Critical Care

CRITICAL CARE

Invasive ventilation modes in children: a systematic review and meta-analysis

Critical Care 2011, **15**:R24 doi:10.1186/cc9969

Anita Duyndam (a.duyndam@erasmusmc.nl)
Erwin Ista (w.ista@erasmusmc.nl)
Robert Jan Houmes (r.houmes@erasmusmc.nl)
Bionda van Driel (b.vandriel@erasmusmc.nl)
Irwin Reiss (i.reiss@erasmusmc.nl)
Dick Tibboel (d.tibboel@erasmusmc.nl)

ISSN 1364-8535

Article type Research

Submission date 7 June 2010

Acceptance date 17 January 2011

Publication date 17 January 2011

Article URL http://ccforum.com/content/15/1/R24

Invasive ventilation modes in children: a systematic review and meta-analysis

Anita Duyndam, Erwin Ista, Robert Jan Houmes, Bionda van Driel, Irwin Reiss, Dick Tibboel

Intensive Care Unit, Erasmus MC – Sophia Children's Hospital, PO Box 2060, 3000 CB Rotterdam, The Netherlands.

Corresponding author:

Erwin Ista

Email: w.ista@erasmusmc.nl

Abstract

Introduction: The purpose of this study was to critically review the existing body of evidence on ventilation modes for infants and children up to the age of 18 years.

Methods: The databases PubMed and EMBASE were searched using the search terms: 'artificial respiration', 'instrumentation', 'device', 'devices', 'mode', 'modes'. The review included only studies comparing two ventilation modes in a randomized controlled study (RCT) and reporting one of the following outcome measures: length of ventilation (LOV), oxygenation, mortality, chronic lung disease and weaning. We quantitatively pooled the results of trials where suitable.

Results: Five trials met the inclusion criteria. They addressed six different ventilation modes in 421 children: high frequency oscillation (HFO), pressure control (PC), pressure support (PS), volume support (VS), volume diffusive respirator (VDR) and biphasic positive airway pressure. Overall there were no significant differences in LOV and mortality or survival rate associated with the different ventilation modes. Two trials compared HFO versus conventional ventilation. In the pooled analysis, mortality rate did not differ between these modes (odds ratio (OR) 0.83, 95% confidence interval (CI) 0.30 to 1.91). High-frequency ventilation (HFO and VDR) was associated with a better oxygenation after 72 hours than was conventional ventilation. One study found a significantly higher PaO2/FiO2 ratio with the use of VDR versus PC ventilation in children with burns. Weaning was studied in 182 children assigned to either a PS protocol, VS protocol or no protocol. Most children could be weaned within two days and weaning time did not significantly differ between the groups.

Conclusions: The literature provides scarce data for the best ventilation mode in critically ill children beyond the newborn period. However, there is no evidence that high-frequency ventilation reduced mortality and LOV. Longer-term outcome measures such as pulmonary

function, neurocognitive development, and cost-effectiveness should be considered in future studies.

Introduction

Ventilator-induced lung injury in critically ill children suffering from acute respiratory failure should be counteracted by adapting ventilation management to the cause of respiratory failure [1]. Ideally, management should be based on proven effective strategies. In a multicenter study bronchiolitis was the most frequent cause of respiratory failure in infants (43.6%); pneumonia that in older children (24.8%) [2]. Mortality in that study was rare (1.6%); the median duration of ventilation was 7 days. Randolph et al. [1] suggested that in pediatric clinical trials, long-term morbidity would be a more sensitive indicator of the effects of clinical ventilation interventions than mortality or duration of ventilation.

Pediatric intensive care units (PICUs) worldwide use a wide variety of ventilation modes: high frequency oscillation (HFO), pressure control (PC), synchronized intermittent mandatory ventilation (SIMV), pressure support (PS), pressure regulated volume control (PRVC) and, more recently, neurally adjusted ventilator assist (NAVA) [3, 4]. The ventilation mode is often not targeted specifically to the underlying disease but rather determined by the intensive care physician's experience, local PICU policy and protocols, or outcomes of studies in adults [1, 2, 5]. An unambiguous international guideline is still lacking [1, 5].

The objective of this article is to systematically review the randomized controlled trials (RCTs) comparing ventilation modes used in critically ill children (term born up to 18 years of age) on the following outcome measures: length of ventilation, oxygenation, mortality, chronic lung disease and weaning. We aimed to answer the question whether there is sufficient evidence to decide on the better mode.

Materials and methods

Search and selection

A systematic search was performed in PubMed and EMBASE in September 2010. MeSH terms and keywords searched for in the titles, abstracts and keywords areas were: 'artificial

respiration', 'instrumentation', 'device', 'devices', 'mode', 'modes', combined with Boolean operators AND, OR. (Additional file 1 provides the complete search strategy). The search was limited to RCTs or quasi-experimental studies, with age limit > 28 days until 18 years. Only articles comparing at least two ventilation modes were selected for review. Articles on non-invasive ventilation, studies in premature neonates (< 37 weeks), and articles in other languages than English or Dutch were excluded. No limits were imposed on publication date. Two authors (AvD, EI) independently reviewed abstracts and full-text articles to identify eligible studies. Reference lists of retrieved studies were hand searched for additional articles.

Quality assessment

Study quality and level of evidence were assessed on criteria established by the Dutch Institute for Healthcare Improvement CBO in collaboration with the Dutch Cochrane library (See Additional file 2 and Table 1) [6]. The major criteria were: 1) was assignment to study group randomized?; 2) were investigators blinded?; 3) was it an intention-to-treat analysis?; 4) were the study groups comparable?; and 5) was there appropriate report of outcome results for each group and the estimated effect size. Consensus between the authors on the interpretation of the extracted data was achieved.

Data abstraction

Authors AvD and EI each independently recorded patient characteristics (sample size, age, respiratory failure), details of the ventilation mode and period over which outcome variables were measured. Outcome variables considered were the following: length of ventilation (LOV), oxygenation, chronic lung disease (CLD), mortality and weaning.

Statistical methods

We quantitatively pooled the results of individual trials, where suitable. We expressed the treatment effect as an odds ratio (OR) for dichotomous outcomes and as a weighted mean difference (WMD) for continuous outcomes with 95% confidence intervals. The pooled OR was estimated with the Mantel-Haenszel method which is generally the most robust model [7]. Differences were considered statistically significant if $p < 0.05$ or if the 95% confidence interval did not include the value 1. The analyses were performed with Microsoft ® Excel, Office 2007 for Windows.

Results

Search and selection

After filtering out duplicate studies, titles and abstracts of 461 potentially relevant articles were screened (Figure 1). The reference lists yielded one other study that had been missed because the keywords were not in the title or abstract. Eventually, nine full-text articles were retrieved and assessed for eligibility. Four RCTs were excluded for any of the following reasons: focus on triggering instead of ventilation; inclusion of infants below 37 weeks of gestational age; not comparing two ventilation modes [8-11]. This review therefore includes five RCTs [12-16].

Tabulated details of these five RCTs are presented in Tables 2 and 3.

Length of ventilation

Length of ventilation (LOV) served as outcome measure in four studies (Table 2). First, Arnold and colleagues [12] in a multi center trial compared HFO and conventional ventilation (CV) in 58 children with either diffuse alveolar disease and/or air leak syndrome; 29 had been randomized to HFO; 29 to CV. During the first 72 hours of study the mean airway pressure was significantly ($p<0.001$) higher in the HFO group. The HFO strategy entailed aggressive increases in mean airway pressure to attain the ideal lung volume and to achieve an arterial oxygen saturation of > 90% with $FiO2 < 0.6$. The CV strategy entailed stepping up

the end-expiratory pressure and inspiratory time to increase mean airway pressure and to limit peak inspiratory pressure increases. Crossover to the alternate ventilator was required if the patient met defined criteria for treatment failure. LOV did not significantly differ between the CV and HFO groups (weighted mean difference (WMD) 2.0 days, 95% confidence interval (CI) -9.61 to 13.61).

Second, Dobyns et al. [14] in a multi center study compared HFO and CV in 99 children with acute hypoxemic respiratory failure. Seventy-three were treated with CV (38 without iNO, 35 with iNO); 26 with HFO (12 without iNO, 14 with iNO). Mechanical ventilation and FiO2 were adjusted to maintain SaO2 at 90% and pCO2 between 45 and 55 mmHg. Higher pCO2 values were tolerated as long as the arterial pH was 7.20. In the CV strategy the positive end-expiratory pressure was increased incrementally to improve oxygenation while avoiding clinical and radiographic signs of lung hyperinflation. The peak airway pressure was maintained at < 35–40 cm H2O by limiting the level of tidal volume and positive end-expiratory pressure. The initial HFO settings were: FiO2 of 1.0, 33% inspiratory time, frequency of 10 Hz, and mean airway pressure set at 2–4 cm H2O above that used on CV. Pressure amplitude was set to achieve perceptible chest wall motion and was adjusted if possible to optimize ventilation.

In this study HFO did not lead to a significantly shorter LOV (Table 2). However, for the two ventilation groups without iNO, LOV significantly differed between CV and HFO (WMD -30.0 days, 95%CI -45.89 to -14.11). Third, Carman et al. [16] compared the Volume Diffusive Respirator (VDR) with PC ventilation in burned children with inhalation injury. The VDR is a high-frequency, time cycled pressure ventilator that can ventilate, oxygenate and promote secretion removal. SaO2 was maintained at or above 90%; PaCO2 at <55 mmHg. Thirty-two children with a mean age of 5.5 years (SD±0.9) were treated with VDR; 32 children with a mean age of 9.4 years (SD±1.0) with PC ventilation (p=0.04 for mean age). LOV was significantly different between the study groups (WMD -1.0 days, 95%CI -1.98 to -0.02).

Fourth, Jaarsma et al. [13] randomized 18 children with respiratory failure to either BIPAP

(n=11) or PSV (n=7); their median age was 4 months (range 4 weeks to 10 years). Initial ventilator settings depended on age and the cause of respiratory failure and were adjusted according to thoracic excursions and measured tidal volume. Adjustments were made afterwards aiming at a pCO2 of 4–5 kPa and a pO2 of 8–11 kPa. LOV did not significantly differ between BIPAP (9.8 ± 9.2 days) and PS (6.4 ± 5.8 days).

Pooled analysis resulted in a significantly shorter LOV after CV in comparison with HFO (WMD -2.3 days, 95%CI= -3. 63, -1.04) (Table 4).

Oxygenation

Three studies addressed the effects of different ventilation modes on oxygenation.

In the study by Dobyns et al. [14] the PaO_2/FiO_2 (PF) ratio improved most in HFO mode with iNO after 4 hrs (136mmHg ±21 vs. CV 96±6; p=0.2)) and 12 hrs (HFOV+iNO 184mmHg ±45 vs. CV 107mmHg ±8 and CV+iNO 115mmHg ±9, *p*=0.023; HFOV 136mmHg ±32). After 24 hrs, HFO treatment both with and without iNO provided better oxygenation than CV both with and without iNO (p<0.05). After 72 hrs, HFO treatment was associated with the best improvement in PF ratio (HFO 259 mmHg ±60 vs. CV 148mmHg ±15 and CV+iNO 150 mmHg ±19, *p*=0.027; HFOV+iNO 213 mmHg ±9). The two therapies did not differ in failure rate. Arnold et al. [12] reported a significant (p=0.001) relationship between time and a decreasing oxygenation index in the HFO group but not in the CV group. After crossover (19 patients crossed over from CV to HFO and 11 patients crossed over from HFO to CV) this relationship was significant in both crossover groups (p=0.03 crossover to CV; p=0.02 crossover to HFO).

Carman et al. [16] reported a significantly higher PF ratio in the VDR mode compared with PC (563 mmHg ± 15 vs. 507 mmHg ± 13, p<0.05) but did not specify the time point at which the best PF ratio was measured. As the oxygenation parameters in these three studies were not uniform it was not possible to pool the data.

Mortality, survival

Three studies focused on the outcome measure mortality or survival.

None found a significant difference in mortality between patients treated with HFO and those treated with CV. Arnold et al. [12] reported a mortality rate of 34% (10/29) for HFO versus 41% (12/29) for CV (OR 0.75, 95%CI 0.26 to 2.16). However, the mortality rate in patients not crossed over to CV from HFO or to HFO from CV was significantly better (p=0.003) than that in patients managed with CV only.

Dobyns et al. [14] showed that the survival rate for patients treated with HFO in combination with iNO was higher than that for patients treated with HFO only or with CV (71% vs. 58% in CV, 53% in CV +iNO and 58% in HFO). These differences did not achieve statistical significance. These authors speculated that the improved lung recruitment by HFO enhances the effects of low dose iNO on gas exchange. The mortality rate for HFO without iNO was 42% (5/12) versus 42% (16/38) for CV without iNO (OR 0.98, 95%CI 0.26 to 3.66) [14]. In the study of Carman et al. [16] five of 32 (16%) patients in the PCV group died versus two of 32 (6%) in the VDR group (OR 0.36, 95%CI 0.06 to 2.01).

In the pooled analysis, the mortality rates in HFO mode and CV did not differ (OR 0.70, 95%CI 0.33 to 1.47) (Table 5).

Chronic Lung Disease

Chronic lung disease was examined only in the study of Arnold et al. [12]. The proportion of patients treated with HFO and requiring supplemental oxygen at 30 days was lower than that of patients managed with CV (p=0.039; OR 5.4, 95% CI 1.2 to 23.2).

Weaning

Randolph et al. [15] randomized 182 children aged from 0 to 17 years to either a Pressure support (PS) protocol (n=62), Volume support (VS) protocol (n=60) or a no ventilation weaning protocol in which weaning was at the discretion of the physician (n=60) (Table 3).

The VS and PS protocols dictated that FiO2 and PEEP be adjusted to maintain SpO2 at 95% or higher**.** In the PS protocol, the amount of pressure support was adjusted to achieve an exhaled tidal volume goal of 5 to 7 ml/kg. In the VS protocol, the ventilator automatically adjusted the level of pressure support to achieve an exhaled tidal volume of 5 to 7 ml/kg. Two outcome measures were assessed: weaning time and extubation failure (i.e. any invasive or non invasive ventilator support within 48 hours of extubation). It was hypothesized that VS would result in shorter weaning time as the inspiratory pressures automatically decrease with improvement of lung compliance. Most children could be weaned within two days and weaning time did not significantly differ for the protocols used: PS (1.6 days), VS (1.8 days) and no protocol (2.0 days). Extubation failure rates were not significantly different for PS (15%), VS (24%) and no protocol (17%).

Quality of studies

These five studies compared six different ventilation modes in 421 children [12-14, 16]. Two studies, based on intention to treat analysis, met all CBO quality criteria [14, 15]. Blinding was not possible in any of these studies, because ventilator displays cannot be masked. In four studies patient characteristics and prognostic variables did not differ between the intervention groups. In the study of Carman et al. [16] the mean age differed significantly. Only one study calculated the estimated effect sizes (relative risk of odds ratio) for continuous outcome variables such as LOV, survival or weaning failure [15]. The study by Dobyns et al. [14] is of limited quality because it is a secondary analysis of data obtained from a previous multicenter, randomized trial on iNO treatment in pediatric acute hypoxemic respiratory failure [8]. The mode of ventilation was determined by the attending physician on the guidance of guidelines to maximize oxygenation. The patient was then randomized to treatment with or without iNO [14]. Levels of evidence for the different studies are presented in Tables 2 and 3.

Discussion

This review aimed at identifying the various ventilation modes used in children over the last three decades and searching for any data that would favour a particular mode for pediatric ventilation. The five RCTs included in this review varied in the investigated modes of ventilations, in outcomes and in patient groups.

High-frequency ventilators may use different ventilation modes. Two studies included in this review concerned high-frequency oscillation ventilation [12, 14]; a third concerned the volume diffusive respirator (high-frequency time cycled pressure ventilator) [16]. The evidence from these studies does not allow making a recommendation on preferred type of high frequency ventilator. Two RCTs compared HFO with CV on the outcomes oxygenation, LOV and mortality. Neither study found significant differences in mortality and LOV. However, analysis of the pooled data revealed a significantly lower LOV for the conventional ventilation groups. A confounding factor for this finding is the threefold sample size of conventionally ventilated patients in the study of Dobyns et al. [14]. On the other hand, this analysis only concerned the patients treated with HFO and CV without iNO.

In all studies, oxygenation significantly improved over 72 hours for patients treated with high-frequency oscillators [12, 14, 16]. However, lack of uniform data on oxygenation prevented analysis of pooled data. This finding is in contrast with that reported for preterm neonates. The systematic reviews and meta analyses overall provide no evidence that HFO as the initial ventilation strategy offers important advantages over CV in terms of preventing chronic lung disease in preterm infants with acute pulmonary dysfunction [17-22].

The level of evidence proved moderate to good in three studies [12, 14, 15]. The study of Jaarsma et al. [13] was stopped halfway as both physicians and nurses preferred BIPAP. This, was assigned a 1- level of evidence because of the high risk of bias. Likewise, the study of Carman et al. [16] was assigned a 1- level of evidence because the randomization failed for the demographic variable age.

The strengths of the present review include a comprehensive search strategy, broad inclusion criteria (resulting in a representative, heterogeneous population), and assessment of clinically important outcomes. In addition, we have pooled the data. This statistical approach is also allowed for quasi-experimental, non-randomized studies, such as the study of Dobyns et al. [14] in which randomization of groups was not possible or failed [23]. Meta-analytic techniques in the analysis of nonrandomized studies have been criticized for their potential to perpetuate the individual biases of each study and give a false impression of cohesion in the literature thus discouraging further research [24]. The counter-argument is that statistical quantification and pooling of results from many studies helps to identify reasons for variability, inconsistency or heterogeneity in the literature,
and thus may encourage further research [23, 25]. Nevertheless, the pooled results of this study should be interpreted cautiously in view of the diversity in patient groups, sample sizes, randomization methods, types of ventilators and ventilation strategies.
The reviewed RCTs cannot easily be compared owing to the heterogeneity in age, underlying disease and study outcomes. Therefore, we would recommend to set up studies investigating the best ventilation strategy for specific age categories or underlying pathology [1]. Furthermore, as mortality is rather low, longer-term outcome measures others than the short-term outcome measures studied in this review should be considered, such as pulmonary function, neurocognitive development and cost-effectiveness. Internationally consensus on the most appropriate outcome measures should be reached.

Conclusions

The available literature does not provide sufficient evidence on the best ventilation mode in critically ill children beyond the newborn period. High-frequency ventilation (HFO and VDR) provided better oxygenation after 72 hours than did conventional ventilation. There is no evidence that high-frequency ventilation would reduce mortality and LOV.

Key messages

- There is no evidence for the best ventilation mode in critically ill children beyond the newborn period up to 18 years.
- The different modes have not yet been investigated in (large) groups of children.
- Oxygenation significantly improved over 72 hours for patients treated with high-frequency oscillators.
- Longer-term outcome measures such as pulmonary function and neurocognitive development should be considered.

Abbreviations

PF, Pao_2/Fio_2 ratio; O.I., Oxygenation index; FiO2, Fraction of Inspired Oxygen; SaO2, Saturation of oxygen; pO2, Partial pressure of oxygen; pCO2, Partial arterial pressure of carbondioxide.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AD and DT conceived of and designed the study. AD and EI were involved in data acquisition, analysis, and interpretation and drafted the manuscript. DT and IR critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

The authors thank Ko Hagoort for editing the manuscript. We also thank Professor Dr H Boersma for statistical advice.

References

1. Randolph AG: **Management of acute lung injury and acute respiratory distress syndrome in children.** *Crit Care Med* 2009, **37:**2448-2454.
2. Randolph AG, Meert KL, O'Neil ME, Hanson JH, Luckett PM, Arnold JH, Gedeit RG, Cox PN, Roberts JS, Venkataraman ST, Forbes PW, Cheifetz IM: **The feasibility of conducting clinical trials in infants and children with acute respiratory failure.** *Am J Respir Crit Care Med* 2003, **167:**1334-1340.
3. Bengtsson JA, Edberg KE: **Neurally adjusted ventilatory assist in children: An observational study.** *Pediatr Crit Care Med* 2010, **11:**253-257.
4. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP: **A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population.** *Pediatr Crit Care Med* 2010, **11:**7-11.
5. Turner DA, Arnold JH: **Insights in pediatric ventilation: timing of intubation, ventilatory strategies, and weaning.** *Curr Opin Crit Care* 2007, **13:**57-63.
6. CBO: *Evidence-based Richtlijnontwikkeling. Handleiding voor werkgroepleden.* Kwaliteitsinstituut voor de Gezondheidszorg CBO; 2007.
7. Fleiss JL: **The statistical basis of meta-analysis.** *Stat Methods Med Res* 1993, **2:**121-145.
8. Dobyns EL, Cornfield DN, Anas NG, Fortenberry JD, Tasker RC, Lynch A, Liu P, Eells PL, Griebel J, Baier M, Kinsella JP, Abman SH: **Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure.** *J Pediatr* 1999, **134:**406-412.
9. Guthrie SO, Lynn C, Lafleur BJ, Donn SM, Walsh WF: **A crossover analysis of mandatory minute ventilation compared to synchronized intermittent mandatory ventilation in neonates.** *J Perinatol* 2005, **25:**643-646.

10. Thiagarajan RR, Coleman DM, Bratton SL, Watson RS, Martin LD: **Inspiratory work of breathing is not decreased by flow-triggered sensing during spontaneous breathing in children receiving mechanical ventilation: a preliminary report.** *Pediatr Crit Care Med* 2004, **5:**375-378.

11. Rojas MA, Lozano JM, Rojas MX, Bose CL, Rondon MA, Ruiz G, Pineros JG, Rojas C, Robayo G, Hoyos A, Celis LA, Torres S, Correa J: **Randomized, multicenter trial of conventional ventilation versus high-frequency oscillatory ventilation for the early management of respiratory failure in term or near-term infants in Colombia.** *J Perinatol* 2005, **25:**720-724.

12. Arnold JH, Hanson JH, Toro-Figuero LO, Gutierrez J, Berens RJ, Anglin DL: **Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure.** *Crit Care Med* 1994, **22:**1530-1539.

13. Jaarsma AS, Knoester H, van Rooyen F, Bos AP: **Biphasic positive airway pressure ventilation (PeV+) in children.** *Crit Care* 2001, **5:**174-177.

14. Dobyns EL, Anas NG, Fortenberry JD, Deshpande J, Cornfield DN, Tasker RC, Liu P, Eells PL, Griebel J, Kinsella JP, Abman SH: **Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics.** *Crit Care Med* 2002, **30:**2425-2429.

15. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, Luckett PM, Forbes P, Lilley M, Thompson J, Cheifetz IM, Hibberd P, Wetzel R, Cox PN, Arnold JH: **Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial.** *JAMA* 2002, **288:**2561-2568.

16. Carman B, Cahill T, Warden G, McCall J: **A prospective, randomized comparison of the Volume Diffusive Respirator vs conventional ventilation for ventilation of burned children. 2001 ABA paper.** *J Burn Care Rehabil* 2002, **23:**444-448.

17. Bollen CW, Uiterwaal CS, van Vught AJ: **Cumulative metaanalysis of high-frequency versus conventional ventilation in premature neonates.** *Am J Respir Crit Care Med* 2003, **168:**1150-1155.

18. Cools F, Henderson-Smart DJ, Offringa M, Askie LM: **Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants.** *Cochrane Database Syst Rev* 2009**:**CD000104.

19. Bollen CW, Uiterwaal CS, van Vught AJ: **Systematic review of determinants of mortality in high frequency oscillatory ventilation in acute respiratory distress syndrome.** *Crit Care* 2006, **10:**R34.

20. Bollen CW, Uiterwaal CS, van Vught AJ: **Meta-regression analysis of high-frequency ventilation vs conventional ventilation in infant respiratory distress syndrome.** *Intensive Care Med* 2007, **33:**680-688.

21. Cools F, Askie LM, Offringa M, Asselin JM, Calvert SA, Courtney SE, Dani C, Durand DJ, Gerstmann DR, Henderson-Smart DJ, Marlow N, Peacock JL, Pillow JJ, Soll RF, Thome UH, Truffert P, Schreiber MD, Van Reempts P, Vendettuoli V, Vento G: **Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data.** *Lancet* 2010, **375:**2082-2091.

22. Greenough A, Dimitriou G, Prendergast M, Milner AD: **Synchronized mechanical ventilation for respiratory support in newborn infants.** *Cochrane Database Syst Rev* 2008**:**CD000456.

23. MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AM: **A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.** *Health Technol Assess* 2000, **4:**1-154.

24. Shapiro S: **Meta-analysis/Shmeta-analysis.** *Am J Epidemiol* 1994, **140:**771-778.

25. Greenland S: **Can meta-analysis be salvaged?** *Am J Epidemiol* 1994, **140:**783-787.

Tables

Table 1. Level of Evidence

Level	Description of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort or studies High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant probability that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Table 2. Included RCTs – VENTILATION

Reference	Study population	Intervention/ mode	Outcome measures				Level of evidence
			Mortality / survival	LOV (days)*	Oxygenation	CLD	
Arnold et al, 1994 [12]	58 children (age 2.5±2.5[1] yrs versus 3.1±3.3[2] yrs) With diffuse alveolar disease and/or airleak syndrome	Multi center study (5 centers) Comparison effectiveness of HFO (n=29) with CV (n=29) – crossover Crossover: CV to HFO (n=19) HFO to CV (n=11)	No. survivors at 30 days CV: 17 of 29 (59%); HFO: 19 of 29 (66%); (NS) Death (Ranked) CV: 40% CV to HFO: 42% HFO: 6% HFO to CV: 82% (p=<0.001)	Total CV: 22±17; HFO: 20±27 Survivors (at 30 days) CV: 29±18; HFO: 27±31. Non survivors (at 30 days) CV: 11±9; HFO: 8±6 (NS)	Pao_2/PAo_2 increase over time (72hrs) in HFO compared to CV group (p<0.001) Pao_2/PAo_2: HFO: 0.13 (0 hr) up to 0.26 (72hr); CV: 0.13 (0 hr) up to 0.22 (72hrs). After crossover Pao_2/PAo_2 increase over time (72hrs) in CV to HFO group compared to HFO to CV group (p=0.003)	CV: n=10 (59%); HFO: n=4 (21%). (p=0.039; OR=5.4 95%CI 1.2-23.2) (O_2 at 30 days)	1+
Dobyns et al. [14]	99 children (age 0-23 yrs) With AHRF Oxygenation index > 15	Multi center study (7 centers) Comparisons between patients treated with HFO+iNO (n=14), HFO alone (n=12), CV+iNO (n=35), and CV alone (n=38)	Trend of improved survival in the HFO+iNO. (CV, 22 of 38 (58%); CV+iNO, 20 of 35 (53%); HFO, 7 of 12 (58%); HFO+iNO, 10 of 14 (71%); (p=0.994)	CV: 22±4; CV+iNO: 21±3; HFO: 52±28; HFO+iNO: 17±4; (p=0.098)	Pao_2/Fio_2 (PF) ratio: - After 4 hrs: HFO+iNO 136±21 vs. CV 96±6, p=0.2 - After 12 hrs: HFO+iNO 184±45 vs. CV 107±8 and CV+iNO 115±9, HFO 136±32;p=0.023. - After 24 hrs: treatment both HFO+iNO and HFO resulted in greater improvement in PF ratio than CV or CV+iNO, p=0.005. - After 72 hrs: HFO 259±60 vs. CV 148±15 and CV+iNO 150±19; HFO+iNO 213±29, p=0.027		1+
Jaarsma et al. [13]	18 children (age 0-10 yrs) with respiratory failure for ventilation	Single centre study Compare BIPAP (n=11) with PS (n=7) determining with mode is effective, safe and easy	ND	BIPAP: 9.8±9.2; PS: 6.4±5.8; (p=0.27)	ND		1-
Carman et al. [16]	64 children (mean age7.4±0.7 yrs) with inhalation injury	Single center Compare VDR (n=32) with PC (n=32)	VDR: 2/32 (6%); PC: 5/32 (16%); (NS)	VDR: 12±2; PCV: 11±2; (NS)	Pao_2/Fio_2 (PF) ratio: VDR: 563±16, PC: 507±13; (p<0.05)		1-

1 - HFO group; 2 - CV group; AHRF - acute hypoxemic respiratory failure; iNO –inhaled NO; CV – conventional mechanical ventilation; HFO –High frequency oscillation ventilation; CLD – chronic lung disease; LOV – length of ventilation; BIPAP- biphasic positive airway pressure; PS- pressure support ventilation; ND – no data; yrs - years; hrs – hours; * - mean±sd; VDR – Volume Diffusive Respirator (high-frequency time cycled pressure ventilator); PC – Pressure Controlled Ventilation; NS – not significant; OR – odds ratio; CI – confidence interval; No. – Numbers of.

Table 3. Included RCTs WEANING

Reference	Study population	Intervention/ mode	Outcome measures			Level of evidence
			Duration of weaning (days)*	Extubation failure rate	Oxygenation	
Randolph et al. [15]	182 children (age 0-17 yrs) Weaning of ventilation support for more than 24 hours and who failed a test for extubation readiness on minimal PS	Multicenter study (10 centers) To evaluate weaning protocols comparing: -VS (continuous automated adjustment of PS by the ventilator) (n=59) - PS (adjustment by clinicians) (n=61) - to standard care (no protocol) (n=59)	PS: 1.6(0.9-4.1); VS: 1.8(1.0-3.2); no protocol: 2.0(0.9-2.9), (*p*=0.75)	PS (15%), VS (24%) and no protocol (17%) (p=.44) Male children more frequently failed extubation (OR, 7.86 95%CI:2.36-26.2; p<.001).	ND	1++

* **-** median (interquartile range); ND – no data; PS-Pressure support; VS –Volume support ; OR – Odds Ratio; CI – Confidence Interval.

Table 4. Meta-analysis of trials comparing high frequency ventilation to conventional ventilation: length of ventilation

Study	CV Mean (SD)	N	HFOV Mean (SD)	N	WMD (95%CI)	Z value (p-value)
Length of ventilation						
Arnold (1994)	22 (17)	29	20 (27)	29	2 [-9.61, 13.61]	-0.338 (p=0.74)
Dobyns (2002)	22 (4)	38	52 (28)	12	-30 [-45.89, -14.11]	3.699 (p=0.0002)
Subtotal		*67*		*41*	*-11.51 [-15.14, -7.88]*	*-6.221 (p<0.0001)*
Carman (2002) (VDR)	11 (2)	32	12 (2)	32	-1 [-1.98, -0.02]	-2.0 (p=0.046)
Overall		*99*		*73*	*-2.34 [-3.63, -1.04]*	*-3.542 (p=0.0004)*

WMD – weight mean difference; CI – confidence interval; Volume Diffusive Respirator (high-frequency time cycled pressure ventilator); CV – conventional ventilation; HFOV – High Frequency oscillation ventilation; SD.

Table 5. Meta-analysis of trials comparing high frequency ventilation to conventional ventilation: Mortality

Study	CV n/N		HFOV n/ N		OR (95%CI)
Mortality					
Arnold (1994)	12/29		10/29		0.75 (0.26, 2.16)
Dobyns (2002)	6/38		5/12		0.98 (0.26, 3.66)
Subtotal M-H		*67*		*41*	*0.83 (0.30,1.91)*
Carman (2002) (VDR)	5/32		2/32		
Overall M-H		*99*		*73*	*0.70 (0.33, 1.47)*

M-H - Mantel-Haenszel; OR – Odds Ratio; CI – confidence interval; Volume Diffusive Respirator (high-frequency time cycled pressure ventilator); CV – conventional ventilation; HFOV – High Frequency oscillation ventilation.

Figure legends

Figure 1

Search results.

Additional files

Additional file 1

Title: Search strategy

Description: This file contains the complete search strategy.

Additional file 2

Title: Evaluation form of RCTs

Description: Word file containing a list of criteria for assessing the quality of RCTs.

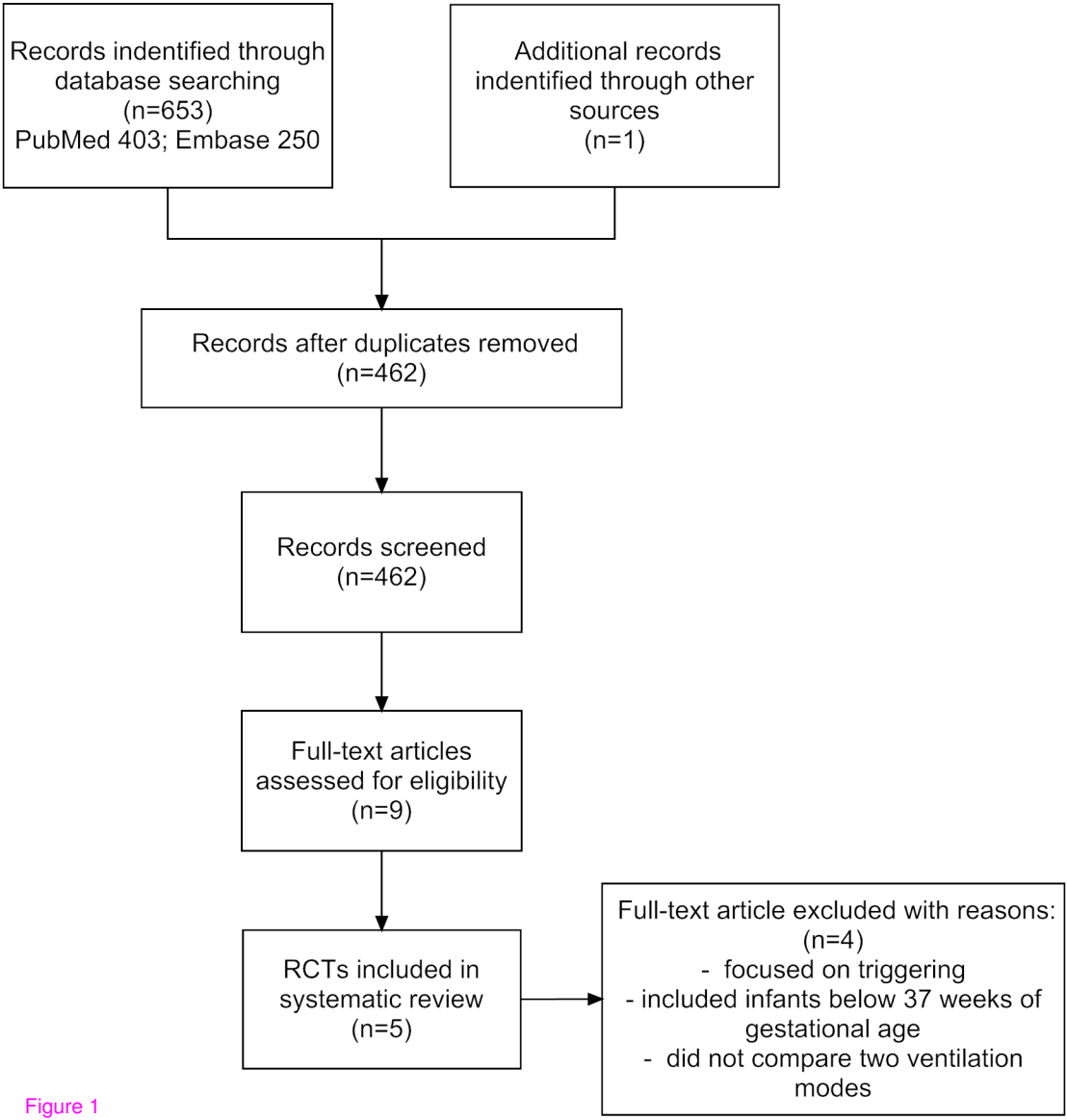
Records indentified through database searching (n=653) PubMed 403; Embase 250
Additional records indentified through other sources (n=1)
Records after duplicates removed (n=462)
Records screened (n=462)
Full-text articles assessed for eligibility (n=9)
RCTs included in systematic review (n=5)
Full-text article excluded with reasons: (n=4)
- focused on triggering
- included infants below 37 weeks of gestational age
- did not compare two ventilation modes

Figure 1

Additional files provided with this submission:

Additional file 1: Additional file 1.doc, 24K
http://ccforum.com/imedia/1885788671507585/supp1.doc
Additional file 2: Additional file 2.doc, 24K
http://ccforum.com/imedia/4695314865075856/supp2.doc