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[Intervention Review]

Synchronized mechanical ventilation for respiratory support in newborn infants

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ABSTRACT

Background

During synchronised mechanical ventilation, positive airway pressure and spontaneous inspiration coincide. If synchronous ventilation is provoked, adequate gas exchange should be achieved at lower peak airway pressures, potentially reducing baro/volutrauma, air leak and bronchopulmonary dysplasia. Synchronous ventilation can potentially be achieved by manipulation of rate and inspiratory time during conventional ventilation and employment of patient-triggered ventilation.

Objectives

To compare the efficacy of:

- (i) synchronised mechanical ventilation, delivered as high-frequency positive pressure ventilation (HFPPV) or patient-triggered ventilation (assist control ventilation (ACV) and synchronous intermittent mandatory ventilation (SIMV)), with conventional ventilation or high-frequency oscillation (HFO);
- (ii) different types of triggered ventilation (ACV, SIMV, pressure-regulated volume control ventilation (PRVCV), SIMV with pressure support (PS) and pressure support ventilation (PSV)).

Search methods

We used the standard search strategy of the Cochrane Neonatal Review group to search the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 5), MEDLINE via PubMed (1966 to June 5 2016), EMBASE (1980 to June 5 2016), and CINAHL (1982 to June 5 2016). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised or quasi-randomised clinical trials comparing synchronised ventilation delivered as HFPPV to CMV, or ACV/SIMV to CMV or HFO in neonates. Randomised trials comparing different triggered ventilation modes (ACV, SIMV, SIMV plus PS, PRVCV and PSV) in neonates.

Data collection and analysis

Data were collected regarding clinical outcomes including mortality, air leaks (pneumothorax or pulmonary interstitial emphysema (PIE)), severe intraventricular haemorrhage (grades 3 and 4), bronchopulmonary dysplasia (BPD) (oxygen dependency beyond 28 days), moderate/severe BPD (oxygen/respiratory support dependency beyond 36 weeks' postmenstrual age (PMA) and duration of weaning/ventilation.

Eight comparisons were made: (i) HFPPV versus CMV; (ii) ACV/SIMV versus CMV; (iii) SIMV or SIMV + PS versus HFO; (iv) ACV versus SIMV; (v) SIMV plus PS versus SIMV; (vi) SIMV versus PRVCV; (vii) SIMV vs PSV; (viii) ACV versus PSV. Data analysis was conducted using relative risk for categorical outcomes, mean difference for outcomes measured on a continuous scale.

Main results

Twenty-two studies are included in this review. The meta-analysis demonstrates that HFPPV compared to CMV was associated with a reduction in the risk of air leak (typical relative risk (RR) for pneumothorax was 0.69, 95% confidence interval (CI) 0.51 to 0.93). ACV/SIMV compared to CMV was associated with a shorter duration of ventilation (mean difference (MD) -38.3 hours, 95% CI -53.90 to -22.69). SIMV or SIMV + PS was associated with a greater risk of moderate/severe BPD compared to HFO (RR 1.33, 95% CI 1.07 to 1.65) and a longer duration of mechanical ventilation compared to HFO (MD 1.89 days, 95% CI 1.04 to 2.74).

ACV compared to SIMV was associated with a trend to a shorter duration of weaning (MD -42.38 hours, 95% CI -94.35 to 9.60). Neither HFPPV nor triggered ventilation was associated with a significant reduction in the incidence of BPD. There was a non-significant trend towards a lower mortality rate using HFPPV versus CMV and a non-significant trend towards a higher mortality rate using triggered ventilation versus CMV. No disadvantage of HFPPV or triggered ventilation was noted regarding other outcomes.

Authors' conclusions

Compared to conventional ventilation, benefit is demonstrated for both HFPPV and triggered ventilation with regard to a reduction in air leak and a shorter duration of ventilation, respectively. In none of the trials was complex respiratory monitoring undertaken and thus it is not possible to conclude that the mechanism of producing those benefits is by provocation of synchronised ventilation. Triggered ventilation in the form of SIMV $\pm$ PS resulted in a greater risk of BPD and duration of ventilation compared to HFO. Optimisation of trigger and ventilator design with respect to respiratory diagnosis is encouraged before embarking on further trials. It is essential that newer forms of triggered ventilation are tested in randomised trials that are adequately powered to assess long-term outcomes before they are incorporated into routine clinical practice.

PLAIN LANGUAGE SUMMARY

Synchronised mechanical ventilation for respiratory support in newborn infants

The majority of newborn babies in need of mechanical assistance to support them also breathe to some degree. If the baby's attempts to breathe are synchronised with the mechanical breaths from the ventilator, less pressure may be needed. This could reduce the chance of air leak or variations in blood flow to the brain. The review of trials found, when compared to conventional mechanical ventilation (CMV), high-frequency positive pressure ventilation (HFPPV) reduced the risk of air leak and triggered ventilation was associated with a shorter duration of ventilation. Compared to high-frequency oscillation, however, certain triggered modes of ventilation resulted in a greater risk of moderate to severe chronic lung disease and a longer duration of ventilation. Newer forms of triggered ventilation have only been evaluated in small randomised trials and have not been demonstrated to have advantages in important clinical outcomes.

BACKGROUND

Description of the condition

The majority of neonates breathe during mechanical ventilation. Those that actively exhale against positive pressure inflation develop pneumothoraces; whereas if positive pressure inflation and spontaneous inspiration coincide (synchrony), oxygenation and carbon dioxide elimination improve. If synchrony occurs, it should be possible to achieve adequate gas exchange at lower inflating pressures, reducing barotrauma, a known risk factor for bronchopulmonary dysplasia. Active expiration is more common if infants have non-compliant lungs and are ventilated with long inspiratory times or relatively slow ventilator rates (30 to 40 bpm), or both. Increasing ventilator rate and reducing inspiratory time, mimicking more closely the preterm infant's respiratory pattern, has been shown in a proportion of infants to stop them actively expiring.

Description of the intervention

Synchronised ventilation can be achieved by HFPPV during which the ventilator rate more closely resembles the spontaneous respiratory rate of very prematurely born infants, and this is more likely to be associated with synchronous ventilation. It can also be achieved by PTV (ACV, SIMV, PRVCV or PSV), during which the infant's respiratory efforts exceeding a critical level trigger a positive pressure inflation. In SIMV only a preset number of the infant's respiratory efforts trigger positive pressure inflations.

How the intervention might work

During mechanical ventilation, infants actively exhale against positive pressure inflation and develop pneumothoraces. Theoretically, by increasing synchronous ventilation, either HFPPV or PTV could reduce air leaks and associated intraventricular haemorrhage and BPD. Indeed, 'triggered ventilation' compared to conventional mechanical ventilation (CMV) has been shown to improve tidal volume ([Jarreau 1996](#)) and oxygenation ([Cleary 1995](#)) and reduce blood pressure fluctuations ([Hummler 1996](#)). Synchronised mechanical ventilation might also reduce barotrauma and hence BPD.

Why it is important to do this review

The aim of this review was to determine whether HFPPV or triggered ventilation were associated with positive outcomes for prematurely born neonates. This review updates the existing review of synchronised ventilation which was published in the *Cochrane Database of Systematic Reviews* Issue 1, 2008 ([Greenough 2008](#)).

OBJECTIVES

To compare the efficacy of:

- (i) synchronised mechanical ventilation, delivered as high-frequency positive pressure ventilation (HFPPV) or patient-triggered ventilation (assist control ventilation (ACV) and synchronous intermittent mandatory ventilation (SIMV)), with conventional ventilation or high-frequency oscillation (HFO);
- (ii) different types of triggered ventilation (ACV, SIMV, pressure-regulated volume control ventilation (PRVCV), SIMV with pressure support (PS) and pressure support ventilation (PSV))

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised clinical trials comparing the use of synchronised ventilation (HFPPV or patient-triggered ventilation) to conventional ventilation or high-frequency oscillation, and randomised trials of different modes of triggered ventilation in neonates were considered for this review.

Types of participants

Neonates (less than four weeks of age) requiring assisted ventilation.

Types of interventions

We considered two forms of ventilation likely to induce synchrony:

high-frequency positive pressure ventilation (HFPPV, ventilator rates ≥ 60 bpm); and triggered ventilation.

Triggered ventilation was divided into:

- assist control ventilation (ACV), otherwise known as synchronous intermittent positive pressure ventilation (SIPPV), the infant being able to trigger a positive pressure inflation with each breath;
- synchronised intermittent mandatory ventilation (SIMV), the infant being able to trigger only a pre-set number of positive pressure inflations;
- pressure-regulated volume control ventilation (PRVCV), a synchronised pressure-limited assist control mode that sequentially varies the delivered pressure to approximate a target inspiratory tidal volume;
- pressure support ventilation, the initiation and end of inflation triggered by the infant's respiratory effort;
- SIMV with pressure support (PS); PS assists every additional spontaneous breath beyond the set SIMV rate.

These modes of ventilation were compared to non-synchronised ventilation either in the form of conventional ventilation (CMV), which for the purpose of this review is defined as pressure pre-set, time-limited ventilation delivered at rates of fewer than 60 bpm, or high-frequency oscillatory ventilation (HFO).

Infants were randomly allocated to receive one or other forms of ventilation (except in [Heicher 1981](#) when alternate allocation was used):

- HFPPV versus CMV;
- ACV or SIMV versus CMV;
- SIMV or SIMV + PS versus HFO.

Triggered modes of ventilation were compared:

- ACV versus SIMV;
- SIMV plus PS versus SIMV;
- SIMV versus PRVCV;
- SIMV versus PSV;
- ACV versus PSV.

Types of outcome measures

Primary outcomes

Data regarding clinical outcomes included:

- mortality;
- air leaks (pneumothorax or pulmonary interstitial emphysema (PIE));
- severe intraventricular haemorrhage (grades 3 and 4);
- bronchopulmonary dysplasia (BPD) (oxygen dependency beyond 28 days);
- moderate/severe BPD (oxygen dependency or respiratory support dependency (or both) at 36 weeks' postmenstrual age);
- duration of weaning/ventilation.

Search methods for identification of studies

Electronic searches

For the 2016 update we used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see [the Cochrane Neonatal Group search strategy for specialized register](#)).

We conducted a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 5) in *The Cochrane Library*; MEDLINE via PubMed (1996 to June 5 2016); EMBASE (1980 to June 5 2016); and CINAHL (1982 to June 5 2016) using the following search terms: (mechanical ventilation[MeSH] OR respiration, artificial[MeSH] OR mechanical ventilation OR triggered ventilation OR SIMV), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictrp/search/en/; and [the ISRCTN Registry](#)).

For the previous version of this review we searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, 2008); Oxford Database of Perinatal Trials; MEDLINE from

1966 to 2008; and EMBASE 1996 to 2008 (MeSH terms: mechanical ventilation; triggered ventilation; artificial respiration; newborn infant).

Searching other resources

We searched previous reviews, abstracts, symposia proceedings as well as conducting handsearches of journals in the English language and establishing contact with expert informants.

Data collection and analysis

Three of the review authors (AS, TR, VM) identified trials that might be included. Each trial was then assessed independently by each review author who completed data collection forms that the review authors had previously agreed upon. The results were then compared and if there was disagreement a fourth and fifth review author (AG, ADM) assessed the results independently. For each included trial, we collected information regarding the method of randomisation, blinding, stratification, number of centres participating in the study, trial inclusion and exclusion criteria and sample size. We also collected demographic data of the trial participants (e.g. gestational age, birth weight, postnatal age, primary diagnosis). We analysed information on clinical outcomes including death, air leaks, intraventricular haemorrhage, chronic lung disease, duration of ventilation or weaning, ventilation mode failure and extubation failure. The denominator for each outcome was the number randomised. In the meta-analyses involving comparison with CMV or HFO, either HFPPV or ACV/SIMV was designated the experimental therapy. In the meta-analyses of ACV or PRVCV versus SIMV, then ACV or PRVCV was designated the experimental therapy. In the meta-analyses of SIMV with PS versus SIMV, SIMV with PS was designated the experimental therapy, and in the meta-analysis of ACV versus PSV, ACV was designated the experimental therapy.

RESULTS

Description of studies

Included studies

We identified twenty-two studies for inclusion in this review (see [Figure 1](#)).

Figure 1. Study flow diagram: review update

1. HFPPV versus CMV ([Heicher 1981](#); [OCTAVE 1991](#); [Pohlandt 1992](#); [Amini 2013](#)).

2. ACV/SIMV versus CMV: [Chan 1993](#) (ACV versus CMV); [Donn 1994](#) (SIMV versus CMV); [Bernstein 1996](#) (SIMV versus CMV); [Chen 1997](#)

(SIMV versus CMV); [Baumer 2000](#) (ACV versus CMV); [Beresford 2000](#) (ACV versus CMV); [Liu 2011](#) (ACV versus CMV).

3. SIMV or SIMV + PS versus HFO ([Courtney 2002a](#); [Craft 2003a](#); [Singh 2012](#); [Sun 2014](#))
4. ACV versus SIMV ([Chan 1994](#); [Dimitriou 1995a](#); [Dimitriou 1995b](#))
5. SIMV plus PS versus SIMV ([Reyes 2006](#))
6. SIMV versus PRVCV ([D'Angio 2005](#))
7. SIMV versus PSV ([Erdemir 2014](#))
8. ACV versus PSV ([Patel 2012](#))

[Pohlandt 1992](#), [Chan 1993](#), [Chan 1994](#), [Dimitriou 1995a](#), [Dimitriou 1995b](#), [Baumer 2000](#) and [Beresford 2000](#) included only preterm infants. [Donn 1994](#) included preterm infants with a birth weight between 1100 grams and 1500 grams. [Courtney 2002a](#) included infants with a birth weight between 601 grams and 1200 grams. [Reyes 2006](#) included preterm infants with a birth weight of 500 grams to 1000 grams. [Singh 2012](#) included infants with a birth weight of greater than 750 grams. [D'Angio 2005](#) included preterm infants with a birth weight of 500 grams to 1249 grams. [Erdemir 2014](#) and [Sun 2014](#) included preterm infants with birth weight less than 1500 grams. [Craft 2003a](#) included preterm infants with birth weight less than 1000 grams. [Bernstein 1996](#), [Heicher 1981](#) and [OCTAVE 1991](#) studied mainly premature neonates. [Chen 1997](#) included term and preterm infants but analysed the groups separately; only the results from the 63 infants with RDS are included in the meta-analysis. [Amini 2013](#) does not make it clear whether term as well as preterm infants were included. [Patel 2012](#) included infants of any gestation who were less than 14 days old.

Information regarding use of antenatal steroids was given only in [Baumer 2000](#), [Beresford 2000](#), [Courtney 2002a](#), [Craft 2003a](#), [D'Angio 2005](#), [Reyes 2006](#), [Patel 2012](#), [Singh 2012](#), [Erdemir 2014](#) and [Sun 2014](#). Data regarding surfactant usage were available in the trials of [Donn 1994](#), [Chan 1994](#), [Dimitriou 1995a](#), [Dimitriou 1995b](#), [Bernstein 1996](#), [Chen 1997](#), [Baumer 2000](#), [Beresford 2000](#), [Courtney 2002a](#), [Craft 2003a](#), [D'Angio 2005](#), [Reyes 2006](#), [Patel 2012](#), [Singh 2012](#), [Amini 2013](#), [Erdemir 2014](#) and [Sun 2014](#). The age at entry varied between studies; the trials of [Chan 1993](#), [Chan 1994](#), [Dimitriou 1995a](#), [Dimitriou 1995b](#), [Reyes 2006](#), [Patel 2012](#) and [Erdemir 2014](#) were weaning studies. Data for the duration of ventilation or weaning were obtained by personal communication with the investigators for [Chan 1993](#), [Chan 1994](#), [Dimitriou 1995a](#), [Dimitriou 1995b](#), [Baumer 2000](#) and [Beresford 2000](#).

Excluded studies

Seventy-two additional studies were detected, but were found to be not eligible for inclusion in this review (see table [Characteristics of excluded studies](#)).

Risk of bias in included studies

All the studies but one were randomised; [Heicher 1981](#) used alternate allocation. The method of randomisation is reported in all but one trial ([Chen 1997](#)). Certain outcomes were only available in some of the trials and therefore only presented for the subgroups in which they were reported for at least two trials, except for the trials assessing PSV, PRVCV and SIMV plus PS.

HFPPV versus CMV: In [Heicher 1981](#) and [OCTAVE 1991](#) analysis was by intention to treat, but in [Pohlandt 1992](#) infants not ventilated strictly according to the technique to which they were randomised were excluded from the analysis.

SIMV/ACV versus CMV: Analysis was according to intention to treat in [Chan 1993](#) and [Baumer 2000](#); in [Bernstein 1996](#), 6% of infants erroneously randomised because of problems including seizures, non-viability and birth weight of less than 500 grams were excluded from the analysis.

SIMV or SIMV + PS versus HFO: Analysis was according to intention to treat in [Courtney 2002a](#) and [Sun 2014](#). In [Craft 2003a](#) an ad-hoc interim analysis was performed due to declining recruitment and the study was curtailed.

ACV versus SIMV: [Dimitriou 1995](#) is presented as two studies ([Dimitriou 1995a](#); [Dimitriou 1995b](#)), as two separate consecutive randomised trials were performed in which ACV was compared to two different methods of delivering SIMV. In [Chan 1994](#), [Dimitriou 1995a](#) and [Dimitriou 1995b](#) weaning failure was defined as no reduction in ventilator settings over a 24 or 48 hour period respectively; extubation failure was defined as a requirement for re-intubation using standardised criteria within a 48 hour period.

SIMV plus PS versus SIMV: In [Reyes 2006](#) analysis was by intention to treat; five infants who were randomised met exclusion criteria and their results were not included in the analysis.

PRVCV versus SIMV: In [D'Angio 2005](#) analysis was by intention to treat; one infant did not receive the allocated intervention.

SIMV vs PSV: In [Erdemir 2014](#) weaning and extubation was performed according to standardised criteria. Analysis was not stated to be by intention to treat; however there were no failures of weaning reported in either arm.

ACV vs PSV: In [Patel 2012](#) analysis was by intention to treat. Weaning was by standardised criteria.

Effects of interventions

HFPPV versus CMV (comparison 1)

Death (Analysis 1.1): Four trials reported this outcome ([Heicher 1981](#); [OCTAVE 1991](#); [Pohlandt 1992](#); [Amini 2013](#)). None demonstrated a significant effect. The meta-analysis indicates a trend towards reduction in death rate using HFPPV but this does not reach statistical significance (relative risk (RR) 0.78, 95% confidence interval (CI) 0.61 to 1.00).

Air leaks (Analysis 1.2 and Analysis 1.3): Three trials reported pneumothorax as an outcome ([Heicher 1981](#); [OCTAVE 1991](#); [Pohlandt 1992](#)); one trial reported a significant effect, with a lower rate of pneumothorax in the HFPPV group ([Heicher 1981](#)). The meta-analysis supports a significant reduction in the risk of pneumothorax (typical RR for pneumothorax was 0.69, 95% CI 0.51 to 0.93). [Pohlandt 1992](#) reported a significant reduction in PIE in the HFPPV group (RR 0.68, 95% CI 0.49 to 0.94). [Amini 2013](#) reported total air leaks as outcome variable, with a non-significant trend favouring HFPPV (RR 0.25, 95% CI 0.06 to 1.08).

BPD (oxygen dependency at 28 days) (Analysis 1.4): Four trials reported this outcome ([Heicher 1981](#); [OCTAVE 1991](#); [Pohlandt 1992](#);

Amini 2013). None demonstrated a significant effect. The meta-analysis found no evidence of effect.

IVH (Analysis 1.5): One trial reported this outcome, with a significantly lower rate of IVH in the HFPPV group (RR 0.13, 95% CI 0.02 to 0.94) (Amini 2013).

Other outcomes: The incidence of PDA post randomisation was given in two trials (Heicher 1981; Pohlandt 1992); in neither did it differ significantly.

ACV/SIMV versus CMV (comparison 2)

Death (Analysis 2.1): Six trials reported this outcome (Donn 1994; Bernstein 1996; Chen 1997; Baumer 2000; Beresford 2000; Liu 2011). None demonstrated a significant effect. The meta-analysis indicates a trend towards an increase in death rate using ACV/SIMV but this does not reach statistical significance (typical RR 1.17, 95% CI 0.94 to 1.47).

Air leaks (Analysis 2.2): Seven trials reported this outcome (Chan 1993; Donn 1994; Bernstein 1996; Chen 1997; Baumer 2000; Beresford 2000; Liu 2011). None demonstrated a significant effect. The meta-analysis found no evidence of effect.

Duration of ventilation (hours) (Analysis 2.3): Five trials reported this outcome (Donn 1994; Chen 1997; Baumer 2000; Beresford 2000; Liu 2011). Bernstein 1996 also reported the duration of ventilation, but the data are presented as the median and 95% CIs (SIMV 103 hours, 95% CI 94 to 118 versus CMV 120 hours, 95% CI 101 to 142), and the results, therefore, could not be meta-analysed in the relevant Outcome (2.3). A significantly shorter duration of ventilation was noted in Chen's study (Chen 1997) and Donn's study (Donn 1994). The meta-analysis of the five studies supported a significant reduction in ventilation duration (MD -38.30 hours, 95% CI -53.90 to -22.69). Chan 1993 reported the duration of weaning: ACV mean 39 hours, SD 45 versus CMV mean 65 hours, SD 75 (the results are not presented in Outcome 2.3).

Extubation failure (Analysis 2.4): Four trials reported this outcome (Chan 1993; Donn 1994; Chen 1997; Baumer 2000). One trial reported a significant effect in favour of ACV/SIMV (Chen 1997). The meta-analysis of the results of the four trials, however, did not demonstrate a significant effect, the typical RR being 0.93 (95% CI 0.68 to 1.28).

Severe IVH (Analysis 2.5): Six trials reported this outcome (Donn 1994; Bernstein 1996; Chen 1997; Baumer 2000; Beresford 2000; Liu 2011). None demonstrated a significant effect. The meta-analysis found no evidence of effect.

BPD (oxygen dependency at 28 days) (Analysis 2.6): Four trials reported this outcome (Baumer 2000; Bernstein 1996; Chen 1997; Donn 1994). None demonstrated a significant effect. The meta-analysis found no evidence of effect.

Moderate/severe BPD (Oxygen dependency at 36 weeks postmenstrual age) (Analysis 2.7): Two trials reported this outcome (Baumer 2000; Beresford 2000). Neither demonstrated a significant effect. The meta-analysis found no evidence of effect.

Other outcomes: In two trials the incidence of PDA is given post randomisation (Chen 1997; Beresford 2000). In one trial only the incidence of PDA requiring indomethacin and/or ligation was

higher in the conventional group for both survivors ($P < 0.05$) and the whole population of infants ($P < 0.05$) (Beresford 2000).

SIMV OR SIMV + PS versus HFO (comparison 3)

Death (Analysis 3.1): Four trials of SIMV OR SIMV + PS VS HFO reported this outcome (Courtney 2002a; Craft 2003a; Singh 2012; Sun 2014). Sun 2014 reported a significant effect in favour of HFO (RR 3.21, 95% CI 1.07 to 9.67). No other trials reported a difference in this outcome, and the meta-analysis found no evidence of effect.

BPD: oxygen dependency at 28 days (Analysis 3.2): One trial reported this outcome with no significant effect (Singh 2012).

Moderate/Severe BPD (Analysis 3.3): Three trials reported this outcome (Courtney 2002a; Craft 2003a; Sun 2014). Sun 2014 reported a significant effect in favour of HFO (RR 2.24, 95% CI 1.20 to 4.18) and Courtney 2002a reported a trend in favour of HFO (RR 1.24, 95% CI 0.96 to 1.60). The meta-analysis showed a significant effect in favour of HFO (RR 1.33, 95% CI 1.07 to 1.65).

Death or BPD (Analysis 3.4): Only one study reported this combined outcome, with a significant effect in favour of HFO (RR 2.38, 95% CI 1.41 to 4.03) (Sun 2014).

Duration of mechanical ventilation (Analysis 3.5): Two trials reported this outcome with both showing a significant effect in favour of HFO (Singh 2012; Sun 2014). The meta-analysis demonstrated a significant effect in favour of HFO (Mean difference 1.89 days, 95% CI 1.04 to 2.74).

Air Leaks (Analysis 3.6): One trial reported PIE as an outcome and showed a significant decrease of this outcome in the SIMV group (RR 0.66, CI 0.44 to 0.99) (Courtney 2002a). Three trials reported pneumothorax as an outcome with no significant difference (Courtney 2002a; Craft 2003a; Sun 2014).

IVH Grade 3 or 4 (Analysis 3.7): Four trials reported this outcome (Courtney 2002a; Craft 2003a; Singh 2012; Sun 2014). No trial found a significant difference.

ACV versus SIMV (comparison 4)

Duration of weaning (hours) (Analysis 4.1): Three trials of ACV versus SIMV reported this outcome (Chan 1994; Dimitriou 1995a; Dimitriou 1995b). None demonstrated a significant effect. In all three, however, the duration of weaning tended to be shorter in infants supported by ACV rather than SIMV. The meta-analysis supported a trend in this direction which, however, did not reach statistical significance.

Weaning failure (Analysis 4.2): Three trials of ACV versus SIMV reported this outcome (Chan 1994; Dimitriou 1995a; Dimitriou 1995b). None demonstrated a significant effect. The meta-analysis found no evidence of effect.

Extubation failure (Analysis 4.3): Three trials of ACV versus SIMV (Chan 1994; Dimitriou 1995a; Dimitriou 1995b) reported this outcome. None demonstrated a significant effect. The meta-analysis found no evidence of effect.

Air leaks (Analysis 4.4): Three trials of ACV versus SIMV (Chan 1994; Dimitriou 1995a; Dimitriou 1995b) reported this outcome. None demonstrated a significant effect. The meta-analysis found no evidence of effect.

SIMV PLUS PS versus SIMV (comparison 5)

Only [Reyes 2006](#) reports on SIMV plus PS compared to SIMV alone.

Death ([Analysis 5.1](#)): There was no significant effect with regard to death at 28 days or death prior to discharge.

Air leaks ([Analysis 5.2](#)): The occurrence of PIE and pneumothorax are reported separately; there were no significant differences in either outcome.

BPD, oxygen dependency at 28 days (Outcome 5.3.1): There was no significant effect.

Moderate/severe BPD, oxygen dependency at 36 weeks postmenstrual age (Outcome 5.3.2): There was no overall significant effect.

Severe IVH (Grade III and IV) ([Analysis 5.4](#)): There was no significant effect.

Other outcomes: There was no significant effect re PDA. Days on mechanical ventilation and supplementary oxygen did not differ by ventilation status, but in the subgroup of infants with birth weight of 700 grams to 1000 grams, the days of supplementary oxygen were lower in the SIMV plus PS group ($P = 0.034$).

PRVCV versus SIMV (comparison 6)

Death prior to discharge ([Analysis 6.1](#)): One trial ([D'Angio 2005](#)) reported this with no significant difference between intervention.

BPD, oxygen requirement at 36 weeks' postmenstrual age in survivors ([Analysis 6.2](#)): One trial reported this with no significant difference between intervention ([D'Angio 2005](#)).

Airleak (PIE (Outcome 6.3.1) or Pneumothorax (Outcome 6.3.2)): In the PRVCV versus SIMV trial there were no significant effects with regard to either pneumothorax or PIE ([D'Angio 2005](#)).

Severe IVH ([Analysis 6.4](#)): One trial reported this outcome with no significant difference between intervention ([D'Angio 2005](#)).

SIMV versus PSV (comparison 7)

Duration of weaning ([Analysis 7.1](#)): One trial reported this outcome ([Erdemir 2014](#)). There was no significant difference.

Extubation failure ([Analysis 7.2](#)): One trial reported this outcome ([Erdemir 2014](#)). There was no significant difference.

Air leaks (total) ([Analysis 7.3](#)): One trial reported this outcome ([Erdemir 2014](#)). There was no significant difference.

Moderate/Severe BPD; Oxygen requirement at 36 weeks postmenstrual age ([Analysis 7.4](#)): One trial reported this outcome ([Erdemir 2014](#)). There was no significant difference.

ACV versus PSV (comparison 8)

Duration of weaning (Outcome 8.1): One trial reported this outcome ([Patel 2012](#)). The data were reported as median and range. No significant difference was reported.

DISCUSSION

Physiological studies have demonstrated in prematurely born neonates that both high-frequency positive pressure ventilation and triggered ventilation are more likely to provoke a synchronous respiratory interaction; that is, the infant's inspiratory efforts coincide with positive pressure inflations. When compared to CMV, those ventilation modes were shown to be associated with improved ventilation. Unfortunately, in none of the subsequent randomised trials is it reported whether synchronous ventilation was achieved and few outcome measures are consistently reported in all relevant trials. Nevertheless, the meta-analyses demonstrate a significant decrease in air leak and a shorter duration of ventilation with HFPPV and triggered ventilation respectively. However, no significant effect on the incidence of BPD or death has been shown using either HFPPV or trigger ventilation modes.

No deleterious effects of those two ventilatory modes were highlighted. Some positive effects have been demonstrated of the newer triggered modes PRVCV and SIMV plus PS, but both modes have each only been examined in one randomised trial; further trials are required which incorporate long-term outcomes.

A meta-analysis of the studies comparing SIMV or SIMV + PS with HFO show a significant decrease in moderate or severe BPD, and significantly shorter duration of mechanical ventilation with HFO. Whether other trigger modes such as ACV have similar results to HFO requires investigating.

AUTHORS' CONCLUSIONS

Implications for practice

Comparative trials of assisted ventilation in neonates demonstrate that, compared to CMV, HFPPV is associated with a reduced risk of air leak and triggered ventilation with a shorter duration of ventilation. On clinical grounds, those ventilatory modes would seem preferable for preterm neonates to 'conventional' ventilation delivered at rates of less than 60 bpm. In addition, HFO resulted in a reduced risk of BPD and duration of ventilation compared to SIMV with or without pressure support. It is important to determine if other triggered modes such as ACV have similar poor results compared to HFO.

Comparative trials demonstrated that in preterm infants in the recovery stage of respiratory distress, ACV compared to SIMV is associated with a shorter duration of ventilation; thus, ACV would seem the more desirable mode of weaning for preterm neonates. There are insufficient randomised trials of PRVCV or pressure support versus SIMV to make any conclusions to their efficacy with regard to long-term efficacy.

Implications for research

Further trials are encouraged to assess whether ventilation modes likely to provoke synchronous ventilation will have other benefits and whether the mechanism of such effects is by provoking synchrony. Optimisation of trigger and ventilator performance with respect to respiratory diagnosis is essential. Randomised trials of the newer triggered modes with long-term outcomes are essential to determining their efficacy.

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Greenough 2004

Greenough A, Milner AD, Dimitriou G. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: [10.1002/14651858.CD000456.pub2](https://doi.org/10.1002/14651858.CD000456.pub2)]

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Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory supporting newborn infants. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: [10.1002/14651858.CD000456.pub3](https://doi.org/10.1002/14651858.CD000456.pub3)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Amini 2013
Study characteristics
Synchronized mechanical ventilation for respiratory support in newborn infants (Review)

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Amini 2013 (Continued)

Methods	Randomised Single centre trial Randomisation method: block randomisation Blinding of randomisation: unclear Blinding of intervention: no Blinding of outcome measurement: no Complete follow-up: yes
Participants	All neonates admitted to NICU with respiratory failure requiring mechanical ventilation (respiratory failure and gestational age not defined). All infants received surfactant. Exclusion criteria include: complex congenital heart disease, genetic syndromes, major anomalies, hypoxic ischaemic encephalopathy or birth asphyxia. HFPPV 31; CMV 31
Interventions	HFPPV or CMV
Outcomes	No primary outcome stated. Outcomes reported were IVH, air leak, mortality, treatment failure, duration of mechanical ventilation, number of doses of surfactant administered, oxygen requirement at 28 days, PVL
Notes	Ventilator types: Bearcub 750 used for both interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Block randomisation"; no further details given
Allocation concealment (selection bias)	Low risk	"Block randomisation"; no further details given.
Blinding (performance bias and detection bias) All outcomes	High risk	Clinician aware of intervention
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinicians likely to be aware of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up of recruited infants

Baumer 2000

Study characteristics

Methods	Randomised Multicentre trial Randomisation method: randomly allocated by telephone Stratified by centre. Within each centre, randomisation in blocks to ensure a similar distribution of babies in each arm of the study Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Gestational age < 32 weeks. Assisted ventilation within 72 hours of birth Not ventilated for more than 6 hours at randomisation RDS Exclusion: major congenital malformation or inhalational pneumonitis Sample size: 924 PTV: 465 CMV: 459
Interventions	PTV vs CMV
Outcomes	Primary: Hospital mortality or need for oxygen treatment at 36 weeks of gestation; pneumothorax cerebral ultrasound abnormality nearest to 36 weeks of gestation; duration of ventilation in survivors
Notes	Ventilator types: PTV: SLE 2000 (airway pressure trigger) Draeger baby log 8000 (airway flow trigger) CMV: SLE 2000, Draeger Babylog, Sechrist 423 of those randomised to PTV and 422 infants randomised to CMV had cranial ultrasound examination

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly allocated by telephone"
Allocation concealment (selection bias)	Low risk	"Within each centre, randomisation was performed in blocks" Probably done
Blinding (performance bias and detection bias) All outcomes	High risk	"Form of ventilation to which they were assigned from birth to final extubation" Comment: no blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Clinicians were allowed the discretion to change the baby from the assigned mode of ventilation" Comment: no blinding as clinicians aware of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: clinicians likely to be aware of the intervention

Baumer 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome for death (912/924); pneumothorax(922/924); cranial USS (848/924)
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Beresford 2000
Study characteristics

Methods	Randomised Multicentre trial Randomisation method: computer generated sequence hidden in sequentially numbered, opaque envelopes Stratified by BW Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Birth weight 1000 to 2000 grams Assisted ventilation within 24 hours of birth RDS Exclusion: major malformations, congenital heart disease, MAS Sample size: 386 PTV: 193 CMV: 193
Interventions	PTV vs CMV
Outcomes	Primary: Incidence of CLD Secondary: Death Pneumothorax IVH Cystic PVL Shunt insertion
Notes	Ventilator types: SLE 2000 (airway pressure trigger)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated sequence".
Allocation concealment (selection bias)	Low risk	"Hidden in sequentially numbered, sealed, opaque envelopes".
Blinding (performance bias and detection bias) All outcomes	High risk	"Study design was such as to preclude crossover of treatment strategy". Comment: clinician aware of the mode of intervention
Blinding of participants and personnel (performance bias)	High risk	Comment: clinicians aware of the intervention

Beresford 2000 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: clinicians aware of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: complete data present

Bernstein 1996

Study characteristics

Methods	Randomised Multicenter trial Intention-to-treat basis Randomisation method: sealed, opaque envelopes. Stratified by BW Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	BW > 500 grams Assisted ventilation Age < 36 hours RDS, congenital pneumonia, MAS CXR with abnormal lung parenchyma, $\text{FiO}_2 > 0.4$ (all BW) and $\text{MAP} > 7 \text{ cmH}_2\text{O}$ (for infants with BW > 1250 grams). Duration of CMV prior randomisation < 12 hours, spontaneous breathing rate > 20 bpm and in-dwelling arterial line Exclusion: infants with air leak, seizures, IVH grade III or IV, neuromuscular disease affecting respiration, major malformations including chromosomal abnormalities, CDH, CHD (except PDA), lung hypoplasia, septic shock or severe skin disease Sample size: 350* SIMV: 178 (167 analysed) CMV: 172 (160 analysed) *23 excluded post randomisation
Interventions	SIMV vs CMV
Outcomes	Primary: Acute effect on oxygenation Sedative/analgesic drug requirements Duration of ventilation Air leaks Secondary: Severe IVH Death Need for pharmacological paralysis ECMO or long-term supplemental oxygen The age at which infants undergoing long-term ventilation (> 14 days) regained their BW
Notes	Ventilator types: Infant Star with Star Sync module (abdominal movement monitor)

Risk of bias

Bernstein 1996 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation schedules were generated for each centre by computer"
Allocation concealment (selection bias)	Low risk	"Sequential, opaque, sealed envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Intention-to-treat protocol"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: clinicians aware of intervention (intention-to-treat protocol)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Data were collected prospectively" Comment: clinicians probably aware of intervention (intention-to-treat protocol)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome for all participants reported

Chan 1993

Study characteristics

Methods	Randomised Single centre trial Randomisation method: sealed, opaque envelopes Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Gestational age < 36 weeks. Age: 1 to 21 days. RDS. In the recovery stage of the respiratory disease (at 40 bpm) Sample size: 40 PTV: 20 CMV: 20
Interventions	PTV vs CMV
Outcomes	Primary: Hours of ventilation from entering the study until first extubation (weaning) Secondary: Number of infants who failed weaning Number of infants who failed extubation
Notes	Ventilator types: SLE 2000 (airway pressure trigger), Sechrist IV-100B

Risk of bias

Chan 1993 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Sealed, opaque envelopes"
Allocation concealment (selection bias)	Low risk	Not revealed to clinician
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "protocol for weaning from ventilation was similar in both groups" Comment: clinicians not blinded to the method of weaning.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "not possible to "blind" the clinicians" Comment: different ventilators used for the two study groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: clinicians aware of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome for all participants reported

Chan 1994
Study characteristics

Methods	Randomised Single centre trial Randomisation method: sealed, opaque envelopes Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	GA < 35 weeks Age < 1 to 23 days Weaning – loaded with aminophylline Exclusion: apnoea, failure to trigger Sample size: 40 SIMV: 20 CMV: 20
Interventions	PTV vs SIMV
Outcomes	Primary: Duration of weaning Secondary: Number of infants who failed weaning Number of infants who failed extubation
Notes	Ventilator types: SLE 2000 (airway pressure trigger) CMV

Chan 1994 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised" By sealed opaque envelope
Allocation concealment (selection bias)	Low risk	"Consecutively drawing cards from sealed envelope" Comment: clinicians blinded to allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"protocol for weaning from ventilation was similar in both groups" Comment: clinicians aware of intervention
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: clinicians aware of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: clinicians aware of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome for all participants reported

Chen 1997

Study characteristics

Methods	Randomised Single centre trial Blinding of randomisation: not stated Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	BW < 1.75 kg, GA < 34 weeks and RDS Assisted ventilation Exclusion: congenital malformation, inherited metabolic abnormalities, sepsis, treatment with muscle relaxants Sample size: 77 SIMV: 38 CMV: 39 RDS sample size: 62 SIMV: 31 CMV: 31 MAS sample size: 15 SIMV: 7 CMV: 8 Term infants (MAS) excluded from the analysis
Interventions	SIMV vs CMV

Chen 1997 (Continued)

Outcomes	Primary: Duration of ventilation Need of reintubation Air leaks PDA IVH Secondary: BPD ROP Death
Notes	Ventilator types: Infant Star with Star sync module (airflow trigger) (CMV) Bear Cub

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised"
Allocation concealment (selection bias)	Unclear risk	Comment: the evaluator was unaware of the treatment status of the patients
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: not possible to assess
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not possible to assess
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not possible to assess
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome for all participants reported

Courtney 2002a

Study characteristics

Methods	Randomised controlled multicentre study randomised by off-site clinical coordination centre
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Courtney 2002a (Continued)

Participants	<p>BW 601 to 1200 grams</p> <p>appropriately developed for gestational age</p> <p>< 4 hours of age and expected to require ventilation for at least 24 hours</p> <p>Exclusion: if Apgar at 5 minutes < 4; a base deficit of 15 or more prior to study; severe hypotension; chromosomal or genetic abnormalities; congenital heart disease or known neuromuscular disease</p>
Interventions	HFO with Sensormedics 3100a or SIMV with either VIP Bird, Babylog 8000, Bear Cub with neonatal monitoring or Bear Cub 750vs
Outcomes	<p>Primary outcome: death or BPD (oxygen requirement at 36 weeks)</p> <p>successful extubation</p> <p>IVH, PVL, pneumothorax, PIE, pulmonary haemorrhage, bacteraemia, PDA, NEC, ROP</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by off-site clinical coordination centre. Probably done
Allocation concealment (selection bias)	Low risk	Off-site allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of clinicians: different ventilators used for different arms
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding possible as above
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinicians likely to be aware of intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 infants from HFOV and 4 from SIMV withdrawn – data analysed until point of withdrawal

Craft 2003a

Study characteristics

Methods	<p>Multicentre randomised controlled trial</p> <p>Randomised using random number sequence with assignments in opaque sealed envelopes</p> <p>Block randomisation (units of 10)</p>
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Craft 2003a (Continued)

	crossover to alternative method in event of failure – analysis by intention to treat
Participants	23 to 34 weeks gestation weighing < 1000 grams requiring mechanical ventilation No exclusion criteria stated Grouped 500 to 750 g and 750 to 1000 grams – data combined for meta-analysis
Interventions	SIMV or high-frequency flow interruption (HFFI)
Outcomes	Days of mechanical ventilation Days of CPAP days of oxygen requirement BPD (Oxygen requirement at 36 weeks) Airleak PDA Grade 3 or 4 IVH Grade 3 or 4 ROP Death
Notes	Infant Star ventilator. Graseby capsule used for synchronisation. Extubation when rate reduced to 8 to 12 bpm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Infants were randomly assigned by a sealed opaque envelope, with a previously generated random number sequence"
Allocation concealment (selection bias)	Low risk	Clinicians blinded to allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind clinician to treatment arm
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind clinician to treatment arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors likely aware of treatment arm
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition unclear. Study terminated at ad-hoc interim analysis

D'Angio 2005

Study characteristics

Methods	Randomised Single centre trial Randomisation method: block randomisation scheme by one of the investigators Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Ventilated infants BW of 500 to 1249 grams Less than six hours of age Gestational age > 24 weeks Sample size: 212 PRVCV: 104 SIMV: 108
Interventions	PRVCV vs SIMV
Outcomes	Primary: proportion of infants alive and extubated at 14 days Secondary: death Moderate/severe BPD Air leaks Severe IVH (grades 3 and 4)
Notes	Ventilator type: Servo 300, infants who required slow rates > 40 bpm (maximum for the Servo 300) were transferred to the BIRD VIP ventilator

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "randomly assigned " Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: probably done (Failure and Weaning protocol followed)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: clinicians likely to be aware of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: clinicians likely to be aware of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: respiratory outcomes for all participants reported

Dimitriou 1995a

Study characteristics

Methods	Randomised Single centre trial Randomisation method: sealed, opaque envelopes Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	GA < 35 weeks Age < 15 days Weaning – loaded with aminophylline Exclusion: apnoea, failure to trigger Sample size: 40 PTV: 20 SIMV: 20
Interventions	PTV vs SIMV
Outcomes	Primary: Duration of weaning Secondary: Number of infants who failed weaning Number of infants who failed extubation
Notes	Ventilator types: SLE 2000 (airway pressure trigger)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random selection"
Allocation concealment (selection bias)	Low risk	"Drawing a card"
Blinding (performance bias and detection bias) All outcomes	Low risk	Done as protocol followed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: clinicians likely to be aware of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome of all trial participants reported.

Dimitriou 1995b

Study characteristics

Methods	Randomised.
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Dimitriou 1995b (Continued)

Single centre trial
Randomisation method: sealed, opaque envelopes
Blinding of randomisation: yes
Blinding of intervention: no
Complete follow-up: no
Blinding of outcome measurement: no

Participants	GA < 35 weeks Age < 15 days Weaning – loaded with aminophylline Exclusion: apnoea, failure to trigger Sample size: 40 PTV: 20 SIMV: 20
Interventions	PTV vs SIMV
Outcomes	Primary: Duration of weaning Secondary: Number of infants who failed weaning Number of infants who failed extubation
Notes	Ventilator types: SLE 2000 (airway pressure trigger)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Random selection"
Allocation concealment (selection bias)	Low risk	"Drawing a card"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Done as protocol followed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: clinicians likely to be aware of the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: outcome of all trial participants reported.

Donn 1994

Study characteristics

Methods	Randomised Single centre trial Randomisation method: lottery (sampling without replacement) Blinding of randomisation: not reported
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Synchronized mechanical ventilation for respiratory support in newborn infants (Review)

Donn 1994 (Continued)

	Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Preterm infants. BW between 1.1 to 1.5 kg RDS, SRT Sample size: 30 PTV: 15 CMV: 15
Interventions	PTV vs CMV
Outcomes	Primary: Duration of ventilation Secondary: Air leaks IVH CLD
Notes	Ventilator types: PTV V.I.P. BIRD (airflow trigger) CMV Sechrist IV-100B, V.I.P. BIRD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised"
Allocation concealment (selection bias)	Low risk	"lottery (sampling without replacement)"
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not possible to assess
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome of all trial participants reported

Erdemir 2014

Study characteristics

Methods	Randomised
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Synchronized mechanical ventilation for respiratory support in newborn infants (Review)

Erdemir 2014 (Continued)

	Single centre trial
	Sealed envelope randomisation
Participants	60 prematurely born infants 30 SIMV 30 gestation < 33 weeks or birth weight < 1500 grams requiring mechanical ventilation for RDS Exclusion criteria: admission after 6 hours of age congenital cardiac, respiratory or CNS malformation congenital metabolic disease congenital pneumonia or sepsis perinatal asphyxia leak around ET tube of < 20%
Interventions	Received surfactant placed on PTV, then randomised to SIMV or PSV + VG when FiO ₂ < 0.4, RR < 60, PIP 16 cmH ₂ O, PEEP 4 cmH ₂ O with adequate blood gases
Outcomes	Duration of weaning time to extubation PIP, MAP, Vt, RR at start, during and at end of weaning
Notes	58 recruited, 45 reported
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk "Sealed envelope randomisation": sequence generation unclear
Allocation concealment (selection bias)	Low risk "Sealed envelope randomisation"
Blinding (performance bias and detection bias) All outcomes	High risk No blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk All outcomes reported for all participants

Heicher 1981

Study characteristics

Methods	Quasi-randomised Single centre trial Patients alternatively assigned to one of the two study ventilatory modes Blinding of randomisation: no Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Birth weight > 750 grams. No gross anomalies. Abnormal lung fields on chest radiograph. Respiratory distress syndrome, pneumonia Exclusion: infants with chromosomal abnormalities or meconium aspiration Sample size: 102 Rapid rates: 51 Slow rates: 51
Interventions	HFPPV. Rapid rates (60 bpm) with IT: 0.5 sec versus slow rates (20 to 40 bpm) with IT: 1sec
Outcomes	Clinical improvement Need for pharmacological paralysis Hours of assisted ventilation Hours of $\text{FiO}_2 > 0.6$. CLD Mortality
Notes	Ventilator types: Baby Bird, Bird Co

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "were alternately assigned" Comment: not randomised
Allocation concealment (selection bias)	High risk	Comment: assigned not randomised
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "remained constant throughout the study period" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes reported for all trial participants

Liu 2011

Study characteristics

Methods	Randomised trial Single centre Randomisation method: random number table Blinding of randomisation: unclear Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: not clear
Participants	GA < 35 weeks Mechanical ventilation RDS Age < 12 hours old Arterial blood gas pH < 7.25; PaO ₂ < 50mmHg; PaCO ₂ > 50 mmHg PaO ₂ /FiO ₂ ≤ 250 mmHg; a/APO ₂ ≤ 0.22 Exclusion criteria: congenital lung abnormalities, pulmonary haemorrhage, pneumothorax, congenital pneumonia, meconium aspiration, wet lung, complex congenital heart disease, grade 3/4 intracranial haemorrhage Sample size: 84 SIPPV + VG: 31 CMV: 30 HFOV: 23
Interventions	SIPPV +VG vs CMV vs HFOV
Outcomes	Primary: Duration of mechanical ventilation Oxygenation status Secondary: Death Air leak Ventilation associated pneumonia Intraventricular haemorrhage (Grade 3/4)
Notes	Ventilator types: Babylog 8000 plus, Sensormedics 3100 A

Risk of bias

Bias	Authors' judgement	Support for judgement
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Liu 2011 (Continued)

Random sequence generation (selection bias)	High risk	Comment: random number table used
Allocation concealment (selection bias)	High risk	Comment: probably not used
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: probably not done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes of all participants reported.

OCTAVE 1991
Study characteristics

Methods	Randomised Multicentre trial Randomisation method: sealed, opaque envelopes Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: no
Participants	Age < 72 hours. Assisted ventilation Exclusion: meconium aspiration Sample size: 346 HFPPV: 174 CMV: 172
Interventions	HFPPV (60 bpm) versus CMV (20 to 40 bpm)
Outcomes	Incidence of pneumothorax Incidence and severity of CLD Mortality Neurodevelopmental outcome
Notes	Ventilator type: Sechrist IV 100B

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random assignment"

OCTAVE 1991 (Continued)

		Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "sealed, opaque, serially numbered envelope" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: clinicians probably aware of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: clinicians probably aware of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: short-term outcome reported for all participants

Patel 2012

Study characteristics

Methods	Randomised Single centre study Randomisation: sequential opaque sealed envelopes with contents generated by random number table Randomised at initiation of weaning ventilation
Participants	Ventilated, less than 14 days old excluding: congenital heart disease or HIE Evaluation of weaning: randomised when $\text{FiO}_2 < 0.4$; $\text{PIP} \leq 20 \text{ cmH}_2\text{O}$ if ≥ 29 weeks' gestation; $\leq 17 \text{ cmH}_2\text{O}$ if between 26 and 29 weeks' gestation; or $\leq 15 \text{ cmH}_2\text{O}$ if ≤ 26 weeks' gestation 18 ACV, 18 PSV
Interventions	ACV Vs PSV (backup 40 bpm, trigger 0.6 to 1.0 litre/min)
Outcomes	Duration of weaning, time to extubation
Notes	All infants ventilated with SLE5000 Data in paper expressed as median and range

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised using a sequential opaque sealed envelope system, the contents having been determined by random number table generation": low risk
Allocation concealment (selection bias)	Low risk	As above; block allocation with six in each block

Patel 2012 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding of clinician. Analysis by intention to treat
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not all short term outcomes measured at all time points, but relevant outcomes reported for all participants

Pohlandt 1992

Study characteristics

Methods	Randomised (with stratification for gestational age) Method of randomisation: random number table. Blinding of randomisation: not reported Blinding of intervention: no Complete follow-up: no Blinding of outcome measurement: no
Participants	Gestational age < 32 weeks Assisted ventilation Supplemental FiO ₂ > 0.4 Sample size: 181 HFPPV: 91 CMV: 90
Interventions	HFPPV (60 bpm with IT: 0.3 sec) vs CMV (30 to 40 bpm with IT: 1 sec)
Outcomes	Incidence of extra-alveolar air leaks Mortality
Notes	Ventilator types: AIV Loosco MKII, Biomed MVP 10, Babylog-Draeger, Sechrist IV-100B, Siemens Servo-B and Servo-C, Stephan 181 infants were enrolled into the study, but only 137 fulfilled the criteria and their results were analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "random number table" Comment: probably not followed
Allocation concealment (selection bias)	High risk	Comment: probably not done

Pohlandt 1992 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: clinicians probably aware of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: primary outcomes of all participants reported

Reyes 2006
Study characteristics

Methods	Randomised Single centre Randomisation method: sequential Sealed opaque envelopes from a computer-generated randomised list Blinding of randomisation: no Complete follow-up: yes Blinding of outcome measurement: no
Participants	Birth weight 500 to 1000 grams appropriate birth weight for gestational age Mechanical ventilation requirement < 12 hours after birth until 7 days Exclusion: congenital anomalies; neuromuscular disease; lung hypoplasia; congenital heart disease; hypotension requiring intravenous medication; PIE or pneumothorax; required HFOV > 24 hours; received sedation or muscle relaxation Sample size: 107 53: SIMV plus PS 54: SIMV
Interventions	SIMV plus PS versus SIMV
Outcomes	Primary: Proportion of infants requiring supplementary oxygen at 28 days Secondary: Death Air leaks BPD IVH (Grades III and IV) (Grade III and IVH)
Notes	Ventilator type: Pressure-limited flow triggered VIP ventilator

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomisation" Comment: probably done

Reyes 2006 (Continued)

Allocation concealment (selection bias)	High risk	Comment: probably not followed
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "study protocol was actively followed" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Caregivers were not blinded to the assigned modality" Comment: not followed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: clinicians probably aware of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcomes of all trial participants reported

Singh 2012
Study characteristics

Methods	Randomised controlled single centre study Randomisation: web-based random number generator generated allocation sequence, which was placed in sequential sealed opaque envelopes
Participants	preterm neonates requiring mechanical ventilation excluding: BW < 750 grams; major congenital anomaly; perinatal asphyxia; shock; prior air leak If did not undergo 24 hours of ventilation the patient was excluded from analysis 66 HFO, 84 SIMV
Interventions	SIMV or HFOV
Outcomes	FiO ₂ , MAP, OI at 1, 6 and 24 hours Duration of ventilation Oxygen dependency at 28 days Hospital stay Survival IVH, PVL, PDA, ROP, pulmonary haemorrhage, ventilator associated pneumonia
Notes	SIMV delivered with SLE2000, HFOV with Draeger Babylog 8000

Risk of bias

Bias	Authors' judgement	Support for judgement
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Singh 2012 (Continued)

Random sequence generation (selection bias)	Low risk	"Simple randomisation using a web-based random number generator": probably done
Allocation concealment (selection bias)	Low risk	"slip of paper bearing the intervention was kept in serially numbered opaque sealed envelopes": probably done
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	HFOV arm 17 died/left study; SIMV 23 died/left study

Sun 2014

Study characteristics

Methods	Randomised single centre study computer-generated randomisation after consent stratified by sex and gestational age
Participants	admitted to NICU with gestational age < 32 weeks; birth weight < 1500 grams; requiring mechanical ventilation for respiratory distress syndrome with PaO ₂ /FiO ₂ < 200 mmHg exclusion: genetic metabolic diseases; congenital abnormalities; pneumothorax or grade III or IV IVH prior to randomisation randomised: 336 — 184 to SIMV, 182 to HFOV
Interventions	SIMV + PS vs HFOV
Outcomes	Primary outcome: mortality and BPD Secondary outcomes: days of mechanical ventilation; hospital stay; surfactant requirement; ROP; pulmonary haemorrhage; PDA; NEC; pneumothorax. Moderate or severe disability at 18 months
Notes	SLE5000 and Servo-i ventilators not analysed: 41 in SIMV, 37 in HFOV group

Risk of bias

Bias	Authors' judgement	Support for judgement
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Sun 2014 (Continued)

Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation plan": probably done
Allocation concealment (selection bias)	Low risk	Randomisation stratified by centre, by sex and gestational age using variable block size block randomisation: probably done
Blinding (performance bias and detection bias) All outcomes	High risk	Different ventilators used, no blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different ventilators used, no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different ventilators used, no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High risk for long-term outcomes with approximately 30% lost to follow-up Low risk for short-term outcomes

ACV: assist control ventilation
BPD: bronchopulmonary dysplasia
BW: birth weight
CDH: congenital diaphragmatic hernia
CHD: congenital heart disease
CLD: chronic lung disease
CMV: conventional mechanical ventilation
CPAP: continuous positive airway pressure
ECMO: extracorporeal membrane oxygenation
GA: gestational age
HFO: high-frequency oscillation
HFOV: high frequency oscillatory ventilation
HFPPV: high-frequency positive pressure ventilation
IT: inspiratory time
IVH: intraventricular haemorrhage
MAP: mean airway pressure
MAS: meconium aspiration syndrome
NEC: necrotising enterocolitis
OI: oxygenation index
PDA: patent ductus arteriosus
PIE: pulmonary interstitial emphysema
PIP: peak inspiratory pressure
PRVCV: pressure-regulated volume control ventilation
PS: pressure support
PTV: patient-triggered ventilation
PVL: periventricular leukomalacia
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity
SIMV: synchronised intermittent mandatory ventilation
SRT: surfactant replacement therapy
VG: volume guarantee

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abd El-Moneim 2005	Short-term cross over study
Abubakar 2005	Randomised short-term cross over study
Amitay 1993	Not assigned respiratory support mode by randomisation
Bernstein 1993	Not assigned respiratory support mode by randomisation
Bitondo 2012	Adult crossover study of PSV controlled automatically or by clinician
Chan 1993b	Not assigned respiratory support mode by randomisation
Cheema 2001	Short-term comparison of volume guarantee synchronised ventilation to PTV or SIMV
Clavieras 2013	Adult study comparing methods of pressure support
Cleary 1995	Acute effects of synchronised ventilation
Dani 2006	Short-term randomised comparison of PSV with VG to HFOV
de la Oliva 2012	Non-randomised cross-over study in the paediatric population
De Luca 2009	Cross over trial comparing ACV in time-cycled and flow-cycled modality
deBoer 1993	Not assigned respiratory support mode by randomisation
Dimitriou 1998	Comparison of triggering devices
Duman 2012	Comparison of volume targeting vs pressure limited ventilation in one mode of triggered ventilation
Durand 2001	Randomised pilot study comparing HFOV to SIMV
Estay 2009	Assess the effects of flow sensor dead space during SIMV
Firme 2005	Randomised short-term cross-over study
Friedlich 1999	Nasopharyngeal SIMV versus CPAP
Greenough 1986	Not assigned respiratory support mode by randomisation
Greenough 1987a	Not assigned respiratory support mode by randomisation
Greenough 1987b	Not assigned respiratory support mode by randomisation
Greenough 1988a	Not assigned respiratory support mode by randomisation
Greenough 1988b	Not assigned respiratory support mode by randomisation
Greenough 1991	Not assigned respiratory support mode by randomisation
Gupta 2008	Quasi-experimental cross-over study
Guthrie 2005	Randomised short-term comparison of SIMV and mandatory minute volume

Study	Reason for exclusion
Guven 2013	Comparison of volume guarantee versus pressure-limited ventilation in one mode of triggered ventilation
Herrera 2002	Acute effects of volume-guaranteed SIMV
Hird 1990a	Not assigned respiratory support mode by randomisation
Hird 1990b	Not assigned respiratory support mode by randomisation
Hird 1991a	Not assigned respiratory support mode by randomisation
Hird 1991b	Not assigned respiratory support mode by randomisation
Hird 1991c	Not assigned respiratory support mode by randomisation
Hird 1991d	Not assigned respiratory support mode by randomisation
Hummler 1996	Acute effects of synchronised ventilation
Hummler 1997	Acute effects of mechanical ventilation
Hummler 2006	Randomised short-term cross-over study
Jaber 2005	Randomised short-term cross-over comparison of PSV and volume support ventilation
Jarreau 1996	Acute outcome of synchronised ventilation
John 1994	Comparison of triggering devices
Kapasi 2001	Short-term randomised comparison of ventilation modes
Keszler 2004	Short-term randomised comparison of ventilation modes with ACV with or without volume guarantee
Laubscher 1997	Comparison of triggering devices
Lista 2006	Acute effects of different levels of volume targeting during synchronised intermittent positive pressure ventilation within the context of a randomised trial
Luyt 2001	Acute effects of PTV and conventional ventilation compared within the context of a randomised trial
McCallion 2007	Observational study studying the effects of spontaneous breathing, triggered and untriggered inflations
Migliori 2003	Non randomised comparison of pressure support synchronised ventilation and SIMV
Mitchell 1989	Not assigned respiratory support mode by randomisation
Mizuno 1994	Not assigned respiratory support mode by randomisation
Moretti 1999	Nasal SIPPV to nasal CPAP
Mrozek 2000	Randomised comparison (short-term) of volume-targeted synchronised ventilation and CMV

Study	Reason for exclusion
Nacoti 2012	Paediatric study comparing PSV to PSV with sighs. Non-randomised.
Nafday 2005	Randomised comparison (short-term) of pressure support with volume guarantee
Nakae 1998	Comparison of triggering devices
Nikischin 1996	Comparison of triggering devices
Nishimura 1995	Comparison of triggering devices
Olsen 2002	Cross-over trial comparing pressure support with volume guarantee synchronised ventilation to SIMV
Osorio 2005	Cross-over short-term comparison of SIMV with or without pressure support
Patel 2009	Cross-over trial comparing SIMV and SIMV with pressure support
Polimeni 2006	Short-term cross-over study
Scopesi 2007	Short-term cross-over study
Servant 1992	Not assigned respiratory support mode by randomisation
Smith 1997	Acute outcome of synchronised ventilation
Takeuchi 1994	Not assigned respiratory support mode by randomisation
Thiagarajan 2004	Comparison of triggering devices
Upton 1990	Not assigned respiratory support mode by randomisation
Vishveshwara 1991	Not assigned respiratory support mode by randomisation
Wheeler 2012	Randomised cross-over trial to study the effects of differing back up rates within one mode of triggered ventilation

DATA AND ANALYSES

Comparison 1. HFPPV vs CMV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death	4	647	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 1.00]
1.2 Air leaks	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Pneumothorax	3	585	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.51, 0.93]
1.2.2 Pulmonary interstitial emphysema	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.49, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Total air leak	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.08]
1.4 BPD (oxygen dependency at 28 days)	4	647	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.46]
1.5 IVH	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.94]

Analysis 1.1. Comparison 1: HFPPV vs CMV, Outcome 1: Death

Analysis 1.2. Comparison 1: HFPPV vs CMV, Outcome 2: Air leaks

Analysis 1.3. Comparison 1: HFPPV vs CMV, Outcome 3: Total air leak

Analysis 1.4. Comparison 1: HFPPV vs CMV, Outcome 4: BPD (oxygen dependency at 28 days)

Analysis 1.5. Comparison 1: HFPPV vs CMV, Outcome 5: IVH

Comparison 2. ACV/SIMV vs CMV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Death	6	1790	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.94, 1.47]
2.2 Air leaks	7	1830	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.27]
2.3 Duration of ventilation (hours)	5	1463	Mean Difference (IV, Fixed, 95% CI)	-38.30 [-53.90, -22.69]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Extubation failure	4	1056	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.68, 1.28]
2.5 Severe IVH	6	1790	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
2.6 BPD (oxygen dependency at 28 days)	4	805	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.12]
2.7 Moderate/Severe BPD (oxygen dependent at 36 weeks PCA)	2	1310	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.08]

Analysis 2.1. Comparison 2: ACV/SIMV vs CMV, Outcome 1: Death

Analysis 2.2. Comparison 2: ACV/SIMV vs CMV, Outcome 2: Air leaks

Analysis 2.3. Comparison 2: ACV/SIMV vs CMV, Outcome 3: Duration of ventilation (hours)

Analysis 2.4. Comparison 2: ACV/SIMV vs CMV, Outcome 4: Extubation failure

Analysis 2.5. Comparison 2: ACV/SIMV vs CMV, Outcome 5: Severe IVH

Analysis 2.6. Comparison 2: ACV/SIMV vs CMV, Outcome 6: BPD (oxygen dependency at 28 days)

Analysis 2.7. Comparison 2: ACV/SIMV vs CMV, Outcome 7: Moderate/Severe BPD (oxygen dependent at 36 weeks PCA)

Comparison 3. SIMV or SIMV + PS vs HFOV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Death	4	996	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.91, 1.71]
3.2 BPD: oxygen requirement at 28 days	1	110	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.37, 27.83]
3.3 Moderate/ Severe BPD: Oxygen requirement at 36 weeks PCA	3	869	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.07, 1.65]
3.4 Death or BPD	1	356	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.41, 4.03]
3.5 Duration of mechanical ventilation	2	466	Mean Difference (IV, Fixed, 95% CI)	1.89 [1.04, 2.74]
3.6 Air leaks	3	1398	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.70, 1.19]
3.6.1 Pulmonary interstitial emphysema	1	498	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.44, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6.2 Pneumothorax	3	900	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.82, 1.64]
3.7 IVH Grade 3/4	4	1010	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.24]

Analysis 3.1. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 1: Death

Analysis 3.2. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 2: BPD: oxygen requirement at 28 days

Analysis 3.3. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 3: Moderate/ Severe BPD: Oxygen requirement at 36 weeks PCA

Analysis 3.4. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 4: Death or BPD

Analysis 3.5. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 5: Duration of mechanical ventilation

Analysis 3.6. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 6: Air leaks

Analysis 3.7. Comparison 3: SIMV or SIMV + PS vs HFOV, Outcome 7: IVH Grade 3/4

Comparison 4. ACV vs SIMV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Duration of weaning (hours)	3	120	Mean Difference (IV, Fixed, 95% CI)	-42.38 [-94.35, 9.60]
4.2 Weaning failure	3	120	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.31, 1.93]
4.3 Extubation failure	3	120	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.37, 2.67]
4.4 Air leaks	3	120	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.23, 2.83]
4.4.1 Total air leaks	3	120	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.23, 2.83]

Analysis 4.1. Comparison 4: ACV vs SIMV, Outcome 1: Duration of weaning (hours)

Analysis 4.2. Comparison 4: ACV vs SIMV, Outcome 2: Weaning failure

Analysis 4.3. Comparison 4: ACV vs SIMV, Outcome 3: Extubation failure

Analysis 4.4. Comparison 4: ACV vs SIMV, Outcome 4: Air leaks

Comparison 5. PS + SIMV versus SIMV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Death during first 28 days	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.08, 2.01]
5.1.2 Death prior to discharge	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.31, 2.43]
5.2 Air leaks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 Pneumothorax	1	107	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2.2 Pulmonary interstitial emphysema	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.25, 2.15]
5.3 BPD	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.3.1 BPD (oxygen dependency at 28 days)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.23]
5.3.2 Moderate/Severe BPD (oxygen dependency at 36 weeks PMA)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.18]
5.4 Severe IVH (grade III and IV)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.41, 2.08]

Analysis 5.1. Comparison 5: PS + SIMV versus SIMV, Outcome 1: Death

Analysis 5.2. Comparison 5: PS + SIMV versus SIMV, Outcome 2: Air leaks

Analysis 5.3. Comparison 5: PS + SIMV versus SIMV, Outcome 3: BPD

Analysis 5.4. Comparison 5: PS + SIMV versus SIMV, Outcome 4: Severe IVH (grade III and IV)

Comparison 6. PRVCV vs SIMV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Death prior to discharge	1	211	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.50, 2.11]
6.2 BPD: oxygen requirement at 36 weeks in survivors	1	185	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.55, 1.27]
6.3 Air leak	1	424	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.51, 2.13]
6.3.1 PIE	1	212	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.56, 4.91]
6.3.2 Pneumothorax	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.26, 1.88]
6.4 Severe IVH	1	203	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.58]

Analysis 6.1. Comparison 6: PRVCV vs SIMV, Outcome 1: Death prior to discharge

Analysis 6.2. Comparison 6: PRVCV vs SIMV, Outcome 2: BPD: oxygen requirement at 36 weeks in survivors

Analysis 6.3. Comparison 6: PRVCV vs SIMV, Outcome 3: Air leak

Analysis 6.4. Comparison 6: PRVCV vs SIMV, Outcome 4: Severe IVH

Comparison 7. PSV vs SIMV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Duration of weaning	1	60	Mean Difference (IV, Fixed, 95% CI)	-11.30 [-26.53, 3.93]
7.2 Extubation failure	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.57, 2.07]
7.3 Air leaks (total)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.00]
7.4 Moderate/Severe BPD: oxygen requirement at 36 weeks PCA	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.46, 2.17]

Analysis 7.1. Comparison 7: PSV vs SIMV, Outcome 1: Duration of weaning

Analysis 7.2. Comparison 7: PSV vs SIMV, Outcome 2: Extubation failure

Analysis 7.3. Comparison 7: PSV vs SIMV, Outcome 3: Air leaks (total)

Analysis 7.4. Comparison 7: PSV vs SIMV, Outcome 4: Moderate/Severe BPD: oxygen requirement at 36 weeks PCA

Comparison 8. ACV versus PSV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Duration of weaning	1		Other data	No numeric data

Analysis 8.1. Comparison 8: ACV versus PSV, Outcome 1: Duration of weaning

Duration of weaning				
Study	Participants	Duration of weaning ACV (Median (range))	Duration of weaning PSV (Median(range))	Significance
Patel 2012	36	34 (7-100)	27 (10-169)	p=0.88

APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

EMBASE: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

The Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Date	Event	Description
7 July 2020	Amended	We have corrected the Declaration of interest section.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1998

Date	Event	Description
22 August 2016	Amended	Author order corrected
22 September 2015	New citation required and conclusions have changed	Conclusions updated.
24 July 2015	New search has been performed	Seven additional studies incorporated, with new comparisons.
21 May 2012	New search has been performed	This review updates the existing review of "Synchronized mechanical ventilation for respiratory support in newborn infants" published in The Cochrane Library, Issue 4, 2008 (Greenough 2008).
21 May 2012	New citation required but conclusions have not changed	One additional study was identified as eligible for inclusion and additional studies were designated as "excluded studies".
31 August 2007	New citation required and conclusions have changed	Substantive amendment
31 August 2007	New search has been performed	This review updates the existing review of "Synchronized mechanical ventilation for respiratory support in newborn infants" published in The Cochrane Library, Issue 3, 2004 (Greenough 2004). Two additional studies were identified as eligible for inclusion and additional studies were designated as "excluded studies". Two further triggered modes are included: pressure support and pressure regulated volume control ventilation have been included.

CONTRIBUTIONS OF AUTHORS

Professor Anne Greenough and Professor Anthony Milner have co-authored all issues of this review.

Dr. Murthy coauthored this 2012 review update.

DECLARATIONS OF INTEREST

AG received no grants or speaker fees for the three years prior to the publication of this review.

TER has no interest to declare

AS has no interest to declare

VM has no interest to declare

ADM has no interest to declare

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INDEX TERMS**Medical Subject Headings (MeSH)**

High-Frequency Ventilation [methods]; Inhalation [physiology]; Positive-Pressure Respiration [methods]; Randomized Controlled Trials as Topic; Respiration, Artificial [*methods]

MeSH check words

Humans; Infant, Newborn