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Duration of continuous positive airway pressure in premature infants

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SUMMARY

Continuous positive airway pressure (CPAP) has been used for respiratory support in premature infants for more than 40 years and is now a cornerstone of modern neonatal care. Clinical research on CPAP has primarily focused on understanding which devices and pressure sources best implement this therapy. In contrast, less research has examined the optimal duration over which CPAP is administered. We review this aspect of CPAP therapy.

Keywords

Premature infant; Respiratory distress syndrome; Non-invasive ventilation; Continuous positive airway pressure; Oxygen inhalation therapy; Bronchopulmonary dysplasia

1. Introduction

In 1968, Harrison and colleagues reported cessation of grunting and progressive hypoxemia following endotracheal intubation in infants with respiratory distress syndrome (RDS) [1]. This observation led to the use of continuous distending airway pressure to counteract lungs prone to collapse [2]. Nasal continuous positive airway pressure (CPAP) is the most widely used non-invasive continuous distending airway pressure modality and a cornerstone of modern neonatal care. Whereas there has been emphasis on understanding which devices and pressure sources best implement CPAP [3,4], the optimal duration of this therapy is less well studied. At birth, premature infants have life-threatening anatomic and physiologic immaturities of the respiratory system. CPAP attenuates this pathophysiology until sufficient stability develops and continuous distending pressure is no longer needed. But when does this occur? In this review, we summarize the benefits and harms associated with CPAP and describe the clinical considerations that determine CPAP duration. We then describe and synthesize the published evidence on this topic.

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Conflict of interest statement

None declared.

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2. Benefits and harms of CPAP

Gregory proposed that the primary benefit of CPAP is “inflation of the atelectatic lung [2].” CPAP splints the upper airways, decreasing both supraglottic and total pulmonary resistance [5]. The distending pressure increases lung volumes and establishes functional residual capacity while preventing further alveolar collapse and promoting surfactant release [6–8]. Oxygenation is improved through enhanced diffusion, increased ventilation/perfusion matching and decreased shunt [7,9,10]. CPAP may improve respiratory mechanics [11] by improving compliance and stabilizing the compliant chest wall, improving thoracoabdominal synchrony and reducing work of breathing [10]. Upper airway splinting reduces obstructive apnea [12] and may also decrease central apnea by promoting a regular breathing pattern [13].

However, CPAP can also result in harm. Airway distending pressure is a risk factor for air leak syndromes [14,15]. High lung volumes can impair ventilation with resulting hypercarbia [16]. Excessive intrathoracic pressure can decrease venous return and impair cardiac output [17]. Sufficient compromise of pulmonary blood flow may actually worsen ventilation/perfusion mismatch and impair oxygenation [17–19]. Gastric distension [20] – so-called “CPAP belly” – may aggravate feeding intolerance and provoke gastroesophageal reflux, itself a risk factor for ongoing lung injury [21,22]. Prolonged CPAP use may delay initiation of oral feeds, prolong hospitalization, limit infant holding, and constrain developmental therapies [23]. Nasal septum breakdown [24] and perceived infant agitation cause distress in parents and caregivers alike [25,26].

3. Clinical considerations determining CPAP duration

CPAP duration is typically influenced by three clinical considerations:

3.1. Deciding when the infant has met clinical criteria to reduce (“wean”) or discontinue CPAP support

This may be based on the infant’s chronologic or postmenstrual age (PMA), current weight, various clinical markers of respiratory stability or a combination of these factors [27]. The term “stability criteria” describes a set of variably applied clinical characteristics that satisfy this first consideration [28].

3.2. Deciding which is the preferred method to cease CPAP

This includes abrupt discontinuation or gradual reduction. When CPAP is discontinued, approaches include simple removal of CPAP to room air (RA) or transition to a different support strategy, such as nasal cannula.

Widely used methods for gradually decreasing support include [26,28]:

- Gradually reducing CPAP support from a starting pressure to a lower pressure, and then discontinuing support. We refer to this as “pressure weaning.”
- Repeatedly transitioning between periods on and off CPAP support, with a gradual increase in the amount of time off until CPAP support is discontinued. This has

been referred to as “cycling” or “graded-time-off” [29]. We refer to this as “time cycling.”

Gradual methods are based on the notion that they permit respiratory muscle conditioning while attenuating potential harms associated with non-gradual discontinuation [28]. A gradual approach can similarly be followed by discontinuation to RA or transition to an alternative support strategy.

3.3. Deciding which clinical signs indicate that the infant is not tolerating a reduction in or discontinuation of CPAP support

These “failure criteria” are a set of clinical markers of instability, such as worsening apnea or increasing fraction of inspired supplemental oxygen (FiO_2) to maintain arterial oxygen saturation (SpO_2) targets. Meeting such criteria typically results in a return to the previous level of CPAP support.

Together, these three sequential considerations result in a cyclical process that determines total CPAP duration.

4. Duration of respiratory support as an intervention and outcome potential for “wean-time lag” bias

Duration of respiratory support is a widely used outcome measure. Bronchopulmonary dysplasia (BPD) [30] is a prominent example. However, a potential for bias exists in studies that both (i) compare interventions with weaning protocols that mandate unequal durations of respiratory support, and (ii) report duration of respiratory support as an outcome. Consider a hypothetical trial in which infants are randomized either to simple discontinuation of CPAP to RA (Group A) or to gradual time cycling off CPAP support (Group B). Total CPAP duration is measured as an outcome. In this scenario, it is possible that some infants in Group B will be exposed to a longer total duration of CPAP simply due to the differences in the weaning protocol. We term this excess CPAP exposure “wean-time lag” and suggest careful interpretation of outcomes in studies using similar designs. For instance, if the objective is simply to assess whether discontinuation to RA in Group A decreases total CPAP duration compared to the gradual approach of Group B, the outcome is appropriate. In contrast, interpreting a shorter CPAP duration in Group A as evidence of an important clinical benefit might be misleading.

5. Duration of CPAP support: available evidence for best practice

Two surveys describing CPAP duration practice patterns have been published. A 2005 report by Bowe and colleagues [31] describes practice in England, and a 2008 study by Jardine and colleagues [29] reports Australian practice. Both surveys highlight marked practice variability and urge further evidence-based guidance. Key study characteristics and findings are described in Table 1.

Providers at Columbia University Medical Center have pioneered the use of bubble CPAP in neonates. The “Columbia method” describes an expert opinion approach of prolonged CPAP

use [9] in which it is rare to wean CPAP prior to 32 weeks PMA and on average CPAP is continued until 34.5 weeks PMA.

Our review of the literature identified three observational studies [27,32,33] and eight small to medium-sized randomized trials [20,34–40]. Neither of two systematic reviews [28,41] with differing objectives and study inclusions pooled data for meta-analysis due to low data quality and trial heterogeneity. Both emphasized a need for further research.

Tables 2 and 3 summarize the identified randomized trials and observational studies, respectively. For each, we describe population characteristics and compared interventions. We outline stability criteria, weaning methods, and failure criteria. Selected outcomes are displayed, with both point estimates of effect and statistical significance when available. We use these studies to derive clinical practice suggestions.

6. Implications for clinical practice

Despite the limited available evidence to guide clinical practice on this topic, we highlight several recurrent findings:

6.1. The more premature the infant at birth, the later the typical PMA at successful CPAP discontinuation

Compared to more mature infants, those born at lower gestational ages typically require a longer total duration of CPAP support after correction for PMA and are more likely fail CPAP weans when attempted at an equivalent PMA. This finding is noted in the observational data of Rastogi et al. [27], and in prospective data from three trials enrolling a total of 353 infants [35,38,39] (Table 4). Clinicians should expect increasingly premature infants to require CPAP through a later PMA.

6.2. Time cycling as a CPAP weaning method is of unlikely benefit and may cause harm

Each individual trial contributing to this conclusion has limitations. The primary outcome in Todd et al. [38] may be influenced by wean-time lag. Studies by Singh et al. [34] and Soe et al. [35] are only available in abstract form. Chance randomization imbalance without statistical adjustment confounds outcomes in Nair et al. [37]. Nevertheless, studies evaluating time cycling as a weaning approach consistently suggest that it does not result in clinical benefit. The possibility that this approach facilitates respiratory muscle conditioning [28] may be counterbalanced by de-recruitment from repeated cycling off CPAP.

6.3. There is a trade-off between CPAP support and oxygen support

Trials by Abdel-Hady et al. [20,36] supply clinical evidence that prolonged CPAP use improves oxygenation and reduces the need for supplemental oxygen well beyond the immediate postnatal period. This has biologic plausibility and face validity. Infants not requiring supplemental oxygen while on CPAP may require oxygen following CPAP discontinuation [9]. Clinicians wary of oxygen toxicity in recovering lungs may feel inclined to prolong CPAP. This CPAP/oxygen trade-off has significant implications on clinical research when using BPD as an outcome measure. Whereas applied definitions vary, nearly

all include the presence of supplemental oxygen for at least 28 days or at 36 weeks PMA as defining criteria. As CPAP influences the need for supplemental oxygen, practice variability surrounding CPAP duration may strongly influence the need for supplemental oxygen and the perceived incidence of BPD.

6.4. CPAP weaning failure occurs frequently in clinical research. Should this be so in clinical practice?

Failure criteria are a set of clinical markers of instability that prompt a return to CPAP. Most of the studies identified in this review report high weaning failure rates (Fig. 1). As it is desirable to avoid clinical instability, it is reasonable to conclude that the optimal CPAP duration is likely longer than what is typically described in existing trials. It is worth noting that the “Columbia approach” fits this description.

7. Conclusions

Limited evidence exists to guide selection of an optimal CPAP duration for premature infants. Additional trials are needed. Such trials should describe stability criteria, weaning methods, failure criteria and the consequence of failure to facilitate reproducibility and clear interpretation of the study results. The potential for wean-time lag bias should be considered. Future trials should measure long-term respiratory and neurodevelopmental outcomes – no such data currently exist.

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References

1. Harrison VC, Heese HDV, Klein M. Significance of grunting in hyaline membrane disease. *Pediatrics*. 1968; 41:549–59. [PubMed: 5641776]
2. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *N Engl J Med*. 1971; 284:1333–40. [PubMed: 4930602]
3. De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Syst Rev*. 2008; (1):CD002977. [PubMed: 18254011]
4. Chowdhury O, Wedderburn CJ, Duffy D, Greenough A. CPAP review. *Eur J Pediatr*. 2012; 171:1441–8. [PubMed: 22173399]
5. Miller MJ, Difiore JM, Strohl KP, Martin RJ. Effects of nasal CPAP on supraglottic and total pulmonary resistance in preterm infants. *J Appl Physiol*. 1990; 68:141–6. [PubMed: 2179206]
6. Faridy EE. Effect of ventilation on movement of surfactant in airways. *Respir Physiol*. 1976; 27:323–34. [PubMed: 989609]
7. Saunders RA, Milner AD, Hopkin IE. Effects of continuous positive airway pressure on lung-mechanics and lung-volumes in neonate. *Biol Neonate*. 1976; 29:178–86. [PubMed: 782570]
8. Richardson CP, Jung AL. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. *Pediatr Res*. 1978; 12:771–4. [PubMed: 358112]

9. Polin RA, Sahni R. Newer experience with CPAP. *Semin Neonatol.* 2002; 7:379–89. [PubMed: 12464500]
10. Chernick V. Hyaline-membrane disease therapy with constant lung-distending pressure. *N Eng J Med.* 1973; 289:302–4.
11. Andreasson B, Lindroth M, Svenningsen NW, Jonson B. Effects on respiration of CPAP immediately after extubation in the very preterm infant. *Pediatr Pulmonol.* 1988; 4:213–18. [PubMed: 3292996]
12. Miller MJ, Carlo WA, Martin RJ. Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. *J Pediatr.* 1985; 106:91–4. [PubMed: 3917503]
13. Martin RJ, Nearman HS, Katona PG, Klaus MH. Effect of a low continuous positive airway pressure on reflex control of respiration in preterm infant. *J Pediatr.* 1977; 90:976–81. [PubMed: 323448]
14. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *N Eng J Med.* 2008; 358:700–8.
15. Makhoul IR, Smolkin T, Sujov P. Pneumothorax and nasal continuous positive airway pressure ventilation in premature neonates: a note of caution. *ASAIO J.* 2002; 48:476–9. [PubMed: 12296565]
16. Milner AD, Saunders RA, Hopkin IE. Effects of continuous distending pressure on lung volumes and lung mechanics in the immediate neonatal period. *Biol Neonate.* 1977; 31:111–15. [PubMed: 321039]
17. Abdel-Hady H, Matter M, Hammad A, El-Refaay A, Aly H. Hemodynamic changes during weaning from nasal continuous positive airway pressure. *Pediatrics.* 2008; 122:1086–90. [PubMed: 18977991]
18. Shaffer TH, Koen PA, Moskowitz GD, Ferguson JD, Delivoriapapadopoulos M. Positive end expiratory pressure effects on lung-mechanics of premature lambs. *Biol Neonate.* 1978; 34:1–10. [PubMed: 359057]
19. Hobelmann CF, Smith DE, Virgilio RW, Peters RM. Mechanics of ventilation with positive end-expiratory pressure. *Ann Thorac Surg.* 1977; 24:68–76. [PubMed: 327957]
20. Abdel-Hady H, Mohareb S, Khashaba M, Abu-Alkhair M, Greisen G. Randomized controlled trial of discontinuation of nasal-CPAP in stable preterm infants breathing room air. *Acta Paediatr.* 1998; 87:82–7. [PubMed: 9510453]
21. Slocum C, Hibbs AM, Martin RJ, Orenstein SR. Infant apnea and gastroesophageal reflux: a critical review and framework for further investigation. *Curr Gastroenterol Rep.* 2007; 9:219–24. [PubMed: 17511920]
22. Jadcherla SR, Gupta A, Fernandez S, et al. Spatiotemporal characteristics of acid refluxate and relationship to symptoms in premature and term infants with chronic lung disease. *Am J Gastroenterol.* 2008; 103:720–8. [PubMed: 18341491]
23. Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. *Neonatology.* 2012; 102:300–8. [PubMed: 22964658]
24. Yong SC, Chen SJ, Boo NY. Incidence of nasal trauma associated with nasal prong versus nasal mask during continuous positive airway pressure treatment in very low birthweight infants: a randomised control study. *Archs Dis Childh Fetal Neonatal Ed.* 2005; 90:F480–3.
25. Roberts CT, Manley BJ, Dawson JA, Davis PG. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. *J Paediatr Child Health.* 2014; 50:806–10. [PubMed: 24943729]
26. Abdel-Hady H, Shouman B, Nasef N. Weaning preterm infants from continuous positive airway pressure: evidence for best practice. *World J Pediatr.* 2015; 11:212–18. [PubMed: 25846068]
27. Rastogi S, Rajasekhar H, Gupta A, Bhutada A, Rastogi D, Wung JT. Factors affecting the weaning from nasal CPAP in preterm neonates. *Int J Pediatr.* 2012; 416073. [PubMed: 22187570]
28. Jardine LA, Inglis GD, Davies MW. Strategies for the withdrawal of nasal continuous positive airway pressure (NCPAP) in preterm infants. *Cochrane Database Syst Rev.* 2011; (2):CD006979. [PubMed: 21328289]
29. Jardine L, Davies MW. Withdrawal of neonatal continuous positive airway pressure: current practice in Australia. *Pediatr Int.* 2008; 50:572–5. [PubMed: 19143985]

30. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001; 163:1723–9. [PubMed: 11401896]
31. Bowe L, Clarke P. Current use of nasal continuous positive airways pressure in neonates. *Archs Dis Childh Fetal Neonatal Ed*. 2005; 90:F92–3.
32. Fernandez-Alvarez JR, Gandhi RS, Amess P, Mahoney L, Watkins R, Rabe H. Heated humidified high-flow nasal cannula versus low-flow nasal cannula as weaning mode from nasal CPAP in infants <28 weeks of gestation. *Eur J Pediatr*. 2014; 173:93–8. [PubMed: 23942744]
33. Sasi A, Malhotra A. High flow nasal cannula for continuous positive airway pressure weaning in preterm neonates: a single-centre experience. *J Paediatr Child Health*. 2015; 51:199–203. [PubMed: 25039700]
34. Singh S, Bowe L, Clarke P, et al. Is decreasing pressure or increasing time off the better strategy in weaning VLBW infants from nasal CPAP? [Abstract] In: Book of Abstracts, European Academy of Paediatrics; 2006 Oct 7–10; Barcelona, Spain. *Eur J Pediatr*. 2006; 165(Suppl 1):48.
35. Soe A, Hodgkinson J, Jani B, Ducker A. Nasal continuous positive airway pressure weaning in preterm infants [abstract] In: Book of Abstracts European Academy of Paediatrics; 2006 Oct 7–10; Barcelona, Spain. *Eur J Pediatr*. 2006; 165(Suppl 1):48–9.
36. Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: a randomized controlled trial. *Early Hum Dev*. 2011; 87:205–8. [PubMed: 21276671]
37. Nair V, Swarnam K, Rabi Y, et al. Effect of nasal continuous positive airway pressure (NCPAP) cycling and continuous NCPAP on successful weaning: a randomized controlled trial. *Ind J Pediatr*. 2015; 82:787–93.
38. Todd DA, Wright A, Broom M, et al. Methods of weaning preterm babies <30 weeks gestation off CPAP: a multicentre randomised controlled trial. *Archs Dis Childh Fetal Neonatal Ed*. 2012; 97:F236–40.
39. O'Donnell SM, Curry SJ, Buggy NA, et al. The NOFLO trial: low-flow nasal prongs therapy in weaning nasal continuous positive airway pressure in preterm infants. *J Pediatr*. 2013; 163:79–83. [PubMed: 23312683]
40. Rastogi S, Wong W, Gupta A, Bhutada A. Gradual versus sudden weaning from nasal CPAP in preterm infants: a pilot randomized controlled trial. *Respir Care*. 2013; 58:511–16. [PubMed: 22906960]
41. Amatya S, Rastogi D, Bhutada A, Rastogi S. Weaning of nasal CPAP in preterm infants: who, when and how? A systematic review of the literature. *World J Pediatr*. 2015; 11:7–13. [PubMed: 25557597]
42. Broom M, Ying L, Wright A, et al. CeasIng Cpap At standarD criteria (CICADA): impact on weight gain, time to full feeds and caffeine use. *Archs Dis Childh Fetal Neonatal Ed*. 2014; 99:F423–5.

Practice points

- The more premature the infant at birth, the later the typical PMA at successful CPAP discontinuation.
- Time cycling as a CPAP weaning method is of unlikely benefit and may cause harm.
- Prolonged CPAP use diminishes supplemental oxygen need well beyond the newborn period.
- CPAP weaning strategies used in existing clinical studies frequently results in wean failure. An optimal CPAP duration may be longer than the approach described in these trials.

Research directions

- Additional trials assessing optimal CPAP duration are needed.
- Future trials should describe stability criteria, weaning methods, failure criteria, and the consequence of wean failure to facilitate study interpretation and reproducibility.
- The potential for wean-time lag bias should be considered in studies using duration of respiratory support as both an intervention and outcome.
- Future trials should measure long-term respiratory and neurodevelopmental outcomes no such data currently exist.

Fig. 1.

Wean failure is common in clinical trials of continuous positive airway pressure (CPAP) discontinuation methods. Weaning method groups collapsed within each study as $P =$ non-significant for all comparisons; data only available for Group A in Todd et al. GA, BW and PMA are mean central tendency values of collapsed groups. GA, gestational age; w, weeks; BW, birth weight; PMA, postmenstrual age; RA, room air; NC, nasal cannula; FiO_2 , fraction of inspired oxygen; SFA, severe/frequent apnea; RD, respiratory distress; abnl, abnormal; BG, blood gas; d, days; TC, time cycling; MV, mechanical ventilation. Abdel-Hady et al. [36]; O'Donnell et al. [39], Rastogi et al. [40], Nair et al. [37], Todd et al. [38].

Table 1

Surveys on duration of CPAP practice highlight practice variation.

Survey	Findings
Bowe et al. [31]	Weaning methods used: time cycling (66%), pressure weaning (4%)
58 English neonatal units	Adherence to specified weaning protocols: 6%
Jardine et al. [29]	Weaning methods used: time cycling (70%), pressure weaning (74%)
All level 3 Australian neonatal units	Range of responses for selected CPAP duration parameters: <div><div><div>i.</div><div>minimum CPAP prior to discontinuation: 3–6 cmH₂O</div></div><div><div>ii.</div><div>time allowed between pressure weans: 0–5 days</div></div><div><div>iii.</div><div>time off CPAP before full discontinuation (with time cycling): 6–18 h</div></div><div><div>iv.</div><div>increase in FiO₂ required to meet failure criteria: 5–60%</div></div></div>

CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen.

Table 2

Randomized trials on duration of CPAP support: key characteristics and findings.

Study; population	Randomized intervention	Stability criteria	Failure criteria	Selected outcomes	Comments
Abdel-Hady et al. [20] <i>n</i> = 88 GA, cohort: 29 (2) weeks BW, cohort: 1264 (332) g Age at intervention, median (IQR): 7.0 (3–18) vs 7.5 (4–18) days	Group A: continued CPAP support Group B: pressure weaning over 1 h to CPAP 3 cmH ₂ O then off	No supplemental O ₂ , no frequent/severe apnea	Incubator FiO ₂ >0.40; frequent/severe apnea; resulted in return to baseline CPAP support and study termination	i. CPAP duration: 9.5 vs 0 days** ii. Retractions: 0 vs 26%** iii. Change in respiratory rate: +2 vs +7 breaths/min* iv. Arterial to alveolar pO ₂ ratio change at 6 h: (0.01) vs (0.04)* v. Change in abdominal circumference: +0.5 vs 0.5**	Outcomes at 6 h post intervention; 1/44 in Group B met failure criteria within 6 h but 18/44 ultimately returned to CPAP
Singh et al. [34] <i>n</i> = 112; GA: 27 (24–32) vs 28 (24–31) weeks BW: 940 (614–1400) vs 1080 (520–1496) g Age at intervention, cohort: 29 (28–31) weeks PMA	Group A: pressure weaning Group B: time cycling	Supplemental FiO ₂ <0.30	Not detailed	i. Weaning duration: 1.5 vs 8.9 days** ii. Successful weaning (defined as stable off of CPAP for 7 days): 65% vs 37%** iii. Total CPAP duration: 6 vs 13.2 days**	Abstract only; weaning duration difference between groups demonstrates weaning time lag; difference in total CPAP duration largely explained by weaning duration difference.
Soe et al. [35] <i>n</i> = 98 GA, cohort: (24–31) weeks BW: not reported Age at intervention: not detailed	Group A: pressure weaning over 6 days Group B: time cycling over 6 days	Not detailed	Not detailed	i. Successful weaning (not defined); 24–27 weeks GA: 82% vs 55%* 27–31 weeks GA: NS ii. CPAP duration: 24–27 weeks GA: 10 vs 15 days* 27–31 weeks GA: NS	Abstract only
Abdel-Hady et al. [36] <i>n</i> = 60 GA: 31 (2.6) vs 31 (2.4) weeks BW: 1600 (390) vs 1600 (380) g Age at intervention: not reported	Group A: CPAP discontinuation to RA Group B: CPAP transitioned to NC with FiO ₂ 0.30 when FiO ₂ 0.21, NC flow weaned from 2 L/min by 0.5 L/min every 6	Supplemental FiO ₂ 0.21 (Group A) or <0.30 (Group B) and CPAP 5 cmH ₂ O for 24 h, no frequent/severe apnea, no respiratory distress, no abnormal blood gas	FiO ₂ >0.60; frequent/severe apnea, respiratory distress, abnormal blood gas; resulted in return to CPAP, 24 h of stability criteria prior to repeat weans	i. CPAP duration: 11.2 vs 7.6 days* ii. Oxygen duration: 5 vs 14 days** iii. Respiratory support duration: 10.5 vs 18 days* iv. Length of hospitalization: 36 vs 36.7 days (NS)	Stability criteria unequal between groups, PMA at intervention between groups not reported

Study; population	Randomized intervention	Stability criteria	Failure criteria	Selected outcomes	Comments
Todd et al. [38], Broom et al. [42] (secondary analysis) <i>n</i> = 177 Groups A vs B vs C GA: 27.1 (1.4) vs 26.9 (1.6) vs 27.3 (1.5) weeks BW: 988 (247) vs 987 (249) vs 1015 (257) g Age at intervention: 29.6 (1.7) vs 30.5 (2.3) vs 29.7 (1.9) PMA	Group A: CPAP discontinuation to RA Group B: time cycling between RA and 6 h CPAP with increasing time off by 2–4 h to 16 h off CPAP then discontinued Group C: time cycling off CPAP as per Group B but to 0.5 L/min NC; additional 24 h NC before discontinuation to RA	Supplemental FiO ₂ <0.25 and down-trending, CPAP 4–6 cmH ₂ O for 24 h, no frequent/severe apnea, no respiratory distress; no sepsis or patent ductus arteriosus undergoing treatment	Two of: FiO ₂ >0.25; frequent/severe apnea, respiratory distress, abnormal blood gas; for Group A resulted in return to CPAP for minimum of 48 h; for Groups B and C resulted in return to CPAP “for 6 h or until stability criteria was met”	Groups A vs B vs C (i) (ii) (iii) (iv)	Randomization chance imbalance on covariates of gender and Apgar score adjusted through multivariate analysis Authors speculate that return to CPAP for minimum 48 h after failure in Group A compared to “6 h or until stability criteria was met” in B and C may have allowed “full recruitment of the lung” following CPAP failure in Group A but not B and C and may have mediated observed outcomes CPAP duration: 11 vs 17 vs 19 days** Oxygen duration: 24 vs 49 vs 34** PMA at discharge: 35.8 vs 36.9 vs 36.9** BPD: 13% vs 42% vs 19%* (A vs B only) 68% of Group A failed at least once (within 5 days), 28% required 4–13 attempts; likelihood of wean failure inversely correlated with GA; equivalent data not provided for Group B or C Secondary data analysis: (v) Time to full feeds (NS) and duration of caffeine (NS) when using adjusted multivariate analysis as per original study
O'Donnell et al. [39] <i>n</i> = 78 Group A vs B GA, cohort: median 28 (24–32) weeks BW: 1060 (590–1430) vs 1090 (510–1440) g Age at intervention, median: 31 (28–37) vs 31 (27–37)	Group A: CPAP discontinuation to RA Group B: CPAP transitioned to 1 L/min NC with RA oxygen	No supplemental FiO ₂ with CPAP 3–5 cmH ₂ O for 24 h	Any supplemental FiO ₂ need, frequent/severe apnea, respiratory distress; resulted in return to CPAP	i. ii. iii.	Wean failure within 5 days; 31% vs 41% (NS) Respiratory rate: 58 vs 54 breaths/min* BPD: 11% vs 0% (NS) Infants failing wean of similar PMA but lower GA (27 vs 29 weeks, <i>P</i> = 0.002) and BW (920 g vs 1230 g, <i>P</i> = 0.0001) than infants not failing
Rastogi et al. [40] <i>n</i> = 56 Group A vs B GA: 28 (1.6) vs 28 (1.8) weeks BW: 1131 (221) vs 1080 (219) g Age at intervention, cohort: ~32 weeks	Group A: CPAP discontinuation to RA Group B: time cycling to RA starting 3 h on and 3 h off CPAP for 48 h, then 3 h on and 6 h off for 48 h before CPAP discontinuation	No supplemental FiO ₂ on CPAP 5 cmH ₂ O for 48 h, no frequent/severe apnea, no respiratory distress	Any supplemental FiO ₂ need, frequent/severe apnea, respiratory distress; resulted in return to CPAP, weaning reconsidered after 48 h, unclear if subsequent weans	i. ii.	No failure for 7 days (primary outcome); 46% vs 43%, <i>P</i> = 0.65; length of hospital stay: 61 vs 66 days, <i>P</i> = 0.48

Study; population	Randomized intervention	Stability criteria	Failure criteria	Selected outcomes	Comments
Nair et al. [37]; $n = 30$ All subjects previously on mechanical ventilation Group A vs B GA (median) 27 IQR (26–27) vs 27 IQR (26–28) BW (median) 914 (840–980) vs 970 (800–990) g Age at intervention: 16 (6–26) vs 6 (6–10) days	Group A: continuation of baseline CPAP with transition to 1 L/min NC after 72 h Group B: time cycling to 1 L/min NC starting 10 h on and 2 h off CPAP; gradually progressed to 4 h on and 8 h off CPAP with transition to 1 L/min NC after 72 h	CPAP use for >72 h post extubation, supplemental $\text{FiO}_2 < 0.25$ on CPAP 4 cm H_2O	adhered to initial intervention arms $\text{FiO}_2 > 0.30$; frequent/severe apnea, respiratory distress, abnormal blood gas	Group A vs B i. No failure for 3 days: 41% vs 31% (NS) ii. CPAP duration: 28 vs 35 days (NS) iii. BPD: 35% vs 62% (NS)	Randomization chance imbalance between groups on covariates of age at intervention, mechanical ventilation duration, and gender; statistical adjustments not described

RCT, randomized controlled trial; GA, gestational age; BW, birth weight; CPAP, continuous positive airway pressure; PMA, postmenstrual age; FiO_2 , fraction of inspired oxygen; pO₂, partial pressure of oxygen; BPD, bronchopulmonary dysplasia; IQR, interquartile range.

Population demographics and study outcome measures represented as mean and (standard deviation) or (range) and compare Group A vs Group B unless otherwise specified. Data stratified by intervention when available, measures representative of entire study cohort when specified. NS, non-significant.

* $P < 0.05$,

** $P < 0.01$.

Table 3

Observational studies on duration of CPAP support: key characteristics and findings.

Study; population	Comparison	Stability criteria	Failure criteria	Selected outcomes
Rastogi et al. [27] Descriptive cohort study <i>n</i> = 454 GA: 29.3 (2.2) weeks BW: 1357 (392) g	N/A; descriptive report of weight and PMA at successful CPAP discontinuation (defined as stable on RA with no respiratory support for 7 days)	No supplemental O ₂ for 48 h	Not detailed	Mean weight and PMA at discontinuation: 1611 g and 32.9 weeks BW strongest predictor of CPAP duration, with mean decrease of 0.2 weeks PMA for every 100 g (1 week PMA for every 500 g) increase
Fernandez-Alvarez et al. [32] Matched pair cohort analysis <i>n</i> = 79 GA (median): 27 IQR (26–28) vs 27 IQR (26–28) weeks BW (median): 930 (782–1170) vs 980 (840–1078) g Age at wean: not recorded	Group A: transition to 8 L/min HFNC, wean stepwise by 1 L/min every 12–24 h to 2 L/min then wean to NC Group B: transition to NC, wean “as much as tolerated” every 12–24 h	Supplemental FiO ₂ <0.40 on CPAP 4 cmH ₂ O	FiO ₂ >0.40; frequent/severe apnea, respiratory distress, abnormal blood gas	i. CPAP duration: 13 vs 25 days** ii. Duration of non-invasive support: 37 vs 34 days (NS) iii. BPD: 28% vs 23% (NS) iv. Nasal bridge injury: 0% vs 13%**
Sasi et al. [33] Epoch study <i>n</i> = 1286 GA: 28.1 (2.2) vs 28.5 (2.2) weeks BW: 1155 (374) vs 1199 (396) g Age at wean: not recorded	Group A: 2004–2007: no HFNC available Group B: 2008–2011: HFNC available and used to transition from CPAP; HFNC weaned to RA when flow <4 L/min	Only described for Group B: supplemental FiO ₂ <0.30 on CPAP 6 cmH ₂ O	Only described for Group B: increase in FiO ₂ >0.1	Adjusted for covariate differences between epochs; no difference in primary outcome of BPD (adjusted OR: 0.6 (0.2–1.6))

GA, gestational age, BW, birth weight, CPAP, continuous positive airway pressure, PMA, postmenstrual age, FiO₂, fraction of inspired oxygen, BPD, bronchopulmonary dysplasia; HFNC, high-flow nasal cannula; OR, odds ratio.

Population demographics and study outcome measures represented as mean and (standard deviation) or (range) and compare Group A vs Group B unless otherwise specified. Data stratified by intervention when available, measures representative of entire study cohort when specified. NS, non-significant.

* *P* < 0.05,

** *P* < 0.01.

Table 4
Lower gestational age and birth weight are associated with longer duration of CPAP support.

Study	Influence of GA and BW on CPAP duration or wean failure
Rastogi et al. [27]: retrospective observational study of standardized clinical practice; <i>n</i> = 454.	Using linear regression analysis, CPAP duration decreased by 1 weeks PMA for every 500 g increase in birth weight and 0.4 weeks PMA for every 1 week increase in birth GA ^{**}
Soe et al. [35]: randomized trial abstract; pressure weaning vs time cycling; <i>n</i> = 98	Percent weaning failure stratified by GA (collapsed across interventions): 24–27 weeks: 32% vs 27–31 weeks: 2%
Todd et al. [38]: randomized trial; CPAP discontinuation vs time cycling vs time cycling with NC; <i>n</i> = 177	Analysis stratified by GA; median wean failure count: 24–25 weeks: 3; 26 weeks: 3; 27 weeks: 3.5; 28 weeks: 2; 29 weeks: 1 ^a
O'Donnell et al. [39]: randomized trial; CPAP discontinuation to RA or NC; <i>n</i> = 78	At equivalent PMA (all medians) ^{**} ; Characteristics of infants successfully weaning: 29 weeks GA, 1230 g BW; characteristics of infants failing wean: 27 weeks GA, 920 g BW

CPAP, continuous positive airway pressure; GA, gestational age; BW, birth weight; PMA, postmenstrual age.

* *P* < 0.01.