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HIGH FREQUENCY PERCUSSIVE VENTILATION IN ACUTE RESPIRATORY FAILURE

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ABSTRACT (204 words)

Introduction: High-Frequency Percussive Ventilation (HFPV) is a ventilation mode characterized by high-frequency breaths. This study investigated the impact of HFPV on gas exchange and clinical outcomes in acute respiratory failure (ARF) patients during spontaneous breathing, non-invasive ventilation (NIV), and invasive mechanical ventilation (iMV).

Methods: This systematic review included randomized and nonrandomized studies up to August 2023. Inclusion criteria focused on adult ARF patients, HFPV application, comparisons with other ventilation modes, and outcomes related to oxygenation and clinical parameters. A pooled data analysis was performed comparing HFPV with iMV concerning gas exchange, pulmonary infection, and mortality.

Results: Of the 51 identified records, 29 met the inclusion criteria. HFPV was safely and effectively applied to ARF patients during spontaneous breathing or NIV, improving oxygenation. For patients who underwent iMV, HFPV significantly enhanced oxygenation and the arterial partial pressure of carbon dioxide, reduced pulmonary infection occurrence, and improved survival. Barotrauma rates were not elevated with HFPV, and hemodynamic stability remained unaffected. HFPV was also utilized in patients undergoing Extra-Corporeal Membrane Oxygenation, resulting in improved lung recruitment and oxygenation.

Conclusion: HFPV had favourable effects on physiological and certain clinical outcomes in ARF patients. However, the overall evidence quality remains weak, necessitating large-scale randomized controlled trials for definitive conclusions.

KEYWORDS: Acute Respiratory Failure; High-Frequency Percussive Ventilation; Invasive Mechanical Ventilation; Oxygenation; Clinical outcomes.

ABREVIATION LIST

ARF: Acute Respiratory Failure

CPAP: Continuous Positive Airway Pressure

CPT: chest physiotherapy

ECMO: Extra-Corporeal Membrane Oxygenation

HFPV: High-Frequency Percussive Ventilation

HFOV: High-Frequency Oscillatory Ventilation

HFJV: High-Frequency Jet Ventilation

ICU: Intensive Care Unit

iMV: invasive Mechanical Ventilation

NIV: non-invasive ventilation

$PaCO_2$: arterial partial pressure of carbon dioxide

PaO_2/FiO_2: arterial partial pressure to inspired fraction of oxygen ratio

VAP: Ventilator Associated Pneumonia

INTRODUCTION

High-Frequency Percussive Ventilation (HFPV) is a pneumatically driven ventilation mode characterized by time-cycled and pressure-limited mechanics that was introduced in the late 1970s as a new mode to reduce complications occurring during conventional modes of ventilation. This approach amalgamates the favourable attributes of standard mechanical ventilation alongside the traits of low-frequency breathing cycles (approximately 10-15 breaths per minute) and rapid high-frequency breaths (approximately 400 cycles per minute) [1]. This ventilation mode results in a reduced respiratory time and maintains an inspiratory-to-expiratory ratio of 2:1. HFPV involves regular interruptions in the ventilation cycle to allow the airway pressure to return to baseline before repeating the process.

In patients with hypoxemic acute respiratory failure (ARF), HFPV may represent a significant advantage compared to conventional modes of ventilation. HFPV delivers positive pressure, which restores and maintains lung volume and enhances alveolar ventilation [2-3]. In addition, it efficiently ensures proper oxygenation while operating at reduced airway pressures and tidal volumes [4] and mitigating the likelihood of barotrauma and volutrauma [4-6].

Indeed, critically ill patients are also at increased vulnerability to pulmonary complications such as pulmonary atelectasis, pneumonia, and respiratory failure [7-8]. Respiratory dysfunctions, encompassing factors such as excessive airway secretion, compromised mucociliary clearance [9-11], and an ineffective cough reflex[12-13], increase the risk of ventilator associated pneumonia (VAP) and lung atelectasis [10, 14-15], and the probability of unsuccessful extubation [16-17] and affect the intensive care unit (ICU) length of stay [14, 18-19] and mortality [16-17].

In this context, HFPV can be utilized either as an independent method or in conjunction with other ventilation approaches to effectively address conditions such as hypoxemia, pulmonary atelectasis, and airway clearance in patients with chronic obstructive pulmonary disease [20-21], cystic fibrosis [22-24], chest trauma [25-26], burns and inhalation injury [27-30] as well as in obese patients or those who have undergone lung surgery [31]. It has also been shown that HFPV improves gas exchange in mechanically ventilated patients who exhibit inadequate responses to conventional ventilation [32].

We conducted a systematic review to assess the impact of HFPV on oxygenation (principal aim) and other secondary physiological and clinical outcomes in adult patients with ARF.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (see the PRISMA Checklist in the Supplementary Material) [33]. The review protocol has been registered in Prospero (CRD42023440119).

Study selection and inclusion criteria

We included all randomized, quasi-randomized, prospective and retrospective studies, published in indexed scientific journals from inception to August 2023. We excluded papers published in languages other than English, case reports or series (including < 5 patients), reviews, systematic reviews or meta-analyses and studies published in abstract form. The references of included papers, reviews, systematic reviews, and meta-analyses were also examined to identify potential studies of interest missed during the primary search.

Search strategy and data extraction

Two authors (A.B. and E.G.) independently searched MEDLINE, EMBASE, and the Scopus Database of Systematic Reviews using the following keywords and their related MeSH terms: "nonconventional ventilation", "percussive ventilation", "acute respiratory failure", and "guidelines". Controlled vocabulary terms, text words, and keywords were variably combined. Blocks of terms per concept were created. These authors also independently checked all the articles and selected those meeting the following Population, Intervention, Comparison, Outcomes and Study (PICOS) criteria:

P) adult (aged 18 years or older) patients with ARF, as defined per study or with an arterial partial pressure to inspired fraction of oxygen ratio (PaO_2/FiO_2) < 300mmHg[34];

I) application of HFPV;

C) other ventilation modes (e.g., conventional mechanical ventilation, non-invasive ventilation) or spontaneous breathing;

O) oxygenation (e.g., PaO_2/FiO_2), arterial blood gases, airway pressures applied by the ventilator, ventilator-free days, ICU length of stay, complications (e.g., barotrauma, pneumothorax) and hospital mortality;

S) randomized, quasi-randomized, prospective and retrospective studies.

In particular, the screening process comprised two stages: the first stage involved the screening of titles and abstracts, while the second stage involved a comprehensive review of the complete texts of pertinent papers. The data were separately extracted by the two reviewer authors and collected in a dedicated spreadsheet (Excel, Microsoft Corporation, Redmond, WA, United States).

In cases of disagreement, the opinion of a third examiner (F.L.) was requested for a conclusive decision.

Risk of bias assessment

The methodological quality of the included studies was independently assessed by two authors (AB and EG), using Review Manager software (RevMan 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). We evaluated all studies for randomized sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias.

Outcome definition

We analysed whether the application of HFPV could modify some physiological and clinical outcomes in patients during spontaneous breathing, non-invasive ventilation (NIV),

conventional invasive Mechanical Ventilation (iMV), or extracorporeal membrane oxygenation (ECMO). In particular, we recorded:

1) the improvement of oxygenation (i.e., PaO_2/FiO_2) and carbon dioxide removal (i.e., arterial partial pressure of carbon dioxide; $PaCO_2$), as assessed through arterial blood gases, at the longest reported time point, up to 72 hours from the start of treatment;

2) changes in the mechanical properties of the respiratory system (i.e., airway peak pressure);

3) effects of HFPV on hemodynamics;

4) ventilator-free days, ICU length of stay, complications (i.e., barotrauma, pneumothorax), pulmonary infections (i.e., lower respiratory tract infections such as ventilator associated pneumonia and ventilator associated tracheobronchitis) [35-36], ICU and hospital mortalities.

Statistical analysis

Statistical analysis was conducted on the summary statistics of the selected articles (e.g., means, medians, proportions). As a result, the statistical unit of observation for all the selected variables was the single study and not the patient. Descriptive statistics of individual studies used different statistical indicators for central tendency and variability, such as means and standard deviations (SD), whereas absolute and relative frequencies were adopted for qualitative variables [37-38].

When pooled data analysis was performed, we presented dichotomous outcomes as risk ratio (RR) with 95% confidence intervals (CIs). For normally distributed continuous data, we calculated mean difference (MD) with corresponding 95% CIs. We used medians and interquartile ranges for continuous data that were not normally distributed. The meta-analyses were performed using random-effects models. We assessed heterogeneity by visually inspecting the forest plots to determine the closeness of point estimates to each other and the overlap of CIs. We used the χ^2 test with a P value of 0.10 to indicate statistical significance,

and the I^2 statistic to measure heterogeneity. We also considered the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P value from the χ^2 test), when determining the importance of the observed I^2 value. P values <0.05 were considered to indicate statistical significance. The assessment and graphical editing processes were facilitated by Review Manager software (RevMan 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

After launching the search strategy, we identified 51 records; after title and abstract screening and assessment for eligibility, 29 articles met the inclusion criteria. The detailed screening process is depicted in Figure S1 (in the Supplementary Materials).

The characteristics of the included studies are summarized in Table 1. Seventeen out of 29 (58%) studies were conducted in the United States, 10 (34%) in Europe, 1 (4%) in Australia and 1 (4%) in Japan. All studies but one were single-centre studies; six studies (21%) were randomized controlled trials. A total of 3506 patients were included. The characteristics of the patients included in every single study and the HFPV settings are summarized in Table 2. Finally, the results of the risk of bias assessment for each included study are presented in Figures S2 and S3 (in the Supplementary Materials), highlighting the overall risk of bias for each domain.

HFPV during spontaneous breathing

HFPV has been applied in patients with [39-40] or recovering from [41] ARF during spontaneous breathing. Vargas et al. investigated the impact of adding HFPV (30 minutes twice daily) to standard medical treatment and oxygen for 33 exacerbated COPD patients without respiratory acidosis. They found that combining HFPV with standard treatment reduced the exacerbation worsening rate (from 35% to 0) and length of hospital stay (from 7.9 to 6.8 days) compared to standard treatment alone. Additionally, in 16 patients receiving HFPV, there were significant improvements in gas exchange and respiratory rate compared to baseline [40].

In a study by Clini et al., 46 tracheostomized patients who recovered from ARF (mean PaO_2/FiO_2 ~240 mmHg) were randomized to receive two daily sessions of chest physiotherapy (CPT) with or without HFPV. Patients receiving the combination of HFPV and

CPT showed significant improvements in oxygenation and maximal expiratory pressure, while those receiving CPT alone did not. The incidence of pulmonary complications did not differ between the two treatments [41].

A recent retrospective study by Hassan et al. compared HFPV to CPT alone in 35 critically ill patients. HFPV sessions were shorter (10-15 minutes) and administered once or twice daily, while CPT sessions were longer (10-20 minutes) and administered once daily. Both treatments led to progressive improvements in peripheral oxygen saturation and chest X-ray findings, with a reduction in the inspired oxygen fraction. The length of stay in the ICU was similar between the HFPV and CPT groups (9.6 ± 5.9 days vs. 11.1 ± 9.3 days), and no major adverse events were reported in either group [39].

HFPV during non-invasive ventilation

Two studies investigated the use of HFPV in patients with ARF and Non-Invasive Ventilation (NIV).

Antonaglia et al. conducted a randomized controlled trial with 40 COPD exacerbation patients requiring NIV [21]. They compared HFPV to CPT in combination with NIV through a helmet starting from the second day of ICU admission. A historical control group of 40 patients receiving NIV through a mask was also included. Patients receiving HFPV had greater PaO_2/FiO_2 at ICU discharge than did patients in the historical and CPT groups. HFPV also reduced the time spent on ventilatory assistance and the length of ICU stay, with no associated complications [21].

Dimassi et al. conducted a prospective study with a randomized crossover design involving 17 patients at risk of extubation failure. They compared a session of HFPV to NIV. Both HFPV and NIV helped respiratory muscles by reducing the diaphragmatic workload and

respiratory rate. NIV decreased $PaCO_2$, while HFPV did not, and there were no significant changes in oxygenation [42].

HFPV during invasive Mechanical Ventilation

HFPV has been widely compared with conventional modes of invasive mechanical ventilation (iMV) in patients with ARF or ARDS of varying aetiology, trauma related ARF or inhalation injury.

Oxygenation

In April 1989, Gallagher et al. first described a significant improvement in oxygenation after 30 minutes of HFPV application in a series of 7 patients who underwent iMV for ARDS [43]. Several subsequent studies have described and compared iMV with HFPV. Consistent with Gallagher et al. [43], successive studies have demonstrated that HFPV improves oxygenation in patients with ARDS [44-45] or ARF of varying aetiology not responding to conventional iMV [32], in obese patients with the indication of prone positioning [31] or not responding to conventional iMV [46], and in cardiac surgery patients soon after the surgery [47] or failing conventional iMV [48]. In contrast, only one study did not show differences in gas exchange among 100 surgical patients admitted to the ICU who were randomized to receive conventional iMV or HFPV [49].

Oxygenation improvement was also reported in patients with post-traumatic ARDS refractory to conventional iMV [50-51] and in patients with severe traumatic brain injury and ARDS [52]. Only one study by Hurst et al. reported no differences in oxygenation between HFPV and conventional iMV in a group of 38 patients with severe traumatic brain injury and ARF [53].

Another area of application for HFPV is in the treatment of inhalation injury. Inhalation injury is a complication commonly observed in burn patients, who predisposes to bacterial infections and increases their morbidity and mortality. In comparison with iMV, HFPV improved oxygenation in patients with inhalational injury when applied as an alternative to conventional iMV [54-56] or as a salvage therapy after its failure [57]. Noteworthy, as shown in two observational studies by Reper et al. in patients, the degree of improvement in $PaO_2/FiO_2$is influenced by the increased frequency of percussion [58] without exacerbating the lung inflammation [5].

Figure 1 illustrates the comparison between HFPV and conventional iMV regarding the PaO_2/FiO_2 ratio at the longest reported time point, which extended up to 72 hours. The data revealed that HFPV led to a substantial improvement in PaO_2/FiO_2(Mean Difference 109 [95%CI: 77; 140] mmHg; $p<0.00001$; I^2 96%).

Secondary physiological outcomes

The effects on $PaCO_2$ were assessed in multiple studies, which yielded inconsistent results. Some studies observed a reduction in $PaCO_2$ during HFPV, in comparison to conventional iMV [32, 43-45, 52, 56-58], whereas other studies did not report similar results [46-47, 51, 53-55]. We also conducted a pooled data analysis based on available data, which is presented in Figure 2. In accordance with Figure 1, we included the reported values at the longest reported time point, up to 72 hours from the start of treatment. The pooled data analysis demonstrated that compared to conventional iMV, HFPV significantly reduced the $PaCO_2$ (Mean Difference -5.7 [95% CI: -8.1; -3.3] mmHg; $p<0.00001$; I^2 88%).

Several studies have investigated the impact of HFPV on applied airway pressures and hemodynamic status with varying results. Some studies have reported a significant reduction in applied airway pressure during HFPV [45, 53, 56-58]. Conversely, other studies did not

find a significant change in applied airway pressure during HFPV [32, 43, 47, 50-51, 54-55]. Notably, Hurst et al. reported that HFPV reduced peak inspiratory pressure only in patients with ARDS [49]. Importantly, all studies consistently reported that HFPV did not adversely affect the hemodynamic status of patients [31-32, 43, 45, 47, 49, 53, 55-56, 58]. Additionally, two studies demonstrated that HFPV significantly reduced intracranial pressure in patients with severe traumatic brain injury [52-53], secondary to a simultaneous reduction in $PaCO_2$ [52].

Secondary clinical outcomes

Clinical outcomes in studies of HFPV have been reported by a limited number of authors, primarily due to the observational design of most published studies.

Many studies have not reported cases of pneumothorax or air-leaks related to barotrauma during the application of HFPV [31-32, 44, 50, 53-56]. In contrast, a few studies reported a very low rate of such adverse events, such as those occurring during conventional iMV [29-30, 49, 57].

Two studies reported a lower rate of pneumonia complications in patients with inhalational injury receiving HFPV than in patients in a comparison group receiving conventional iMV [30, 59]. However, other studies found no difference between the modes of ventilation with respect to the incidence of pulmonary infection [29, 54-55]. As shown in Figure S4 (in the Supplementary Materials), the pooled data analysis showed a trend toward a reduction in the development of pulmonary infection in patients receiving HFPV compared to those receiving conventional iMV (Risk Ratio 0.74 [95% CI: 0.54; 1.00]; p=0.05; I^2 39%).

The number of days spent under iMV was not different between HFPV and conventional iMV in some studies [29, 49]. The number of ventilator-free days were also similar between HFPV and conventional iMV in other studies [32, 54]. Additionally, the ICU and hospital

lengths of stay were not significantly different between treatments in several studies [29, 49, 54].

Mortality rates varied across studies. Some reported a reduction in ICU and overall mortality in patients receiving HFPV, particularly in those with inhalational injuries or minor burns [29-30, 59]. However, other studies found no significant differences in mortality between HFPV and conventional iMV [32, 49, 54-55].The pooled data analysis showed a reduction in mortality in patients receiving HFPV compared to those receiving conventional iMV (Risk Ratio 0.62 [95% CI: 0.46; 0.84]; p=0.002; $I^2$20%) (see Figure S5 in the Supplementary Materials).

HFPV during Extra-Corporeal Membrane Oxygenation (ECMO)

In individuals suffering from severe ARDS and unresponsive respiratory failure, the use of veno-venous Extracorporeal Membrane Oxygenation (vv-ECMO) plays a pivotal role in their treatment [60]. During vv-ECMO, blood is drained through a venous cannula, which is typically placed within the femoral vein. Subsequently, the blood is oxygenated by an artificial membrane lung and reintroduced into the circulation via another cannula (reinfusion), which is positioned either in the femoral or jugular vein. Numerous trials have shown promising outcomes and advantages that support the utilization of vv-ECMO in treating the most severe cases of ARDS, regardless of its underlying cause[61-65]. During vv-ECMO, the lungs are ventilated with a protective or ultra-protective strategy. In this scenario, HFPV has been also been attempted in patients undergoing ECMO for ARDS. Michaels et al. reported the data recorded in 39 patients receiving ECMO in combination with HFPV [66]. The characteristics of the patients were similar to those reported by other investigators adhering to the Extracorporeal Life Support Organization (ELSO). In fact, pre-ECMO and post-ECMO respiratory characteristics and clinical outcomes were reported by

the authors to be similar to those of other previous investigations [66]. Moreover, the research also indicated that HFPV assists in alveolar recruitment and enhances the inherent pulmonary function of individuals undergoing ECMO treatment. This finding implies that incorporating HFPV in conjunction with an active lung recruitment approach could shorten the recovery and weaning period for adults with ARDS receiving ECMO therapy [66].

Kulgarov et al. also reported their experience with HFPV in five patients undergoing veno-arterial ECMO for cardiopulmonary arrest [67]. Although patients were not strictly speaking admitted for ARF, HFPV was applied to facilitate weaning from ECMO after weaning failed with conventional modes of ventilation. The duration of HFPV combined with ECMO was 5.4 ± 5.6 days, whereas the duration of ECMO alone was 6.0 ± 5.1 days and that of HFPV alone was 2.2 ± 2.2 days. At 24 hours after application, HFPV significantly improved the oxygenation (PaO_2/FiO_2) from 44 ± 16 to 170 ± 70 mmHg, while maintaining $PaCO_2$ and pH within normal ranges [67]. All patients were successfully weaned from ECMO, and only one died before ICU discharge due to progressive heart failure after ECMO discontinuation [67].

DISCUSSION

This systematic review described the physiological benefits of the application of HFPV in patients with ARF during spontaneous breathing, CPAP or NIV, conventional iMV or ECMO. HFPV was applied as adjunctive therapy for tracheobronchial secretion management (during spontaneous breathing, CPAP or NIV) or as ventilatory support combined with conventional modes (during iMV and ECMO).

HFPV is a ventilation mode within the family of high-frequency ventilation strategies. Other modalities within this family include High-Frequency Oscillatory Ventilation (HFOV) and High-Frequency Jet Ventilation (HFJV). All these modalities deliver small tidal volumes at high frequencies, but they have different technical characteristics and operational principles

[68-69]. HFOV includes the active insufflation and exsufflation of gas from the lungs with a ventilator equipped with a large vibrating membrane. The active exhalation phase is believed to enhance the release of gas, thereby enabling the use of a higher frequency and smaller tidal volume compared to devices with passive exhalation [70-71]. On the opposite, HFJV delivers a high-velocity jet of gas through a small catheter into the patient's airway at a very rapid rate, creating a brief positive pressure in the airway to facilitate ventilation. This is followed by an expiratory release with a rapid decrease in pressure, enabling quick exhalation of air from the lungs [69]. Noteworthy, ventilators differ in terms of ventilatory efficacy [68]. For these reasons, in order also to provide a clear point, we focused only on HFPV. HFPV is characterized as a ventilation method that regulates airflow and timing, generating controlled pressure while delivering a series of high-frequency subtidal volumes alongside low-frequency breathing cycles [72]. More specifically, the ventilator operates as a pneumatically driven high-frequency pulse generator, combining oscillatory breaths at frequencies ranging from 0.6 to 15 Hz to reach a chosen peak airway pressure. It includes regular interruptions, typically occurring every 2 seconds, with a passive exhalation phase ending at a designated level of oscillatory continuous positive airway pressure (CPAP), usually set at 5 to 10 cm H_2O [72]. The peculiarity of this mode of ventilation is the presence of the “Phasitron”, a sliding Venturi system generating percussion in the form of rapid airflow fluctuations [72]. Oscillatory modes of ventilation aim to open the collapsed alveola and to guarantee protective ventilation by delivering small tidal volumes [73].It has been widely demonstrated that low tidal volumes (i.e. 6 ml/kg of predicted body weight) and driving pressure (< 13 cmH_2O) are associated with improved survival in patients with ARDS [74-76]. Two large trials have shown that HFOV has no significant effect on 30-day mortality [71] and may even increase hospital mortality [70] in patients undergoing mechanical ventilation for ARDS. However, since the literature remains inconclusive, some authors have reopened the

discussion on this mode of ventilation, suggesting the need for more clinical investigation [73, 77-78]. In keeping with these authors, our results suggest the same indication in the field of HFPV. In our pooled data analysis, we have observed an improvement in oxygenation, that may be primarily attributed to a recruitment effect on compression atelectasis. Indeed, this has been suggested for obese patients with compression atelectasis, as evidenced by enhancements in respiratory system compliance and confirmed by chest computer tomography scans [31]. In addition, we also demonstrated that the application of HFPV during iMV promoted alveolar recruitment and improved oxygenation in hypersecretive tracheostomized patients [1]. However, a clear assessment of lung aeration and tidal distribution within the lung currently lacks; this could be assessed and monitored with some bedside advance respiratory monitoring such as electrical impedance tomography or lung ultrasonography [79-80]. In addition, the clinical outcomes associated with HFPV have shown a degree of variability in different patient populations, with some studies indicating potential benefits in terms of reduced complications and mortality, particularly in specific patient subgroups. Indeed, it should be noted that there is considerable heterogeneity in the aetiology of ARF (i.e. COPD, trauma, inhalational injury, ARDS, …) among the patients included in these studies.

The current evidence is insufficient to establish a general indication for the use of HFPV in hypoxemic patients with ARF. Noteworthy, a panel of experts has recently published an opinion document on diagnosis and management of inhalational injury [81]. Based on the limited literature assessing and supporting the use of HFPV, the experts currently regard HFPV as inappropriate [81].

Before drawing conclusions, it is essential to acknowledge a significant limitation of this systematic review. A comprehensive pooled data analysis of all predefined outcomes was hindered by several factors, including the relatively small amount of data and studies,

population and methodological heterogeneity, low-quality study designs (as shown by the risk of bias assessments in the ESM), and sometimes the lack of control groups, together with the unavailability of additional data and information from corresponding authors. Consequently, pooled data analysis was feasible for only a few outcomes in intubated patients, and only narrative summaries were possible for those who breathed spontaneously or who were receiving NIV, necessitating cautious interpretation of any conclusions. Therefore, it is mandatory to design large RCTs in specific populations of patients with ARF to draw definitive conclusions. Indeed, a question still exists: "Is HFPV an abandoned or forgotten mode of ventilation in patients with ARF?"

CONCLUSIONS

The current level of evidence remains insufficient to indicate the use of HFPV in patients with ARF, although potential benefits might occur. Since systematic reviews are only hypothesis generating, further multicentre RCTs are needed to draw definitive conclusions on the effects of HFPV on clinical outcomes (i.e., ventilator associated pneumonia, time spent under mechanical ventilation, survival rate).

TABLES

Table 1 – Characteristics of included studies.

Authors	Year of publication	Study design	Country	Number of centers
Spontaneous Breathing				
Vargas et al. [40]	2005	RCT	France	1
Clini et al. [41]	2006	RCT	Italy	2
Hassan et al. [39]	2021	Retrospective	Australia	1
Non-Invasive Ventilation				
Antonaglia et al. [21]	2006	RCT	Italy	1
Dimassi et al. [42]	2011	Randomized Cross-over	France	1
Invasive Mechanical Ventilation				
Hurst et al. [53]	1988	Prospective Observational pre post	United States	1
Cioffi et al. [57]	1989	Prospective Observational	United States	1
Gallagher et al. [43]	1989	Prospective Observational pre post	United States	1
Hurst et al. [49]	1990	RCT	United States	1
Cioffi et al. [30]	1991	Prospective Observational	United States	1
Rue et al. [59]	1993	Retrospective	United States	1
Reper et al. [56]	1998	Retrospective	Belgium	1
Velmahos et al. [45]	1999	Retrospective	United States	1
Paulsen et al. [51]	2002	Retrospective	United States	1
Reper et al. [55]	2002	RCT	Belgium	1
Reper et al. [58]	2003	Prospective Observational	Belgium	1
Salim et al. [52]	2004	Retrospective	United States	1
Eastman et al.[50]	2006	Retrospective	United States	1
Tsuruta et al. [31]	2006	Prospective Observational	Japan	1
Hall et al. [29]	2007	Retrospective	United States	1
Chung et al. [54]	2010	RCT	United States	1
Lucangelo et al. [32]	2012	Cross-over	Italy	1
Spapen et al. [44]	2014	Retrospective	Belgium	1
Reper et al. [5]	2015	Prospective observational	Belgium	1
Wong et al. [48]	2017	Retrospective	United States	1
Oribabor et al. [47]	2018	Prospective observational	United States	1
Zorzhuk et al. [46]	2020	Retrospective	United States	1
Extra-Corporeal Membrane Oxygenation				
Michaels et al. [66]	2015	Retrospective	United States	1
Gulkarov et al. [67]	2018	Retrospective	United States	1

RCT, Randomized Controlled Trial.

Table 2 – Characteristics of patients and applied treatments.

Authors	Year of publication	N of patients	Type of ARF	Control treatment	HFPV treatment	HFPV settings
Spontaneous breathing						
Vargas et al. [40]	2005	33	COPD exacerbation	Conventional oxygen therapy and standard medical treatment	30-min sessions twice daily	Frequency at 250/minute and Paw at 20 cmH_2O, then adjusted per comfort. I/E ratio at 1:2.5.
Clini et al. [41]	2006	46	Tracheostomized patients recently weaned from iMV	CPT	5-min session of HFPV followed by CPT	Driving pressure (1.6 to 2.0 bar) and frequency (200 up to 300 cycles/min) according to the patient's tolerance. I/E ratio at 1:1.2. Paw limited at 40 cm H_2O.
Hassan et al. [39]	2021	35	ARF of varying aetiology	CPT once daily	10 to 15 min sessions twice daily	Frequency at 170 to 230 breaths/min. Paw between 10 to 20 cmH_2O.
Non-invasive ventilation						
Antonaglia et al. [21]	2006	40	COPD exacerbation	NIV + CPT (25 min once daily)	NIV + HFPV (25 min sessions twice daily)	Frequency at 225/minute. Paw<40 cmH_2O.
Dimassi et al. [42]	2011	17	Post-weaning patients with indication to post-extubation NIV	NIV (20-min session)	HFPV (20-min session)	Frequency at 250/minute Driving pressure at 1.2 bar I/E ratio at 1:2.5.
Invasive Mechanical Ventilation						
Hurst et al. [53]	1988	38	Severe TBI with ICP>15mmHg and ARF	Conventional iMV	HFPV	Frequency at 240 up to 480/minute. Paw<40 cmH_2O. I/E ratio at 1:2.
Cioffi et al. [57]	1989	5 (group 1) 8 (group 2)	Inhalational injury	Conventional iMV	HFPV as salvage treatment (group 1) HFPV as first line treatment (group 2)	Frequency between 200 and 600/minute. I/E ratio at 1:1.
Gallagher et al. [43]	1989	7	ARF of varying aetiology	Conventional iMV	HFPV	Frequency between 350 and 450/minute. I/E ratio at 1:1.
Hurst et al. [49]	1990	100	Patients at risk for ARDS	Conventional iMV	HFPV	Frequency between 200 and

						600/minute. I/E ratio at 1:2.
Cioffi et al. [30]	1991	54	Inhalational injury	//	HFPV as first line	Not specified
Rue et al. [59]	1993	1256	ARF of varying aetiology	HFPV in 926 patients without inhalational injury	HFPV in 330 patients with inhalational injury	Not specified
Reper et al. [56]	1998	11	Inhalational injury	Conventional iMV	HFPV	Frequency between 600 and 800/minute. I/E ratio adjusted according to gas exchange.
Velmahos et al. [45]	1999	32	ARDS	Conventional iMV	HFPV	Frequency >500/minute. I/E ratio at 1:1.
Paulsen et al. [51]	2002	10	ARDS (mainly post-trauma)	Conventional iMV	HFPV as salvage treatment	Not specified
Reper et al. [55]	2002	35	Inhalational injury	Conventional iMV	HFPV	Frequency between 600 and 800/minute. I/E ratio adjusted according to gas exchange.
Reper et al. [58]	2003	8	Postoperative burn patients	2-hours period of Conventional iMV	2-hours period of HFPV	Frequency between 600 and 800/minute. I/E ratio adjusted according to gas exchange.
Salim et al. [52]	2004	10	Severe TBI with ARDS	Conventional iMV	HFPV	Frequency between 200 and 900/minute.
Eastman et al. [50]	2006	12	Post-trauma ARDS	Conventional iMV	HFPV	Frequency between 200 and 900/minute.
Tsuruta et al. [31]	2006	10	Obese patients with ARF	Conventional iMV	HFPV	Frequency at 300/minute.
Hall et al. [29]	2007	222	Inhalational injury	Conventional iMV in 130 patients	HFPV in 92 patients	Frequency at 450/minute. I/E ratio at 1:1.
Chung et al. [54]	2010	62	Burn patients	Conventional iMV	HFPV	Not specified
Lucangelo et al. [32]	2012	35	ARDS	Conventional iMV	12-hours session HFPV	Frequency at 500/minute. I/E ratio at 1:1.
Spapen et al. [44]	2014	42	ARDS	//	HFPV	Frequency at 500/minute. I/E ratio at 1:1.
Reper et al. [5]	2015	15	Inhalational injury	//	HFPV	Frequency between 450 and 650/minute. I/E ratio adjusted according to gas exchange.

Wong et al. [48]	2017	1283	Post-Cardiac Surgery	1267 patients in Conventional iMV	16 patients in HFPV as salvage treatment	Frequency between 500 and 600/minute. I/E ratio at 1:1.
Oribabor et al. [47]	2018	24	Post-Cardiac Surgery	Conventional iMV (Adaptive Support Ventilation mode)	HFPV	Frequency between 500 and 600/minute. I/E ratio at 1:1.
Zorzhuk et al. [46]	2020	12	Morbidly obese patients failing conventional iMV	Conventional iMV	HFPV as salvage treatment	Frequency between 500 and 600/minute. I/E ratio at 1:1.
Extra-Corporeal Membrane Oxygenation						
Michaels et al. [66]	2015	39	ARDS patients receiving ECMO	Conventional iMV + ECMO	HFPV + ECMO	Frequency at 500/minute. I/E ratio at 1:1.
Gulkarov et al. [67]	2018	5	Patients receiving ECMO after cardiac arrest	Conventional iMV + ECMO	HFPV + ECMO	Not specified

COPD, Chronic Obstructive Pulmonary Disease; Paw, airways pressure; iMV, invasive Mechanical Ventilation; CPT, Chest Physiotherapy; HFPV, High Frequency Percussive Ventilation; ARF, Acute Respiratory Failure; NIV, Non Invasive Ventilation; TBI, Traumatic Brain Injury; ICP, IntraCranial Pressure; ARDS, Acute Respiratory Distress Syndrome; ECMO, Extra Corporeal Membrane Oxygenation.

FIGURE CAPTIONS

Figure 1 -Oxygenation.

Sensitivity analysis forest plot for oxygenation for HFPV and conventional iMV, at the longest reported time point up to 72 hours.

Green squares indicate the individual study mean differences whereas the black horizontal lines indicate the 95% confidence interval of single studies. The diamond refers to the overall mean difference (mmHg) with 95% confidence interval.

Figure 2 - Arterial partial pressure of carbon dioxide.

Sensitivity analysis forest plot for arterial partial pressure of carbon dioxide ($PaCO_2$) for HFPV and conventional iMV, at the longest reported time point up to 72 hours.

Green squares indicate the individual study mean differences whereas the black horizontal lines indicate the 95% confidence interval of single studies. The diamond refers to the overall mean difference (mmHg) with 95% confidence interval.

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Conflict of interest: Prof. Federico Longhini contributed to the development of a new helmet for mechanical ventilation, and he is designated as inventor (European Patent number 3320941) not related to the present manuscript. He also received speaking fees from Draeger, Intersurgical and Fisher & Paykel. The remaining authors have no relevant financial or non-financial interests to disclose.

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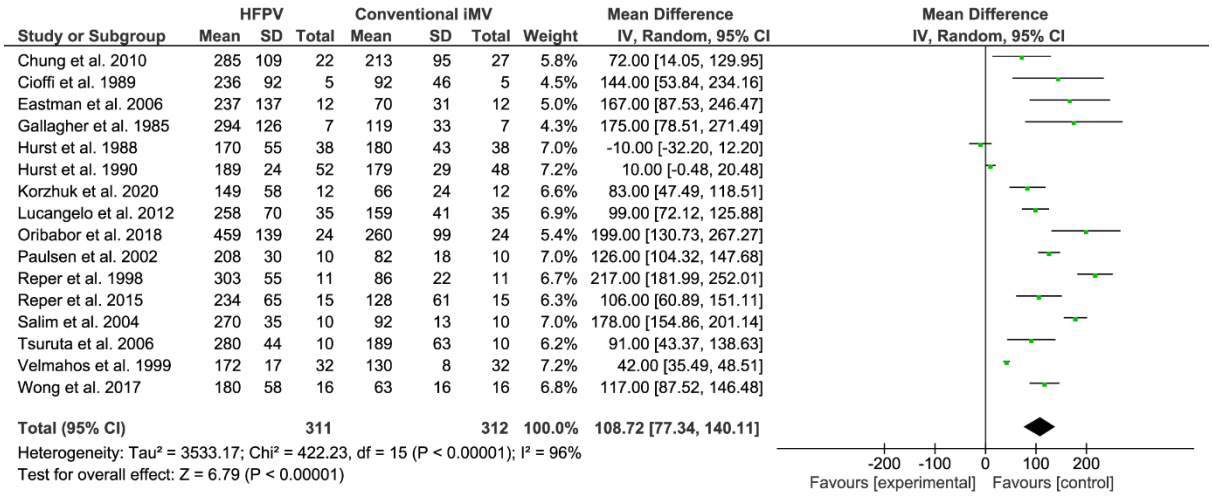

Figure 1

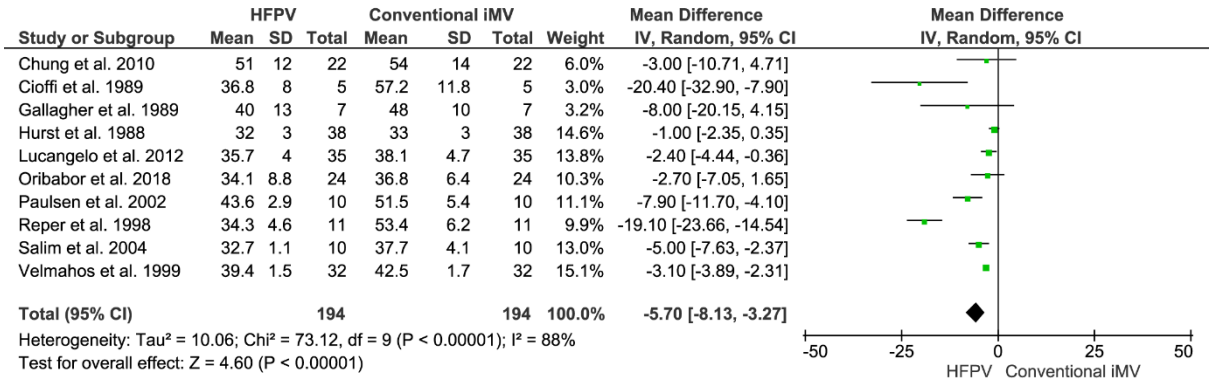

Figure 2

HIGH FREQUENCY PERCUSSIVE VENTILATION IN ACUTE RESPIRATORY FAILURE

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Supplementary Material

PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6-7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8-9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	8-9

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	ESM
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	ESM
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	ESM
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 and 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	ESM
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	10-16
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10-16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	10-16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10-16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	10-16
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	ESM
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	ESM
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16-18
	23b	Discuss any limitations of the evidence included in the review.	16-18
	23c	Discuss any limitations of the review processes used.	16-18
	23d	Discuss implications of the results for practice, policy, and future research.	16-18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	24

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Figure S1. Flow Diagram. Study flow diagram according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols recommendations.

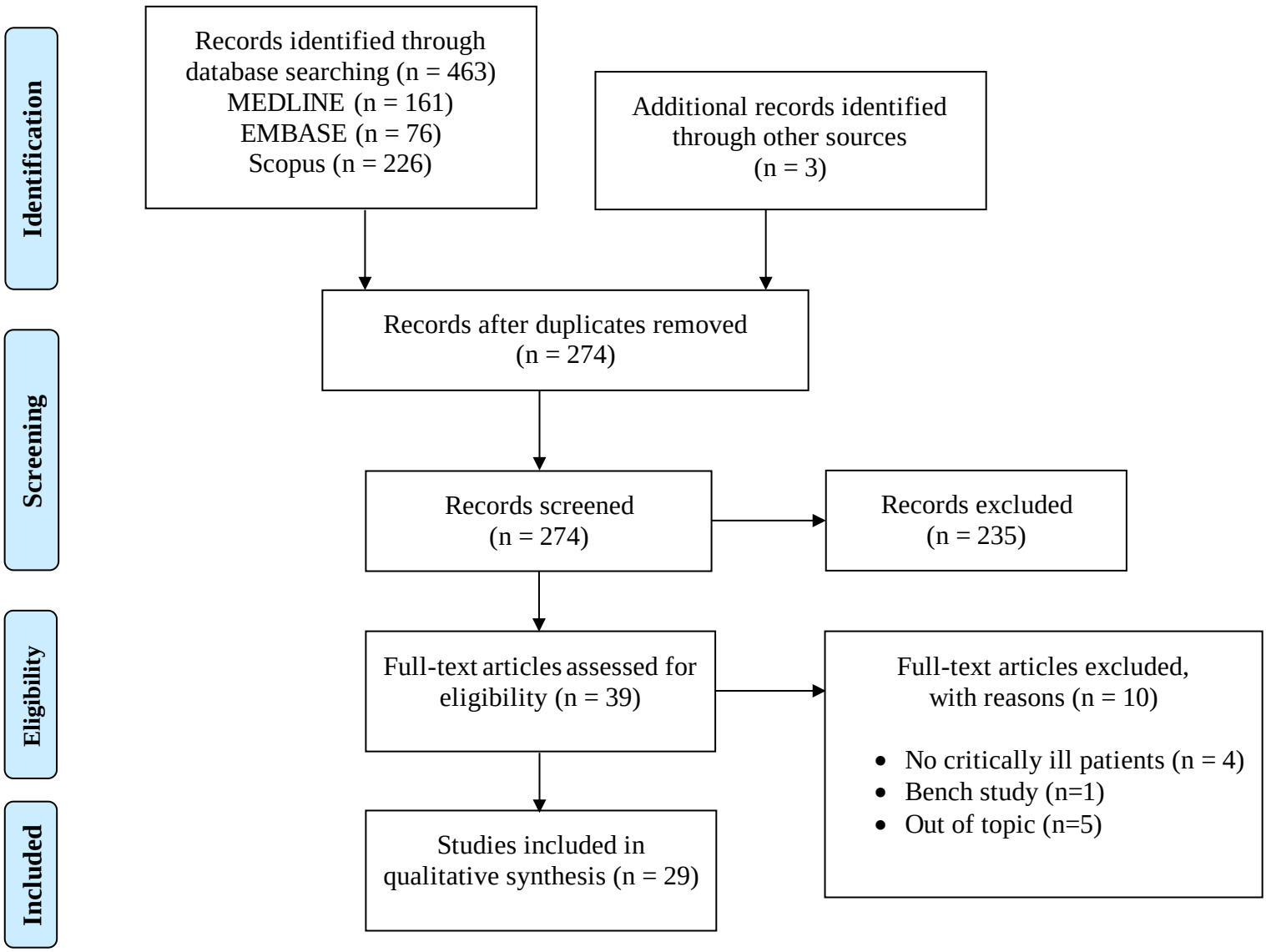


Figure S2. Summary of the risk of bias assessment.

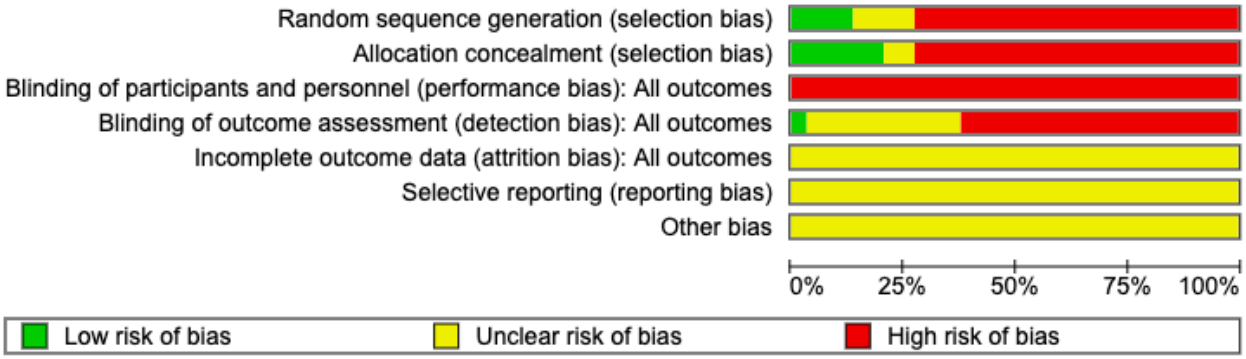


Figure S3. Detailed assessment of the risk of bias.

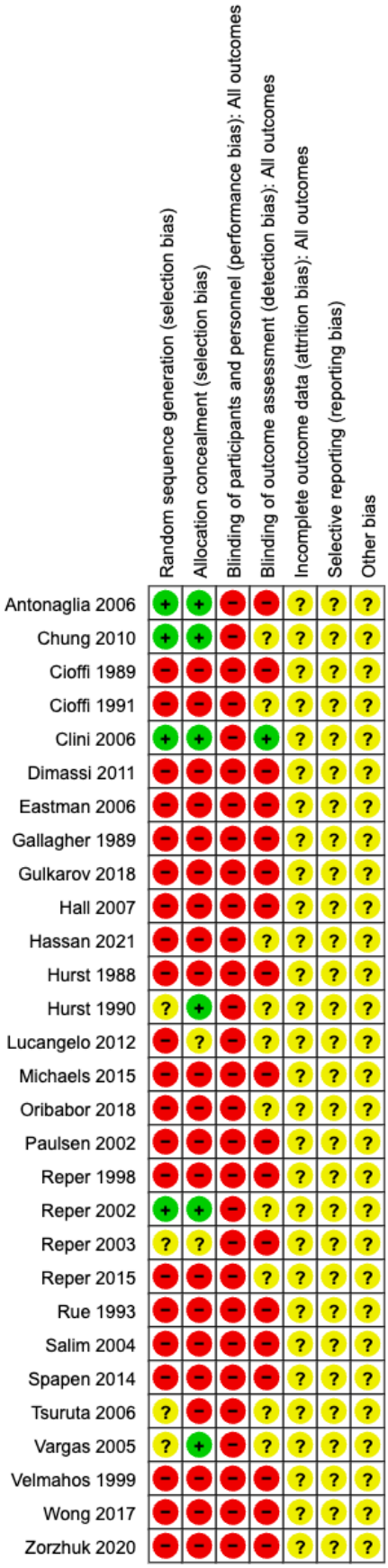
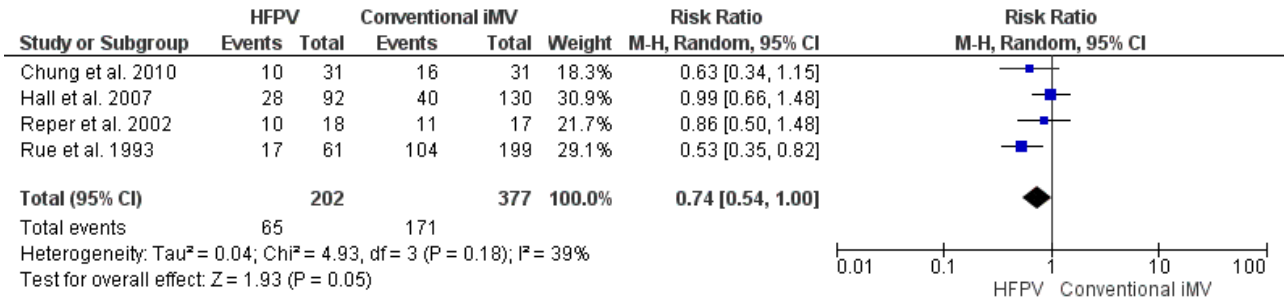
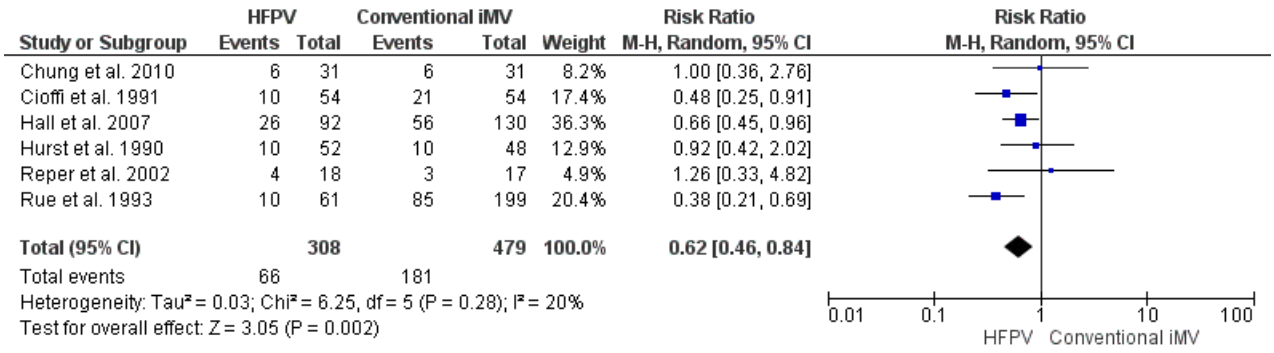


Figure S4. Pooled data analysis for pulmonary infections.



The figure shows the sensitivity analysis forest plot for pulmonary infection occurrence for HFPV and conventional iMV. Blue squares indicate the individual study Risk Ratio whereas the black horizontal lines indicate the 95% confidence interval of single studies. The diamond refers to the overall Risk Ratio with 95% confidence interval.

Figure S5. Pooled data analysis for mortality.



The figure shows the sensitivity analysis forest plot for mortality for HFPV and conventional iMV. Blue squares indicate the individual study Risk Ratio whereas the black horizontal lines indicate the 95% confidence interval of single studies. The diamond refers to the overall Risk Ratio with 95% confidence interval.