

# Weaning strategies for the withdrawal of non-invasive respiratory support applying continuous positive airway pressure in preterm infants: a systematic review and meta-analysis

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## ABSTRACT

**Background** The optimal method to wean preterm infants from non-invasive respiratory support (NIVRS) with nasal continuous positive airway pressure (CPAP) or high-flow nasal cannula is still unclear, and methods used vary considerably between neonatal units.

**Objective** Perform a systematic review and meta-analysis to determine the most effective strategy for weaning preterm infants born before 37 weeks' gestation from NIVRS.

**Method** EMBASE, MEDLINE, CINAHL, Google and Cochrane Central Register of Controlled Trials were searched for randomised controlled trials comparing different weaning strategies of NIVRS in infants born before 37 weeks' gestation.

**Results** Fifteen trials (1.547 infants) were included. With gradual pressure wean, the relative risk of successful weaning at the first attempt was 1.30 (95% CI 0.93 to 1.83), as compared with sudden discontinuation. Infants were weaned at a later postmenstrual age (PMA) (median difference (MD) 0.93 weeks (95% CI 0.19 to 1.67)). A stepdown strategy to nasal cannula resulted in an almost 3-week reduction in the PMA at successful weaning (MD -2.70 (95% CI -3.87 to -1.52)) but was associated with a significantly longer duration of oxygen supplementation (MD 7.80 days (95% CI 5.31 to 10.28)). A strategy using interval training had no clinical benefits. None of the strategies had any effect on the risk of chronic lung disease or the duration of hospital stay.

**Conclusion** A strategy of gradual weaning of airway pressure might increase the chances of successful weaning. Stepdown strategy from CPAP to nasal cannula is a useful alternative resulting in an earlier weaning, but the focus should remain on continued weaning in order to avoid prolonged oxygen supplementation. Interval training should probably not be used.

## INTRODUCTION

Non-invasive respiratory support (NIVRS) is widely used for the management of respiratory disorders in preterm infants. Common indications are neonatal respiratory distress syndrome (RDS), apnoea of prematurity,

## What is known about the subject?

- Non-invasive respiratory support (NIVRS) is a common treatment in preterm infants with respiratory distress syndrome, either as primary support to avoid intubation, or as post-extubation support to facilitate further recovery.
- Different methods have been used to wean the preterm infants from NIVRS with varying success.
- The evidence regarding the optimal strategy for weaning is unclear.

## What this study adds?

- Gradual weaning of nasal continuous positive airway pressure possibly increases the chance of success of the first weaning attempt, but prolongs the weaning process.
- A stepdown strategy to nasal cannula accelerates the weaning process, but is associated with a longer duration of oxygen administration.
- Interval training shows no benefits and should probably not be applied in preterm infants.

post-extubation support and bronchopulmonary dysplasia. Spontaneous breathing can be supported non-invasively either by applying a continuous positive airway pressure (CPAP), or by providing positive pressure inflation breaths with an end-expiratory pressure (non-invasive intermittent positive pressure ventilation or NIPPV). In preterm infants, CPAP is typically applied using a device that controls proximal airway pressure, although nowadays also heated and humidified high-flow nasal cannula (HFNC) with flows between 2L/min and 8L/min is considered as CPAP.<sup>1,2</sup>

Weaning of premature infants from NIVRS to unsupported breathing is usually started as soon as stable conditions are reached.

Weaning too quickly could result in an increased work of breathing (WOB) and a deterioration of respiratory function, which in turn could lead to a prolonged need for respiratory support and a prolonged hospital stay.<sup>3</sup> Weaning too slowly, on the other hand, is associated with unnecessary exposure to respiratory support, and could therefore increase the risk of developing chronic lung disease (CLD) and/or retinopathy of prematurity (ROP). Some studies have suggested that a longer support with CPAP leads to improved structural lung growth resulting in better lung volumes.<sup>4</sup> The optimal method to wean premature infants from CPAP and HFNC is still unclear, and methods used vary considerably between neonatal units. Recent reviews<sup>1 2 4 5</sup> concluded that there is not enough evidence to suggest an optimal strategy for weaning from CPAP or HFNC.

We conducted an updated systematic review and meta-analysis of randomised controlled trials (RCTs) to determine the risks and benefits of different strategies used for the withdrawal of CPAP and HFNC in preterm infants who are stable and may be ready for weaning.

## METHODS

This systematic review and meta-analysis was conducted following a protocol that was registered in PROSPERO (CRD42019125327). MEDLINE, EMBASE, the Cochrane Central Register of controlled trials, CINAHL and Google were searched from inception to December 2019. The search terms included index terms (Mesh or Emtree) as well as free text words for “premature infant”, “continuous positive airway pressure” or “high-flow nasal cannula” and “weaning”.

Ongoing or unpublished trials were searched through trial registers and if needed by contacting the author of the study. The reference lists of retrieved articles were manually screened and studies were selected based on their title, abstract and method. Only studies in English, French, German, Spanish or Dutch were included. Eligibility criteria, study selection, risk of bias and quality of evidence assessments and statistical analysis are described in an online supplemental appendix 1.

The following CPAP systems were accepted for inclusion: (1) any mechanical device that is able to deliver a controlled continuous proximal airway pressure, such as a mechanical ventilator or an infant flow driver; (2) a bubble-CPAP system with underwater column to control proximal airway pressure; or (3) nasal cannula providing heated and humidified flow of gas at rate of at least 2L/min, which has been shown to provide a positive pressure at the airway opening of 2–5 cmH<sub>2</sub>O.<sup>6</sup> Trials had to either compare a specific weaning strategy with no weaning strategy or compare two different weaning strategies. Trials in which intermittent positive pressures were applied, such as (synchronised) NIPPV or bi-level CPAP, were excluded.

The prespecified primary outcome, time to successful weaning, was slightly adjusted after data extraction from a

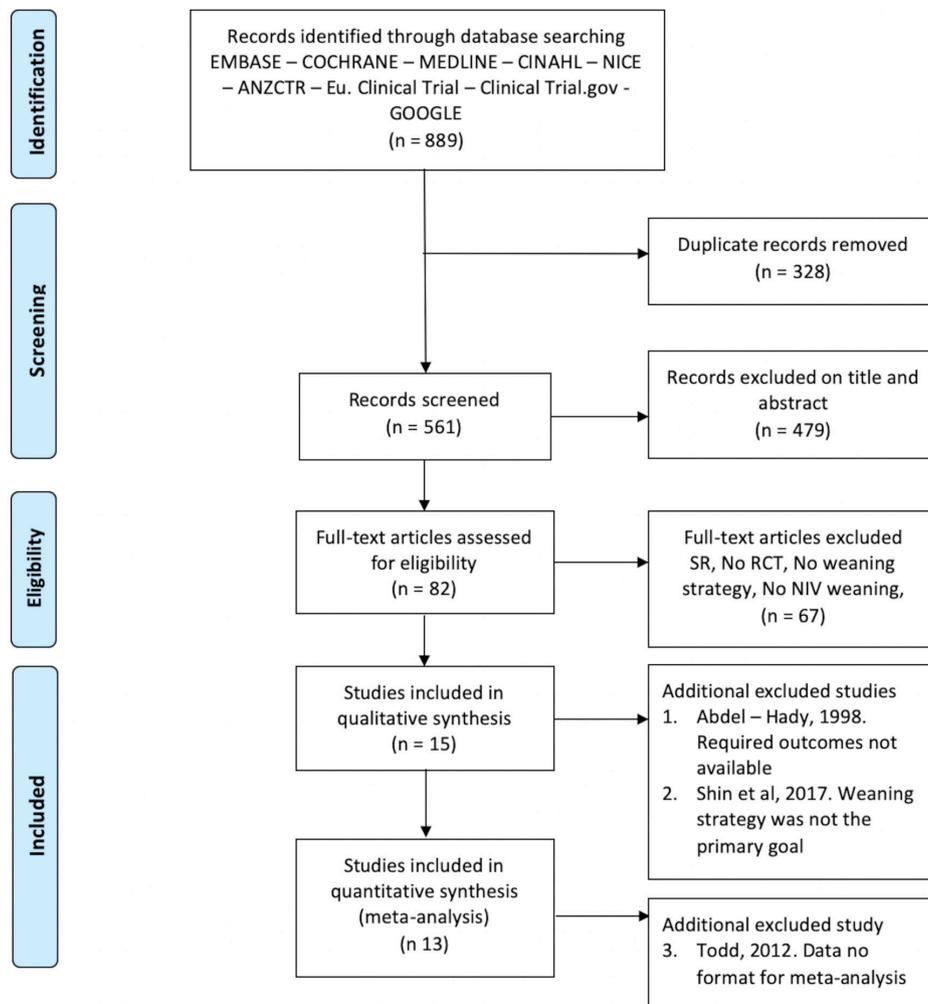
continuous to a dichotomous outcome, namely ‘successful weaning at the first attempt’ (ie, being successfully off NIVRS for at least 72 hours). Other main outcomes were the weaning strategy failure rate (ie, the need to restart the respiratory support after discontinuation or any failure to adhere to the predefined weaning strategy during the course of the study), and respiratory failure during the weaning process (ie, the need for endotracheal intubation and mechanical ventilation). Secondary outcomes were postmenstrual age (PMA) at successful wean (added post hoc), total duration of NIVRS, total duration of supplementary oxygen administration, total duration of hospitalisation, use of caffeine or other respiratory stimulants during weaning time, presence of air leak, presence of CLD, presence of nasal or facial injury and mortality during neonatal hospitalisation.

For the interventions, we considered any strategy that involved the stopping or gradual withdrawal of CPAP and/or HFNC. Possible weaning strategies were: (1) gradual weaning of proximal airway pressure for CPAP or flow rate for HFNC; (2) stepdown weaning, that is, switching from CPAP to either high-flow or low-flow nasal cannula (LFNC), or from HFNC to LFNC, based on prespecified criteria; (3) interval-based weaning that is, removing nasal CPAP or HFNC for short periods over 24 hours and gradually increasing the time off positive airway pressure based on prespecified criteria until the respiratory support is completely stopped. The complete and sudden discontinuation of support, independently of the level of pressure or flow was considered as control group. In order to assess the effects of each specific type of weaning strategy separately (stepdown vs gradual weaning vs interval training), trials were grouped by type of weaning strategy for analyses.

## RESULTS

The search retrieved a total of 889 citations (figure 1). Following removal of duplicates and ineligible citations, we included 15 studies for the qualitative analysis of which 13 were eligible for the quantitative analysis. One trial<sup>7</sup> could not be included in the quantitative analysis because data could not be extracted in the required format.

A summary of the included trials is presented in online supplemental appendix 2. The trials investigated various weaning strategies of CPAP: (1) gradual weaning of CPAP pressure,<sup>8 9</sup> (2) stepdown from CPAP to a lower level of respiratory support, being either HFNC, LFNC or a combination of both,<sup>10–13 14</sup> (3) interval training where CPAP was cycled off with periods of either no support or a lower level of support, gradually increasing the time off until discontinuation of CPAP<sup>7 10 15–19</sup> and (4) a combination of the described methods. In most studies these strategies were compared with sudden discontinuation of CPAP, although some variation existed in how the control intervention was applied. Only one study made a direct comparison of two specific strategies: stepdown strategy versus gradual



**Figure 1** PRISMA flow diagram. Qualitative refers to qualitative assessment of the study methodology and quantitative is the number of studies included in the meta analysis. NIV, non-invasive ventilation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SR, systematic review.

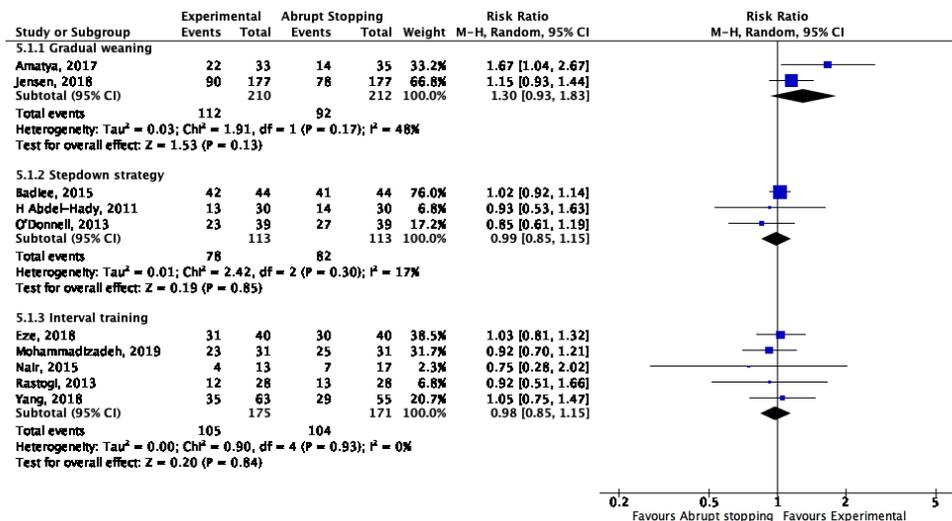
pressure weaning.<sup>14</sup> Three studies<sup>7 10 18</sup> investigating interval training as weaning strategy, had two interventional arms, whereby the respiratory support during periods off CPAP varied from no support at all to LFNC with either 0.2 or 1.5L/min,<sup>18</sup> or HFNC with 6L/min.<sup>14</sup> In two trials with multiple interval training arms,<sup>10 18</sup> we excluded the intervention group where during the pauses of CPAP nasal cannula with a higher flow was applied<sup>10b 18b</sup> from the meta-analysis, because they were considered to be less consistent with the review question. All other comparisons were included in the meta-analyses. Readiness to wean was usually defined as a combination of a critical CPAP pressure, a low fractional inspired oxygen (FiO<sub>2</sub>) and signs of clinical stability. Criteria for weaning failure were reported in all studies and showed good consistency across studies. Results of the risk of bias assessment of included studies are given in online supplemental appendix 1.

### Successful weaning at the first attempt and respiratory failure during the weaning period

Successful weaning was reported in 10 studies<sup>8 9 11–13 15–19</sup> (figure 2). There was a non-significant trend towards

an increased chance of successful weaning at the first attempt when CPAP pressure was gradually reduced as compared with abruptly stopped (2 trials, 422 infants, risk ratio (RR) 1.30 (95% CI 0.93 to 1.83)). No differences were found in the chance of successful weaning when a stepdown strategy (3 trials, 226 infants, RR 0.99 (95% CI 0.85 to 1.15)) or interval training (5 trials, 346 infants, RR 0.98 (95% CI 0.85 to 1.15)) was used compared with sudden weaning. There was no significant heterogeneity across trials in the meta-analysis.

The PMA in weeks at which the infant was successfully weaned was significantly higher with gradual CPAP weaning as compared with abrupt stopping of CPAP (2 trials, 422 infants, mean difference (MD) 0.93 weeks (95% CI 0.19 to 1.67)). On the contrary, applying a step-down strategy resulted in an almost 3-week reduction in PMA at successful weaning from CPAP as compared with abrupt stopping (2 trials, 118 infants, MD -2.70 weeks (95% CI -3.87 to -1.52)) (figure 3). Of note, both trials did not find a significant difference in the PMA when infants came off any respiratory support (CPAP, HFNC



**Figure 2** Successful weaning at the first weaning trial (gradual weaning, stepdown strategy and interval training vs abrupt stopping).

or oxygen). For interval training, marked heterogeneity existed across studies for this outcome ( $I^2=87\%$ ), with studies showing earlier weaning<sup>17 18</sup> as well as delayed weaning.<sup>10</sup>

Respiratory failure during the weaning period was only reported in three trials.<sup>10 13 14</sup> Badiee *et al*<sup>13</sup> reported more respiratory failure when CPAP was abruptly stopped compared with a stepdown approach (4/44 vs 0/44,  $p=0.05$ ). In the study by Soonsawad *et al*,<sup>14</sup> comparing a stepdown strategy to HFNC and further weaning of flow to a strategy of weaning of CPAP pressure, only 1 infant (from the stepdown strategy group) out of the 101 included infants had respiratory failure.

### Weaning failure during the course of the study

There is no significant difference in weaning failure rate when a stepdown strategy is compared with abrupt stopping of CPAP (4 trials, 327 infants, RR 1.25 (95% CI 0.79 to 1.97)) (online supplemental appendix 3).<sup>11-14</sup>

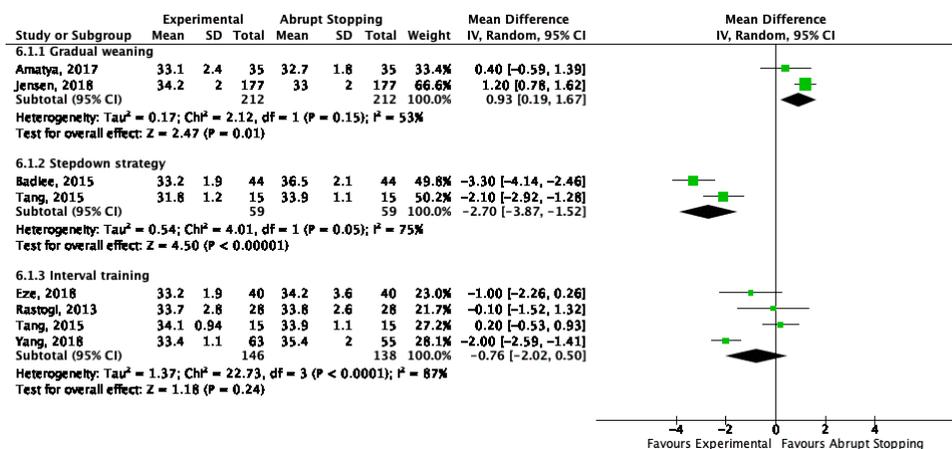
### Total duration of NIVRS

There was a modest, but statistically significant increase in the duration of CPAP treatment when CPAP was gradually decreased as compared with abruptly stopped (2 trials, 422 infants, MD 1.52 days (95% CI 0.73 to 2.30)) (online supplemental appendix 4).

The two studies (90 infants) comparing a stepdown strategy to HFNC (flow of 2L/min or 6L/min) with abrupt stopping of CPAP both showed a significant reduction in CPAP duration but the effect size differed markedly: -3.60 days (95% CI -6.98 to -0.22) for the study by Abdel-Hady *et al*<sup>11</sup> versus -17.7 days (95% CI -21.00 to -14.40) for the study by Tang *et al*.<sup>10</sup> Interval training resulted in a significant increase in duration of NIVRS compared with the abrupt stopping of CPAP (4 trials, 240 infants 1.66 days (95% CI -0.86 to 2.46)).

### Total duration of oxygen supplementation

As compared with abrupt stopping CPAP, both gradual weaning (2 trials, 422 infants, MD 1.45 days (95% CI



**Figure 3** Postmenstrual age in weeks at the first successful weaning trial (gradual weaning, stepdown strategy and interval training vs abrupt stopping).

0.38 to 2.53)) as well as a stepdown strategy (2 trials, 148 infants, MD 7.80 days (95% CI 5.31 to 10.28)) resulted in a significant increase in the total duration of oxygen supplementation (online supplemental appendix 5). For interval training, no significant effect of interval training on the duration of oxygen supplementation was found (3 trials, 236 infants, MD -0.03 days (95% CI -0.16 to 0.10)).

### Weaning of CPAP and use of caffeine

Five<sup>8-11 15</sup> trials reported on the use of caffeine and four<sup>11 13 18 19</sup> on the use of xanthine for the treatment of apnoeas of prematurity as baseline therapy. There was no significant relationship between the need of caffeine or xanthine and a specific weaning strategy of CPAP in any of the trials.

### Length of hospital stay

Length of hospital stay (online supplemental appendix 6) was reported in 10<sup>8-11 13-15 17-19</sup> studies. A strategy of gradual pressure weaning had no significant effect on the duration of hospitalisation (2 trials, 422 infants, MD 0.26 days (95% CI -8.44 to 8.96)). Using a stepdown strategy resulted in a significantly earlier discharge as compared with abrupt stopping (3 trials, 178 infants, MD -3.51 days (95% CI -4.04 to -2.98)). For interval training, the meta-analysis showed a not significant increase in the length of hospital stay (5 trials, 346 infants, MD 1.26 days (95% CI -1.88 to 4.40)).

### Adverse events

For adverse events, only four studies<sup>10 11 14 19</sup> reported air leaks and/or facial/nasal injuries. Soonsawad *et al* showed less nasal trauma in the HFNC compared with the CPAP group (20% vs 42%). In Tangs' study, there was no significant difference in nasal injury between the weaning groups. Presence of air leak was only described by Abdel-Hady *et al* and Mohammadzadeh *et al*. In both RCTs there was no difference between the abrupt

stopping group compared with the stepdown strategy and interval training.

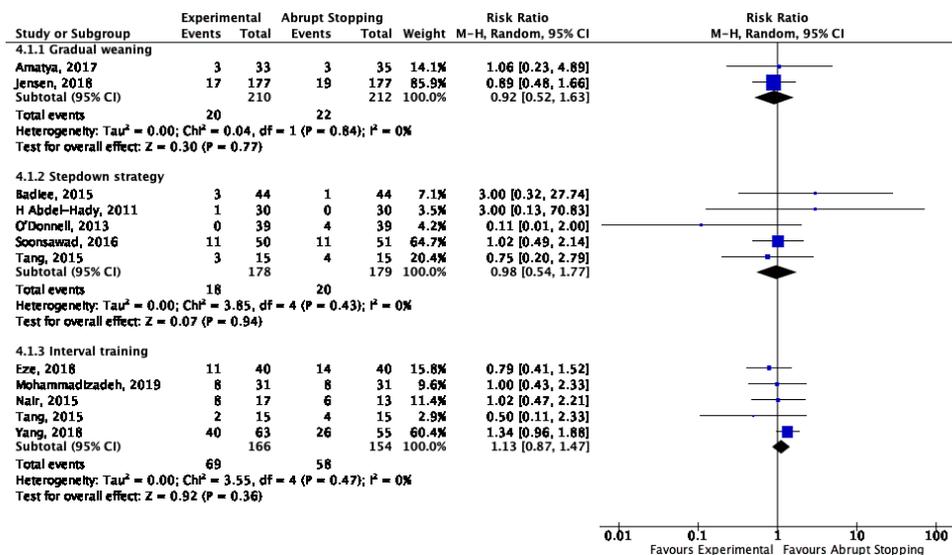
### Chronic lung disease

The effect of using a certain CPAP weaning strategy on the risk of CLD, defined as the need of respiratory support or oxygen need at 36 weeks' PMA, was reported in 12 studies. For none of the weaning strategies a significant effect was seen on the risk of CLD (figure 4). This finding was consistent across all trials.

### DISCUSSION

This systematic review and meta-analysis identified 13 RCTs where different weaning strategies were studied for successful weaning of nasal CPAP in preterm infants. Except for one study,<sup>14</sup> weaning strategies were always compared with the sudden discontinuation of CPAP. Three categories of weaning strategies could be distinguished: (1) gradual weaning of CPAP pressure, (2) stepping down from CPAP to a lower level of respiratory support and (3) interval training with a prespecified schedule of cycling off CPAP. Both the short-term success or failure of the different strategies (primary outcomes) as well as the more clinically relevant longer-term effects on CLD or ROP (secondary outcomes) were assessed.

With gradual pressure wean, which was addressed by the largest included trial,<sup>9</sup> infants were possibly more successful in their first attempt to be weaned off CPAP as compared with sudden discontinuation, but they remained on CPAP for 1 week longer in terms of their PMA. This prolonged CPAP treatment did not affect the duration of hospitalisation. A recent study suggested that extended CPAP application on itself may have a stimulatory effect on lung growth, resulting in larger functional residual capacity (FRC). This positive effect of CPAP on FRC development may in fact explain the higher



**Figure 4** Chronic lung disease at 36 weeks' gestation (gradual weaning, stepdown strategy and interval training vs abrupt stopping).



success rate of a first weaning trial. The higher PMA at the weaning attempt could of course by itself be responsible for the higher success rate. The main challenge with this strategy is knowing the optimal CPAP pressure for each individual infant at each individual time point of the disease. An adequate positive airway pressure is essential to maintain an optimal FRC, which is reflected by adequate oxygenation, minimal WOB and haemodynamic stability.<sup>20–23</sup> Unfortunately, there is only limited evidence to suggest a single approach to initiate or adjust the CPAP level in preterm infants recovering from RDS.

Stepping down from CPAP to a lower level of support, either HFNC or LFNC, clearly reduced the time on CPAP as compared with sudden discontinuation. Infants were on average 2.7 weeks younger in PMA when they were successfully weaned off CPAP, and success rates of the first attempt were similar. However, infants remained significantly longer on oxygen supplementation (on average 1 week). Possible explanations are the lack of beneficial effects of CPAP on lung development in the group where CPAP was stopped earlier, or the lack of focus on continued strict weaning once infants were on nasal cannula because it causes less discomfort to the infant. Although this was not associated with a prolonged hospital stay or an increased risk of CLD, it is uncertain whether or not it could increase the risk of developing ROP. In the study by Yang *et al*,<sup>18</sup> infants in the group of 100% oxygen LFNC (0.2L/min) had a significantly increased risk of ROP as compared with the other two groups (52% vs 38% in the CPAP group and 44% in the nasal cannula group with air flow,  $p < 0.05$ ). This finding was not confirmed in the other four studies<sup>10 14 16 17</sup> that reported on the incidence of ROP.

In most of the studies investigating the stepdown strategy, infants were switched from CPAP to HFNC although flows varied between 2L/min and 6L/min. Nasal CPAP provides a consistent positive pressure at the proximal airway which is monitored continuously in order to keep the alveoli open and maintain an optimal FRC.<sup>24–27</sup> Studies have demonstrated that flows as low as 2L/min can generate a positive pressure up to 6 cmH<sub>2</sub>O, but also that this pressure is highly variable.<sup>6 18 28–30</sup> Inconsistent pressure generation during HFNC could lead to micro-atelectasis, contributing to a prolonged need of respiratory support and oxygen need. HFNC has become commonly used alternative for nasal CPAP in neonatal units, mostly because of the comfort it offers to the infant and parents (less nasal trauma, ease of care, facilitating infant–parent bonding and kangaroo care).<sup>31–33</sup> However, studies on how to wean HFNC are completely lacking.<sup>30</sup>

Interval training, although most frequently studied, does not seem to offer any benefit as compared with sudden discontinuation of CPAP. It was not associated with a higher success rate of the first weaning attempt, and infants were weaned off CPAP at a similar PMA, although for the latter outcome significant between-study heterogeneity existed. It is likely that the interval training schedule itself has a major impact on its success.

In some trials, respiratory support during times off CPAP was completely removed or restricted to an LFNC. This could have resulted in intermittent de-recruitment of lung volume, and, hence, to increased WOB.<sup>34 35</sup> Intermittent withdrawal of positive airway pressure during interval training may be detrimental for the development of immature lungs.

An important factor in the weaning process and in the success of a specific strategy is undoubtedly the way infants are being assessed to be ready or not for (further) weaning. In all studies, clear readiness-to-wean criteria were defined in the protocol. Besides a minimally required level of CPAP pressure and FiO<sub>2</sub>, those criteria also consisted of clinical signs of respiratory stability, such as ‘WOB’ or ‘chest retractions’. The clinical assessment of an infant’s respiratory condition requires committed and trained nursing staff. It is known that the clinical expertise of the nursing staff is an important factor determining CPAP success.<sup>27 36</sup> Probably, it is of equal importance during the weaning phase of CPAP. Also, readiness-to-wean should be assessed in a very consistent way. Therefore, it is important that each unit develops its own specific weaning protocol and invests in adequate training of nursing staff.

The strengths of this systematic review are the comprehensiveness of the literature search and the fact that a prespecified, strict methodology, published in PROSPERO, was followed. In addition, the majority of the included trials in this review were published in the past 5 years representing well current clinical practice about CPAP weaning.

This review has also some limitations. Some predefined outcomes required minor adjustments after data extraction. For some studies, imputation was required in order to have the data in the correct format. Especially in meta-analyses with only few studies, this could have an impact on the meta-analysis result. We were unable to include two RCTs<sup>37 38</sup> which were published only in abstract form, even after having contacted the authors. For some of the trials, the data could not be obtained in the correct format for meta-analysis, even after contacting the authors, making it impossible to include those studies in the meta-analyses. Due to the fact that the interventions were technically very difficult or even impossible to blind for caregivers, all included trials are at risk of performance bias. Finally, not all factors that possibly modify the effects of a weaning strategy (eg, severity of RDS, use of antenatal steroids, use of device and interfaces) could be taken into account in this review.

## CONCLUSION

This systematic review and meta-analysis showed that a weaning strategy of progressive reduction of CPAP pressure possibly increases the chances of success at first weaning attempt, but that the weaning process takes more time and discontinuation comes at a later PMA. Stepping down from CPAP to an HFNC shortens the

duration of CPAP treatment but is associated with a longer duration of oxygen administration. Whether one strategy is superior to another should be further investigated in a head-to-head comparative study. Studies on how to wean HFNC further are currently lacking. No major benefits were found for a weaning strategy based on interval training. None of the weaning strategies had any effect on the development of CLD.

Neonatal units should make their own specific weaning protocol with prespecified readiness-to-wean criteria and provide adequate training for nursing staff, so that CPAP weaning is consistent and transparent within a certain unit.

Future studies are needed on CPAP pressure during the weaning process to maintain optimal lung volume at all times, on the objective assessment of readiness to be weaned and on possible strategies to safely wean HFNC.

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## Supplementary appendix 1: Methodology

### Eligibility criteria

We included all RCT's and quasi-RCT's in which either individual newborn infants or clusters of newborn infants were randomized to CPAP and/or HFNC withdrawal strategies. Infants had to be born before 37 weeks' gestation, receiving noninvasive respiratory support with CPAP or HFNC and be ready for a weaning attempt. Noninvasive respiratory support could be applied by different interfaces: via face mask, nasal mask, nasal prongs, or a single nasopharyngeal tube.

### Search methods

We searched MEDLINE, EMBASE, the Cochrane Central Register of controlled trials and CINAHL from inception to December 2019. Ongoing or unpublished trials were searched through trial registers (clinicaltrials.gov, EU clinical trial register, Australia and New Zealand's clinical register) and if needed by contacting the author of the study. References lists were also searched.

We used the following strategy: MeSH search terms "infant, premature", "infant", "very low birth weight" OR the text word "VLBW", "infant\*", "preterm\*", "premature\*", "low birth weight", "neonat\*", "newborn\*" AND MeSH search terms "continuous positive airway pressure", "oxygen inhalation therapy", "noninvasive ventilation" OR the text words "CPAP", "high-flow", "nasal cannula", "NC", "high-flow nasal cannula", "HFNC", "heated humidified high-flow nasal cannula", "HHHFNC", "positive pressure", "distending pressure", "positive expiratory pressure", "positive end expiratory pressure", "PEEP" AND MeSH search term "ventilator weaning" OR the text words "wean\*", "decreas\*", "ceasing", "cessation", "stop\*", "stopping", "discontinue", "withdraw\*"

### Study selection, Risk of bias and quality of the evidence

On search completion and following duplicate removal, two investigators (BVD/FVGD) independently performed the first screening of the retrieved studies based on title and abstract, and subsequently also the following screening based on full-text. Data were extracted by one author (BVD) and checked for accuracy by a second author (CVD). Extracted data included characteristics regarding the study (setting, publication year, etc.), the population, the intervention and the outcomes. A third author (FC) acted as adjudicator when an agreement could not be reached.

Two investigators (BVD/JL) assessed independently the risk of bias in individual studies using the Cochrane tool for bias assessment in RCT's [1]. We assessed studies using the following criteria: random sequence generation, allocation concealment, blinding of intervention, completeness of follow-up and blinding of outcome measurement assigning a rating of "Yes" (no risk), "No" (high risk) or "Unknow" for each category.

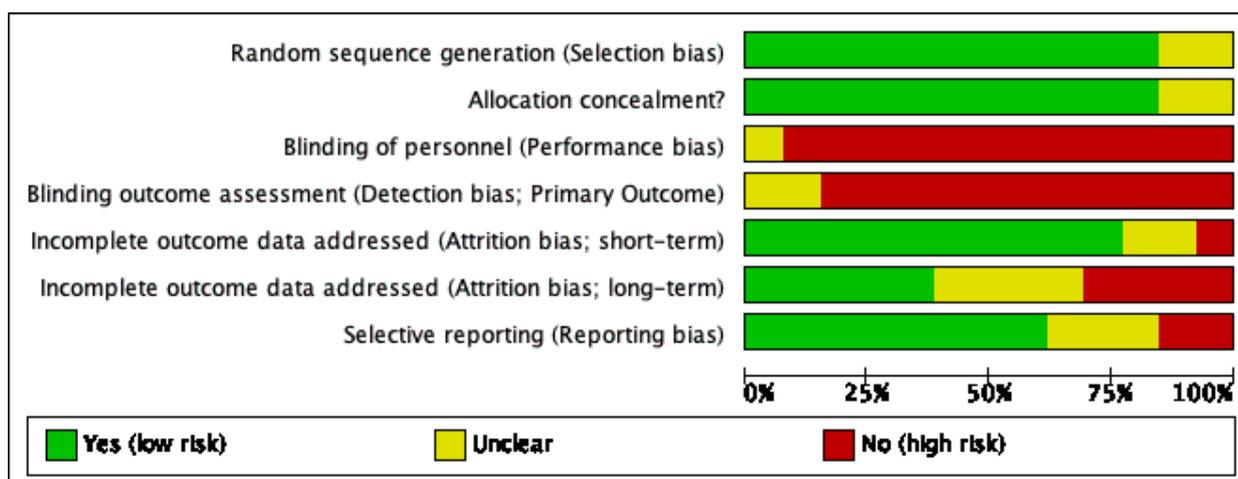
Under the assumption that true heterogeneity between studies would be present, the random-effects model was used for all meta-analyses.

### Statistical analysis

The statistical analyses were performed using RevMan 5.3 (Cochrane Collaboration). Under the assumption that true heterogeneity between studies would be present, the random-effects model was used for all meta-analyses. Treatment effects for categorical data were expressed as a risk ratio (RR) and for continuous outcomes as a mean differences (MD) using the Mantel-Haenzel and inverse variance method. For studies [9–11,16,17] only reporting medians and interquartile (IQR), we estimated the mean and standard deviation (SD) using the methods proposed by Hozo et al [2]. Studies with multiple intervention arms for the same weaning strategy were handled as follows: either only one intervention arm of that study was included in the meta-analysis (i.e. when the other intervention arm was considered to be less consistent with the review question), or both arms were included in the same meta-analysis, thereby splitting the control group in equal parts (i.e. in case both intervention arms were considered to be of equal importance to the review question). The 95% confidence interval (CI) was reported on all estimates. We assessed heterogeneity using the chi-squared test for homogeneity and the  $I^2$  statistic. If statistical heterogeneity was found (chi-square values of  $p < 0.10$  or  $I^2$  values  $> 50\%$ ) we explored the possible reason for this heterogeneity.

### Risk of bias and Quality of evidence assessments

Eleven trials [7–10, 15 – 17] have a low risk of bias for group allocation. Random-sequence was generated using a computer-based system, and allocation was concealed using sealed envelopes in the majority of the studies. Yang et al [18] and Mohammadizadeh et al [19] did not clearly describe the methodology of their study. The type of intervention did not allow for blinding, hence, all included trials are at risk of performance bias. The number of participants with missing data was not or insufficiently described in eight trials.





## Supplementary appendix 2: Characteristics of the included studies

Author & Year Country	N	Study population	Weaning readiness criteria	Intervention		Weaning failure criteria	Primary Outcomes
				Experimental group	Control group		
Abdel-Hady et al 2011 <sup>[11]</sup> Ireland	60	Mean GA 31.1 $\pm$ 2.6 and 31.0 $\pm$ 2.4 weeks in both study groups CPAP	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 <u>Clinically stable:</u> 1. Respiratory rate <60/min 2. No significant chest recession 3. No single apnea requiring bagging 4. Not more than 6 episodes of apnea requiring stimulation during the preceding 24h 5. Satisfactory arterial bloodgases (pH>7.25, PCO <sub>2</sub> <60 and base deficit <8)	<u>Stepdown strategy:</u> Switch to HFNC with 2L/min; first reduction of FiO <sub>2</sub> to 0.21, then reduction of flow with 0.5L/min every 6h until discontinuation	Reduction of FiO <sub>2</sub> on CPAP to 0.21, then stop CPAP	1. Decreased SpO <sub>2</sub> <87% despite increasing FiO <sub>2</sub> to max 0.60 2. Increased WOB 3. Increased frequency of apnea and BC (>6 requiring stimulation/24h) 4. Severe apnea or BC that required PPV 5. Worsening bloodgases (PaCO <sub>2</sub> >65mmHG or pH<7.2)	1. Duration of oxygen
Todd et al 2012 <sup>[7]</sup> Australia	154	Mean GA 26.9 $\pm$ 1.6, 27.3 $\pm$ 1.5 and 27.1 $\pm$ 1.4 weeks in the 3 groups CPAP with FiO <sub>2</sub> >0.25 for at least 24h	CPAP of 4-6 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.25 <u>Clinically stable:</u> 1. Respiratory rate < 60/min 2. No significant chest recession 3. <3 episodes of self-reverting apneas (<20") and/ or BC (<100/min) and/or desaturation (<86%) in 1h for previous 6h 4. Average SpO <sub>2</sub> >86% most of the time or PaO <sub>2</sub> / TPao <sub>2</sub> >45mmHg 5. Not currently treated for PDA or sepsis 6. Tolerated time off CPAP during cares (>15min)	<u>Interval training (A):</u> CPAP 6h on and increasing periods of time off (starting with periods of 2h); when 16h off, trial stop CPAP  <u>Interval training (B):</u> Similar as group 1, but with support of LFNC at 0.5L/min during times off. When trial of stop CPAP, continuation of LFNC for 24h	Stop CPAP	1. Increased WOB with RR >75/min 2. Increased apnea and/or BC and/or desaturations >2 in 1 hour for the previous 6h period 3. Increased FiO <sub>2</sub> >0.25 to maintain SpO <sub>2</sub> >86% and/ or PaO <sub>2</sub> / TPao <sub>2</sub> >45mmHg 4. pH <7.2 5. PaCO <sub>2</sub> / TPaco <sub>2</sub> >65mmHg 6. Major apnea or BC requiring resuscitation	1. Time to wean off CPAP 2. CPAP duration
Rastogi et al 2013 <sup>[15]</sup> USA	56	Mean GA 28.12 $\pm$ 1.67 weeks CPAP (primary or post-extubation) for at least 48h	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21 <u>Clinically stable:</u> 1. No evidence of increased WOB 2. Stable for at least for 48h	<u>Interval training:</u> CPAP 3h on and 3h off for 48h; if tolerated, periods of CPAP off increased to 6h for the next 48h; if tolerated, stop CPAP	Stop CPAP		Success rate of the first trial to wean
O'Donnell et al 2013 <sup>[12]</sup> United Kingdom	78	Median GA 28 weeks (range 24-32) CPAP for at least 24h	CPAP of 3-5 cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21	<u>Stepdown strategy:</u> Switch to LFNC (1L/min) with room air	Stop CPAP	1. >1 self-correcting apneic episode/hrs. 2. 1 apneic episode requiring moderate stimulation or bag-and-mask ventilation 3. Need for oxygen to maintain SpO <sub>2</sub> >85% 4. A score of 6-10 on the Silverman-Anderson Respiratory Scale	Weaning failure
Badiee et al 2015 <sup>[13]</sup> Iran	88	Mean GA 31.2 $\pm$ 2.6 weeks CPAP at 5 – 8cmH <sub>2</sub> O	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 <u>Clinically stable:</u> 1. Lack of apnea 2. No signs of respiratory distress	<u>Stepdown strategy</u> Switch to HFNC 2L/min with FiO <sub>2</sub> 0.30; once FiO <sub>2</sub> weaned to 0.21, reduction of flow (0.5L/min every 1h) until flow of 0.5L/min; then stop HFNC	Continuation of CPAP 5 cmH <sub>2</sub> O and weaning of FiO <sub>2</sub> to 0.21; stop CPAP if stable for 6h	1. Increased WOB 2. Significant retraction 3. Increased apnea 4. Abnormal blood gases (2 samples with an interval of >2hrs with pH<7.2, pCO <sub>2</sub> >65mmHg and paO <sub>2</sub> <50mmHg with FiO <sub>2</sub> >60%)	Duration of oxygen requirement

**AcoRN:** Acute Care of at-Risk Newborn – **BC:** bradycardia – **CLD:** Chronic lung disease – **CPAP:** Continuous Positive Airway Pressure – **FiO<sub>2</sub>:** Fractional inspired oxygen concentration – **GA:** Gestational Age – **HFNC:** High flow nasal cannula – **IQR:** Inter quartile range – **kPa:** kiloPascal – **LFNC:** Low flow nasal cannula – **PaO<sub>2</sub>:** Partial arterial oxygen – **PaCO<sub>2</sub>:** Partial arterial carbon dioxide – **PCO<sub>2</sub>:** Partial carbon dioxide – **PDA:** Persistent ductus arteriosus – **PMA:** Post Menstrual Age – **PNA:** postnatal age – **PPV:** Positive pressure ventilation – **SpO<sub>2</sub>:** Pulse oximetry saturation – **TPaO<sub>2</sub>:** Transcutaneous partial arterial oxygen – **TPaCO<sub>2</sub>:** Transcutaneous partial arterial carbon dioxide – **WOB:** Work of breathing

## Supplementary appendix 2: Characteristics of the included studies (continued)

Author & Year Country	N	Study population	Weaning readiness criteria	Intervention Experimental group	Control group	Weaning failure criteria	Primary Outcomes
Tang et al 2015 <sup>[10]</sup> Australia	60	Mean GA 27.5 weeks (range 24.0 – 29.9) CPAP Mean PMA at enrollment 31 weeks (range 27 – 37)	CPAP <5 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.25 <u>Clinically stable:</u> 1. Respiratory rate <60/min 2. No significant chest recession, 3. <3 episodes of apnea, BC, oxygen desaturation in 1h for the previous 12h, 4. SpO <sub>2</sub> >86% most of the time or PaO <sub>2</sub> >45mmHg and 5. Not currently treated for PDA or sepsis	1. <u>Stepdown strategy:</u> Switch to HFNC starting at flow 6L/min  2. <u>Interval training (A):</u> CPAP 6h alternated with ambient air/oxygen or LFNC during off periods; first progressive increase of time on air/LFNC and then decrease of time on CPAP  3. <u>Interval training (B):</u> Similar as A but CPAP 6h alternated with HFNC for 1h;	Stop CPAP to ambient air/oxygen (up to 25%) or to LFNC (<1L/min)	1. Increased WOB with respiratory rate >75 per minute, 2. Increased apnea and/or BC and/or desaturations >2 in 1h for the previous 6h period 3. FiO <sub>2</sub> >0.25 to maintain SpO <sub>2</sub> >86% and/or PaO <sub>2</sub> >45mmHg 4. pH <7.2, 5. PaCO <sub>2</sub> >65mmHg 6. Apnea or BC requiring resuscitation	1. CLD, 2. Days respiratory support (CPAP or HFNC or Oxygen) 3. Days of hospital stay 4. Days to achieve full suck feeds
Nair et al 2015 <sup>[16]</sup> Canada	30	Median GA 27 weeks (IQR 26-28) and 27 weeks (IQR 26-27) in both study groups Post-extubation CPAP for at least 72h	CPAP of 4 cmH <sub>2</sub> O	<u>Interval training:</u> Weaning schedule over 72h of CPAP alternated with LFNC (1L/min) with decreasing time on CPAP and increasing time on LFNC	Continuation of CPAP 4 cmH <sub>2</sub> O for 72h; then switch to LFNC (1L/min)	1. ACoRN respiratory score of 5 or more, or increase in previous score 2. FiO <sub>2</sub> >0.30 3. Acidosis (pH < 7.20) 4. Apnea with BC/desaturation requiring stimulation (>1/h) 5. Apnea requiring bag and mask ventilation	Successful weaning
Soonsawad et al 2016 <sup>[14]</sup> Thailand	101	Median GA 29 weeks (IQR 27-30) PNA at enrollment median 8 days (IQR 4-28) and 7.5 days (IQR 3-20) in both groups	CPAP ≤6 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 <u>Clinically stable:</u> 1. Sat 88 - 93% 2. <3 Apnea or BC in 1h 3. No clinical signs of RDS 4. Being able to take off devices during nursing care 5. no clinical sign of hemodynamic significant PDA	<u>Stepdown strategy:</u> Switch to HFNC at 4 L/min (<1000g) or 5-6 L/min (>1000g) First decrease FiO <sub>2</sub> then decrease flow rate (1 L/min for 24h) until 3 L/min (>1000g) or 2 L/min (<1000g); then stop or switch to LFNC	<u>Gradual weaning</u> First decrease FiO <sub>2</sub> , then decrease CPAP pressure (1cmH <sub>2</sub> O for 24h) until 4 cmH <sub>2</sub> O; then stop or switch to LFNC	1. Increased WOB 2. Apnea or BC or desaturation >3 times within 1h during 6h under observation 3. Apnea requiring positive pressure ventilation 4. FiO <sub>2</sub> >0.6 to keep SpO <sub>2</sub> 88-93% 5. pH <7.25 or pCO <sub>2</sub> >65mmHg	Time to wean
Amataya et al 2017 <sup>[8]</sup> USA	68	Mean GA 28.7 ± 1.8 and 28.5 ± 1.9 weeks in both study groups CPAP (primary or post-extubation) for at least 48h Days to reach FiO <sub>2</sub> 0.21 on CPAP 5.6 ± 12.4 and 5.7 ± 12.6 days in both study groups	CPAP of 5cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21 for at least 48h <u>Clinically stable:</u> 1. Normal WOB, no persistent tachypnea, no marked retractions 2. No apnea associated with BC or cyanosis with >2 episodes in 12h or >3 in 24h with at least one requiring bag and mask ventilation 3. SpO <sub>2</sub> >90% 4. Not currently treated for PDA or sepsis at the time of weaning 5. Tolerated time off CPAP during nursing cluster care up to 15 minutes or more	<u>Gradual weaning:</u> Weaning over 24h, i.e. reduction of CPAP pressure with 1 cmH <sub>2</sub> O every 8h, up to 3 cmH <sub>2</sub> O; then stop CPAP	Stop CPAP	1. Increased WOB: persistent tachypnea (>60 for 2h) and marked retractions 2. Apnea (cessation of respiration >20s) associated with BC or cyanosis with >2 episodes in 12h or >3 in 24h with at least one requiring bag and mask ventilation 3. FiO <sub>2</sub> >0.21 to maintain sat. >90% for over 2h in 24h 4. Abnormal blood gases (2 arterial samples >2h apart) with low pH<7.2, PaO <sub>2</sub> >65mmHg, PaO <sub>2</sub> <50mmHg	Success rate of the first trial of CPAP weaning

**AcORN:** Acute Care of at-Risk Newborn – **BC:** bradycardia – **CLD:** Chronic lung disease – **CPAP:** Continuous Positive Airway Pressure – **FiO<sub>2</sub>:** Fractional inspired oxygen concentration – **GA:** Gestational Age – **HFNC:** High flow nasal cannula – **IQR:** Inter quartile range – **kPa:** kiloPascal – **LFNC:** Low flow nasal cannula – **PaO<sub>2</sub>:** Partial arterial oxygen – **PaCO<sub>2</sub>:** Partial carbon dioxide – **PCO<sub>2</sub>:** Partial carbon dioxide – **PDA:** Persistent ductus arteriosus – **PMA:** Post Menstrual Age – **PNA:** postnatal age – **PPV:** Positive pressure ventilation – **SpO<sub>2</sub>:** Pulse oximetry saturation – **TPaO<sub>2</sub>:** Transcutaneous partial arterial oxygen – **TPaCO<sub>2</sub>:** Transcutaneous partial arterial carbon dioxide – **WOB:** Work of breathing

## Supplementary appendix 2: Characteristics of the included studies (continued)

Author & Year Country	N	Study population	Weaning readiness criteria	Intervention		Weaning failure criteria	Primary Outcomes
				Experimental group	Control group		
Eze et al 2018 <sup>[17]</sup> USA	80	Mean GA 26.5 weeks (range 23.6-30.6) and 27.4 weeks (range 23.9-30.7) in both groups CPAP for at least 24h PNA at enrollment 37 days (range 3-100) and 31 days (range 3-67) in both groups	CPAP of 5-6 cmH <sub>2</sub> O and FiO <sub>2</sub> ≤0.30 for at least 24h And: 1. PMA ≥ 26 0/7 w 2. loaded with caffeine 3. stable respiratory assessment and Hb ≥ 8 g/dL	<u>Interval training</u> CPAP alternated with LFNC (< 2 L/min): 9h CPAP and 3h LFNC for 24h; then 6h CPAP and 6h LFNC for 24h; then 3h CPAP and 9h LFNC for 24h; then room air or LFNC after 24h of re-recruitment with CPAP	If CPAP 6 cmH <sub>2</sub> O: weaned to 5 cmH <sub>2</sub> O for 96h, then stop or switch to LFNC (≤ 2 L/min)  If CPAP 5 cmH <sub>2</sub> O: continued for 96h, then stop or switch to LFNC	1. Increased WOB 2. RR >70/min over 1h 3. FiO <sub>2</sub> >0.30 and/or >2 l/min via NC to keep SaO <sub>2</sub> levels over 86% 4. Apnea or BC requiring resuscitation, ranging from bag and mask ventilation to intubation	Successful wean off CPAP during the first trial (=total 7 days: 4 days weaning, 3 days observation) without failure
Yang et al 2018 <sup>[18]</sup> Taiwan	181	Mean GA 28.8 ± 2.4 weeks Positive pressure respiratory support for at least 24h Mean PMA at enrollment 33.3 ± 2.4 and 34.3 ± 2.4 weeks	CPAP of 5-7 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.25 for 24h And: 1. weight > 1250 g 2. Hb >10 g/dL 3. No use of vasoactive or sedative agents	<u>Interval training (A)</u> CPAP alternated with LFNC oxygen at 0.2 L/min: increasing time off CPAP every 24h (4-8-12h); then stop CPAP  <u>Interval training (B)</u> CPAP alternated with LFNC air flow at 1.5 L/min: increasing time off CPAP every 24h (4-8-12h); then stop CPAP	Continuation of CPAP at 4 – 6 cmH <sub>2</sub> O for 5 days, then stop to room air or LFNC oxygen as needed	1. Increased WOB 2. Increase apnea and/or BC events and/or 2 desaturation periods in 1h for the previous 6h-period 3. Increase FiO <sub>2</sub> >0.25 to maintain SpO <sub>2</sub> >86% 4. pH <7.2 5. PaO <sub>2</sub> / TPaO <sub>2</sub> of >65mmHg 6. Major apnea or BC episode requiring resuscitation	1. Length of weaning duration 2. Body weight and post conceptional age of successful weaning
Jenssen et al 2018 <sup>[9]</sup> Denmark	354	Median GA 30 weeks (IQR 29-31) CPAP for at least 24h Median PMA at enrollment 32 weeks (IQR 31-32)	CPAP <8 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 And: 1. PMA ≥ 29 0/7 weeks 2. Respiratory rate <70/min 3. <3 episodes of BC or desaturations in 24hrs 4. Tolerate CPAP off during nursing procedures (up to 15 min)	<u>Gradual weaning group</u> Reduction of CPAP pressure with 1 cmH <sub>2</sub> O every day, down to 4 cmH <sub>2</sub> O; then stop CPAP	Stop CPAP	1. RR >70 per minute 2. Difficult breathing with retractions 3. Increased oxygen requirement by more than 10% 4. >3 episodes of oxygen sat <70% or heart rate <70 BPM in 24hrs 5. Major apnea or BC requiring resuscitation 6. TCO <sub>2</sub> >2kPa starting point	Weight gain velocity (g/kg/d)
Mohammadzadeh 2019 <sup>[19]</sup> Iran	62	Mean GA 30.5 ± 2.6 and 30.1 ± 1.8 weeks in both study groups CPAP (primary for RDS or post-extubation) for at least 24h Mean PMA at enrollment 31.0 ± 2.4 and 31.1 ± 3.7 weeks	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21 for 24h <u>Clinically stable:</u> 1. RR <60/min 2. Absence of diaphragmatic or sternal retraction 3. <6 episodes of apnea and BC within 24h 4. Absence of apnea requiring PPV 5. SpO <sub>2</sub> most of the time >86% 6. No PDA or sepsis 7. Tolerability of separation from CPAP for nursing care episodes (>15 min.)	<u>Interval training:</u> CPAP (ON) alternated with room air or ambient oxygen (OFF): increasing time off CPAP every 24h (4h - 8h - 12h); then stop CPAP	Stop CPAP	1. SpO <sub>2</sub> <87% and increased oxygen need 0.60 2. Increased WOB 3. >6 episodes of apnea and BC within 24h improving with slight stimulation 4. 1 episode of severe apnea or BC requiring PPV 5. Arterial pH<7.2 or PCO <sub>2</sub> >65mmHg	Successful CPAP weaning at first attempt

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Study or Subgroup	Stepdown strategy		Abrupt stopping		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Badlee, 2015	2	44	3	44	6.8%	0.67 [0.12, 3.80]
H Abdel-Hady, 2011	7	30	6	30	22.1%	1.17 [0.44, 3.06]
O'Donnell, 2013	16	39	12	39	56.8%	1.33 [0.73, 2.44]
Soonsawad, 2016	6	51	4	50	14.2%	1.47 [0.44, 4.90]
Total (95% CI)		164		163	100.0%	1.25 [0.79, 1.97]
Total events	31		25			
Heterogeneity: $\tau^2 = 0.00$ ; $\text{Chi}^2 = 0.64$ , $\text{df} = 3$ ( $P = 0.89$ ); $I^2 = 0\%$						
Test for overall effect: $Z = 0.97$ ( $P = 0.33$ )						

