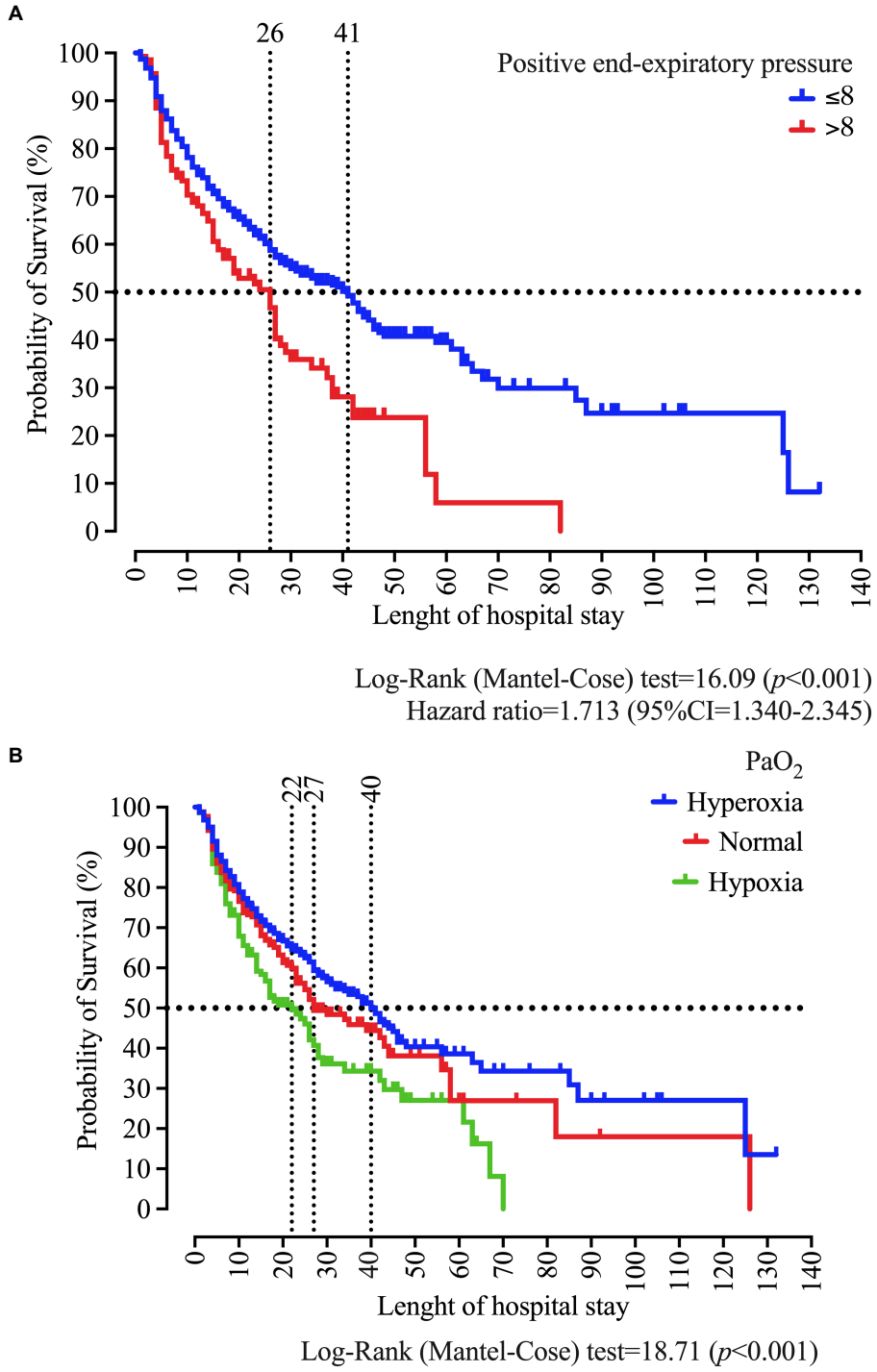

FIGURE 7
Survival curve of patients who were intubated at the University Hospital according to the positive end-expiratory pressure (PEEP) **(A)**, and the arterial oxygen pressure (PaO_2) classification as normal, hypoxemia, and hyperoxemia **(B)**. We carried out the statistical analysis using the Log-Rank (Mantel-Cose) test. We calculated the Hazard ratio using the PEEP ≤8 cmH_2O as the numerator parameter and we adopted a 0.05 alpha error. PaO_2 values at admission in the ICU were categorized using the following distribution: hypoxia (<80 mmHg), normal (between 80 and 100 mmHg), and hyperoxia (>100 mmHg).

For example, these actions aim to reduce the incidence of obesity, systemic arterial hypertension, and diabetes mellitus and, consequently, might reduce the occurrence of cardiovascular events (46).

Regarding diagnosis at admission, our study shows that patients in treatment with sepsis, cerebrovascular accident, and kidney disorders also present a higher death risk than individuals diagnosed with traumatic brain injury, polytrauma, elective surgeries, and those that evolved to tracheostomy. Some findings in our study disagree with those in the literature since patients with traumatic brain injury and polytrauma were younger than other patients. For example, the cerebrovascular accident, along with the need for mechanical ventilation, presents a high mortality rate (56.6%) and tends to

TABLE 2 Multivariate binary logistic regression analysis predicts the death of adult and old patients admitted to an intensive care treatment unit.

Predictors	B	SE	Wald	df	Sig	Exp(B)	95%CI	
							Lower limit	Upper limit
Age (Elderly)	0.800	0.129	38.329	1	<0.001	2.226	1.728	2.867
Sex (Male)	−0.283	0.123	5.307	1	0.021	0.754	0.593	0.959
Sepsis (Positive)	0.673	0.143	22.136	1	<0.001	1.961	1.481	2.595
Elective surgery (Presence)	−0.757	0.132	32.774	1	<0.001	0.469	0.362	0.608
Cerebrovascular accident (Positive)	0.834	0.218	14.615	1	<0.001	2.304	1.502	3.534
Length of hospital stay (days)	−0.056	0.006	99.131	1	<0.001	0.946	0.935	0.956
PaO_2 (normal)			14.712	2	0.001			
PaO_2 (Hyperoxemia)	−0.273	0.157	3.016	1	0.082	0.761	0.560	1.036
PaO_2 (Hypoxemia)	0.492	0.239	4.245	1	0.039	1.635	1.024	2.611
PEEP (>8 cmH_2O)	0.767	0.210	13.320	1	<0.001	2.153	1.426	3.250
Constant	0.525	0.200	6.853	1	0.009	1.690		

Variables not inserted in the equation using the stepwise forward method: patient's origin (surgery or clinic); traumatic brain injury; polytrauma; cerebrovascular accident; the presence of ventilation-associated pneumonia; the need for tracheostomy; diabetes mellitus; systemic arterial hypertension; and alcoholism. B, regression coefficient estimated for the predictor; SE, regression coefficient standard error; df, degrees of freedom; Exp(B), odds ratios for the predictors; CI, confidence interval; PEEP, positive end-expiratory pressure; PaO_2, arterial oxygen pressure. PaO_2 values at admission in the ICU were categorized using the following distribution: hypoxia (<80 mmHg), normal (between 80 and 100 mmHg), and hyperoxia (>100 mmHg).

predominate among male patients (52.7%) with a mean age of 60 yo (47, 48). We confirmed this data in our study, which showed that male sex, diagnosis of cerebrovascular accident, and age are more frequent among our patients; however, male sex was not a death predictor in our data.

When considering death risk markers, sepsis is responsible for ~30–60% of deaths in the ICU (49). The highest death risk due to sepsis results from organ failure caused by the host's deregulated response to the infection. Despite all efforts made to prevent infections and treat patients affected by them, sepsis is still one of the most common causes of death worldwide, with varied rates according to the region (South Africa and Asia are the most affected regions), age (older age is more associated with death risk), and sex (male) (24, 50, 51). As for treatment, empirical antimicrobial therapy is still the base treatment, and its start is indicated in the first 6 h of the diagnosis. Each hour of delay in the treatment represents a 6% increase in the death risk. The literature described that prescribing unsuitable antimicrobial drugs increases death rates and bacteria resistant to antibiotic medication. In addition, antibiotic medicine might eliminate the bacteria from the blood plasma. However, it might not be efficient in preventing pathogen proliferation in the erythrocyte, which might cause the inefficiency of some treatments against sepsis (52). The sepsis profile described is similar to the profile observed in patients assisted at the University Hospital where we carried out the study.

Elective surgeries that require ICU admission represent 9.7% of this treatment. Of those, ~50.4% also present postoperative complications [e.g., pulmonary embolism and cardiac arrest], with a mortality rate from 2.4 to 9.7% (53). We can associate the lower death risk after elective surgery with the preparation that precedes the procedure.

4.2. Death risk associated with PEEP and PaO_2

This study described the highest death risk of patients receiving ventilation with PEEP >8 cmH_2O, maintaining hypoxemia. On the other hand, patients with hyperoxemia showed a lower death risk. Some studies have pointed out that PEEP does not reduce the incidence of pulmonary complications and should not be considered a protective factor for a favorable outcome. In addition, PEEP might increase oxygenation; however, in other cases, it might lead to static stretching, resulting in lesions (18, 54). A study carried out the analysis of surgical patients. It showed that PEEP use resulted in a 5% death risk reduction due to decreased postoperative pulmonary complications such as atelectasis and hypoxemia. However, those findings were inconclusive due to research limitations (small sample) (55). Concomitantly, we observed a higher survival rate in patients that used PEEP ≤8 cmH_2O. However, the outcome does not seem to be associated with the PEEP cut-off point in the literature (22, 23). Gatinoni and co-workers (2015) concluded that there is not "a PEEP correct value" and that it must be titrated by taking into consideration several factors (e.g., oxygenation and hemodynamics) (19). In addition, PEEP is not the only risk factor associated with worse outcomes among the ventilator parameters. In this context, it is important to evaluate parameters such as tidal volume, driving pressure, and plateau pressure that can improve the risk of ventilator-induced lung injury (known as barotrauma and volutrauma), which in turn increase the risk of death (56). Importantly, the two terms–barotrauma and volutrauma–reflect the two sides of the same phenomenon: lung injury due to a large distending volume and/or to a high airway pressure.

In extreme cases, hypoxemia might lead to organ failure (57). In contrast, hyperoxemia might lead to acute hyperoxic and acute lung injury, damaging the epithelium and endothelium due to the release of pro-inflammatory cytokines [e.g., Tumor Necrosis Factor Alpha (TNF-α) and Interferon Gamma (IFN-g)], which might start a pulmonary injury process (25, 58). Although hyperoxemia in the first 24 h of hospital admission does not seem to increase death risk in severe trauma patients (59), it is associated with a higher death risk in patients with cardiorespiratory arrest (60). The literature associated the use of supplementary oxygen in patients with hyperoxemia (PaO_2 over 150 mmHg) with the worst clinical outcome, possibly due to

vasoconstriction, reduction in the coronary blood flow, and cardiac output, the release of free radicals, and microvascular perfusion modulation (58, 61).

Despite the general reduction in death risk in patients with PaO_2 over 150 mmHg in the first 24 h of ICU admission, high PaO_2 values should not be recommended when we know the etiology of the tissue oxygenation decrease (e.g., due to hampered transportation). Thus, it might not be wise to state that high levels of arterial oxygenation are always beneficial or might cause harmful side effects (62). In addition, the goals of applying PEEP are to improve gas exchange and increase functional residual capacity, but the effects of PEEP on heart function include reduced venous return, increase pulmonary vascular resistance, and afterload to the right heart, which can lead to worsening oxygenation (63).

4.3. Multivariate binary logistic regression analysis

We identified the following markers as the main predictors for death: female sex, elderly, sepsis, cerebrovascular accident, hypoxemia, and PEEP >8 cmH_2O. Concomitantly, patients undergoing elective surgery and male sex presented lower chances of death.

We developed the study at a trauma referral center in the region. This fact could lead to an increase in the death risk in male patients, which would confirm other epidemiological studies on trauma centers in Brazil (located in Parana, Bahia, and Paraiba states). However, the male sex was associated with the lowest death incidence. A fact that could explain our findings is that these male patients might have had their age as the primary protective factor since they were all younger patients (data not presented).

Among the elderly, traumatic brain injury might increase mortality when associated with several comorbidities, such as falls, which can even contribute to the cause of trauma (64–66). A retrospective cohort study that analyzed data from 8,598 patients reported that most ICU admissions were male patients. However, the analysis did not show a difference between the sexes when comparing the length of hospital stays, but the hospital discharge rate was higher for female patients (67). In addition, older patients are more vulnerable and might develop multiple organ failures faster, leading to an increased death rate in that population (68).

Sepsis is accountable for 25% of ICU admissions in Brazil and shows high mortality rates, which might reach 65%, while sepsis mortality means around the world might reach 40% (69). Being an organ failure caused by the deregulated and unsuitable host response to infection, sepsis is potentially fatal, and its mortality rate is higher in environments of low or medium resources (70).

Elective surgeries usually present a low mortality rate (between 1 and 4%), and pre-operative care procedures are essential for safe surgical treatment. However, the ideal level of such care has not been defined yet, and death still occurs, mainly due to postoperative complications, for example, pulmonary embolism and cardiac arrest (53).

Both hypoxemia and the use of PEEP >8 cmH_2O were factors that increased mortality rates in our analysis. A study developed with rats that analyzed PEEP to prevent postoperative pulmonary complications reported that PEEP >8 cmH_2O prevented such complications (71). However, that study reported a postoperative analysis only. In addition, regarding PaO_2, health professionals are most concerned with hypoxemia than with the harmful effects of hyperoxemia. For this reason, PaO_2 at admission is oftenly higher than recommended. However, the mortality curve related to PaO_2 at admission presents a U shape. The mortality risk increases as much with low PaO_2 as with high. Also, it is relevant to highlight that the oxygen supplementary offer and the PEEP influence the PaO_2 (72). Although PEEP reduces the collapse of alveolar units and the incidence of atelectasis, one of the factors causing hypoxemia (73), the use of high PEEP values might lead to injury induced by static stretching of alveolar units, mainly when we consider the time in mechanical ventilation support since it is usually longer in patients of clinical or trauma origin (18, 74). The PEEP ideal value remains an unanswered question, and if underestimated, it might collapse the alveoli hampering gas exchange. On the other hand, if overestimated, it might lead to alveolar hyperdistention, inhibiting gas exchange, and venous return (19, 20). Therefore, we must compare PEEP titration to the drug administration, which must be applied rationally based on the patient's condition.

PEEP increases linearly the mechanical power, which is the energy delivered to the alveolus because of the ventilatory parameters set (75). The mechanical power equation might help the clinical team to estimate injuries associated with mechanical ventilation support by observing the variables present in its formula (current volume, respiratory rate, and inspiratory time). Since PEEP increases the mechanical power volume linearly, it also increases the risk of injury associated with ventilation and death (56). Our study showed increased death risk with PEEP >8 cmH_2O, which might be related to lesions caused by the ventilation, which agrees with the literature.

A recent study incorporated PEEP into the PaO_2/FiO_2 ratio to evaluate the mortality predisposition of patients receiving mechanical ventilation, and it was seen to be a good marker. That study also reported that PEEP incorporated into the PaO_2/FiO_2 ratio alters the classification of gas exchange severity in critical patients (76). The pandemic caused by the new coronavirus (COVID-19) raised great interest in PEEP since this disease affects the lungs severely in some cases leading to a condition like that of acute respiratory discomfort syndrome, requiring better mechanical ventilation performance (77).

5. Limitations

The limitations of our study include a small sample and missing data such as the absence of severity score (e.g., APACHE II or III, Sequential Organ Failure Assessment and Simplified Acute Physiology Score II) and some values for BMI, and pneumonia associated with ventilation. Data such as tidal volume, driving pressure, and oxygenation index were not collected because the objective of this study was to evaluate the PEEP influence and PaO_2 separately from the other parameters. We performed an observational study, which might lead to confounding factors. In addition, due to the COVID-19 pandemic, the 2020 and 2021 data were not included since the pandemic modulated and affected ICU admissions, including referred ICU (78–81). Finally, our study is a picture coming from the Brazilian scenario and this could or could not match exactly the worldwide scenario, including access to the health system and/or the standard of admissible patients to treatment in ICU, together with code-status regulations. Also, in the future, it is important to perform other observational studies as those performed by National

Institute for Health and Care Research Global Health Unit on Global Surgery and COVIDSurg Collaborative to improve the world's capacity to deal with conditions such as COVID-19 pandemic and its impact on the health system, including ICUs collapse during the COVID-19 pandemic and the comparison between time-lapse periods (before-, during-, and after-COVID-19 pandemic) (78–82).

6. Conclusion

The death rate of the studied ICU was equivalent to that of other similar units. Regarding risk predictors, several demographic and clinical characteristics were associated with enhanced mortality in ICU patients under mechanical ventilation, such as diabetes mellitus, systemic arterial hypertension, and older age. The PEEP >8 cmH_2O at admission was also associated with increased mortality since this value is a marker of initially severe hypoxia.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The Ethics Committee of São Francisco University approved the research [CAAE no 29718820.9.0000.5514]. Written informed consent from the [patients/participants OR patients/participants legal guardian/next of kin] was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1064120/full#supplementary-material

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Effect of protective lung ventilation on pulmonary complications after laparoscopic surgery: a meta-analysis of randomized controlled trials

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Introduction: Compared with traditional open surgery, laparoscopic surgery is widely used in surgery, with the advantages of being minimally invasive, having good cosmetic effects, and having short hospital stays, but in laparoscopic surgery, pneumoperitoneum and the Trendelenburg position can cause complications, such as atelectasis. Recently, several studies have shown that protective lung ventilation strategies are protective for abdominal surgery, reducing the incidence of postoperative pulmonary complications (PPCs).Ventilator-associated lung injury can be reduced by protective lung ventilation, which includes microtidal volume (4–8 mL/kg) ventilation and positive end-expiratory pressure (PEEP). Therefore, we used randomized, controlled trials (RCTs) to assess the results on this topic, and RCTs were used for meta-analysis to further evaluate the effect of protective lung ventilation on pulmonary complications in patients undergoing laparoscopic surgery.

Methods: In this meta-analysis, we searched the relevant literature contained in six major databases—CNKI, CBM, Wanfang Medical, Cochrane, PubMed, and Web of Science—from their inception to October 15, 2022. After screening the eligible literature, a randomized, controlled method was used to compare the occurrence of postoperative pulmonary complications when a protective lung ventilation strategy and conventional lung ventilation strategy were applied to laparoscopic surgery. After statistical analysis, the results were verified to be statistically significant.

Results: Twenty-three trials were included. Patients receiving protective lung ventilation were 1.17 times less likely to develop pulmonary complications after surgery than those receiving conventional lung ventilation (hazard ratio [RR] 0.18, 95% confidence interval [CI] 1.13–1.22; $I^2 = 0\%$). When tested for bias ($P = 0.36$), the result was statistically significant. Patients with protective lung ventilation were less likely to develop pulmonary complications after laparoscopic surgery.

Conclusion: Compared with conventional mechanical ventilation, protective lung ventilation reduces the incidence of postoperative pulmonary complications. For patients undergoing laparoscopic surgery, we suggest the use of protective lung ventilation, which is effective in reducing the incidence of lung injury

and pulmonary infection. Implementation of a low tidal volume plus moderate positive end-expiratory pressure strategy reduces the risk of postoperative pulmonary complications.

KEYWORDS

protective lung ventilation, small tidal volume, moderate PEEP, laparoscopic surgery, pulmonary complications, meta-analysis

Introduction

Laparoscopic surgery is a technique that uses a laparoscope in the abdominal cavity to monitor and guide surgery from outside the abdomen to complete the exploration of diseased tissue, haemostasis, electrocoagulation, suturing and other operations. Laparoscopic surgery is widely used because of its low rate of bleeding, low postoperative pain (1), fast recovery, and short hospital stays. Compared with traditional open surgery, laparoscopy is widely used in surgery with the advantages of minimal invasiveness, good cosmetic effects and short hospital stays. However, during laparoscopic surgery, pneumoperitoneum and Trendelenburg positions can cause postoperative pulmonary complications (PPCs), such as atelectasis (2), resulting in severe perioperative respiratory dysfunction. Studies have shown that the incidence of PPCs after general surgery is 5%, while the incidence of PPCs after abdominal surgery is between 12% and 58% (1).

Mechanical ventilation is a routine surgical form of ventilation that used to use high tidal volume ventilation (10 to 15 mL/kg) to prevent hypoxaemia and atelectasis. However, experiments have shown that mechanical ventilation under high tidal volume ventilation conditions can cause alveolar hyperexpansion, worsen lung injury, and cause ventilator-related lung injury (3). Recently, several studies have shown that certain lung ventilation strategies are protective for abdominal surgery, reducing the incidence of PPCs (4, 5).

Protective lung ventilation minimizes lung injury and circulatory suppression due to mechanical ventilation while improving hypoxaemia. Intraoperative protective ventilation strategies can maintain alveolar dilation, reduce alveolar collapse or over dilation, and decrease the incidence of atelectasis. The core components of protective pulmonary ventilation include small tidal volume ventilation [Vt 6–8 mL/kg (6, 7)], moderate positive end-expiratory pressure [PEEP 5–10 cm H_2O (6, 8)], and pulmonary recruitment.

A high tidal volume can be used to reopen an area of the lung where the end of the expiratory has collapsed and repair arterial oxygenation injury, but it is considered safe only for short periods of mechanical ventilation. Appropriate positive end-expiratory pressure can be effective in preventing PPCs. High PEEP can promote alveolar hyperexpansion, pulmonary vascular resistance can increase accordingly (1), and ventilatory blood flow ratio imbalance can impair haemodynamics, causing postoperative pulmonary complications, and the ideal PEEP value is currently unclear. However, all relevant studies have recommended small tidal volumes, and there is clear evidence that protective lung ventilation in patients with acute lung injury and acute respiratory distress syndrome is effective in reducing morbidity and mortality (8). Nevertheless, the effect is not obvious in the general patient population, and there is a lack of strong evidence and clear mechanisms to prove that protective lung ventilation can be effective in reducing the occurrence of pulmonary complications when applied to laparoscopic surgery.

Therefore, we used randomized, controlled trials (RCTs) to assess the results on this topic and for meta-analysis to further assess the effects of protective lung ventilation (low tidal volume ventilation and PEEP) on pulmonary complications in laparoscopic surgery patients.

Methods

Search strategy

In this systematic review and meta-analysis, we submitted a registration for this study on the PROSPERO website and is currently being assessed. We followed the PRISMA (9) guidelines (PRISMA Checklist can be seen in Appendix 1) and collected articles from six Chinese and English literature databases—CNKI, Medical Wanfang, CBM, Cochrane, PubMed, and Web of Science—as well as relevant subject literature from the China Clinical Trial Registry through a literature search, without language restrictions. Randomized, controlled trials were searched for according to the corresponding keywords and extended terms in Chinese and English, and all relevant articles from the establishment of the database up to November 2022 were retrieved.

The complete detailed search string for PubMed was as follows: ((“Laparoscopes”[Mesh]) OR ((((((((((Peritoneoscope[Title/Abstract]) OR (Celioscope[Title/Abstract])) OR (Laparoscope[Title/Abstract])) OR (Laparoscopic surgery [Title/Abstract])) OR (Porous laparoscopy[Title/Abstract])) OR (Single-port laparoscopy[Title/Abstract])) OR (Transumbilical laparoscopy[Title/Abstract])) OR (Transumbilical single-port laparoscopy[Title/Abstract])))) AND ((“Pulmonary Ventilation”[Mesh]) OR ((((((((((((Ventilation, Pulmonary[Title/Abstract]) OR (Airflow, Respiratory[Title/Abstract])) OR (Airflow, Expiratory[Title/Abstract])) OR (Protective pulmonary ventilation[Title/Abstract])) OR (Protective ventilation[Title/Abstract])) OR (Pulmonary protective ventilation[Title/Abstract])) OR (Lung protective ventilation[Title/Abstract])) OR (Lung protective strategies[Title/Abstract])) OR (Lung-protective ventilation therapy[Title/Abstract])) OR (Pulmonary protective ventilation mode[Title/Abstract])) mechanical ventilation[Title/Abstract]))))AND(((randomized controlled Trial[Publication

Type] OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])). The search strategies of other search engines can be seen in Appendix 2.

Inclusion criteria and exclusion criteria

After completing the initial search of the literature, preliminary screening was performed by removing duplicate literature; excluding reviews, meta-analyses, systematic reviews, and literature with inconsistent research content by reading titles and abstracts; and selecting the literature that needed to be obtained in the original language by formulating inclusion and exclusion criteria and final evaluation indicators. The inclusion criteria were the following: (1) Study subjects: patients undergoing laparoscopic surgery; (2) Interventions: conventional lung ventilation strategies were in the control group and protective lung ventilation strategies used in the experimental group; (3) Outcome measures: at least one of the following: pulmonary complications: atelectasis, hypoxia, and hypoxaemia; (4) Study design: randomized, controlled trials (RCTs). Patients were randomly assigned to two groups, and the results of the two groups were compared. One group (experimental group) received an intervention with a protective lung ventilation strategy, while the other group (control group) received a conventional ventilation strategy. The two groups were compared for postoperative outcomes to determine the effectiveness of the intervention in the experimental group.

The exclusion criteria were: (1) repeatedly reported studies; (2) valid outcome measures not being obtained, e.g. atelectasis, hypoxia, and hypoxaemia; (3) additional measures added to the experimental group intervention; (4) the experimental design not matching in that protective lung ventilation strategies were used in the intervention group, and conventional pulmonary ventilation was used in the control group. Finally, by reading the original texts, the final relevant documents were obtained by eliminating the documents that did not meet the requirements.

In this review, we define:P as a patient who requires laparoscopic surgery; I means: the use of protective lung ventilation strategy as an intervention; C means: the control group uses the conventional lung ventilation strategy; O means: The outcomes of this meta-analysis are pulmonary complications; S means: the experimental design protocol is a fully randomized controlled trial. Pulmonary complications include: Pneumonia, Respiratory failure, Pulmonary embolism, Pulmonary embolism, Bronchopleural fistula, Pleural empyema. To investigate the effects of protective lung ventilation on pulmonary complications after laparoscopic surgery. Primary outcomes are: pulmonary infection, atelectasis; Secondary outcomes are: cough, lung injury, etc.

Data extraction and quality analysis

We read the extracted data and further confirmed the relevant data extracted. The following data were extracted from each entry: first author, year of publication, group and number of participants, population characteristics (weight, sex, age), tidal volume and PEEP value in the experimental group (protective lung ventilation group) and control group (conventional lung ventilation group). The main evaluation indicators were pulmonary complications, such as lung infection and atelectasis, and the secondary indicators were cough, lung injury, etc. [PPCs are defined in Table 1 (10)].

TABLE 1 Standardized PPCs according to the european perioperative clinical outcome definitions.

Pneumonia	Patient received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count $>12 \times 10^9 \cdot L^{-1}$
Respiratory failure	Postoperative arterial oxygen partial pressure <8 kPa (60 mm Hg) on room air, an arterial oxygen partial pressure to oxygen fraction ratio <40 kPa (300 mm Hg) or arterial oxyhaemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy
Pulmonary embolism	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area and compensatory overinflation in the adjacent non-atelectoic lung
Pulmonary embolism	Diagnosed by CT angiography without severity grading
Bronchopleural fistula	Diagnosed by flexible bronchoscopy, persistently requiring reoperation
Pleural empyema	Fever, white blood cell count $>12\times10^9 \cdot L^{-1}$ and CT scan

The results of this study were dichotomous variables, and we calculated the relative risk (RR) using 95% confidence intervals. Heterogeneity was quantified by the I^2 statistic. If the I^2 value was >50%, the heterogeneity was considered significant. A bias test was also performed. All statistical analyses were processed using Review Manager software (RevMan, version 5.3) and Stata software, version 14.

RCT methods were used in this study. The studies were assessed for complete random allocation, allocation concealment, blinding of participants and staffs, data integrity, selective reporting of study results, and other sources of bias (small sample size, conflict of interest, unbalanced baseline), completed literature quality assessment, heterogeneity testing, and bias testing.

Results

Literatures search

After a well-developed literature screening strategy, 646 articles were obtained. Two students read the titles and abstracts of these 646 articles alone, screened according to the inclusion and exclusion criteria formulated in advance, and summarized the articles screened by the two students together. By reading the title and summary, we excluded 173 duplicate articles. Then 574 articles were excluded due to non-compliance (Figure 1). The last 23 RCTs met the inclusion criteria for this meta-analysis.

The main characteristics of the 23 articles (1, 9, 11–31) of this study are shown in Table 2.

Data analysis

Of the 23 articles included in this meta-analysis, 1 described pediatric laparoscopic surgery, and 22 described laparoscopic

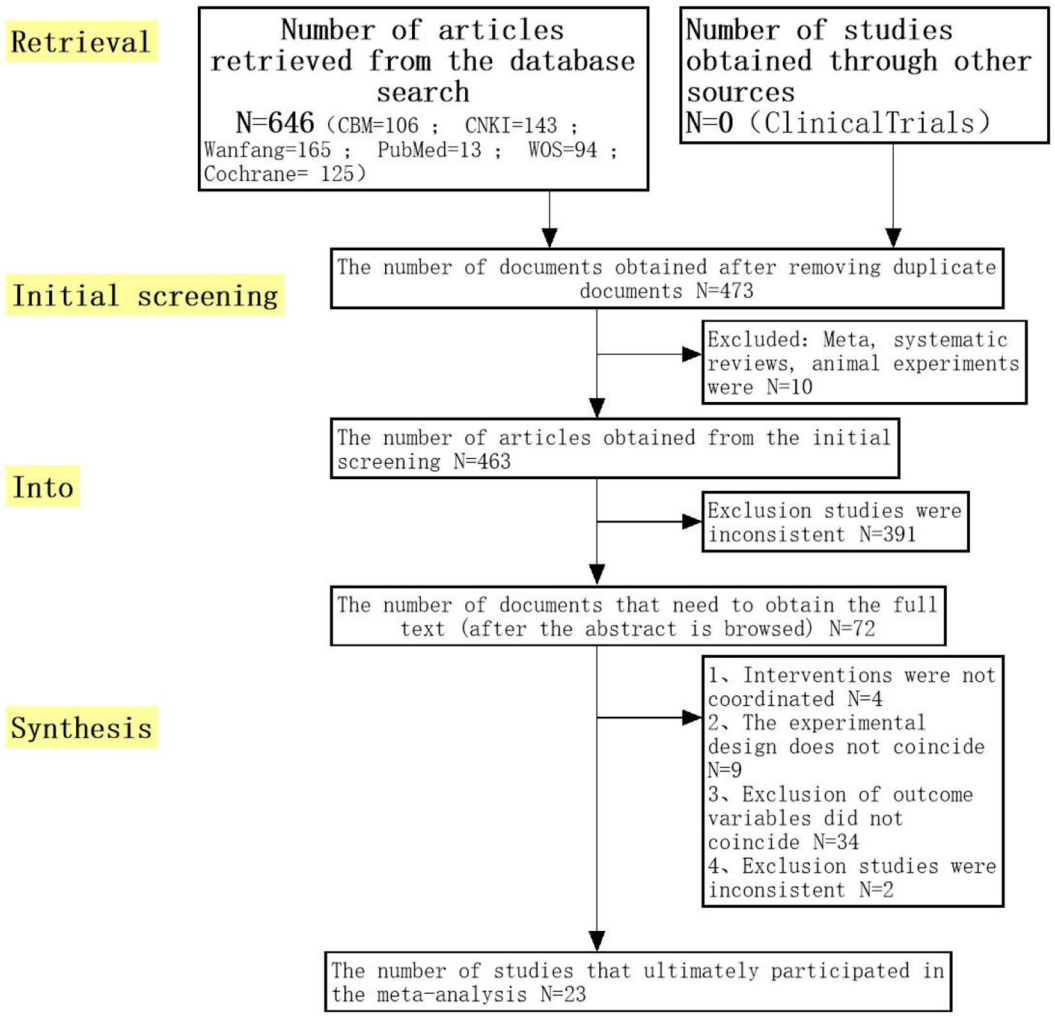

FIGURE 1
Selected randomized controlled trials (RCTs) for meta-analysis.

surgery in adult patients, of whom 2 underwent gynecological laparoscopic surgery, and 3 described laparoscopic surgery in overweight patients. The summary data in Table 1 were processed in Review Manager (version 5.3) software to complete the data bias assessment. We assessed the certainty of the evidence using the GRADE approach, which is presented in Appendix 2. Figure 2 summarizes the details of the risk of bias assessment. Two trials were judged to be at low risk of bias, 18 were at unclear risk, and three were at high risk of bias. All trials produced appropriate random sequences, and nine trials reported appropriate allocation concealment.

After the heterogeneity test ($I^2 = 0\%$ and $P = 0.86 > 0.1$), the Q test indicated that there was no heterogeneity between the selected literature in this study (the heterogeneity was not statistically significant), and the fixed effect was selected for pooled effect size. Twenty-three studies used a fixed-effect pooled RR = 1.17 (95% CI 1.13 to 1.22) and were statistically significant (Z = 7.95 and $P = 0.00001 < 0.05$), suggesting that protective lung ventilation is less likely to have pulmonary complications when applied to laparoscopic surgery than conventional lung ventilation and that protective lung ventilation is 1.17 times less like to cause complications than conventional lung ventilation. Figure 3 provides for details.

By plotting funnel plots to investigate whether there was publication bias in the 23 articles of this study, visual findings showed that the funnel plots were symmetrical (Figure 4) and that there was no publication bias. The funnel plots were then evaluated in Stata software, version 14.0 to obtain $P = 0.36 > 0.1$, further confirming that the data were unbiased, and the conclusions of this study were accurate and reliable, as shown in Figure 5 with details.

Then, we further studied the subgroup analysis of the effects of different PEEP plus small tidal volume ventilation on pulmonary complications (Figure 6), and the results showed that when PEEP was in 6 cm H_2O, RR = 2.71, $I^2 = 0\%$, $P = 0.84$, when PEEP was in 7 cm H_2O, RR = 2.81, $I^2 = 0\%$, P = 0.56, there was no heterogeneity between the literature in the above two groups. We can conclude that different levels of PEEP plus small tidal volume ventilation reduce the incidence of pulmonary complications after laparoscopic surgery. The results of the between-group comparison

TABLE 2 Characteristics of randomized, controlled trials included in the meta-analysis.

	Age		Gender (male/female)		Vt (ml/kg)		PEEP (cmH2O)		Number		Pulmonary complication (*N*)	
	P group	C group	P group	C group	P group	C group	P group	C group	P group	C group	P group	C group
1	59.0 ± 9.0	55.0 ± 12.0	9/22	13/18	7	10	10		31	31	10	11
2	51.1 ± 8.9	50.3 ± 9.8	/	/	7	9	30		44	43	4	11
3	/	/	/	/	6–8	8–10	6		35	35	0	7
4	69.7 ± 5.8	70.8 ± 5.8	98/42	102/38	6	10	5		130	130	24	41
5	52.8 ± 16.5	57.4 ± 10.1	14/7	9/10	6	10	5		21	19	3	9
6	63.8 ± 9.7	68.2 ± 8.3	18/14	15/9	7	9	5		32	28	2	4
7	69.9 ± 6.3	68.6 ± 4.0	11/9	12/8	6	6	7	12	22	22	1	4
8	64.0 ± 6.0	62.0 ± 4.0	23/22	26/19	8	8	5		45	45	3	11
9	70.7 ± 7.1	71.1 ± 6.7	10/13	20/16	6–8	8–10	8–10		36	36	1	7
10	70.6 ± 9.3	70.2 ± 9.4	40/22	39/23	7	8–10	5		62	62	9	21
11	69.3 ± 3.0	70.2 ± 4.3	22/18	25/15	6	10	6		40	40	2	5
12	66.5 ± 8.3	66.1 ± 9.2	35/23	34/23	7	10	7		58	57	1	8
13	55.4 ± 10.7	56.0 ± 12.9	17/18	18/12	6–8	6–8	2		35	30	2	4
14	47.8 ± 12.0	50.0 ± 10.0	12/8	14/6	6	10	5		20	20	2	7
15	51.3 ± 10.3	54.4 ± 6.8	/	/	7	9	7		30	30	0	4
16	43.2 ± 7.3	43.2 ± 7.3	/	/	6	10	8–10		45	45	1	5
17	/	/	/	/	6	10	8–10		30	30	3	8
18	53.3 ± 7.3	52.5 ± 7.0	36/13	32/17	6	9	5		49	49	9	15
19	57.6 ± 5.0	56.9 ± 5.2	12/8	10/10	6	6	5		20	20	1	2
20	68.4 ± 4.0	69.1 ± 4.7	16/14	13/17	6	8	5		30	30	2	3
21	56.2 ± 4.3	57.5 ± 4.8	25/15	21/19	6–8	6–8	10	5	40	40	5	6
22	63.0 ± 6.0	63.0 ± 8.0	56/24	52/28	6	9	5		80	80	14	25
23	1.5 ± 0.5	1.7 ± 0.3	12/8	11/9	7	10	6		20	20	1	2

were I^2 = 0%, P = 0.91, which indicated that there was no heterogeneity between the groups.

We summarized specific pulmonary complications: atelectasis, hypoxemia, pneumonia, respiratory infections, as shown in Table 3. We found that the experimental groups with protective lung ventilation had significantly fewer PPCs than the control groups with conventional ventilation. Patients with PPCs are mainly characterized by atelectasis, hypoxemia, and pneumonia. And a few number of patients had respiratory infection, diffuse infiltrate, localized infiltrate, pleural effusion, increased thickness of interstitium, etc. Therefore, we can conclude that, when protective pulmonary ventilation is used in laparoscopic surgery, the probability of no pulmonary complications is 1.17 times that with conventional pulmonary ventilation, so laparoscopic surgery patients can have a better ventilation effect, with a reduced incidence of postoperative pulmonary complications, and protective ventilation can promote patient prognosis by adopting a protective lung ventilation strategy (small tidal volume + PEEP).

Discussion

For patients who require laparoscopic surgery under general anesthesia, there might not be a variety of serious lung diseases, but various factors, such as anesthetic drugs, mechanical ventilation, pneumoperitoneal pressure, special positioning, and surgical trauma used during surgery, can cause damage to the patient's lung tissue. Studies have found that when pneumoperitoneum pressure is at the level of 11–13 mm Hg it can lead to an average increase of 66% in atelectasis, greatly increasing the incidence of postoperative pulmonary complications.

Mechanical ventilation is one of the important conditions for the successful completion of laparoscopic surgery, but it can also cause ventilator-induced lung injury (VILI) while providing life support to patients. In the past, it was believed that the length of mechanical ventilation was directly proportional to the incidence of pulmonary complications. However, the latest research shows that even a short period of mechanical ventilation can cause VIIL and even ARDS in healthy lungs.

FIGURE 2
Risk of bias of included trials was assessed using the Cochrane risk of bias tool. Low risk = bias, if present, unlikely to significantly change results; unclear risk = bias raises some doubt about results; high risk = bias might significantly change results.

Protective lung ventilation strategies include small tidal volume ventilation and continuous positive airway pressure (PEEP). Relevant studies have shown that excessive tidal volume, blood transfusion, infection, and extracorporeal bypass during mechanical ventilation can lead to damage to healthy lungs (32). In animal experiments, it was found that, if healthy animals were subjected to mechanical ventilation with a large tidal volume for several hours, it caused deformation, necrosis, and exfoliation of alveolar epithelial cells and vascular endothelial cells, increased the level of inflammatory mediators in bronchoalveolar lavage, and significantly increased the expression of various cytokines (such as TNF). In this study, it was found that the use of small tidal volume protective pulmonary ventilation during mechanical ventilation could indeed reduce the incidence of pulmonary complications (33, 34), providing definitive evidence for clinical work.

Continuous positive airway pressure (PEEP) and the use of appropriate PEEP during mechanical ventilation can assist in collapsed alveolar remanoeuvres (35). Studies have shown that alveolar remanation can increase the functional residual gas volume and lung compliance of the lungs from a physiological point of view, improve the ventilation status and oxygenation status of patients, and reduce functional shunts in the lungs. The study found that, comparing small tidal volumes plus lower level PEEP and low tidal volumes plus high level PEEP, the former had a relatively large area of alveolar collapse and atelectasis during surgery and basically no tensile lung tissue. In the latter, there was hypertense lung tissue (36). Therefore, although small tidal volumes plus low-level PEEP cannot adequately maintain alveolar remanoestasis, it will not cause alveolar hypertension. However, small tidal volumes plus high-level PEEP can satisfactorily achieve the purpose of alveolar remanoeuvres, but at the same time, there is alveolar hypertonic damage, which has an impact on circulatory function. Therefore, too low or too high a level of PEEP has certain adverse effects. Choosing an appropriate PEEP is particularly important for mechanical ventilation and preventing postoperative pulmonary complications.

Protective lung ventilation strategies have received a lot of attention in recent years as a new approach to mechanical ventilation-related lung injury. Many studies have shown that protective lung ventilation has high clinical value for the treatment of patients with acute respiratory lung injury (ALI) and acute respiratory distress syndrome (ARDS), while there is a lack of clear clinical evidence in relevant studies in patients with better physical condition. In this study, we concluded that the use of protective lung ventilation strategies in general patients can effectively reduce the incidence of postoperative pulmonary complications by including patients of different ages and physical conditions. This demonstrates that the protective ventilation strategy with a small tidal volume plus moderate PEEP is also suitable for mechanical ventilation in general patients. The evidence shows that a target tidal volume of 6 mL/kg causes mild hypercapnia in patients with relatively normal lung function and gas exchange. Studies have shown that mild hypercapnia is permissible during ventilation because respiratory acidosis due to hypercapnia can increase respiratory motility, although this is based on the absence of craniocerebral lesions or cardiovascular diseases. In addition, in

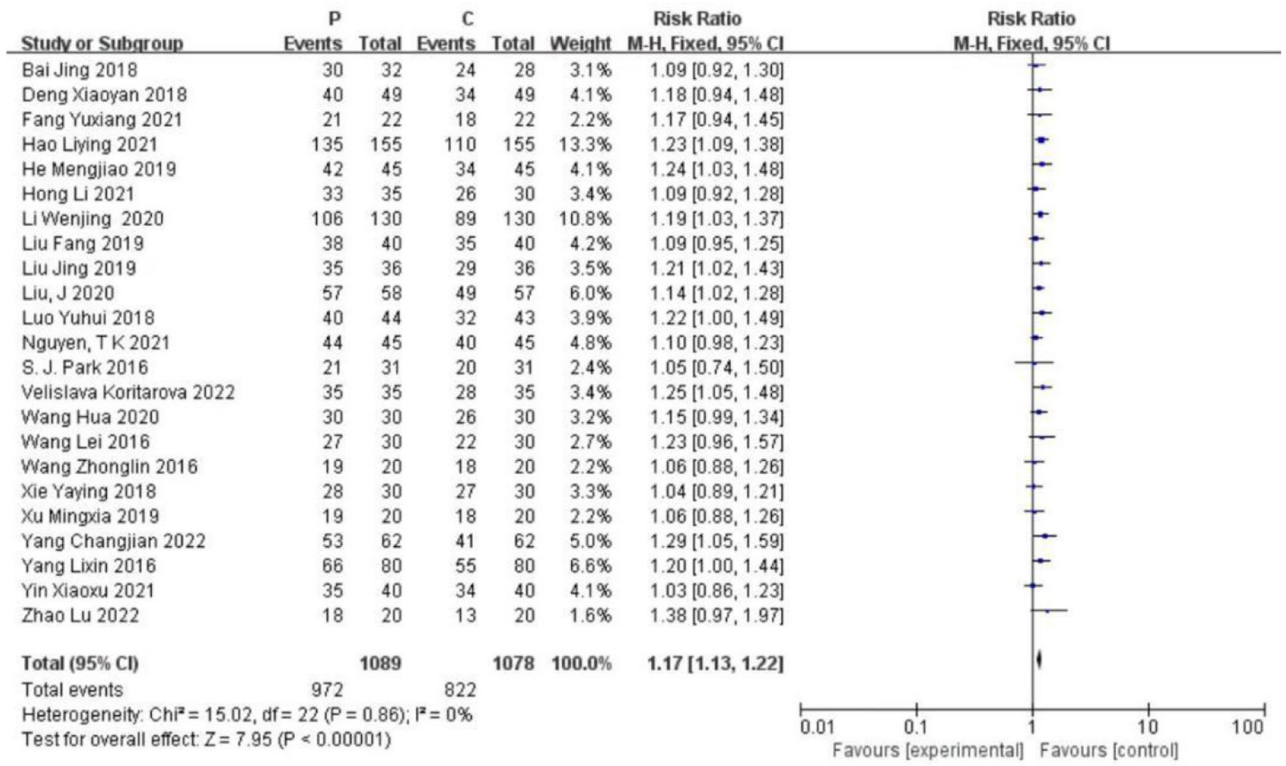

FIGURE 3
Effect of protective lung ventilation on pulmonary complications after laparoscopic surgery. A risk ratio >1.0 indicates a favorable effect on postoperative lung recovery. CI, confidence interval; event, number of people without pulmonary complications. $I^2 = 0\%$, P = 0.86.

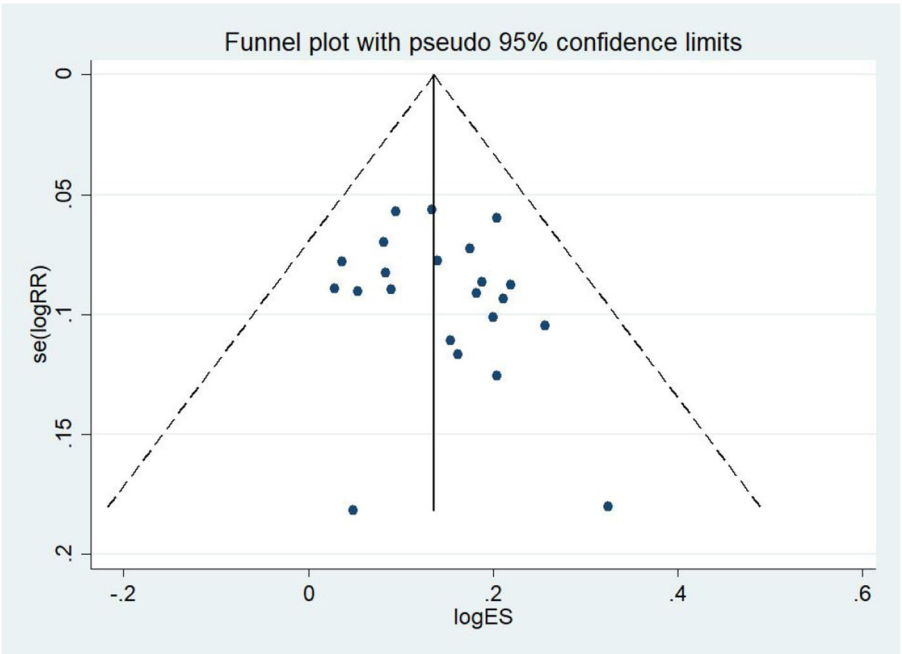

FIGURE 4
Test for bias (funnel plot). Preliminary judgement of bias was determined by whether it was symmetrical.

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0884708	.0526785	1.68	0.108	-.0210802	.1980217
bias	.5845151	.6240449	0.94	0.360	-.7132574	1.882288

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FIGURE 5
Protective lung ventilation test for bias of pulmonary complications after laparoscopic surgery. $P > 0.1$, the included data were unbiased and statistically significant.

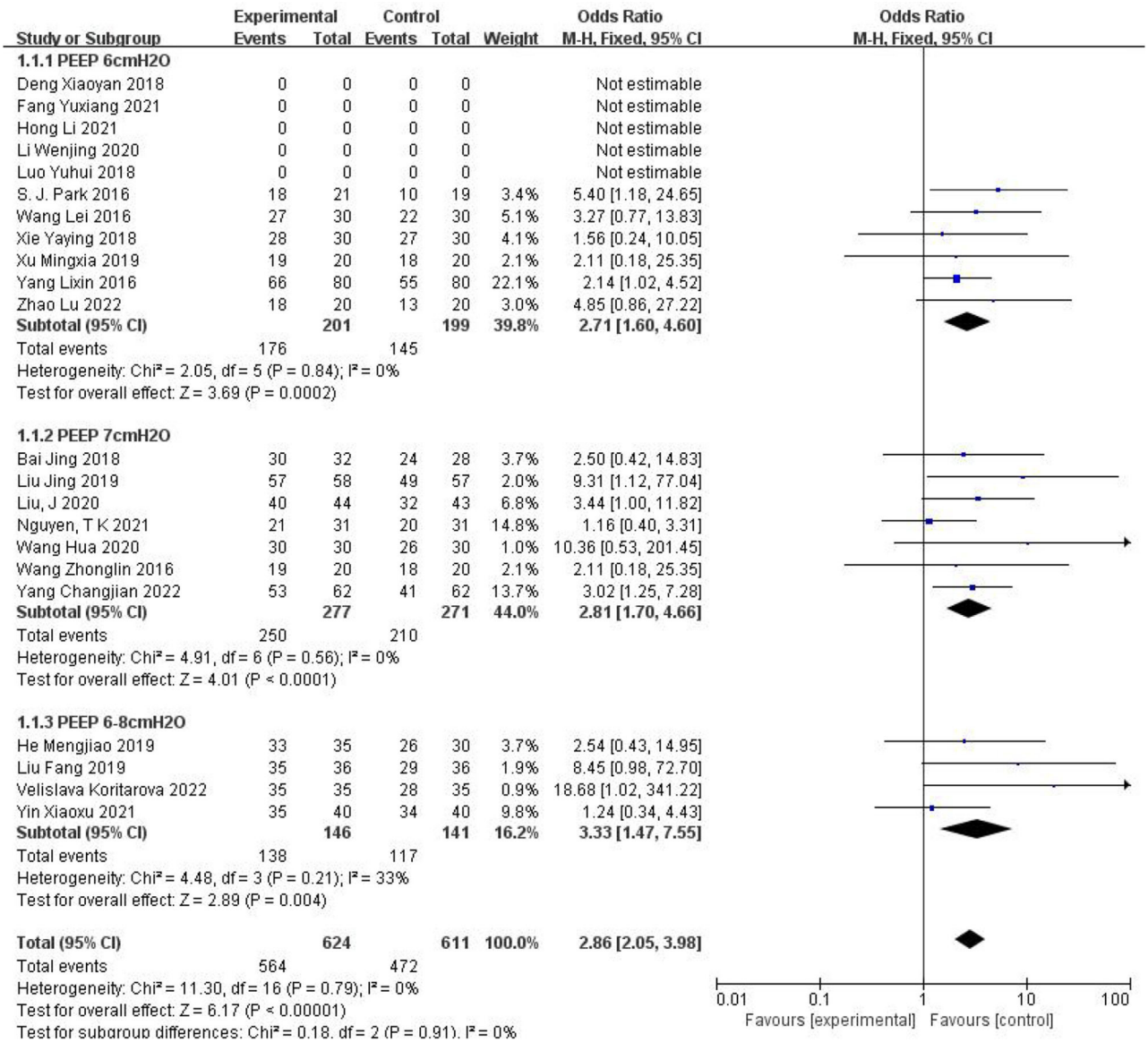

FIGURE 6
Subgroup analysis of different PEEP plus small tidal volume on the pulmonary complications. A risk ratio >1.0 indicates a favorable effect on postoperative lung recovery. CI, confidence interval; event, number of people without pulmonary complications.

TABLE 3 Summary of specific pulmonary complications.

Number	Atelectasis		Hypoxemia		Pneumonia		Respiratory infection	
	P group	C group	P group	C group	P group	C group	P group	C group
1		2						
2		4					3	5
3		7						
4	24	41						
5	3	8				1		
6								
7		2					1	1
8								
9					1	7		
10								
11		4			2	1		
12								
13								
14	1	3	1	3				
15						4		
16		1	1	3				
17								
18	3	8	6	12				
19		1			1	1		
20		0	4	11	2	3		
21	2	1						
22	6	13	10	20	7	16		
23						1		
Total	39	95	22	49	13	34	4	6

this study, we also analyzed the effect of small tidal volume plus different levels of PEEP on postoperative pulmonary complications in patients. Through subgroup analysis, we found that when PEEP was set to 6 or 7 cm H_2O, compared with conventional ventilation group, it can effectively reduce the occurrence of postoperative pulmonary complications in patients, which provides the effective evidence for subsequent clinical work.

In summary, a protective lung ventilation strategy with a small tidal volume plus moderate levels of PEEP can be used to minimize ventilator-associated lung injury when mechanical ventilation is performed during laparoscopic surgery (3). Postoperative pulmonary complications, including atelectasis, pneumonia, and lung injury, are the most common complications and the main causes of morbidity and mortality, affecting the prognosis and prolonging the hospital stay. Therefore, we recommend the use of protective lung ventilation strategies during mechanical ventilation, which can effectively reduce the incidences of lung injury and lung infection. A strategy of low tidal volume + moderate positive end-expiratory airway pressure reduces the risk of lung injury and infection. In addition, the occurrence of VILI is also related to various factors, such as inspired oxygen concentration, ventilation mode, and pulmonary recruitment maneuvers, so we still require further research to optimize the protective lung ventilation strategy by adjusting the inspired oxygen concentration, improving the ventilation mode, and selecting a reasonable lung recruitment method.

Limitations

This study has certain limitations. Firstly, in the process of screening the literatures, two people completed the process separately and summarized them, and there was a degree of subjectivity. Secondly, the 23 articles included patients of different ages, including children, adults, and the elderly, and the outcome indicators were inevitably affected by age, physical condition, lung function and other factors, which had an impact in our conclusion that the protective lung ventilation strategy used in laparoscopic surgery can effectively reduce the incidence of PPCs. In addition, we used pulmonary complications as an independent and complete indicator to demonstrate that protective lung ventilation strategies used in laparoscopic surgery are effective in reducing the incidence of PPCs after surgery. However, there

was no detailed comparison of interventions for pneumonia, atelectasis, etc.

Conclusion

Compared with conventional mechanical ventilation, protective lung ventilation reduces the incidence of postoperative pulmonary complications. For patients undergoing laparoscopic surgery, we suggest the use of protective lung ventilation, which is effective in reducing the incidence of lung injury and pulmonary infection. Implementation of a low tidal volume plus moderate positive end-expiratory pressure strategy reduces the risk of postoperative pulmonary complications. Postoperative pulmonary complications, including atelectasis, pneumonia, and lung injury, are the most common complications and the main causes of morbidity and mortality, affecting the prognosis and prolonging the hospital stay. Therefore, the use of protective lung ventilation strategy can facilitate the patient's recovery more quickly.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YW and LJ proposed and designed this study. MS and BY retrieved and selected the data and responsible for the extraction of the data and the quality assessment of all study data. MS performed a statistical analysis and summarized the data and drafted the manuscript. YW, BY, and TW revised it. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1171760/full#supplementary-material

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New and personalized ventilatory strategies in patients with COVID-19

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Coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus and may lead to severe respiratory failure and the need for mechanical ventilation (MV). At hospital admission, patients can present with severe hypoxemia and dyspnea requiring increasingly aggressive MV strategies according to the clinical severity: noninvasive respiratory support (NRS), MV, and the use of rescue strategies such as extracorporeal membrane oxygenation (ECMO). Among NRS strategies, new tools have been adopted for critically ill patients, with advantages and disadvantages that need to be further elucidated. Advances in the field of lung imaging have allowed better understanding of the disease, not only the pathophysiology of COVID-19 but also the consequences of ventilatory strategies. In cases of refractory hypoxemia, the use of ECMO has been advocated and knowledge on handling and how to personalize strategies have increased during the pandemic. The aims of the present review are to: (1) discuss the evidence on different devices and strategies under NRS; (2) discuss new and personalized management under MV based on the pathophysiology of COVID-19; and (3) contextualize the use of rescue strategies such as ECMO in critically ill patients with COVID-19.

KEYWORDS

COVID-19, noninvasive respiratory support, invasive mechanical ventilation, prone position, recruitment maneuvers, extracorporeal membrane oxygenation

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus and can lead to respiratory failure (1, 2). COVID-19 may manifest with different degrees of respiratory failure, up to acute respiratory distress syndrome (ARDS), named "C-ARDS" (3). Initially interpreted as viral pneumonia, its radiologic picture includes ground-glass opacities (GGOs), with large alveolar edema and consequent collapse and increase in blood volume and interstitial space. GGOs also have dilated vessels (4), with a risk of microthrombosis and endotheliitis (5). At hospital admission, patients can present with severe hypoxemia even under conventional oxygen therapy (COT) and dyspnea, which may require ventilatory support. The disease can develop heterogeneity among patients, and COVID-19 can assume different phenotypes (6). Three phenotypes have been described: L-type, characterized by low lung elastance; H-type, characterized by high lung elastance (7–9); and F-type, the final evolution of COVID-19 characterized by lung fibrosis (10–13).

However, depending on the severity of the disease, the need for supportive strategies may evolve to mechanical ventilation (MV) with the use of low tidal volumes (V_T) (14, 15). If hypoxemia persists, prone position (PP) and alveolar recruitment maneuvers (ARM) can be considered (9, 12, 16–19). In addition, extracorporeal membrane oxygenation (ECMO) should be considered in the most severe cases of C-ARDS (17, 20–22). Recently, the literature has focused on individualization of ventilatory strategies, according to a broad range of patient variables (9, 10), including physiological data, lung imaging, laboratory data, biomarkers, and even omics data (10). However, some of these tools are not routine practice in many hospitals. Nevertheless, adopting personalized medicine could better implement the therapy in the patients with C-ARDS.

The aim of this narrative review are to: (1) discuss the evidence on different devices and strategies for noninvasive respiratory support (NRS); (2) discuss new and personalized management under MV based on the pathophysiology of COVID-19; and (3) contextualize the use of rescue strategies such as ECMO in critically ill patients with COVID-19 (Figure 1).

2. Physiopathology and phenotypes

In the early stages of COVID-19, the virus targets nasal, bronchial, and pneumocytic epithelial cells. The spike protein of the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor (23), which allows the virus to enter the host cells, mainly into type II pneumocytes, where the virus starts to replicate. Subsequently, damage to endothelial cells occurs with consequent damage to the alveolar-capillary barrier, resulting in increased cell permeability (23).

The late phase is characterized by a large inflammatory cascade mediated by neutrophils and monocytes, which leads to large diffuse alveolar lesions (4, 5). In this phase, vascular lysis is often observed, with extensive destruction of the lung parenchyma and pneumocytes, alveolar collapse, and the formation of hyaline tissue (5). At the vascular level, dysregulation with stasis, microthrombi, microhemorrhages, and pulmonary embolism are commonly observed due to the high vascular permeability. The alveolar-capillary destruction caused by vascular lysis results in progressive hypoxemia and hypercapnia (4, 9, 24). At first, hyperventilation is noted. However, with progression of the inflammatory cascade, arterial partial pressure of carbon dioxide ($PaCO_2$) levels increase and pH becomes acidic (5).

Faced with great alveolar damage, COVID-19 presents as a disease with severe hypoxemia (4, 5, 9, 24, 25). The development of the disease is characterized by the predominance of non-aerated lung tissue, mainly in the dependent regions of the lung. Under normal conditions, these regions have normal blood flow. However, in COVID-19, perfusion is observed to be antigravity, diverting to non-dependent (normally aerated) lung regions (8, 26, 27), with loss of the hypoxic vasoconstriction reflex (4, 6, 8, 27). One hypothesis is that there is a loss of response of sensitive chemoreceptors to low arterial partial pressure of oxygen (PaO_2). Another possibility is dysregulation of mitochondria and the pathways involved in oxygen sensing (26). Ventilation/perfusion (V/Q) dysregulation is observed, which is initially due to the presence of hyperperfused ground-glass regions (8, 9, 24, 26, 27). In later stages, the formation of atelectasis is observed, distributed non-homogeneously. V/Q irregularity remains due to the presence of extremely non-aerated areas (8, 9, 24, 26, 28). In autopsy studies, lungs with confirmed SARS-CoV-2 infection exhibit paste within the alveolar cavity, fibrinous exudation, proliferation of type II alveolar epithelial

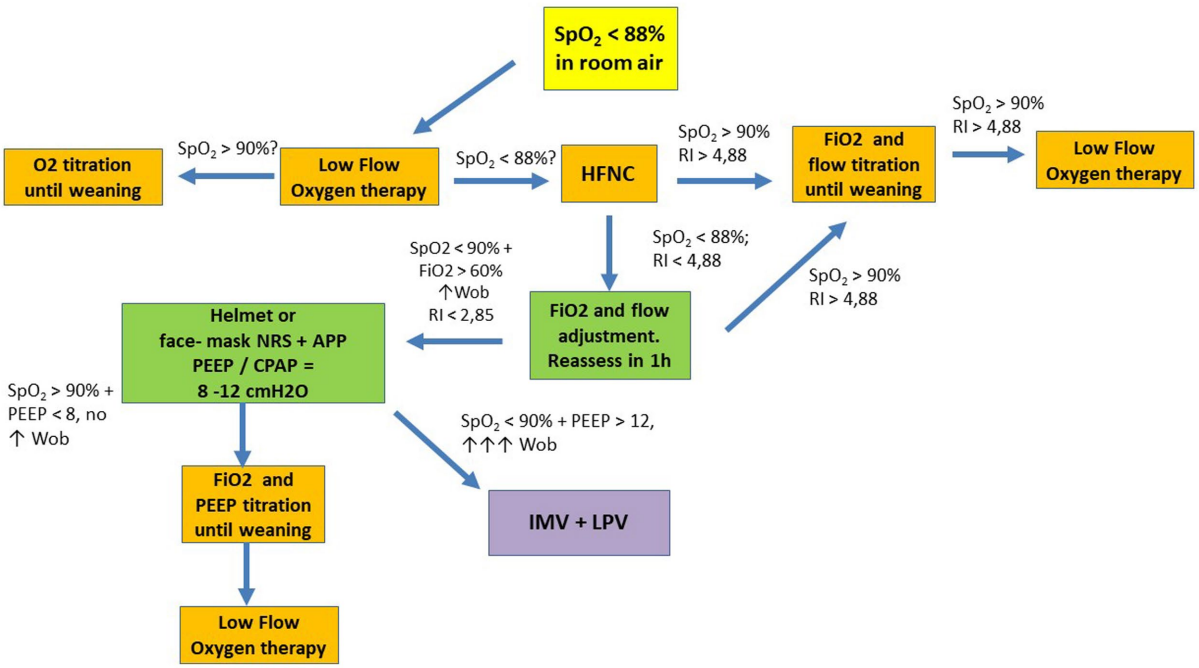

FIGURE 1
Suggested flowchart for noninvasive ventilatory management in COVID-19. APP, awake prone position; HFNC, high flow nasal cannula; LPV, lung protective ventilation; NRS, noninvasive respiratory support; P/F, PaO_2 to FiO_2 ratio; RI, ROX Index; SpO_2, oxygen saturation; WOB, work of breathing; CPAP, continuous positive airway pressure; IMV, invasive mechanical ventilation; PEEP, positive end expiratory pressure.

cells and macrophages, vascular congestion of the alveolar septum, and vascular thrombi (23). This points to the importance of the vascular bed in the development of COVID-19 pneumonia (Figure 2).

Some authors divide the histopathology of COVID-19 into three phases that resemble pulmonary ARDS due to the presence of diffuse alveolar damage; (1) the acute/early phase, characterized by intra-alveolar edema and interstitial widening, with peak hyaline membrane formation, both diffuse and focal, which occurs between 4 and 5 days after the initial insult; (2) the organizer stage, also called myeloproliferative, characterized by intense cell proliferation of fibroblasts and hyperplasia of type II epithelial cells; (3) the late/fibrous stage with honeycombing (8, 23, 26).

Three COVID-19 phenotypes can be established to broaden understanding of the pathophysiology (4, 8, 9, 24–27), although the literature does not recommend this (9).

2.1. COVID-19 phenotypes

2.1.1. The L phenotype

The L phenotype occurs in mild to moderate cases, mainly in the early stages. It is classified as low respiratory system elastance, low ventilation-to-perfusion ratio, low lung weight, low lung recruitability (25). It is the longest surviving phenotype (25). It is characterized by hyperperfused subpleural focal GGOs maintaining lung areas that are normally aerated (4, 8, 9, 24–27). Increased perfusion can lead to capillary collapse and hypercoagulability/microthrombosis, leading to deviation of blood flow to the non-dependent regions of the lung (very aerated) and resulting in loss of the hypoxic vasoconstriction reflex (4). Thus, an increase in poorly perfused dependent areas is observed. This situation decreases the V/Q ratio. The clinical picture includes severe hypoxemia with satisfactory ventilatory mechanics ("happy hypoxemia") (4, 5). Low lung weight is observed, and compliance of the respiratory system is normal or minimally reduced. Therefore, the percentage of poorly aerated tissue is low, as is recruitability. Zubieta-Calleja et al. (23) suggest that this happy hypoxemia may be due to a reduced ventilatory drive, commonly found in this phenotype. Given the dissociation between the extent of hypoxemia and normal compliance, two explanations have been proposed to characterize the severe hypoxemia. The first is the focality of the lung lesion, as demonstrated by the ground-glass pattern. This partially reduces ventilation without affecting elastic recoil. Because there is great lung perfusion, low V/Q areas are diffusely distributed throughout the lung from ventral to dorsal and cranial to caudal (4, 5, 8, 9, 24–27). Pulmonary involvement is low at this stage, therefore the patient's ventilatory work is still normal. A second explanation is that gas exchange abnormalities arise primarily from vascularly mediated injury, which is not observed at this stage (25). Gattinoni et al. (6) suggest that hypoxemia is due to perfusion irregularity and that vasoplegia is also responsible for low PaO_2. In addition to diverting blood flow, ventilation is directed toward non-dependent regions, which allows the creation of dead space areas (5). In conjunction with low V/Q lung units, this phenotype is considered to have wasted ventilation, which does not substantially affect oxygenation (8). Patients with this phenotype may be candidates for NRS or high flow nasal oxygen to correct hypoxemia (8, 29). This phenotype can also be found in promptly intubated patients.

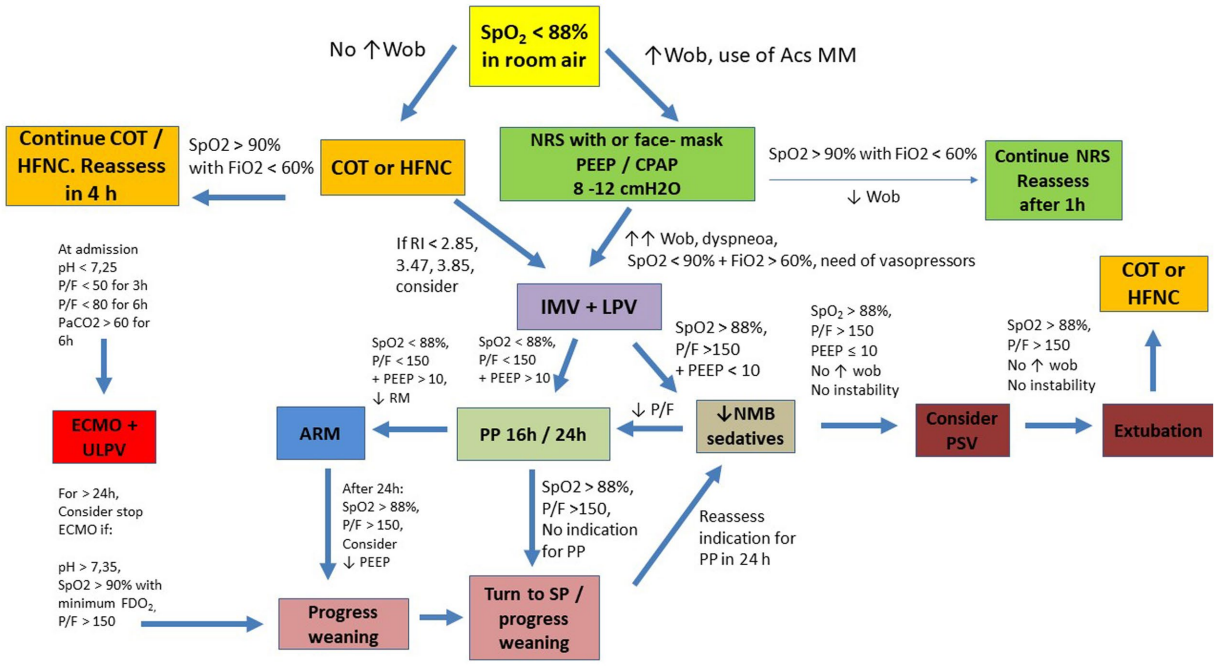

FIGURE 2
Suggested flowchart for ventilatory management in COVID-19. Acs MM: Accessories Muscles; ARM, alveolar recruitment maneuver; COT, conventional oxygen therapy; ECMO, Extracorporeal Membrane Oxygenation; IMV, invasive mechanical ventilation; HFNC, high flow nasal cannula; LPV, lung protective ventilation; NMB, neuromuscular blocker; NRS, noninvasive respiratory support; P/F, PaO_2 to FiO_2 ratio; PP, prone position; PSV, pressure support ventilation; RI, ROX Index; SP, supine position; SpO_2, oxygen saturation; ULPV, ultra lung protective ventilation; WOB, work of breathing; CPAP, continuous positive airway pressure; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; FDO_2, fraction of oxygen in the sweep gas stream; PEEP, positive end-expiratory pressure.

As the disease progresses, the L phenotype may progress to the H phenotype, characterized by low lung compliance. One of the signs of transition between phenotypes is the need for a high fraction of inspired oxygen (FiO_2) and increased ventilatory drive (8, 25). Increases in inspiratory efforts are directly associated with worsening of inflammation and, in turn, with increased V_T and increased vascular permeability with the formation of alveolar edema. This is one of the mechanisms of patient self-inflicted lung injury (P-SILI) (discussed in Section "Patient self-inflicted lung injury in NRS"). In addition, NRS should be considered with utmost caution in patients with L phenotype, because progression from type L to type H phenotype can be also caused by mechanisms of inflammatory amplification overlapping the host inflammatory response phase (25). Over time, alveolar edema increases and lung volume decreases, reducing the lung area available for gas exchange (8, 9, 24–27). Thus, the inspiratory volumes generated for a given inspiratory pressure decrease, resulting in dyspnea. At this time, transition from the L to the H phenotype is expected (8, 25).

2.1.2. The H phenotype

The H phenotype represents evolution of the L phenotype and is found in critically ill patients (8, 9, 24–27). In this phase, there is amplification of the inflammatory response, allowing greater cellular permeability and formation of alveolar edema (25). As a result of the decrease in gas volume during the evolution of the L phenotype, an increase in lung weight is observed due to the presence of irregularly distributed consolidated areas, predominantly in the dependent regions. This leads to an increase in lung elastance and, in turn, a decrease in lung compliance, with the development of a restrictive pattern of ventilation. Alveolar units of low V/Q ratio are increased (8, 9, 24–27). In this phenotype, however, this happens due to increased lung consolidation, unlike the L phenotype, where the explanation rested on GGOs (8). By increasing pulmonary edema and the pressure exerted on the lung parenchyma, the cardiac output perfusing non-aerated lung areas contributes to the formation of a right-to-left shunt (6). As in the L phenotype, wasted ventilation persists to a great extent (8). The H phenotype has a high capacity for alveolar recruitment (Section "Alveolar recruitment maneuvers and PEEP titration").

2.1.3. The F phenotype

Faced with the ventilatory dysfunctions found in the two previous phenotypes, Tonelli et al. (25) considered the final pathway of COVID-19 to be the development of pulmonary fibrosis, namely the F phenotype (8, 25, 30).

The evolution of the L to H phenotype is mediated by an intense inflammatory cascade (24). During its evolution, there is activation of multiple aberrant inflammatory pathways that unbalance the relationship between pro-fibrotic and anti-fibrotic mediators (25). In the F phenotype, fibroproliferation occurs so that the lung resembles a patchwork quilt. This causes the alveolar units to have different lung elasticities, with different capacities for volumetric accommodation (8, 9, 24–27).

During spontaneous ventilation, some alveolar units may be more distensible than others, generating high transpulmonary pressures with a high risk of lung injury and pneumocyte rupture (8, 9, 24–27). Furthermore, the pulmonary fibrotic pattern found in this phenotype reduces carbon dioxide diffusing capacity, leading to hypercapnia (8, 25). Rescue therapies such as alveolar recruitment and PP are not very effective because there is a high density of collagen, which is not easily distensible.

3. Noninvasive respiratory support

At hospital admission, patients with COVID-19 may present with low PaO_2 and dyspnea. Both can be explained by silent hypoxemia and the presence of non-ventilated areas, as shown by computed tomography, with important ventilation-perfusion inequalities (2, 31). NRS is able to correct hypoxemia, reduce the work of breathing, and improve poor ventilated areas (28), and, even in some scenarios, endotracheal intubation can be avoided (31).

3.1. The choice of NRS interface

Overall, two strategies have been adopted: continuous positive airway pressure (CPAP) and BILEVEL, i.e., pressure support (PS) +: positive end expiratory pressure (PEEP) with the use of two interfaces: facemask and helmet (1, 2, 15, 28, 31, 32). Both interfaces improve oxygenation and reduce aerosolization compared with a high flow nasal cannula (HFNC) and COT.

Patients with COVID-19 may require prolonged NRS therapies (due to low oxygenation on admission) to avoid MV. In this case, there might be a need to apply high PS of up to 12 cmH_2O (15, 29, 32), PEEP values between 8 and 12 cmH_2O (2, 15, 29, 32), reaching up to 15 cmH_2O (33) and as little air leakage as possible. The helmet is one of the best interfaces to promote patient comfort (1, 2, 15, 34). It is also associated with reduced intubation rates and better correction of hypoxemia (35). However, the helmet is associated with greater rebreathing of CO_2, requiring intensive monitoring (36). Furthermore, a randomized clinical trial by Arabi et al. (34) divided 320 patients into two groups: half used a helmet and the other half received COT. No differences in mortality were observed after 28 days, but helmet mortality was observed at day 180. Compared with COT, no differences in mortality were observed (37).

3.2. Parameter adjustments during NRS

The best comfort level can be achieved by adjusting ventilation parameters, such as PS and PEEP levels. The PS level is associated with the generation of V_T necessary to ensure adequate aeration; the PEEP level is responsible for ensuring oxygenation. A retrospective study reported the use of CPAP in 46 patients with PEEP ranging between 8 and 12 cmH_2O. The PEEP level was adjusted according to clinical tolerance, air leakage, and peripheral saturation of oxygen (SpO_2) (31). Only nine patients were intubated between days 7 and 14, and the authors recommended the use of CPAP to avoid intubation. Similar results were found in another study that compared HFNC with CPAP in 151 patients (98% with helmet) and NRS in 72 patients (15 with a helmet and 57 with a facemask) (1). One hundred sixty-three patients received HFNC. For the first two interfaces, the authors established a mean PEEP level of 10.2 cmH_2O during CPAP and 9.5 cmH_2O in NRS. Although all the interfaces were shown to improve oxygenation, there was no difference in intubation rates and

length of stay (1). In an important randomized clinical trial, COT (low or high flow) was compared with CPAP adjusted to a mean PEEP of 8.2 cmH_2O. Only 36% of the patients in the CPAP group were intubated compared with 44% of the HFNC group. In addition, CPAP reduced mortality compared with COT (26). More recently, Colaianni-Alfonso et al. (35) studied 112 patients with moderate to severe COVID-19 who failed HFNC; the patients were divided into two groups for CPAP: one group used a facemask interface with median PEEP of 12 cmH_2O and the other a helmet interface with median PEEP of 14 cmH_2O. The groups remained on continuous CPAP for 24 h. It was observed that the helmet group had lower intubation rates and a more marked improvement in oxygenation compared with the facemask group, which had higher intubation rates and longer length of stay. Although these data favor the helmet, caution is required in the interpretation, because the PEEP value applied must be consistent with the clinical condition of the patient.

Adjustments other than PS and PEEP can be fine-tuned at the bedside. In 2009, a study (36) evaluated 13 patients after extubation and randomly performed three 20-min periods of NRS with three interfaces: facemask, helmet, and helmet with a 50% increase in PS and PEEP associated with a high rate of pressurization (rise time). Using the first two interfaces, PS had a mean level of 10 cmH_2O, PEEP of 5 cmH_2O and 0.2 s of pressurization time. In the third group, PS had a mean level of 15 cmH_2O, PEEP of 8 cmH_2O, and the shortest possible pressurization time, i.e., 0.05 s. The authors analyzed transdiaphragmatic pressure (Pdi), which is a surrogate of inspiratory effort through an esophageal catheter. Pdi was reduced in the helmet group with higher PS (15 cmH_2O) and PEEP (8 cmH_2O) and fast pressurization time (0.05 s). This highlights an important comparison between the facemask and helmet interfaces. Keeping the same cycling-off (25%), the helmet had more asynchrony events at the end of inspiration compared with the facemask, with ventilator cycling sooner or later compared with the end of the patient's inspiratory time. In this case, the ventilator's inspiratory time was shorter than the patient's neural time. The authors point out that an overlap exists between the PS applied by the ventilator and the patient's neural time. As an explanation, the authors hypothesize that cycling with the helmet seems to occur due to changes in flow caused by the mechanical characteristics of the interface and not by the characteristics of the patient. With the patient's inspiratory time longer than that of the helmet, the interface promotes minimal reduction in ventilatory overload. Further studies on patients with COVID-19 comparing the two interfaces are necessary for a better understanding of their ventilatory repercussions.

The choice of the ideal interface, as well as fine ventilator adjustments, should aim to achieve patient-ventilator synchrony, reduce the work of breathing, especially with the helmet interface and to ensure comfort. A multicenter randomized clinical trial randomized 54 patients (mean age, 66 years) to NRS and 55 to HFNC (15). The NRS group underwent therapy for at least 48 h and used a helmet interface with PS and PEEP levels ranging between 10 and 12 cmH_2O, no pressurization time (rise time), expiratory trigger between 10 and 50% to avoid double trigger, inspiratory trigger to avoid auto-triggering, and maximum inspiration time between 1 and 1.2 s. PS was titrated individually to ensure high flows to the patient. The NRS group showed lower intubation rates and more MV-free days compared with the HFNC group. This allows us to conclude that the success of NRS is based on fine ventilatory adjustments.

Typically, NIV is a therapy performed in the ICU. However, with the pandemic exceeding the capacity of available beds, this tool gained space outside the ICU. Cammarota et al. (37) conducted a systematic review with meta-analysis including 17 articles containing 3,377 patients which showed the effectiveness of NIV outside the ICU environment as an adequate tool to deal with the demand for ventilatory assistance.

3.3. NRS therapeutic targets

The literature is not concordant regarding the therapeutic objectives of NRS. Perkins et al. (28) indicated different factors as therapeutic targets, such as: $SpO_2 > 90\%$, respiratory rate ≤ 25 bpm, and a reduction in the work of breathing (26). Aliberti et al. (2) stated that NRS weaning can be performed if the patient's $SpO_2 > 94\%$ with $FiO_2 < 50\%$ and PEEP ≤ 5 cmH_2O. Arabi et al. (34) stated that application of PEEP should target SpO_2 between 92 and 98%, and that the respiratory rate should be <25 bpm. More recently, Colaianni-Alfonso et al. (35) state that application of PEEP should target an SpO_2 between 92 and 96%.

3.4. Predictors of NRS failure

After starting NRS, patient monitoring must be constant to assess its effectiveness or failure. Arabi et al. (34) suggest assessment every 1 to 3 h, but this may vary according to the intensive care unit (ICU). In case of therapy refractoriness, the literature indicates that MV should not be postponed. Some signs of failure mentioned in the literature are: respiratory rate > 40 bpm, respiratory acidosis with pH <7.25–7.30, use of accessory muscles, dyspnea, swallowing disturbance, $SpO_2 < 88$–90% for more than 5 min, PaO_2/FiO_2 ratio < 100, persistent requirement for $FiO_2 > 70\%$, hemodynamic instability (systolic blood pressure < 90 mmHg or mean blood pressure < 65 mmHg, even with volume resuscitation), deterioration in the level of consciousness (2, 15, 34, 35). Contrary to the data, the intubation criteria in the randomized clinical study by Perkins et al. (28) are stricter. These authors compared CPAP with low and high flow oxygen therapy and considered an $SpO_2 \leq 94\%$ with an FiO_2 of at least 40% to be a ventilatory risk. Robba et al. (27) suggest immediate intubation if the PaO_2/FiO_2 ratio does not improve and/or $PaCO_2 < 30$ mmHg and/or respiratory rate > 28 bpm using accessory muscles for more than 3 h. More recently, the study by Colaianni-Alfonso et al. (35), who compared helmet CPAP and helmet facemask (discussed earlier), considered pH <7.35 as a criterion for intubation, in addition to all previous signs. These data indicate that there is no clear guideline for the signs of NRS failure, allowing the use of some scales to help diagnose it (Figure 1).

3.5. NRS failure prediction scales

The literature presents some scales/indices that help in the diagnosis of therapeutic failure during NRS:

- ROX Index (38–40)
- Sepsis-related Organ Failure Assessment (SOFA) (41)

- HACOR Score (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) (42–45)
- Simplified Acute Physiology Score (SAPS) (46)

3.5.1. ROX index

Originally developed to assess the effectiveness of HFNC, the ROX Index has been used as a predictor of the success or failure of NRS. It consists of dividing the SpO_2/FiO_2 quotient by the respiratory rate. It must be calculated in periods of time not yet defined in the literature, but which may be the same as the HFNC. Values < 2.85, <3.47, and < 3.85 after 2, 6, and 12 h, respectively, have been demonstrated to be predictors of therapy failure (38). At the same cutoff points, values ≥ 4.88 indicate success of NRS (38). A recent article applied CPAP with a mean PEEP of 12 cmH_2O in 112 patients with a facemask interface. All patients remained on CPAP for 24 h (39). The researchers calculated the ROX Index after 2, 6, 12, and 24 h of positive airway pressure, and values <6.64 after 24 h of therapy were associated with therapeutic failure. The cutoff periods of 2, 6, and 12 h showed low specificity and sensitivity (39). Higher cutoff points were found in an American study in 2022 (40). The researchers applied CPAP in 95 patients with an initial PEEP of 5 cmH_2O. FiO_2 was adjusted individually by SpO_2. The ROX Index was measured after 2, 6, 12, 18, and 24 h of positive airway pressure, and values < 8.76, <9.08, <9.50, <8.58, and < 7.77, respectively, were predictors of NRS failure. However, details of the interfaces were not given (34).

3.5.2. Sepsis-related organ failure assessment

SOFA was developed in 1996 (41) to assess multiorgan failure, which is a characteristic of COVID-19 (30). It includes six domains each with scores between 1 and 4: breathing, coagulation, liver, cardiovascular, neurologic, and renal. Values > 2 indicate the presence of sepsis and, therefore, a risk of mortality. A recent prospective study (47) evaluated 1,491 patients, 158 of whom received NRS; the rest received low flow or high flow oxygen therapy. Mean PS was 8 cmH_2O, mean PEEP was 7 cmH_2O, and mean FiO_2 was 60%. Patients on NRS had a mean SOFA score of 3. This group had higher intubation and mortality rates at 28, 60, and 90 days. Although the authors did not provide a cutoff point for NRS failure, they showed that most patients had a score > 3 in the cardiovascular domain after 24 h in the ICU. Previously, another prospective study (48) included 58 patients received NRS. Twenty-seven patients who progressed to intubation had an average of 4 points on the SOFA; the group who were not intubated had 3 points. Furthermore, the authors showed that high scores on the scale were associated with low oxygenation. Although the authors did not explain this association, within the respiratory domain of SOFA, a score of 4 indicates a PaO_2/FiO_2 ratio < 100, suggesting therapeutic failure. They concluded that high SOFA was related to intubation but did not provide data on mortality. These data are in agreement with previous studies (1). With the facemask and helmet interfaces, the average SOFA values were 3.3 and 4, respectively. The difference in scores between the interfaces remains unknown.

3.5.3. HACOR score

Originally developed in 2017 (42), the HACOR Score consists of five parameters easily collected at the bedside: heart rate, acidosis, consciousness, oxygenation and respiratory rate. Of these domains, four are included in the evaluation of the effectiveness of NRS, which makes this score very accurate in detecting therapeutic failure (43). The authors reported that the cutoff point for NRS failure must be ≥5. The study by Innocenti et al. (44) evaluated 135 patients who underwent CPAP with a full-face or oronasal mask. The HACOR Score, ROX Index, and SOFA scales were applied 3 days and 1 day before the start of NRS, on the day of admission, and on days 1, 2, 5, 8, and 11 after NRS. The authors did not provide information about PEEP adjustments. FiO_2 was titrated to achieve an SpO_2 of 94%. Thirty-five patients died (considered as a therapeutic failure) given the presence of several comorbidities. This group had a HACOR Score > 5, ROX Index <4.88, and SOFA scores ≥4.

An observational study by Guia et al. (43) evaluated the HACOR Score of 128 patients with a mean age of 61 years after performing 1 h of CPAP with a mean PEEP of 10 cmH_2O. Thirty-two patients had a HACOR Score ≥ 5, and 22 failed therapy; i.e., 69% of the positive predictive value. On the other hand, 96 patients had a HACOR Score < 5 points. Of these, 83 had successful CPAP; i.e., 86% of the negative predictive value.

3.5.4. Simplified acute physiology score

Originally developed in 1993 by Le Gall et al. (46), SAPS includes cardiorespiratory and renal parameters, laboratory analysis of red and white blood series, and electrolytes. It is a larger scale than the previous ones. Values vary between 0 and 163 points. Higher scores are associated with worse prognosis. According to the original study, a SAPS of 29 points is associated with 10% of deaths, and values of 40 are correlated with 25% of deaths. Very few studies on COVID-19 included in this review used SAPS. Patients in the study by Oranger et al. (31) showed SAPS of 26 points, whereas the study by Grieco et al. (15) reported mean values of 32 points. The multicenter study by Schmidt et al. (47) reported that patients with COVID-19 on NRS had a mean SAPS of 33 points. It is reasonable to conclude that there is a correlation between SOFA, SAPS II, HACOR Score, and the ROX Index regarding the diagnosis of NRS failure.

3.6. Patient self-inflicted lung injury in NRS

At the beginning of the pandemic, the initial recommendation was early intubation to protect the lungs (3, 49). Due to the urgency caused by the pandemic, limited staff, and few noninvasive ventilatory resources to meet the demand, many patients experienced worsening respiration and consequent intubation.

With the reduction in the number of cases, noninvasive ventilatory support such as NRS and HFNC was introduced with the aim of reducing ventilatory effort and avoiding intubation (29). However, when instituting noninvasive therapy, adequate monitoring is required to avoid P-SILI (8, 27, 50). In patients with COVID-19, reduced lung compliance and heterogeneous distribution of inspired V_T are observed due to the presence of areas of low V/Q ratio that are distributed irregularly throughout the lung (4, 8, 24, 25, 51). In spontaneous ventilation, during the inspiratory phase, sufficient diaphragmatic contraction is required to counteract pulmonary elastic recoil forces (8, 24, 25, 27, 50). This generates large variations in transpulmonary pressure (P_L).

In the early stages of COVID-19 (L phenotype), when there are no large pulmonary consolidations, no variations in transpulmonary pressure are observed, which allows the application of NRS with

greater safety (6, 25, 29). Under normal conditions of spontaneous breathing, during the inspiratory phase, pleural pressure decreases uniformly, whereas PL increases uniformly (50). In situations of increased ventilatory drive, greater inspiratory efforts are observed to generate a given V_T caused by greater negative pleural pressure, increasing P_L, which reflects inspiratory efforts. This allows non-homogeneous distribution of lung pressures and volumes, leading to P-SILI (8, 25, 50). Expiratory efforts can also cause P-SILI (50). During intense expiratory activity, pleural pressure increases, drastically reducing P_L, with alveolar collapse occurring in most dependent lung regions and peripheral airways. Battaglini et al. (50) suggest a study of stress/strain for a better understanding of the disease. Stress is the distribution of force applied per unit of lung area, and strain evaluates the stretching of this alveolar unit and is directly proportional to stress (25, 50). During the development of COVID-19, ventilatory efforts become more vigorous, leading to regional hyperdistention, especially in non-dependent regions, and further compromising dependent regions (8, 24, 25, 50). Therefore, both stress and strain are increased. This is associated with the development of pneumothorax and pneumomediastinum (50).

3.6.1. Pendelluft phenomenon

Inspiratory pendelluft is a phenomenon found in the development of COVID-19 and contributes to the genesis of P-SILI (8, 25, 50, 52). It is defined as the disorganized distribution of gas when the inspiratory effort has not yet produced an inspiratory flow at the airway opening. It occurs due to different regional time constants or negative fluctuations in pleural pressure in patients who are breathing spontaneously. This allows irregular distribution of V_T and, consequently, of P_L (8, 25). In the pendelluft phenomenon, the gas moves from the non-dependent region to the dependent region, which remains under significant recruitment and hyperdistention and may release inflammatory mediators. Analyzing the transition of phenotypes is also useful to monitor P-SILI.

In the L phenotype, when lung compliance is normal or slightly reduced, a fluid-like behavior is predominant. Thus, the distribution of pleural pressure is homogeneous along the lung surface (25). With the worsening of inflammation and alveolar edema, this pulmonary phenotype can progress to type H (25). One of the signs of phenotypic transition is an increased respiratory rate (even in NRS), resulting in intense respiratory efforts (8, 25). Another sign of phenotypic transition is an increase in PEEP and an increase in FiO_2 to maintain $SpO_2 > 90\%$ (50). The generation of high V_T values can also indicate a phenotypic transition. When positive airway pressure is applied, P_L may increase with consequent production of high V_T outside the protective concept, i.e., between 6 and 8 mL/kg of predicted body weight (PBW) (33, 47, 50). This increases the chances of barotrauma.

Considering the pendelluft effect, the chances of P-SILI also increase. The gold standard for detecting ventilatory effort is esophageal pressure through a catheter that rests just above the diaphragm. However, its use is still restricted to experimental studies, not yet viable at the bedside (50). Tonelli et al. (52) proposed that measuring the variation in nasal pressure (P_{nos}) is directly related to the variation in esophageal pressure (P_{es}). For this, they studied 61 patients, of which 83% tested positive for COVID-19. The authors calculated both pressures. They used a nose clip for the analysis of P_{nos} and asked the patients to keep their mouth closed throughout the evaluation. On the third day of NRS, the authors observed that patients who evolved to invasive MV had a mean ΔP_{es} of 14 cmH_2O and a mean ΔP_{nos} of 6.5 cmH_2O. The values for those who remained in NRS were 12 and 5.6 cmH_2O, respectively. This was an early cohort study. New studies are important to confirm this information.

In addition, asynchrony events are also associated with the genesis of P-SILI; double triggering is the most common. In patients with COVID-19, the expiratory phase is marked by a significant increase in pleural pressure, reducing pleural pressure, causing collapse of most dependent lung regions and peripheral airways. Hence, P-SILI is also influenced by the pendelluft effect. This leads to alveoli with different regional time constants.

3.6.2. Squishball phenomenon

During the transition from the H to F phenotype, a severe increase in esophageal pressure is observed as the lung is assuming a pattern of fibrosis or a patchwork. There is deposition of collagen and elastin, poorly contractile proteins, therefore the chance of P-SILI and ventilator-induced lung injury (VILI) increases dangerously if the patient remains on NRS (8, 25). During the inspiratory phase, fibrotic lungs present heterogeneous behavior, because lung tissue does not have the same mechanical properties in all directions when a given transpulmonary pressure is applied (8, 25). In addition, the application of PEEP or high V_T can determine hyperdistention of more distensible lung areas (34). This is called the squishball phenomenon, which increases regional stress and strain (25). Its understanding is similar to the pendelluft effect.

3.6.3. Mechanical power for monitoring P-SILI

Considering that the amount of energy to which the lung is subjected, even during assisted spontaneous breathing, can be crucial in the development of P-SILI, application of inappropriate ventilator pressure or the phenotypic evolution of the disease increase the patient's esophageal pressure, resulting in VILI. Mechanical power can be assessed at the bedside to evaluate this phenomenon in a simple way (8) using the formula $0.098 \times \text{respiratory rate} \times V_T \times (P_{peak} - 0.5\Delta P_{aw})$, where P_{peak} is the peak pressure and P_{aw} is the airway pressure. This index may represent a reliable estimate of the amount of energy transferred from the respiratory muscles and ventilatory assistance to the lung during assisted spontaneous breathing (8). Thus, the need for ventilatory adjustments, such as increased PS or PEEP, can be assessed.

The use of mechanical power is useful to assess pulmonary recruitability at the bedside (8). Decreased dynamic compliance is correlated with increased mechanical power and may suggest limited lung recruitability and predict the risk of local overdistention (8).

3.6.4. P-SILI and perfusion irregularities

Another factor that increases the chances of P-SILI is the irregularity of lung perfusion (4, 5, 24, 26, 50). With increased inspiratory effort, pulmonary capillaries can be compressed, increasing pulmonary resistance. This leads to increased transalveolar and transcapillary pressures recruiting previously collapsed capillaries (50). On the other hand, it leads to hyperdistention of those located in healthy areas and in ground-glass regions, which can lead to increased blood flow in injured regions and damage to the alveolar-capillary membrane (50). This predisposes the formation of interstitial and alveolar edema, increasing the risk of P-SILI (25). With this, the phenomenon of pendelblut is observed, in which traction forces

applied to vessels adjacent to stress generators can generate a blood siphon effect toward areas of greater P_L (8).

All these factors may lead to higher lung perfusion and predispose the formation of interstitial and/or alveolar edema and worsening lung inflammation (47). This may explain why patients intubated at a late stage are not responsive to PEEP and have low static compliance, increasing mortality (51). Despite the signs of NRS failure mentioned earlier, and considering the heterogeneous development of the disease among patients, the decision to intubate needs to be taken after discussion with a multidisciplinary team (2).

3.6.5. Early versus late intubation

The decision to intubate should be made considering the course of the disease and the patient's clinical condition. It should be performed in cases of complete refractoriness to NRS. However, with the reduction in the number of cases, patients under NRS can be better monitored, allowing for a lower rate of intubation.

The L phenotype normally appears hypoxemic, with no change in compliance. In this case, HFNC and NRS are first-choice interventions, because the patient still benefits from the therapy (25) and orotracheal intubation can be postponed.

With evolution from the L to the H phenotype, consolidations and alveolar collapse, which need to be reopened to ensure adequate oxygenation and reduction of ventilatory work, are present (8, 25). The problem is that the patient must develop extra diaphragmatic force due to the increase in elastic recoil (25). NRS at this point starts to become contradictory because the patient increases inspired V_T to overcome the elastic recoil leading to P-SILI. Robba et al. (27) stated that patients who remain on NRS for a long time may develop the H phenotype, which may result in diaphragmatic dysfunction. At this point, orotracheal intubation is recommended.

It is difficult to ventilate patients who have the F phenotype because the lungs present great heterogeneity in gas distribution, leading to the pendelluft effect (8, 25, 27). Maintaining spontaneous ventilation in this phenotype may increase the release of inflammatory mediators, and therefore intubation is recommended (8, 25).

Prolonged endotracheal intubation is associated with a worse prognosis, the need for emergency airway management (27), and increased mortality (18, 38, 47). Wendel-Garcia et al. (42) showed that compromised respiratory system mechanics during prolonged endotracheal intubation may explain the increase in mortality observed under NRS. It may also make it difficult to maintain protective ventilation and contraindicate ARM or PP due to increased areas of pulmonary consolidation and/or a radiologic pattern similar to fibrosis.

In a study by Ball et al. (41), 52 patients with a mean age of 64 years who failed helmet CPAP after a minimum of 2 h were divided into two groups: early intubation and late intubation, with a cutoff point of 2 days. After endotracheal intubation, patients underwent computed tomography imaging with two levels of PEEP: 8 and 16 cmH_2O to assess ARM. The late intubated group had lower static compliance and a lower P/F ratio. Regarding ventilation distribution, the late intubated group had a higher percentage of poorly and non-aerated areas. Furthermore, this group did not respond to increased PEEP (8 to 16 cmH_2O), requiring higher FiO_2, indicating that these patients were not recruitable. There was no difference in mortality between the groups.

There is still a lack of studies in the literature that quantify the results of patients intubated early or late after NRS failure. The research carried out for this paper allowed the creation of Table 1.

3.6.6. Aerosol risk during NRS

At the beginning of the pandemic, there was great concern about the production of aerosols which would spread the SARS-CoV-2. The current recommendation stated that the patient should be allocated in a room with negative pressure, and undergo NIV therapy with a double branch circuit and antibacterial filter (54, 55). Whittley et al. (56) at the beginning of the pandemic, when comparing low and high flow oxygen therapy devices with NIV reported that high flow oxygen with NIV had the greatest particle dispersion capacity. After the reduction in the number of cases, the therapy became flexible to meet the demand. In the current scenario, NIV is no longer considered to be a large-scale aerosol-producing therapy (57, 58). Dell'Olio et al. (57) carried out a study that evaluated the production of aerosols in 4 regions around patients undergoing NIV with total face interface. The regions were 50, 80, 150 and 200 meters from the patients' mouths. The results showed that only 21% of these regions were contaminated by SARS-CoV-2, indicating that NIV is a safe therapy.

Winslow et al. (58) compared COT, NRS, and HFNC in terms of virus shedding rates. Each group had 10 patients and the analysis was performed with the patient ventilating properly and with a cough stimulus. The authors concluded that NRS and HFNC have a low dispersion rate when compared to COT.

4. Prone position

Patients with COVID-19 who have an indication for MV need to be protectively ventilated to prevent VILI. For this, a plateau pressure (P_{plat}) <30 cmH_2O, driving pressure (ΔP) <15 cmH_2O, and V_T between 6 and 8 mL/kg of PBW are recommended (59). However, within the pathophysiology of COVID-19, the patient may have poorly or non-ventilated lung areas, mainly in the basal and dorsal regions, in contrast to great aeration in the ventral regions, leading to hyperinflation (8). This is called pulmonary heterogeneity and may lead to low respiratory compliance. As a result, there is intrapulmonary shunt formation, mismatching the V/Q ratio (60). Thus, some patients may not respond to lung protective ventilation (LPV), requiring rescue maneuvers, such as PP (19, 20).

Recent studies have shown that COVID-19 has features of ARDS (61), allowing the Surviving Sepsis Campaign panel to recommend that the treatment of COVID-19 be similar to that of ARDS (12).

4.1. Effects of PP

PP is a non-pharmacologic strategy widely adopted in moderate/severe cases of ARDS with inadequate gas exchange (i.e., PaO_2/FiO_2 ratio < 150, with FiO_2 > 60%) even with PEEP optimized within the concept of LPV. In ARDS, PP redistributes air volume from ventral to dorsal areas, promoting lung homogeneity (19, 20) because lung ventilation is dependent on gravity (20). PP also reduces regional lung stress/tension by displacing non-ventilated areas ventrally (20, 62, 63). Recruitment of the dorsal region of the lung is observed with subsequent increase in regional oxygenation and de-recruitment of the ventral region, leading to a decrease of the hyperinflated tissue (63, 64). In this case, a reduction of the dorsal shunt is observed, improving oxygenation (19, 20). Grasselli et al. (62) state that oxygenation can improve between 60 and 80%.

TABLE 1 Selected NRS studies.

Trial	Population		Intervention		Outcome	
(sample size)	Inclusion criteria	Exclusion criteria	Treatment	Control	Primary	Secondary
1) Retrospective Studies (n = 4)						
Franco et al. (1) (n = 670)	- SpO_2 < 94%, - RR > 20 and Poor response to 10–15 L/min COT - Requiring CPAP / NRS with high FiO_2 - P/F < 200 requiring IMV	- SpO_2 > 94%, - RR < 20 without need of COT or SpO_2 < 94%, RR > 20 but responds to 10–15 L/min COT	CPAP or NRS or HFNC Interface: Helmet or Face mask PP applied in patients with bilateral posterior infiltrates.	No control group	↑ Oxygenation ↔ Mortality at 30th day; ↔ IMV %; ↔ Hospital LOS	No described
Aliberti et al. (2) (n = 157)	Pneumonia as the only cause of hARF; P/F ratio < 300 during COT	- Immediate IMV; - GCS <15; - Respiratory acidosis; - Need of Vasopressors; - Risk of aspiration pneumonia; - Inability to protect airways	CPAP using helmet interface. PEEP = 10.8±2.3 cmH2O	No control group	↑ IMV % ↑ Mortality in ICU	↑ CPAP success ↑ Mortality at 30th day;
Oranger et al. (31) (n = 52)	COT > 6 L/min to $SpO_2 \geqslant 92\%$	No described	CPAP 8-12 cmH_2O Interface: Face mask.	COT up to 15 litres/min.	↓ IMV % at 7th and 14thday ↓ Mortality in DNI patients	No described
Wendel-Garcia et al. (33) (n = 1093)	- bilateral infiltrates in the chest X-ray - need COT to keep $SpO_2 \geq 90\%$	- IMV before and after ICU admission - COT or combination with HFNC and NRS	NRS Group Interface: Not mentioned PS: The necessary to generate V_T of 5.7-7.6 ml / PBW PEEP: 12-15 cmH_2O	COT: Litrage not mentioned HFNC: Flow: Not mentioned FiO_2: 50-70%	↓ IMV in HFNC ↔ ICU LOS ↔ ICU Mortality ↓ VFD in COT	No mentioned
2) Prospective Studies (n = 3)						
Ranieri et al. (32) (n = 315)	- hARF - Bilateral opacities on chest X-ray - P/F ratio < 300 mmHg - Previous treatment for hARF with HFNC or NRS for 12 hours.	- IMV since the onset of hARF - treated with more than one therapy (e.g., HFNC/ NIV/CPAP) at the onset of hARF - awake PP - DNI order	NRS Group Interface: Not mentioned - PEEP 10-12cmH_2O - PS 10-12 cmH_2O	HFNC Group - Flow: 50-60 L/min	↔ IMV % ↔ Oxygenation	↑ 28-day Mortality in NRS Group
Colaianni-Alfonso et al. (35) (n = 112)	COVID Patients that failed in maintain RR < 30; SpO2 ⩾ 94% with FiO_2 < 60% by HFNC	Pregnancy, hypercapnic patients and DNI patients	CPAP with face-mask (n = 57)	CPAP with Helmet (n = 55)	Helmet Group - ↓ IMV % - ↑ Oxygenation	Face-Mask Group: ↑ Mortality, LOS ↓ S / F, PEEP, Time to IMV
			CPAP: 10 – 14 cmH2O, FiO_2 to SpO2 = 92-96%. 24h with continuous CPAP. After that, CPAP and HFNC were used alternatively			
Schmidt et al. (47) (n = 1491)	- No IMV on admission - > 16 years	IMV on the day of admission	COT, NIV, HFNC, or combined therapy Interface: bucconasal or facemask COT: 4-10 L/min NIV: PS 6–10 cmH2O, PEEP 6–8 cmH2O FiO2 50–80%. HFNC: Flow: 40–60 L/min and FiO_2 was 60–90 %.	No control Group	↔ IMV % ↑ Mortality in ICU for NRS ↔ Hospital LOS ↑ Mortality at 28,60, 90th day for NRS; ↔ for COT or HFNC	No described

(Continued)

TABLE 1 (Continued)

Trial	Population		Intervention		Outcome	
Sivaloganathan et al. (48) (n = 101)	hARF	No described	NRS or IMV Group NRS only, NRS + IMV or IMV only	NRS Ceiling NRS as ceiling of treatment	↑ IMV in NRS or IMV Group ↓ Mortality in ICU in NRS or IMV Group ↑ Discharge in NRS or IMV Group	No described
3) Randomized Controlled Trials (n = 3)						
Grieco et al. (15) (n = 109)	- P/F ratio ≤ 200 mmHg - $PaCO_2$ ≤ 45 mmHg, No history of chronic respiratory failure or moderate to severe cardiac insufficiency (NYHA > II or LVEF <50%),	- Acute exacerbation of chronic pulmonary disease; - Kidney failure - Previous treatment with NRS or HFNC at the time screening - Hemodynamic instability - Urgent IMV - DNI order - BMI > 40 - pH < 7,30 - Recent Thoracic or abdominal surgery - Cardiogenic oedema	NRS Group (48h continuous) Interface: Helmet - PEEP 10-12 cmH_2O - PS 10-12 cmH_2O - Esens: 10%-50% - FiO_2 to SpO_2 92-98%	HFNC group (At least 48h - Flow: 60L/min initially. After 48h, FiO_2 were titrate to maintain SpO_2 92-98%	↑ VFD at 28th day in NRS Group	↓ IMV % in NRS Group; ↓ VFD at 60th day in NRS Group; ↔- 28 and 60-day ICU Mortality ↔ 28 and 60-day Hospital Mortality ↔ ICU LOS ↔ Hospital LOS.
Perkins et al. (28) (n = 1273)	- hARF with SpO_2 ≤ of 94% despite receiving COT with FiO_2 ≥ 40%	- Immediate IMV - Known Pregnancy	CPAP Group Interface: Not mentioned - PEEP: 8.1-8.5 cmH_2O	COT Group + HFNC Group Flow: 51.4-53.5 L/min	↓ IMV within 30 days in CPAP Group ↔ 30-day Mortality	↓ IMV % in CPAP Group ↔ Time in IMV ↔ ICU Mortality ↔ ICU LOS ↔ Hospital Mortality ↔ ICU Mortality
Arabi et al. (34) (N = 320)	- P/F ratio < 200 mmHg despite COT - COT > 10 L/min or above	- Immediate IMV - GCS < 12 - $PaCO_2$ > 45mmHg - Pregnancy - Unstable Hemodynamic - Cardiopulmonary arrest - DNI Patients	NRS Interface: Helmet - PEEP 8-10 cmH_2O - PS 10 cmH_2O - FiO_2 = 100% - Flow Rate > 50L/min - Rise time of 50ms - Esens of 50% - Maximum Pp = 30 cmH_2O - PP - Light sedation if needed	Usual Respiratory Group: NRS with mask, HFNC or COT	↔ 28-day Mortality	↔ ICU Mortality ↔ Hospital Mortality ↔ ICU free days ↔ VFD ↔ IMV % ↔ Hospital LOS ↔ Time to IMV ↔ Kidney replacement ↔Vasopressin free days

(Continued)

TABLE 1 (Continued)

Trial	Population		Intervention		Outcome	
Arabi et al. (37) (n = 317)	- P/F ratio < 200 mmHg despite COT - COT > 10 L/min or above - Suspected or confirmed COVID-19 pneumonia	Immediate IMV - GCS < 12 - $PaCO_2$ > 45mmHg - Pregnancy - Unstable Hemodynamic - Cardiopulmonary arrest - DNI Patients	NRS Interface: Helmet - PEEP 8-10 cmH_2O - PS 10 cmH_2O - FiO_2 = 100% - Flow Rate > 50L/min - Rise time of 50ms - Esens of 50% - Maximum Pp = 30 cmH_2O - PP - Light sedation if needed	Usual Respiratory Group: NRS with mask, HFNC or COT	180-day mortality ↔ between groups QoF ↔ between groups	Absent

↑: increase, improvement; ↓: worsening, decrease; ↔: No difference; BMI: Body Mass Index; COT: Convention Oxygen Therapy; CPAP: Continuous Positive Airway Pressure; DNI: Do Not Intubate; Esens: Expiratory Sensibility; FiO_2: Fraction of Inspired Oxygen; GCS: Glasgow Coma Scale; GGO: Ground Glass Opacities; hARF: hypoxemic acute respiratory failure; HFNC: High Flow Nasal Cannula; ICU: Intensive Care Unit; LOS: Length of Stay; LUS: Lung Ultrasound; LVEF: Left ventricular ejection fraction; IMV: Invasive Mechanical Ventilation; NRS: Non-invasive Respiratory Support; NYHA: New York Heart Association; P/F ratio: Partial Pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio; $PaCO_2$: Pressure of Arterial Carbon Dioxide; PBW: Predicted Body Weight; PEEP: Positive End Expiratory Pressure; PP: Prone Position; Pp: Plateau Pressure; PS: Pressure Support; RR: Respiratory Rate; S / F: SpO_2 / FIO_2 ratio; V_T: Tidal Volume; VFD: Ventilator Free Days.

4.2. Ventilatory mechanics versus oxygenation

Final PaO_2 is a weighted average of the PaO_2 of blood flowing from different lung units. This means that the number of atelectatic units in the dependent lung regions is proportional to the severity of hypoxemia (63). In a supine position, with an angle of 0°, approximately 60% of the total lung mass is dependent. In COVID-19, perfusion irregularity promotes greater perfusion in these regions, leading to a decrease in the V/Q ratio (20, 62). During PP, however, only 40% are in the dependent position; i.e., fewer lung units are hyperperfused, resulting in better oxygenation (63). The consequence, in terms of ventilatory mechanics to the PP, is a decrease in total compliance of the chest wall, due to the functional stiffening of the anterior chest wall (63, 64). Thus, an improvement in lung compliance values and a more homogeneous V/Q distribution are expected (64). This also reduces VILI, resulting in improved parameters of ventilatory mechanics (49).

4.3. Patients eligible for prone position

The correct indication for PP is directly correlated with the duration of the disease and the patient's clinical status. The L phenotype is characterized by moderate to severe hypoxemia, even with normal lung compliance (6). This phenotype is considered unresponsive to PP, and the observed improvement in oxygenation is due to the redistribution of blood flow from dorsal to ventral areas, without any alveolar recruitment, as seen in ARDS (42). This, PP in this phenotype does not bring great benefits, because this phenotype has no or little recruitment capacity. However, better aeration of dorsal regions is noted, reducing the chances of atelectrauma (64). Furthermore, COVID-19 is progressive, evolving to the H phenotype, which is more recruitable (6, 25). In this phenotype, there may be a worsening of lung compliance, without any relationship with the conduct. It is at this point that PP becomes more indicated. There is also an improvement in oxygenation, but at the expense of directing blood flow to dorsal regions with alveolar recruitment between patients (62). The ventilatory difficulty of the F phenotype contraindicates PP, because the benefits will be few. This is due to organizing pulmonary fibrosis (25, 27, 63). At this time, protective ventilation is prioritized (25).

The study by Fossali et al. (64) provides information relevant to the topic. The authors studied 21 patients with a mean age of 67 years. They performed chest computed tomography in a supine position and PP. Afterward, within the ICU, the authors performed electric impedance tomography (EIT) to verify distribution and ventilation and perfusion. All were protectively ventilated, without adjustments, in pressure regulated volume-controlled mode with PEEP maintained at 10 cmH_2O. The authors described that there was no difference in the compliance of the respiratory system in both decubitus positions. The authors hypothesizes that in supine position, there may be alveolar units subject to cyclic openings and closings, which would be reduced in PP. In addition, another possible reason is that there was a decrease in lung elastance associated with increased chest wall rigidity. In addition, there was recruitment of dorsal regions, with perfusion improvement in these regions and de-recruitment of ventral regions. This allowed reduction in barotrauma and atelectrauma, reduction of areas with dead space, reducing the number of alveolar units with low V/Q, which improved V/Q matching. This dorsal de-recruitment is called spongelung (65) and is characterized by a reduction in dorsal pulmonary tension and ventral hyperdistention. The authors also point out that there was a reduction in the dead space/shunt ratio in PP and that this is also a marker of lung protection. However, the patients included in this study had been ill for an average of 8 days. Considering that COVID-19 is a progressive disease, it can be inferred that the patients were in phenotype transition to H and F, when the PP has few benefits.

The retrospective study by Langer et al. (66) divided 1,057 patients ventilating protectively into two groups (PP and supine position) with a mean age of 63 years. The average time to perform the first PP was 2 days. The authors observed that there was no difference in

oxygenation and ventilatory mechanics between the groups. This can be explained by the high compliance at baseline. Therefore, the effect of PP may not work solely by recruitability, but through the redistribution of pulmonary blood flow.

Weiss et al. (19) studied 42 patients with a mean age of 59 years, but with significant obesity (body mass index (BMI) > 34 kg/m^2), also under LPV. The researchers performed three PP sessions. In contrast to the article mentioned earlier, there was improvement in oxygenation after the first PP session, but a similar effect was not observed during the second and third PP sessions. This can be attributed to disease progression.

Recently, the COVID-19 Veneto ICU Network research group developed the PROVENT-C19 Registry, a large multicenter protocol specifically for patients with COVID-19 with the aim of describing the population that most benefits from PP (67). On admission, anthropometric data, data on comorbidities, and the type of ventilatory support used before EIT will be collected. The outcomes to be analyzed include differences in gas exchange and the PaO_2/FiO_2 ratio and ventilatory parameters before and after PP, prone duration, and ICU and hospital mortality. Considering the expected large population of this study, there will be an important improvement in clinical practice.

4.4. Duration of PP

The recommended duration of PP is at least 16 h (61, 68, 69). However, some studies have reported durations longer than 16 h of PP with different outcomes. The prospective study by Engerström et al. (70) evaluated 1,714 patients with a mean age of 64 years. The mean time between intubation and first PP session was 20.4 h. No association between early PP and survival was observed. Protti et al. (20) studied 15 patients with a mean age of 69 years and a mean BMI of 29 kg/m^2. Patients were intubated within 2 days and were placed in PP within 3 days. There was a reduction in the volume of non-aerated gas and hyperventilated areas, indicating a lower possibility of VILI and an increase in respiratory compliance. An important point in this study is that the patients did not experience delayed intubation. This certainly has effects on the outcomes.

Encouraging results were also found in the study by Page et al. (60). The authors studied 52 obese patients (BMI >32 kg/m^2) with a mean age of 62 years. They were randomized between conventional prone (16 h) and extended prone (24 h). There was no change in respiratory mechanics, but patients who remained prone longer had more ventilator-free days.

A longer time in the prone position was reported by Rezoagli et al. (71). The standard PP group lasted for 16 h, while extended PP consisted of 40 h. Although the extended PP group was younger than standard PP group, extended PP was feasible and was able to reduce the workload of health professionals. Taking into account the oppressive condition during pandemic, the reduction in workload is an important issue to consider. Furthermore, no benefits or harm in terms of gas exchange or respiratory mechanics were found when extended PP was compared to the standard PP group.

On returning to supine position, some patients may experience a decrease and loss of oxygenation gain (59, 72), further favoring extended PP. Recently, the retrospective study by Okin et al. (72) compared 267 patients with a mean age of 62 years who were subjected to 16 h and 24 h of PP in terms of mortality; 157 patients underwent extended PP (>24 h) and 110 underwent conventional PP (up to 16 h). The authors observed that mortality at 30 and 90 days was lower in the extended PP group. In addition, the study highlights that extended PP is safe, because it reduces the number of supine sessions that are associated with alveolar de-recruitment, increased atelectasis, and VILI, contributing to mortality. It also reduces the amount of neuromuscular blockers, reducing diaphragmatic dysfunction (72).

Thus, there is no limit on the number of PP sessions as long as they are recommended. For example, Walter et al. (73) reported that some patients underwent PP 22 times. The same study also suggests that PP should be interrupted when the FiO_2 requirement is ≤60%, when the PaO_2/FiO_2 ratio is >150, and when the PEEP is ≤12 cmH_2O.

4.5. Early or late PP?

Delaying PP is associated with higher mortality. The study by Mathews et al. (74) included 2,338 patients; 702 were placed in PP within 2 days of MV and the other 1,636 within 2 days of MV with a P/F ratio < 200. The authors observed that the early PP group had greater chance of developing shock and use of corticosteroids. However, the risk of death was lower. COVID-19 is a heterogeneous disease, therefore it is not possible to define a suitable time to implement PP. One suggestion is to use the same reasoning used to determine the need to transition from NRS to intubation: the worsening of compliance and the need for high FiO_2 fractions to maintain adequate SpO_2. In this case, it is possible to infer a change from the L to the H phenotype, which has a greater possibility of recruitment, benefiting from PP (25, 63).

With regard to the objectives of prone decubitus, associated articles describe the physiologic and ventilatory changes of the position. However, when analyzing the effects of PP, the increase in survival must be considered. Directing the therapeutic target only to improve oxygenation can be a scientific limitation. To guide the understanding of this topic, Table 2 contains a summary of the included studies and outcomes found.

5. Alveolar recruitment maneuvers and PEEP titration

At the beginning of the pandemic, there were doubts whether the pulmonary presentation of COVID-19 was similar to that of ARDS (51). A common factor is the difficulty in setting an ideal PEEP, although guidelines recommend the use of PEEP >10 cmH_2O due to the large non-aerated area observed in COVID-19 (12). However, in some patients, oxygenation does not normalize, resulting in worse respiratory mechanics (i.e., ΔP >15 cmH_2O; P_{plat} > 30 cmH_2O), even during PP sessions.

5.1. Recruitability assessment

The use of PEEP tables, widely used for ARDS, is an easy alternative to titrate PEEP and sustain ARM (75–78). However, this strategy fails to optimize oxygenation; the PEEP response in patients with COVID-19 is highly heterogeneous due to the facts mentioned

TABLE 2 Selected studies on prone position.

Trial (sample size)	Population		Intervention		Outcome	
	Inclusion criteria	Exclusion criteria	Treatment	Control	Primary	Secondary
Retrospective studies (*n*=4)						
Camporota et al. (13) (*n* = 376)	Patients who received at least one session of PP for ≥12 h Intubated patients who met Berlin definition of ARDS	Not mentioned	COVID-19 ARDS (C-ARDS) group LPV with V_T between 6 and 6.5 mL/kg PBW	ARDS group	↑ RM in COVID-19 group ↔ Oxygenation ↔ Mortality	Absent
Weiss et al. (19) (*n* = 42)	- Intubated COVID-19 patients - Indication to PP	Pregnancy, Reintubation Previous PP at a referring hospital.	PP: ≥16 h LPV High PEEP low FiO_2 tables If P/F in SP >150 mmHg, or ECMO or palliative care was needed, PP was terminated	Absent	↑ Oxygenation in 2nd PP session	↔ Discharge ↔ Hemodynamics ↔ RM
Langer et al. (66) (*n* = 1,057)	Intubated patients who met Berlin definition of ARDS	Age < 18 years Noninvasive respiratory support Missing clinical data regarding the use of PP	PP group LPV with V_T of 6.3–7.8 mL/kg PBW	SP group	SP group ↑ ICU survival ↑ Hospital survival ↑ ICU LOS ↑ Time on MV ↔ Hospital LOS	↑ Oxygenation in SP group ↔ RM, except for P_{plat} which was lower in the SP group ↔ $PaCO_2$
Hochberg et al. (68) (*n* = 512)	Intubated patients who met Berlin definition of ARDS Age > 18 years Indication for PP At least 72 h of IMV	Cardiac arrest Chronic IMV Tracheostomy as first airway IMV <48 h Contraindication for PP	COVID-19 ARDS	ARDS before pandemic	↓ Time to prolonged PP in COVID-19 group	In COVID-19 group ↑ Duration of PP ↑ PP sessions
Prospective studies (*n*=5)						
Protti et al. (20) (*n* = 15)	Diagnosis of ARDS Ongoing IMV PP prescribed by the attending physician within 3 days of IMV	Not described	(1) RM + CT in SP (2) PP + new CT + SP No adjustment of PEEP LPV with V_T between 6 and 7.1 mL/PBW	Absent	In PP group ↑ Oxygenation ↑ Lung aeration ↔ RM	Absent
Le Terrier et al. (69)	P/*F* < 300 with PEEP >5 cmH_2O	Not confirmed COVID-19 even with radiologic pattern	Early PP group	Non-early PP group	↔ Mortality at 60th day	↔ Mortality at 28th and 90th day In non-early group: ↓ VFD until 28th day ↓ ECMO ↓ NO ↓ Static compliance at 3rd day ↓ P/F at 3rd, 5th and 7th day
Engerström et al. (70) (*n* = 1,714)	P/F ratio < 150 mmHg Patients receiving IMV within 24 h	Confirmed SARS-CoV2 with reason for admission other than COVID-19	Early PP group	Not early PP group	↔ Oxygenation ↔ 30-day mortality	↔ 90-day mortality

(Continued)

TABLE 2 (Continued)

Trial (sample size)	Population		Intervention		Outcome		
	Inclusion criteria	Exclusion criteria	Treatment	Control	Primary	Secondary	
Walter et al. (73) ($n=81$)	ARDS COVID-19 intubated patients who had undergone at least one session of PP of >24 h duration Age ≥ 18 years P/F ratio < 150 mmHg	Missing data about PP session	PP ≥24 h iNO and ECMO were used if necessary LPV with V_T between 6 and 8 mL/kg PBW	Absent	↔ Pressure injuries between stage II and III	↑ Oxygenation ↑ RM	
			Ventilator mode is not described				
Mathews et al. (74)	P/*F* < 200 within 2 days of ICU admission	P/*F* > 200 ECMO on ICU day 1, cardiac arrest or severe arrhythmia Pronation before ICU admission Pregnancy	Early PP group		Late PP group	↓ Hospital deaths in early PP group	Absent
Randomized controlled trials ($n=1$)							
Page et al. (60) ($n=52$)	Patients intubated with: Age > 18 years Indication for PP	DNI patients Prisoner or pregnant IMV >48 h at the time of screening Any contraindication for PP	16 h of PP (traditional) + SP	24 h of PP (prolonged) + SP	↑ Time of PP session in prolonged PP	↔ Differences in RM ↔ Outcomes	
			LPV with V_T between 6 and 7 mL/kg PBW				

↑, increase, improvement; ↓, worsening, decrease; ↔, no difference; ARDS, acute respiratory distress syndrome; CT, computed tomography; DNI, do not intubate; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; iNO, inhaled nitrous oxide; ICU, intensive care unit; IMV, invasive mechanical ventilation; LPV, lung protective ventilation; LOS, length of stay; NO, nitrous oxide; P/F ratio, partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2); $PaCO_2$, pressure of arterial carbon dioxide; PEEP, positive end expiratory pressure; PBW, predicted body weight; PP, prone position; P_{plat}, plateau pressure; RM, respiratory mechanics; SP, supine position; V_T, tidal volume.

earlier (79–82). In this context, some studies chose the recruitment to inflation (R/I) ratio developed by Chen et al. (78) to assess the potential for recruitability in patients with ARDS. It ranges from 0 to 2. R/I < 0.5 indicates low potential for recruitability, increasing the risk of pulmonary overdistension without any benefit. R/I > 0.5 indicates high recruitability (79, 82, 83). After assessing recruitability, the choice of PEEP is based on ARM with decremental PEEP titration. Some studies have used only decremental PEEP titration (8, 78). Briefly, this strategy consists of gradually increasing the airway opening pressure up to 45 cmH_2O and then performing PEEP titration (in steps of 2–3 cmH_2O), maintaining the stability of hemodynamic and airway ΔP and allowing P_L to increase (80–83).

5.2. Effects of PEEP in oxygenation and perfusion

The issue of heterogeneity of oxygenation targets is a topic of discussion. Zerbib et al. (80) states that an SpO_2 between 88 and 92% is satisfactory. Ball et al. (8) suggested that the best PEEP is the one in which PaO_2 remains >60 mmHg. These two studies were less rigid about oxygenation, in contrast to previous studies dealing with ARM and PEEP titration. Randomized studies are needed to confirm whether these oxygenation targets are suitable for COVID-19.

5.3. Effects of PEEP with the L phenotype

For lungs with low recruitability (L-type phenotype; i.e., high static compliance), low levels of PEEP are sufficient to optimize PaO_2 and reduce hyperdistended areas, P_{plat} and airway ΔP.

When high PEEP is applied to the L-type phenotype, it is expected to increase lung volume and reduce lung heterogeneity, at the cost of increased overinflated areas compared with low PEEP (8). Usually, airway pressure increases followed by impairment in respiratory system compliance. In the L phenotype, high PEEP values are not recommended, because this is a poorly recruitable phenotype (6, 8, 25). Increasing PEEP in this phenotype contributes to worsening lung compliance.

Pan et al. (76) studied 12 patients who were protectively ventilated; mean age was 59 years and the mean R/I ratio was 0.21, indicating low pulmonary recruitability. They showed that after applying high PEEP using the PEEP table (>15 cmH_2O), P_{plat} remained high, with a low response in oxygenation. In addition, the authors reported that this patient profile may not respond to high PEEP in the supine position, but that recruitability seems to increase after PP. It can be inferred that this gain is due to displacement of poorly ventilated areas. This reinforces the fact that the PEEP table has partial applicability and seems to suggest that ARM should be performed together with PP.

5.4. Effects of PEEP in the H phenotype

When PEEP is applied incases with the H phenotype, the response is an improvement in lung compliance, with a reduction in P_{plat} and in poorly ventilated or non-ventilated areas, reducing intrapulmonary shunt (8, 25).

Protti et al. (20) studied 40 patients with early COVID-19 in the supine position and performed ARM plus decremental PEEP at three levels: 15, 10, and 5 cmH_2O. With PEEP of 15 cmH_2O, oxygenation improved in 36% of patients, but respiratory compliance improved in only 11%. There was also a reduction in non-ventilated areas and an increase in hyperventilated areas. Furthermore, two different responses were observed as PEEP increased. With an increase in PEEP from 5 to 10 cmH_2O, recruitment was predominantly dorsal, reducing non-aerated tissue, with an improvement in the PaO_2/FiO_2 ratio and an increase in respiratory compliance. However, when PEEP was increased from 10 to 15 cmH_2O, the recruitment obtained previously overlapped with the appearance of hyperventilated areas, predominantly ventral, and a decline in respiratory compliance. Furthermore, the improvement in oxygenation at high PEEP cannot be explained by recruitability, but rather by the improvement in left ventricular function, which decreases cardiac output (50).

–Ball et al. (8) studied a group of 42 recruitable and non-recruitable patients with a mean age of 63 years using LPV. The authors evaluated lung mechanics and oxygenation at two PEEP levels (8 and 16 cmH_2O). The first group benefited from high PEEP by reducing the percentage of non-aerated lung units. However, only the non-recruitable group had a reduction in poorly aerated areas. Both groups showed improved oxygenation via increased hyperaerated areas, with consequent worsening of respiratory compliance. In practical terms, this led to an increase in ΔP, P_{plat}, mechanical power, variables associated with VILI. The authors explained that the improvement in the P/F ratio should be interpreted as redistribution of the V′/Q′ ratio, prioritizing areas with low ventilation, and not as recruitment, even in so-called recruitable patients.

5.5. ARM and obese patients

Some of the studies discussed in this review analyzed obese patients, represented by BMI >30 kg/m^2 (63, 64). Obese patients have a high recruitment potential and can tolerate high PEEP values, as long as the P_{plat} remains up to 30 cmH_2O. Usually, studies have pointed out two main reasons for the need for high PEEP in this population: (1) decreased P_L (79); and (2) predominantly ventral ventilation with a tendency to dorsal alveolar collapse under low PEEP. This scenario can be prone to VILI due to low static compliance. After application of PEEP, the studies have highlighted decreased airway ΔP and dead space, with improvement in static lung compliance, P_L, the PaO_2/FiO_2 ratio, and redistribution of pulmonary blood flow with subsequent reduction of intrapulmonary shunt (81).

Highly specialized centers have introduced EIT to expand understanding of the effect of PEEP levels (75, 81). EIT consists of placing a belt with electrodes between the fourth and fifth ribs to verify the ventilatory distribution (whether predominantly dorsal or ventral) in real time and macroscopically assess the effect of PEEP. The use of EIT during ARM and PEEP titration may guarantee the most adequate value for the patient, which may be two values below or above the values suggested by the PEEP table (75, 81). EIT shows the percentage of well-ventilated, poorly ventilated, collapsed, and hyperinflated areas; the latter two are of interest to the professional at the bedside to avoid VILI (49, 59).

5.6. The balance between oxygenation and ventilatory mechanics

Oxygenation is a therapeutic target, as is the assessment of ventilatory mechanics. Both need to be evaluated together and systematically. This review recommends that the search for the ideal P/F ratio, as well as optimal SpO_2/PaO_2 values, can lead to dangerous maneuvers of alveolar recruitment, exceeding protection limits, with the risk of P-SILI.

Beloncle et al. (10) studied 25 patients with COVID-19, 16 of whom were considered highly recruitable and 9 were considered poorly recruitable. Two PEEPs were applied: 5 and 15 cmH_2O. At high PEEP, the recruitable group showed the same mean compliance for both PEEP levels. However, oxygenation in the recruitable group was higher than in the non-recruitable group. Ball et al. (11) studied 42 patients, 32 non-recruitable and 10 recruitable. The researchers applied two levels of PEEP (8 and 16 cmH_2O). All patients then underwent computed tomography. They found that there was no percentage difference in recruitable areas despite the increase in PaO_2. Therefore, it can be concluded that the compliance of the respiratory system can mitigate oxygenation. The articles of this topic were organized in Table 3, to direct the understanding of ARM.

6. Extracorporeal membrane oxygenation

The administration of low V_T in severely collapsed lungs results in increases in CO_2 levels (i.e., >45 mmHg) leading to the development of respiratory acidosis and extremely severe hypoxemia (84). Patients with extensive alveolar consolidations are likely to be refractory to the PP and ARM maneuver with decremental PEEP (84, 85). Analysis of lung mechanics demonstrates P_{plat} and ΔP above protective limits (30 and 15 cmH_2O, respectively), and pH less than 7.35 (85, 86). This clinical picture could benefit from ECMO.

ECMO is a potentially life-saving strategy recommended in patients who are extremely hypoxemic and acidotic, with the aim of clearing CO_2 levels and allowing the lungs to reduce activity, allowing the ECMO to perform gas exchange. Due to its high complexity, use of ECMO is recommended only in specialized centers and by dedicated staff (87). The studies in this review were based on the ELSO (Extracorporeal Life Support Organization) and EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) definitions to define patients eligible or not for therapy. Among so many recommendations, we highlight: (1) PaO_2/FiO_2 ratio < 50 mmHg over 3 h; (2) PaO_2/FiO_2 ratio < 80 mmHg over 6 h; (3) arterial blood gas pH <7.25 and $PaCO_2$ > 60 mmHg over 6 h (Figure 2).

There are different ventilatory strategies during ECMO. The randomized clinical trial by McNamee et al. (87) studied 412 patients

TABLE 3 Selected studies on alveolar recruitment maneuvers.

Trial (sample size)	Population		Intervention				Outcome	
	Inclusion criteria	Exclusion criteria	Treatment	Control			Primary	Secondary
Retrospective studies ($n = 6$)								
Chiumello et al. (16) ($n = 61$)	Intubated patients who met the Berlin definition of ARDS	Barotrauma COPD Hemodynamic instability	PEEP: 5 cmH_2O	PEEP: 15 cmH_2O			↑ Oxygenation with PEEP of 15 cmH_2O ↓ RM with PEEP of 15 cmH_2O	Not mentioned
			VCV with LPV + RCM					
Sella et al. (75) ($n = 15$)	Intubated patients who met the Berlin definition of ARDS	Not mentioned	EIT-based PEEP group (group A)	PEEP/FiO_2 tables group (group B)			↔ Oxygenation ↓ RM in group B	Not mentioned
			All patients were ventilated in VCV, with lung LPV					
Pan et al. (76) ($n = 12$)	Intubated patients who met the Berlin definition of ARDS	Not mentioned	VCV with 6 mL/kg PBW PEEP was set based on R/I ratio and P_{plat} 24-h session of PP and ECMO were discussed if necessary	Absent			↓ Mortality in PP ↑ Changes in RM in PP	Not mentioned
Van der Zee et al. (81) ($n = 15$)	Intubated patients who met the Berlin definition of moderate to severe ARDS	Not mentioned	Decremental PEEP trial + EIT + compare with PEEP/FiO_2 table Minimum of PEEP of 24 cmH_2O from baseline	Absent			↓ Oxygenation ↔ RM ↑ Lung aeration	Absent
Schulz et al. (83) ($n = 27$)	Intubated patients who met the Berlin definition of ARDS Age > 18 years Moderate or severe ARDS receiving IMV with ≥5 cmH_2O PEEP RCM by increasing PEEP to +50% above the baseline	Pneumoperitoneum Pneumomediastinum undrained Pneumothorax or ongoing air leak Hemodynamic instability	$PEEP_{low}$ responders (group A)	$PEEP_{low}$ nonresponders (group B)	$PEEP_{high}$ responder (group C)	$PEEP_{high}$ nonresponders (group D)	↑ Oxygenation in group C	↔ Lung aeration
			VCV with LPV RR adjusted to permissive hypercapnia					
Bonny et al. (84) ($n = 10$)	Intubated patients who met the Berlin definition of ARDS	Not mentioned	PEEP: 16 cmH_2O	PEEP: 8 cmH_2O			↔ Oxygenation ↔ Hemodynamics ↓ RM with high PEEP	Absent
			VCV with V_T of 6–6.3 mL/kg PBW RR: 23–30 bpm FiO_2: not mentioned					
Prospective studies ($n = 6$)								
Beloncle et al. (10) ($n = 25$)	Intubated patients who met the Berlin definition of ARDS R/I ratio ≥ 0.5	Age < 18 years Pneumothorax ECMO	Highly recruitable	Poorly recruitable			↔ Oxygenation ↔ RM ↔ Changes in hemodynamics	Absent
			Decremental PEEP: 15–10–5 cmH_2O VCV with V_T of 6 mL/kg PBW					

(Continued)

TABLE 3 (Continued)

Trial (sample size)	Population		Intervention			Outcome	
	Inclusion criteria	Exclusion criteria	Treatment	Control		Primary	Secondary
Ball et al. (11) ($n = 42$)	Intubated patients who met the Berlin definition of ARDS	Not mentioned	Recruiters (low compliance)	Nonrecruiters (high compliance)		↔ Alveolar recruitment	↔ Oxygenation ↑ RM
			LPV CT scan at PEEP 8 cmH2O during expiratory breath-hold. Then, PEEP ↑ to 16 + New CT				
Rossi et al. (12) ($n = 25$)	Patients with confirmed COVID-19	Not mentioned	Supine: 5 cmH_2O	Prone: 5 cmH_2O	Supine: 35 cmH_2O	↓ RM in supine: 35 cmH_2O ↑ Lung aeration in supine: 35 cmH_2O	Not mentioned
			(1) CT in SP and PP at 5 cmH_2O of airway pressure (2) CT in SP at 35 cmH_2O of airway pressure				
Somhorst et al. (77) ($n = 75$)	Age ≥ 16 years Intubated patients who met the Berlin definition of ARDS EIT availability	Contraindication to EIT belt Thoracic bandages Undrained pneumothorax Hemodynamic instability	PEEP ↓ to baseline	PEEP ↔ to baseline	PEEP ↑ to baseline	↔ Oxygenation ↑ RM in PEEP ↓ to baseline ↑ Lung aeration in PEEP ↑ to baseline	Not mentioned
			PCV with LPV From baseline PEEP: Use of EIT + decremental PEEP + small RCM				
Perier et al. (79) ($n = 30$)	Intubated patients who met the Berlin definition of ARDS	Contraindication to EIT (pacemaker, implantable defibrillator, skin lesion)	COVID-19 ARDS group	ARDS group		↔ Changes in RM ↔ Time in MV ↔ ICU LOS ↔ Death in ICU ↔ Need of vasopressors ↔ ECMO and tracheotomy %	Not mentioned
			V_T of 6 mL/kg PBW with initial PEEP: 18 cmH_2O if P_{plat} remained <35 cmH_2O Using EIT, PEEP was decreased by 3 cmH_2O until reaching 6 cmH_2O				
Zerbib et al. (80) ($n = 30$)	Intubated patients who met the Berlin definition of ARDS	P/F ratio > 150 mmHg Pneumothorax Pneumomediastinum Hemodynamic instability	Low recruitability (group A)	High recruitability (group B)		↔ Oxygenation ↑ RM in group B	Not mentioned
			VCV with LPV Performed RCM with maximum DP of 15 cmH_2O				
Randomized controlled trials ($n = 1$)							
Protti et al. (82) ($n = 40$)	≤3 days of IMV	Pulmonary air leak Hemodynamic instability	PEEP: 5	PEEP: 10 cmH_2O	PEEP: 15 cmH_2O	↑ Oxygenation with PEEP 10 cmH_2O ↓ RM with PEEP 10–15 cmH_2O ↑ Lung aeration with PEEP 10–15 cmH_2O	Absent
			All patients in SP RCM + CT at AWP of 45 and 5 cmH_2O or CT at AWP of 15 and 5 cmH_2O (group B) + PEEP trial (5, 10, and 15 cmH_2O)				

↑, increase, improvement; ↓, worsening, decrease; ↔, no difference; ARDS, acute respiratory distress syndrome; AWP, airway pressure; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EIT, electrical impedance tomography; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; LPV, lung protective ventilation; LOS, length of stay; P/F ratio, ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2); PEEP, positive end expiratory pressure; PBW, predicted body weight; PCV, pressure-controlled ventilation; PP, prone position; P_{plat}, plateau pressure; R/I ratio, recruitment to inflation ratio; RCM, recruitment maneuver; RM, respiratory mechanics (compliance, P_{plat}, peak pressure); RR, respiratory rate; SP, supine position; VCV, volume-controlled ventilation; V_T, tidal volume.

with severe hypoxemia and < 48 h of intubation and randomized them into two groups: (1) ECMO + LPV and (2) LPV only. The first group showed a reduction in P_{plat} and ΔP and more ventilator-free days, indicating improved lung protection compared with the second group. No difference in mortality was found.

6.1. Time to start ECMO

Considering the inclusion criteria for ECMO, it is pertinent to consider its rapid start after detection of the disorder. There is no consensus in the literature about when to start therapy, because this depends on the availability of equipment and trained staff (85). Even so, the prospective study Mustafa et al. (88) studied 160 patients with a mean age of 49 years. The researchers divided them into two groups: (1) ECMO + LPV; (2) Only MVA. The first group progressed to ECMO within 3.8 days. ECMO + LPV was associated with 68% survival, whereas LPV only was associated with 26% survival. Karagiannidis et al. (89) stated that ECMO should start within 3 days because it is associated with longer patient survival. The multicenter study by Lorusso et al. (90) analyzed 1,215 patients ventilated with a V_T < 3 mL/PBW and concluded that age > 60 years and a time longer than 4 days between the start of MV and the start of ECMO was associated with higher mortality.

Recently, Hajage et al. (91) studied 2,858 patients; 269 (mean age, 53 years) received ECMO within 14 days of hospitalization. Patients were intubated within 1 day of hospitalization, the average time to start ECMO was 6 days, and 89 and 97% of patients received PP and neuromuscular blockers, respectively, before ECMO. All patients were ventilated ultraprotectively, i.e., V_T < 4 mL/kg. It was observed that eligible patients had poor ventilatory mechanics, with a mean ΔP of 18 and a mean P_{plat} of 30 cmH_2O. The results showed that there was a significant improvement in ΔP to 12 cmH_2O and P_{plat} to 18 cmH_2O within 48 h of ECMO. These results are encouraging and reinforce the recommendations for successful ECMO: young age, few days of MV, and few comorbidities.

ECMO is a high-cost strategy that requires highly trained staff (85, 87), which may limit its widespread application and/or late start, when the patient may not benefit from the therapy.

6.2. Eligible patients

Preliminary prospective results from Kon et al. (92) highlighted important issues. The authors studied 27 obese patients with a mean age of 40 years. The authors chose to include only functional independent patients without comorbidities in the study. Before being eligible for ECMO, patients were LPV with a mean PEEP of 14 cmH_2O and FiO_2 > 90%. The primary endpoint of the study was survival during hospitalization and lung recovery (defined by the authors as ECMO weaning). They reported that 11 patients fully recovered on ECMO, and 13 were still on ECMO. The recovered group was successfully decannulated. All patients were tracheostomized with a median time of 24 h, allowing for lower rates of sedation and neuromuscular blockers, in addition to reducing the possibility of nosocomial infections, in contrast to other studies that reported at least 2 days from intubation to ECMO. All patients were ventilated in volume-controlled ventilation mode with 5 mL/kg PBW, with a mean PEEP of 10 cmH_2O. The patients had median low compliance (22 mL/cmH_2O) and ΔP ranging from 14 to 18 cmH_2O. In addition, patients had a mean $PaCO_2$ of 80 mmHg, pH <7.25, and mean serum lactate levels of 2.45 mmol/L. The primary endpoint of the study was 90-day mortality. All these factors were associated with mortality, which was 38.8%. Therefore, the main success factor for ECMO is young age, indicating the need for correct selection of patients (89).

The study by Schmidt et al. (21) included 83 patients, 30 of whom died. Forty-eight patients survived and were discharged from the ICU. The average age was 48 years. Interestingly, the surviving group had higher mean d-dimer values than the group who died. Moreover, 88% of the patients were ventilated in airway pressure release ventilation (APRV) mode, known to ensure alveolar stability and allow for greater pressurization with reduced occurrence of VILI (93). This ventilation mode was not used in almost all of the articles cited that opted for volume-controlled ventilation or pressure-controlled ventilation. Mortality was 31%. There was no information about the association of APRV and the effects of ECMO. But given the purpose of the APRV, it is possible to infer that the association would behave as double lung protection. Other studies associating ECMO and APRV are needed to confirm the positive relationship between them.

6.3. PP on ECMO

Although there are few studies reporting the use of PP in ECMO, recent evidence points to a good response from the combined therapies. Garcia et al. (94) studied 25 patients with COVID-19 that required V/V ECMO. 14 were placed on PP at least once for 16 h on average. All of them were protectively ventilated. In terms of lung mechanics, there were no statistical differences between PP and non-PP patients. However, there was an improvement in oxygenation in the PP group. Massart et al. (95) evaluated 517 patients with a mean age of 55 years on ECMO; 364 were prone during therapy and 153 were not prone. All were protectively ventilated. Lower mortality rates were observed in the PP group. There was no statistical difference between lung compliance and gas exchange values. As with PP, the outcome that should guide clinical practice is mortality. Only randomized studies will be able to confirm if the improvement in oxygenation is due to ECMO or PP or to joint therapy.

6.4. Side effects of ECMO

Despite its beneficial effects, the articles cited here highlight that ECMO presents a high risk of bleeding requiring anticoagulation, and many patients progress to hemodialysis (53, 85–88, 94–98) These facts, added to the fibrotic evolution of COVID, increase the chances of mortality and therapeutic failure with ECMO. However, these factors may have less impact on young patients and/or those with few or no comorbidities. The positive and negative outcomes of the ECMO studies are shown in Table 4.

TABLE 4 Selected ECMO studies.

Trial (sample size)	Population		Intervention		Outcome	
	Inclusion criteria	Exclusion criteria	Treatment	Control	Primary	Secondary
Retrospective studies (*n*=1)						
Herrmann et al. (97) (*n*=673)	Age ≤70 years IMV <8 days before ECMO BMI ≤45 kg/m^2 Absence of malignancies. no history of myocardial infarction Congestive heart failure	Age >70 years Chronic pulmonary disease Kidney disease	In hospital survivors (group A) V/V ECMO PP was applied if necessary LPV with TV ≤6-8 mL/PBW	In hospital nonsurvivors (group B)	↓ Mortality at 6th month in group A	In group A: ↓ Duration of ECMO ↑ ICU LOS ↑ Hospital LOS ↓ In hospital complications In group B: ↑ No. of PP before ECMO ↔ RM ↔ Time to ECMO
Prospective studies (*n*=6)						
Schmidt et al. (22) (*n*=159)	EOLIA/ELSO criteria	>70 years Severe comorbidities Cardiac arrest Multiorgan failure or SAPS II >90 Irreversible neurologic injury IMV for >10 days	Patients alive V/V or V/A ECMO Blood flow: 4.0–5.5 L/min Sweep gas: 3–7 L/min FDO_2 = 100% LPV with V_T between 1.4 and 4.2 mL/kg PBW	Dead patients V/V or V/A ECMO	↑ RM in dead patients group ↔ Oxygenation	Absent
Mustafa et al. (88) (*n*=160)	EOLIA/ELSO criteria	Patients not mechanically ventilated Cardiac arrest Lactate ≥14 mmol/L or pH ≤6.9 Multi-system organ failure Neurologic injury Recent hemorrhagic stroke Refuse to receive blood transfusion DNI patients Chronic organ failure Tumors Severe chronic disease requiring oxygen therapy	V/V ECMO	MVA patients*	↑ Survival ↑ VFD in MVA patients	↓ Time in IMV in MVA patients ↑ % mortality in MVA patients ↔ Oxygenation
Lebreton et al. (96) (*n*=302)	EOLIA/ELSO criteria	Age >70 years Serious comorbidities Multiple organ failure IMV for >10 days Cardiac arrest SAPS >90 Irreversible neurologic injury	Alive patients V/V, V/A, VV/A ECMO sweep gas: 4–8 L/min Blood flow: 4.3–5.5 L/min LPV with V_T ≤4.9–6.2 mL/kg PBW	Dead patients	Dead patients: ↓ ICU LOS ↑ ICU complications ↓Time in ECMO ↓ ECMO complications ↑ Mortality at 90th day after initiation of ECMO ↑ Organ dysfunction ↔ RM and PP sessions	Not mentioned

(Continued)

TABLE 4 (Continued)

Trial (sample size)	Population		Intervention		Outcome	
	Inclusion criteria	Exclusion criteria	Treatment	Control	Primary	Secondary
Yang et al. (85) ($n = 21$)	EOLIA/ELSO criteria No response to PP RR >35 bpm P_{plat} >30 cmH_2O	Not mentioned	V/V ECMO + LPV LPV in PCV with V_T of 4 mL/kg PBW	LPV only	↔ Mortality	↔ Complications associated with ECMO
Garcia et al. (94) ($n = 60$)	IMV + P/F ratio < 80 mmHg with FiO_2 and FDO_2 at 100% Extensive lung consolidation on CT	Not mentioned	V/V ECMO + PP group Ultra LPV with V_T of 1.8–2.7 mL/kg PBW	V/V ECMO + SP group	SP group ↑ ECMO weaning ↓ Duration of ECMO ↓ Mortality at 28th day ↑ ICU discharge ↔ RM	Not mentioned
Whebell et al. (98) ($n = 243$)	EOLIA/ELSO criteria No response to PP in ≥6 h No response to LPV	Non-COVID-19 diagnosis	V/V ECMO LPV with $V^T \leq 6$–8 mL/kg PBW	Conventional care	↓ Hospital mortality in ECMO group ↔ RM	Not mentioned
Randomized controlled trials ($n = 1$)						
McNamee et al. (87) ($n = 412$)	hARF + IMV with PEEP ≥5 cmH_2O 48 h with P/F ratio ≤ 150 mmHg	IMV >7 days Contraindication to heparin Untreated pulmonary embolism Pleural effusion or pneumothorax, or hARF fully explained by left ventricular failure or fluid overload	LPV + V/V ECMO Sweep gas Flow: 10 L/min LPV with V_T of ≤3 mL/kg PBW	Only LPV	↔ Mortality at 90th day	↑ VFD at 28th day in LPV ↔ Time in IMV ↔ Need for ECMO on 7th day ↔ Mortality at 28th day ↑ Adverse event in ECMO group

↑, increase, improvement; ↓, worsening, decrease; ↔, no difference; ARDS, acute respiratory distress syndrome; BMI, body mass index; COT, conventional oxygen therapy; CPR, cardiopulmonary resuscitation; CT, computed tomography; DNI, do not intubate; ECMO, extracorporeal membrane oxygenation; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS; ELSO, Extracorporeal Life Support Organization; FDO_2, fraction of oxygen in the sweep gas flow; FiO_2, fraction of inspired oxygen; hARF, hypoxemic acute respiratory failure; ICU, intensive care unit; IMV, invasive mechanical ventilation; LPV, lung protective ventilation; LOS, length of stay; P/F ratio, ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2); $PaCO_2$, pressure of arterial carbon dioxide; PEEP, positive end expiratory pressure; PBW, predicted body weight; PCV, pressure-controlled ventilation; PP, prone position; P_{plat}, plateau pressure; SP, supine position; RM, respiratory mechanics; SAPS, Simplified Acute Physiology Score; SpO_2, oxygen saturation; TCT, tracheotomy; VCV, volume-controlled ventilation; V/A, venoarterial; V_T, tidal volume; V/V, venovenous; VV/A, venovenoarterial. *MVA, maximized ventilator adjustments: $FiO_2 \geq 80\%$, PEEP ≥ 10 cmH_2O, and V_T 6 mL/kg PBW, keeping $P_{plat} \leq 32$ cmH_2O.

6.5. ECMO in non COVID-ARDS versus COVID-ARDS patients

Some studies compared ECMO in non-COVID-ARDS patients and COVID-ARDS patients. Although similar results were gathered about oxygenation (99, 100), the treatment time and complications were different. Chandel et al. (99) analyzed 9,271 patients who required ECMO between 2017 and 2021. Authors showed that COVID patients remained longer on ECMO when compared to non-COVID patients (19.6 days versus 10 days). Additionally, COVID patients had higher rates of developing kidney failure, requiring hemodialysis. Furthermore, COVID patients remained longer on mechanical ventilation before starting ECMO. This condition may lead to increased diaphragmatic dysfunction and mortality in COVID compared with non-COVID group. Other complications also observed in the COVID group included pneumothorax and intracranial hypertension. This can be explained by the high inflammatory cascade due to COVID.

Similar results were found in the retrospective study by Dave et al. (100). The authors studied 89 patients who used V/V ECMO, divided in two groups: 35 COVID patients and 54 non-COVID patients. COVID patients had higher in-hospital mortality rates (49% versus 24%), longer ECMO and mechanical ventilation time before ECMO (654 h versus 394 h; 3 versus 1 day, respectively) than non-COVID patients.

Conclusion

This narrative review with a literature search strategy concludes that NRS, PP, ARM with decremental PEEP, and ECMO are

therapeutic strategies that should only be applied in strictly selected patients. Noninvasive ventilatory support should be the therapy of choice with the aim of improving hypoxemia and ventilatory work. If no improvement is seen, orotracheal intubation should be instituted with a protective strategy. In cases of inefficient gas exchange, i.e., P/F ratio < 150, PP and ARMs can be performed provided that the patient has recruitability potential. ECMO should only be instituted in patients who, on MV for a short time, have inefficient gas exchange. However, ECMO needs a trained team, and its use is recommended only in highly specialized centers.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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