High-frequency percussive ventilation in acute respiratory failure

Andrea Bruni[1], Giuseppe Neri[1], Gianmaria Cammarota[2], Vincenzo Bosco[1], Eugenio Biamonte[1], Letizia Troisi[1], Annalisa Boscolo[3,4,5], Paolo Navalesi[3,4,5], Federico Longhini[1] and Eugenio Garofalo[1]

[1]Anaesthesia and Intensive Care Unit, Department of Medical and Surgical Sciences, "Magna Graecia" University, Catanzaro, Italy. [2]Department of Translational Medicine, Eastern Piedmont University, Novara, Italy. [3]Department of Medicine-DIMED, University of Padua, Padua, Italy. [4]Anaesthesia and Intensive Care Unit, University Hospital of Padua, Padua, Italy. [5]Thoracic Surgery and Lung Transplant Unit, Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padua, Padua, Italy.

Corresponding author: Federico Longhini (longhini.federico@gmail.com)

Shareable abstract (@ERSpublications)
HFPV can be used to manage tracheobronchial secretions during spontaneous breathing, CPAP or NIV. In intubated patients, HFPV applied with invasive mechanical ventilation improves oxygenation, whereas it may reduce complications and mortality. https://bit.ly/3WGy4ox

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Abstract

Introduction High-frequency percussive ventilation (HFPV) is a ventilation mode characterised 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, noninvasive ventilation (NIV) and invasive mechanical ventilation (iMV).

Methods This systematic review included randomised and nonrandomised 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 haemodynamic stability remained unaffected. HFPV was also utilised in patients undergoing extracorporeal 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 randomised controlled trials for definitive conclusions.

Introduction

High-frequency percussive ventilation (HFPV) is a pneumatically driven ventilation mode characterised 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 (~10–15 breaths·min^{-1}) and rapid high-frequency breaths (~400 cycles·min^{-1}) [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 hypoxaemic 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 utilised either as an independent method or in conjunction with other ventilation approaches to effectively address conditions such as hypoxaemia, pulmonary atelectasis and airway clearance in patients with COPD [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 randomised, quasi-randomised, 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. Bruni and E. Garofalo) 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 (P_{aO_2}/F_{IO_2}) <300 mmHg [34];
I: application of HFPV;
C: other ventilation modes (*e.g.*, conventional mechanical ventilation, noninvasive ventilation (NIV) or spontaneous breathing;
O: oxygenation (*e.g.*, P_{aO_2}/F_{IO_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: randomised, quasi-randomised, 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, USA).

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

Risk of bias assessment

The methodological quality of the included studies was independently assessed by two authors (A. Bruni and E. Garofalo), using Review Manager software (RevMan 5.3; Nordic Cochrane Centre, Cochrane

Collaboration, Copenhagen, Denmark). We evaluated all studies for randomised 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, NIV, conventional invasive mechanical ventilation (iMV) or extracorporeal membrane oxygenation (ECMO). In particular, we recorded:

1) the improvement of oxygenation (*i.e.*, P_{aO_2}/F_{IO_2}) and carbon dioxide removal (*i.e.*, arterial partial pressure of carbon dioxide (P_{aCO_2})), as assessed through arterial blood gases, at the longest reported time point, up to 72 h 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 haemodynamics;
4) ventilator-free days, ICU length of stay, complications (*i.e.*, barotrauma, pneumothorax), pulmonary infections (*i.e.*, lower respiratory tract infections such as VAP 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 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 supplementary figure S1.

The characteristics of the included studies are summarised in table 1. 17 out of 29 (58%) studies were conducted in the USA, 10 (34%) in Europe, one (4%) in Australia and one (4%) in Japan. All studies but one were single-centre studies; six studies (21%) were randomised controlled trials. A total of 3506 patients were included. The characteristics of the patients included in every single study and the HFPV settings are summarised in table 2.

Finally, the results of the risk of bias assessment for each included study are presented in supplementary figures S2 and S3, 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.* [40] investigated the impact of adding HFPV (30 min 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].

TABLE 1 Characteristics of included studies

Authors	Year of publication	Study design	Country	Number of centres
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
Noninvasive ventilation				
Antonaglia *et al.* [21]	2006	RCT	Italy	1
Dimassi *et al.* [42]	2011	Randomised crossover	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	Crossover	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
Korzhuk *et al.* [46]	2020	Retrospective	United States	1
Extracorporeal membrane oxygenation				
Michaels *et al.* [66]	2015	Retrospective	United States	1
Gulkarov *et al.* [67]	2018	Retrospective	United States	1

RCT: randomised controlled trial.

In a study by Clini *et al.* [41], 46 tracheostomised patients who recovered from ARF (mean P_{aO_2}/F_{IO_2} ~240 mmHg) were randomised 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.* [39] compared HFPV to CPT alone in 35 critically ill patients. HFPV sessions were shorter (10–15 min) and administered once or twice daily, while CPT sessions were longer (10–20 min) and administered once daily. Both treatments led to progressive improvements in peripheral oxygen saturation and chest radiograph 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 *versus* 11.1±9.3 days), and no major adverse events were reported in either group [39].

HFPV during NIV

Two studies investigated the use of HFPV in patients with ARF and NIV.

Antonaglia *et al.* [21] conducted a randomised controlled trial with 40 COPD exacerbation patients requiring NIV. 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 P_{aO_2}/F_{IO_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].

TABLE 2 Characteristics of patients and applied treatments

Authors	Year of publication	Patients, n	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/min and P_{aw} at 20 cmH_2O, then adjusted per comfort I/E ratio at 1:2.5
Clini *et al.* [41]	2006	46	Tracheostomised 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^{-1}) according to the patient's tolerance I/E ratio at 1:1.2 P_{aw} limited at 40 cmH_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^{-1} P_{aw} between 10 and 20 cmH_2O
Noninvasive 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/min P_{aw} <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/min 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 >15 mmHg and ARF	Conventional iMV	HFPV	Frequency at 240 up to 480/min P_{aw} <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/min I/E ratio at 1:1
Gallagher *et al.* [43]	1989	7	ARF of varying aetiology	Conventional iMV	HFPV	Frequency between 350 and 450/min 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/min 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/min I/E ratio adjusted according to gas exchange
Velmahos *et al.* [45]	1999	32	ARDS	Conventional iMV	HFPV	Frequency >500/min 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/min I/E ratio adjusted according to gas exchange

Continued

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TABLE 2 Continued

Authors	Year of publication	Patients, n	Type of ARF	Control treatment	HFPV treatment	HFPV settings
Reper *et al.* [58]	2003	8	Post-operative burn patients	2-h period of conventional iMV	2-h period of HFPV	Frequency between 600 and 800/min 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/min
Eastman *et al.* [50]	2006	12	Post-trauma ARDS	Conventional iMV	HFPV	Frequency between 200 and 900/min
Tsuruta *et al.* [31]	2006	10	Obese patients with ARF	Conventional iMV	HFPV	Frequency at 300/min
Hall *et al.* [29]	2007	222	Inhalational injury	Conventional iMV in 130 patients	HFPV in 92 patients	Frequency at 450/min 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-h session HFPV	Frequency at 500/min I/E ratio at 1:1
Spapen *et al.* [44]	2014	42	ARDS		HFPV	Frequency at 500/min I/E ratio at 1:1
Reper *et al.* [5]	2015	15	Inhalational injury		HFPV	Frequency between 450 and 650/min 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/min 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/min I/E ratio at 1:1
Korzhuk *et al.* [46]	2020	12	Morbidly obese patients failing conventional iMV	Conventional iMV	HFPV as salvage treatment	Frequency between 500 and 600/min I/E ratio at 1:1
Extracorporeal membrane oxygenation						
Michaels *et al.* [66]	2015	39	ARDS patients receiving ECMO	Conventional iMV+ECMO	HFPV+ECMO	Frequency at 500/min 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

ARF: acute respiratory failure; HFPV: high-frequency percussive ventilation; I/E ratio: inspiratory to expiratory ratio; P_{aw}: airways pressure; iMV: invasive mechanical ventilation; CPT: chest physiotherapy; NIV: noninvasive ventilation; TBI: traumatic brain injury; ICP: intracranial pressure; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation.

DIMASSI *et al*. [42] conducted a prospective study with a randomised 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 P_{aCO_2}, while HFPV did not, and there were no significant changes in oxygenation.

HFPV during iMV

HFPV has been widely compared with conventional modes of iMV in patients with ARF or acute respiratory distress syndrome (ARDS) of varying aetiology, trauma-related ARF or inhalation injury.

Oxygenation

In April 1989, GALLAGHER *et al*. [43] first described a significant improvement in oxygenation after 30 min of HFPV application in a series of seven patients who underwent iMV for ARDS. 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 randomised 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*. [53] reported no differences in oxygenation between HFPV and conventional iMV in a group of 38 patients with severe traumatic brain injury and ARF.

Another area of application for HFPV is in the treatment of inhalation injury. Inhalation injury is a complication commonly observed in burn patients, predisposing them to bacterial infections and increasing 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 by REPER *et al*. [5, 58] the degree of improvement in P_{aO_2}/F_{IO_2} is influenced by the increased frequency of percussion [58], without exacerbation of the lung inflammation.

Figure 1 illustrates the comparison between HFPV and conventional iMV regarding the P_{aO_2}/F_{IO_2} ratio at the longest reported time point, which extended up to 72 h. The data revealed that HFPV led to a substantial improvement in P_{aO_2}/F_{IO_2} (MD 109 (95% CI: 77–140) mmHg; p<0.00001; I^2 96%).

Secondary physiological outcomes

The effects on P_{aO_2} were assessed in multiple studies, which yielded inconsistent results. Some studies observed a reduction in P_{aCO_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 h from the start of treatment. The pooled data analysis demonstrated that compared to conventional iMV, HFPV significantly reduced the P_{aCO_2} (MD −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 haemodynamic 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*. [49] reported that HFPV reduced peak inspiratory pressure only in patients with ARDS. Importantly, all studies consistently reported that HFPV did not adversely affect the haemodynamic 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 P_{aCO_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.

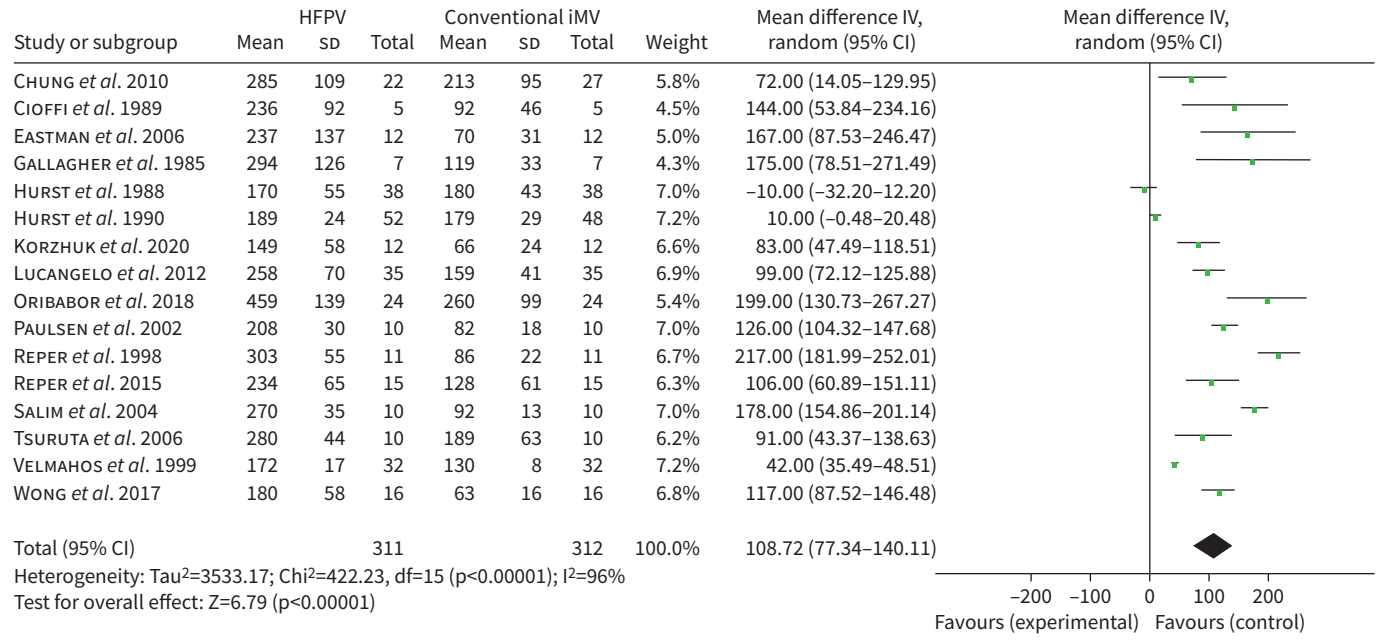

FIGURE 1 Oxygenation. Sensitivity analysis forest plot for oxygenation for HFPV and conventional iMV, at the longest reported time point up to 72 h. Green squares indicate the individual study mean differences, and the black horizontal lines indicate the 95% confidence interval of single studies. The diamond refers to the overall mean difference (mmHg) with 95% confidence interval. HFPV: high-frequency percussive ventilation; iMV: invasive mechanical ventilation; IV: inverse variance.

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 supplementary figure S4, the pooled data analysis showed a trend towards a

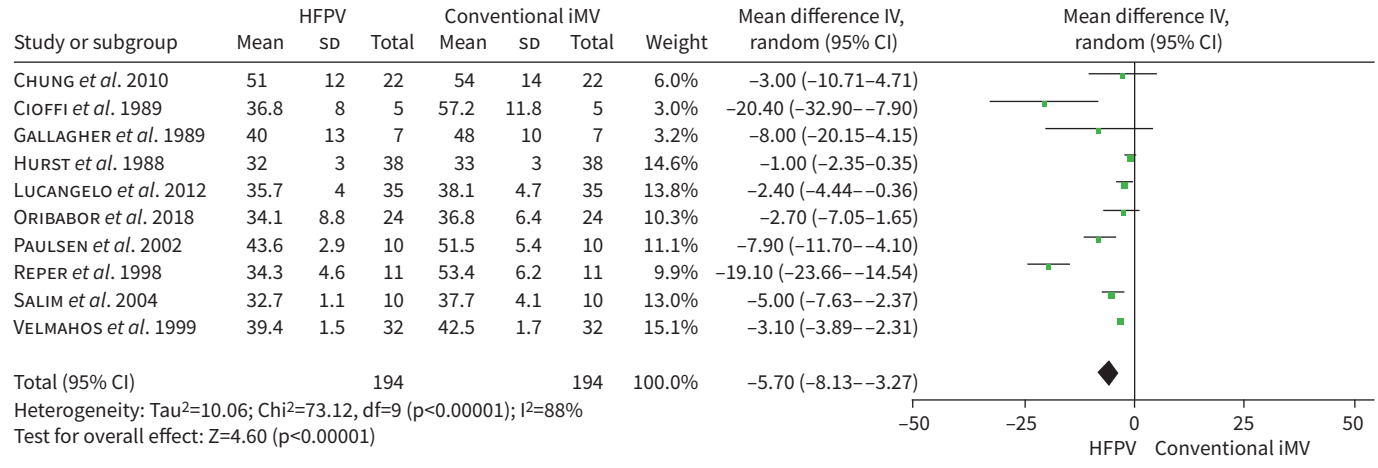

FIGURE 2 Arterial partial pressure of carbon dioxide. Sensitivity analysis forest plot for arterial partial pressure of carbon dioxide (P_{aCO_2}) for HFPV and conventional iMV, at the longest reported time point up to 72 h. Green squares indicate the individual study mean differences, and the black horizontal lines indicate the 95% confidence interval of single studies. The diamond refers to the overall mean difference (mmHg) with 95% confidence interval. HFPV: high-frequency percussive ventilation; iMV: invasive mechanical ventilation; IV: inverse variance.

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 supplementary figure S5).

HFPV during extracorporeal 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 utilisation 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 also been attempted in patients undergoing ECMO for ARDS.

Michaels *et al.* [66] reported the data recorded in 39 patients receiving ECMO in combination with HFPV. 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].

Gulkarov *et al.* [67] also reported their experience with HFPV in five patients undergoing veno-arterial ECMO for cardiopulmonary arrest. 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 h after application, HFPV significantly improved the oxygenation (P_{aO_2}/F_{IO_2}) from 44±16 to 170±70 mmHg, while maintaining P_{aCO_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, continuous positive airway pressure (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 other hand, 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 characterised 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 s, with a passive exhalation phase ending at a designated level of oscillatory CPAP, usually set at 5 to 10 cmH_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 $mL \cdot kg^{-1}$ 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 tracheostomised patients [1]. However, a clear assessment of lung aeration and tidal distribution within the lung is currently lacking; 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 hypoxaemic 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 supplemental material) 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 randomised controlled trials (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.*, VAP, time spent under mechanical ventilation, survival rate).

Provenance: Submitted article, peer reviewed.

Data availability: Data will be available from the corresponding author on reasonable request for scientific reasons.

Author contributions: A. Bruni, A. Boscolo, P. Navalesi, F. Longhini and E. Garofalo substantially contributed to the conception and design of the work. All authors acquired data and information from the study literature, and wrote the drafted manuscript. A. Bruni, G. Cammarota, P. Navalesi, F. Longhini and E. Garofalo wrote and revised the final manuscript, and critically reviewed it for scientific and intellectual content. All authors agree 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 were appropriately investigated and resolved.

Conflict of interest: F. 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 nonfinancial interests to disclose.

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