



CLINICAL RESEARCH ARTICLE

Oxygen saturation histograms predict nasal continuous positive airway pressure-weaning success in preterm infants

Samuel J. Gentle¹, Namasivayam Ambalavanan¹ and Waldemar A. Carlo¹

BACKGROUND: Continuous positive airway pressure (CPAP) is widely used in preterm infants. Identification of readiness for weaning from CPAP can balance benefits with risks of CPAP exposure. We tested the hypothesis that preterm infants that successfully transition off CPAP have higher oxygen saturations prior to weaning compared with infants who fail weaning from CPAP.

METHODS: This was a single-center-matched case-control study in infants ≤ 30 weeks' gestation receiving $\leq 30\%$ FiO_2 weaned off CPAP during the first postnatal week. Cases were infants placed back on CPAP within 7 days of being taken off CPAP, whereas control infants remained off CPAP for 7 consecutive days following CPAP discontinuation. Infants were matched on gestational age at birth (± 10 days). Prospectively collected histograms detailing the distribution of oxygen saturations prior to CPAP discontinuation were compared between cases and controls.

RESULTS: Over a 12-month monitoring period, 36 infants met inclusion criteria. Baseline characteristics, morbidities, and clinical variables did not differ between cases and controls. Controls achieved oxygen saturations of 95–97 and 97–100% for longer duration compared to cases ($p < 0.05$).

CONCLUSIONS: In preterm infants with RDS receiving CPAP and $\leq 30\%$ FiO_2 , infants with higher oxygen saturations had greater success in transitioning off CPAP.

Pediatric Research (2020) 88:637–641; <https://doi.org/10.1038/s41390-020-0772-2>

INTRODUCTION

Preterm infants with respiratory distress syndrome (RDS), a common disease of prematurity, often require respiratory support. Although evidence supports the utility of continuous positive airway pressure (CPAP) for RDS,¹ there is less evidence regarding optimal timing of CPAP discontinuation.² CPAP enables areas of the lung that participate in gas exchange to remain inflated. However, CPAP may also be associated with impaired blood return to the heart,³ pneumothoraces,⁴ and nasal septum injury.⁵ Therefore, discontinuing CPAP upon resolution or improvement of respiratory distress may minimize risks. In randomized controlled trials on approaches to CPAP discontinuation in preterm infants, up to 65% of infants fail their initial wean from CPAP.² This high failure rate provides further confirmation that better criteria are needed to identify infants ready to wean from CPAP as periods of atelectasis that may occur with failed weaning attempts could potentially cause further lung injury.⁶

Oxygen saturation histograms provide a graphic depiction of the distribution of oxygen saturation in different ranges and are available on many bedside monitors in the neonatal intensive care unit (NICU). The use of histograms to follow oxygen saturations in preterm infants may improve outcomes in preterm infants⁷ and provide a clinical tool to identify infants ready to wean from CPAP.⁸ However, baseline clinical variables have differed in prior investigations between infants that fail to wean from support and those that succeed in transitioning off support. The aim of this study was to use a case-control study design to compare achieved oxygen saturation in preterm infants who successfully

transition off of CPAP to those that need prolonged CPAP support. We hypothesized that infants that successfully transition off CPAP would achieve oxygen saturations $>95\%$ for a larger proportion of time compared to those infants that fail to wean from CPAP.

METHODS

Study design

Institutional Review Board approval at the University of Alabama at Birmingham was obtained prior to study initiation. This was a prospective observational case-control study in preterm infants born at ≤ 30 weeks' gestation or < 1250 g at birth. Included infants were born between October 2017 and August 2018. Infants were included if they were managed on CPAP for ≥ 24 h, were weaned off of CPAP within the first 7 postnatal days, were on < 0.30 FiO_2 at the time of weaning, and had 24-hour oxygen saturation histogram data available prior to weaning from CPAP. Twenty-four hour histograms were collected from bedside monitors (Philips IntelliVue MP70) prior to CPAP discontinuation. Infants were excluded if they were never exposed to CPAP, remained on CPAP and/or mechanical ventilation throughout the first postnatal week, had a major congenital anomaly, or did not have histogram data available.

Histograms were available to clinicians from bedside monitors at the time infants were weaned off CPAP; however, specific histogram criteria were not routinely used to determine CPAP-weaning readiness. Goal saturations for this cohort were 90–95%. Respiratory therapists routinely monitored histograms every 6 h

¹Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA
Correspondence: Samuel J. Gentle (sjgentle@uabmc.edu)

Received: 23 October 2019 Revised: 23 December 2019 Accepted: 8 January 2020
Published online: 23 January 2020

on infants requiring respiratory support in our NICU to improve infants' achievement of goal saturations of 90–95%.⁷ Within the NICU, there was no official guideline as to when to wean infants from CPAP in the first postnatal week, however, the practice occurred in this cohort once infants were on low FiO₂ (a median of 0.21 in the cases and 0.22 in controls), with infrequent apneic events (1–2 events/day requiring stimulation), and a CPAP of 4–5 mm H₂O. Infants were not incrementally weaned (e.g., not cycled between CPAP and room air). Infants were weaned to either room air or oxygen environment (servo-controlled supplemental oxygen within the incubator). Infants were typically restarted on CPAP if after weaning they have an increase in apneic frequency, an increase in FiO₂ requirement >0.30, or increased work of breathing.

Cases were infants weaned off CPAP but subsequently placed back on CPAP within 7 consecutive days of discontinuation. Controls were infants weaned off CPAP who remained off CPAP for the following 7 consecutive days. Seven days was chosen as the duration of observation following CPAP discontinuation to reduce potential underestimation of the number of infants subsequently restarted on CPAP. Infants were matched based on gestational age at birth (± 10 days). Baseline characteristics (i.e., gestational age at birth, birth weight, race, sex), major morbidities (i.e., RDS), as well as variables of respiratory support (i.e., amount of oxygen required, number of apneic episodes) were compared between cases and controls. To ensure that results could be subsequently applied clinically, achieved saturations in the 24 h prior to CPAP discontinuation were compared between cases and controls at six default distribution ranges from the Philips monitor (85–87, 87–90, 90–92, 92–95, 95–97, and 97–100%). Histograms were also compared between infants on supplemental oxygen and infants not on supplemental oxygen prior to weaning from CPAP.

Statistical analysis

The hypothesis of this study was that in preterm infants with RDS, infants who successfully wean off CPAP (controls) would achieve oxygen saturations >95% for a greater percentage of time compared to infants who failed weaning from CPAP (cases). Sample size calculations were based on pilot data ($N=15$), wherein controls achieved oxygen saturations >95% for a median of 52% of the time prior to weaning from CPAP compared to cases achieving oxygen saturations >95% for 21% of the time. Using this absolute difference of 31%, a power of 80%, and a confidence level of 95%, we calculated that a total of 34 infants would be required.

Baseline differences between cases and controls were compared using a *t* test or Mann–Whitney tests for continuous variables and the Fisher test for categorical variables. Achieved oxygen saturation distributions were compared between cases and controls using two-way analysis of variance. Forward stepwise multivariate logistic regression was used to determine variables that predicted CPAP-weaning success. The predictive performance of the percentage of time infants achieved oxygen saturations >95% to differentiate cases and controls was analyzed using area under the receiver operating characteristic curve (AUC). Sensitivity and specificity calculations determined the optimal duration of time >95% to predict CPAP-weaning success using the Youden index. Statistical analyses were performed using SPSS version 25.

RESULTS

During the study period, 159 patients were assessed for eligibility during the first postnatal week of whom 48 were weaned off CPAP during the first week after birth (Fig. 1). Of the 48 eligible infants, 12 did not have histogram data available for the 24 h period prior to CPAP discontinuation. Following CPAP discontinuation in the

remaining infants, 12 infants were placed back on CPAP (cases) and 24 remained off CPAP (controls). Given the number of cases and controls, matching was performed with a case:control ratio of 1:2.

Baseline characteristics including antenatal corticosteroid exposure, gestational age, and birth weight as well as morbidities including bronchopulmonary dysplasia, grade 3–4 intracranial hemorrhage, necrotizing enterocolitis, and culture proven sepsis did not differ between cases and controls (Table 1). The median difference in gestational age between cases and controls was 2 days. Respiratory characteristics prior to and after CPAP discontinuation were similar between cases and controls, including the postnatal day when weaned, the number of apneic events requiring intervention, and FiO₂ (Table 2). Achieved oxygen saturations differed between cases and control infants ($p < 0.0001$; Fig. 2). Control infants achieved oxygen saturations for a greater percentage of time between 95 and 97% (32% vs. 19%) and 97–100% (21 vs. 6%) compared with cases ($p < 0.0001$ by Sidak's multiple comparison test). Cases spent more time (66% vs 45%) between goal saturations of 90–95% compared to controls ($p < 0.0002$), although this was secondary to controls achieving higher saturations (Fig. 2). In addition, infants not on supplemental oxygen achieved oxygen saturations of 95–97% (35% vs. 21%) and 97–100% (25% vs. 6%) for more time than infants requiring supplemental oxygen (Supplemental Fig. 1).

By multivariable forward stepwise logistic regression, the percentage of time infants achieved oxygen saturations >95% predicted CPAP-weaning success (OR 1.046; 95% CI 1.006–1.087). No other baseline, clinical, or respiratory variable met inclusion for the equation. The AUC for oxygen saturation achievement >95% was 0.79 (95% CI, 0.63–0.94) (Fig. 3). The optimal value of oxygen saturation achievement >95% to predict CPAP-weaning success by Youden index was 31.6% with a sensitivity of 75% and specificity of 75%.

DISCUSSION

In this case–control study of CPAP weaning in preterm infants, achieved oxygen saturations prior to CPAP discontinuation predicted CPAP-weaning success. In contrast, other baseline characteristics including gestational age, birth weight, and need for mechanical ventilation and respiratory variables including FiO₂ requirement and apneic events prior to CPAP discontinuation did not predict CPAP-weaning success.

Previous studies suggest that baseline characteristics such as gestational age and birth weight differ between infants that successfully wean off of CPAP and infants restarted on CPAP. In a randomized controlled trial in preterm infants comparing cycling on and off CPAP for prespecified periods of time weaning to nasal cannula or weaning to room air, infants born at <28 weeks' gestation took a median of three attempts to wean off CPAP compared with two attempts in infants born at 28–29 weeks' gestation.⁹ In another trial that randomized preterm infants on CPAP to either nasal cannula or room air, infants failing to successfully wean from CPAP had a lower gestational age (27 vs 29 weeks' gestation) and lower birth weight (920 g vs 1230 g).¹⁰ A retrospective observational study in infants born at ≤ 32 weeks' gestation analyzed factors associated with the timing of CPAP discontinuation. Infants were weaned off CPAP at a mean PMA of 33 weeks' gestation and birth weight was inversely related to the PMA at which CPAP was discontinued.¹¹ In the present study, infants were an average of ~28 weeks' gestation in both cases and controls and had a mean birth weight of 895 g in controls and 1019 g in cases. As these variates did not differ between cases and controls, other respiratory variables could be used to predict CPAP-weaning success.

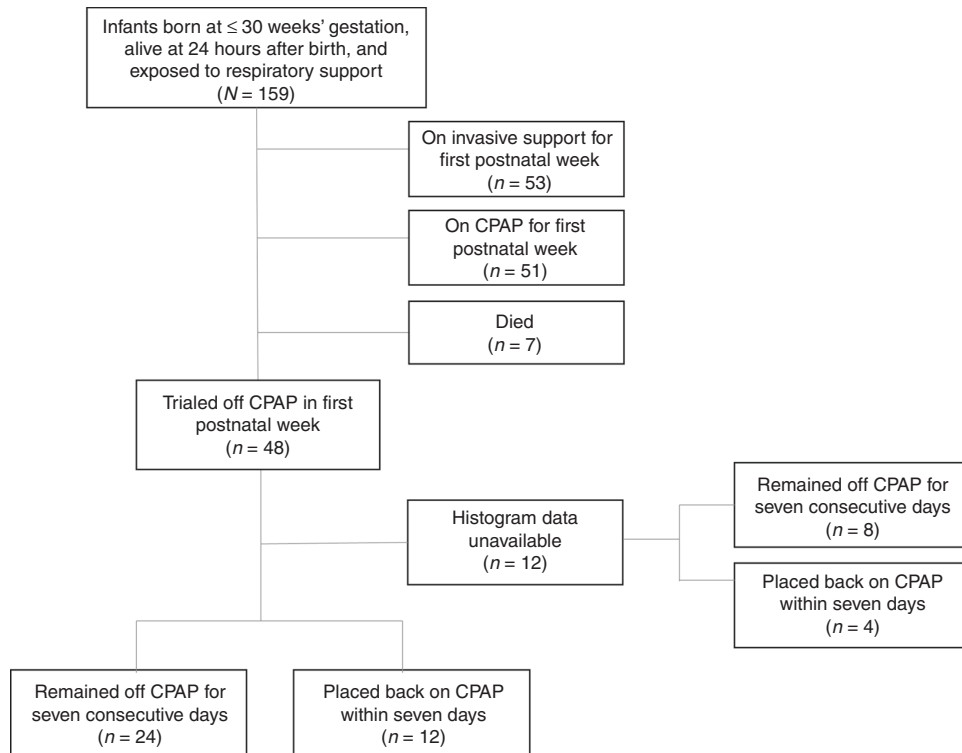


Fig. 1 Flow diagram for included and excluded infants.

Table 1. Characteristics in cases and controls.

	Control (n = 24)	Cases (n = 12)	<i>p</i>
Gestational age, weeks mean ± SD	28.2 ± 1	27.8 ± 1	0.44
Birth weight, grams mean ± SD	895 ± 220	1019 ± 199	0.18
Male sex <i>n</i> (%)	8 (33.3)	5 (41.7)	0.72
Race <i>n</i> (%)			> 0.99
White	9 (37.5)	4 (33.3)	
Black	15 (62.5)	6 (50.0)	
Other	0	2 (16.7)	
Antenatal corticosteroids <i>n</i> (%)	19 (79)	9 (75)	> 0.99
Mechanically ventilated <i>n</i> (%)	9 (38)	4 (33)	> 0.99
Surfactant <i>n</i> (%)	9 (38)	4 (33)	> 0.99
Death <i>n</i> (%)	1 (4.2)	1 (8.3)	> 0.99
Bronchopulmonary dysplasia <i>n</i> (%)	5 (20.8)	4 (33.3)	0.44
Retinopathy of prematurity <i>n</i> (%)	7 (29.2)	4 (33.3)	> 0.99
Grade 3–4 intracranial hemorrhage <i>n</i> (%)	0	1 (8.3)	0.33
Necrotizing enterocolitis stage ≥ 2 <i>n</i> (%)	2 (8.3)	2 (16.7)	0.56
Culture proven sepsis <i>n</i> (%)	3 (12.5)	1 (8.3)	> 0.99

n number, *SD* standard deviation.

Determination of infants' readiness for weaning off CPAP presents a challenge as demonstrated by CPAP-weaning failure rates in randomized controlled trials. RCTs comparing methods of CPAP weaning in preterm infants have used different "stability criteria" prior to randomization. These criteria have included

indicators of work of breathing, parameters of respiratory support, and frequency of apneic events. The oxygen requirement in these trials has ranged from 0.21 FiO₂^{10,12} to <0.25–30 FiO₂.^{9,13,14} Despite the use of these criteria, multiple trials have reported CPAP-weaning failure rates exceeding 50%.^{9,12,15} These failures to successfully wean infants from CPAP suggest that currently used criteria to identify infants ready to wean from CPAP are insufficient. However, weaning success may not only result from the stability criteria used to wean infants but also the failure criteria used to restart CPAP. In these trials, failure criteria ranged from any oxygen requirement^{10,12} to >0.60 FiO₂.¹³ In the RCT with the failure criteria of >0.60 FiO₂, the CPAP-weaning failure rate was the lowest at ~20%. The present study provides additional evidence for the inadequacy of currently used stability criteria. The FiO₂ requirement and apneic event frequency neither differed between cases and controls nor were included in the forward stepwise logistic regression analysis.

Given that additional or refined stability criteria for CPAP-weaning readiness are needed, the present study evaluated oxygen saturation histograms as a potential predictor for CPAP-weaning success. Despite respiratory support and baseline characteristics including FiO₂ and respiratory support that did not differ between cases and controls, control infants achieved oxygen saturations >95% for more time compared with cases. This may suggest improved gas exchange in control infants compared with cases as infants in this study were weaned from CPAP at a median of 4 days after birth, which roughly corresponds to when RDS symptoms and signs typically resolve. Furthermore, in infants with transient to no oxygen requirement, achievement of higher saturations (95–100%) compared with saturations within the limits (90–95%) may not be systematically monitored. Conversely, both control and case infants achieved target saturations for >85% of the time and case infants were not hypoxemic for more time compared with controls as would be expected in infants with little to no oxygen requirement. Analyzing achieved oxygen saturations may therefore provide

Table 2. Respiratory characteristics in cases and controls.

	Control (n = 24)	Cases (n = 12)	P
Postnatal day of CPAP wean, days mean ± SD	4 ± 1.4	4 ± 1.8	0.88
Apneic events with intervention* prior to wean median (IQR)	0 (0–1)	0 (0–1)	> 0.99
Caffeine dose prior to wean, mg/kg mean ± SD	14 ± 5	13.4 ± 4	0.85
Carbon dioxide prior to wean (mmHg) median (IQR)	38 (35–42)	42 (38–43)	0.18
FiO ₂ prior to wean median (IQR)	21 (21–23)	22 (21–25)	0.26
Respiratory support prior to wean n (%)			0.70
CPAP of 4 mm H ₂ O	18 (75)	8 (66.7)	
CPAP of 5 mm H ₂ O	6 (25)	4 (33.3)	
Apneic events with intervention* after wean median (IQR)	0 (0–2)	1 (0–4)	0.23
Carbon dioxide following wean (mmHg) median (IQR)	40 (38–43)	42 (38–43)	0.89
FiO ₂ following wean median (IQR)	21 (21–24)	21 (21–25)	0.37
Respiratory support after wean n (%)			0.50
Room air	9 (37.5)	6 (50)	
Oxygen environment	15 (62.5)	6 (50)	

n number, SD standard deviation, IQR interquartile range, CPAP continuous positive airway pressure, FiO₂ fractional inspired oxygen concentration.
 *Apneic events defined as bradycardic episodes <80 bpm with oxygen desaturation <80% of any duration receiving intervention (e.g., stimulation, increased oxygen).

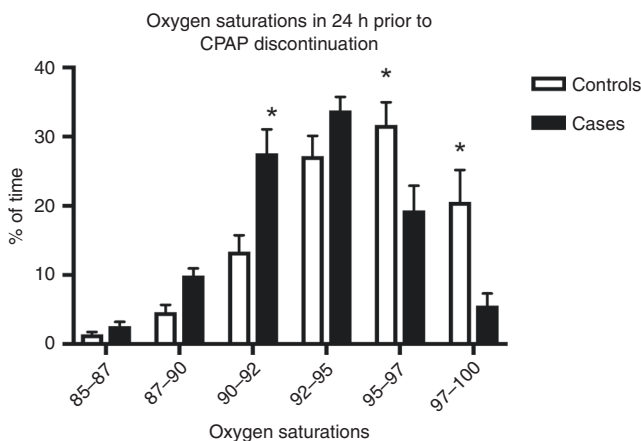


Fig. 2 Achieved oxygen saturations in cases and controls in the 24 h prior to CPAP discontinuation. Controls infants achieved saturations 95–97 and 97–100% for a greater percentage of time than cases. Data represent mean ± standard error of mean. Analysis performed using two-way ANOVA with Sidak's multiple comparisons test.

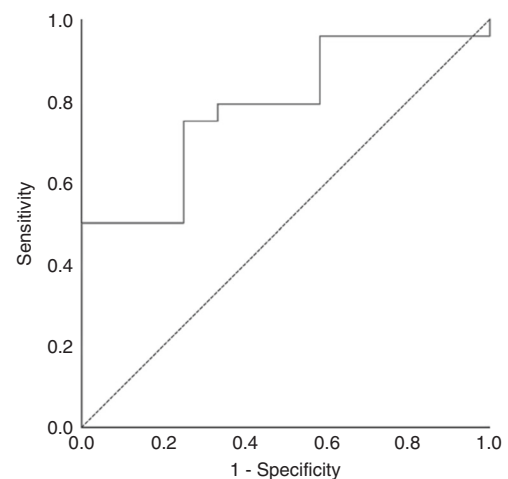


Fig. 3 The area under the curve for oxygen saturation achievement >95% was 0.79 (95% CI, 0.63–0.94). Using a value of 31.6%, the sensitivity and specificity for predicting CPAP-weaning success were 75% and 75%, respectively.

additional, more predictive sensitivity for CPAP-weaning readiness in preterm infants compared with using other respiratory support parameters (e.g., low FiO₂ requirement).

Previous studies have reported the utility of oxygen saturation histogram use in preterm infants. In a previous study comparing oxygen saturation distributions prior to weaning from high flow nasal cannula or CPAP in preterm infants, infants requiring an increase in respiratory support after weaning had oxygen saturations <86% for a longer period of time compared with infants successfully weaned from positive pressure. However, gestational age significantly differed between groups.⁸ A study developing a histogram classification system monitored oxygen saturation stability over the course of hospitalization in preterm infants with FiO₂ >21% and identified five histogram subtypes. Infants with progressively unstable histograms required more respiratory support at term corrected gestation and needed prolonged ventilator support compared with infants achieving

higher oxygen saturations with stable oxygenation patterns.¹⁶ These histogram subtypes cannot be applied to infants in the present study as many infants were on 21% FiO₂ prior to weaning from CPAP. We have also previously reported that systematically monitoring oxygen saturation histogram patterns in preterm infants may reduce death or severe retinopathy of prematurity.⁷

It is unclear whether prolonged CPAP support is lung protective. A trial in preterm infants born at ≤32 weeks' PMA meeting criteria to wean from CPAP were randomized to either 2 weeks of prolonged CPAP or CPAP discontinuation. Infants exposed to prolonged CPAP had improved pulmonary mechanics compared with those infants in which CPAP was discontinued.¹⁷ In a multicenter randomized trial in infants born at <30 weeks' gestation (N = 177), infants were weaned off CPAP using three different strategies: sudden wean to room air, cycled between CPAP and room air with incremental increases

in time in room air, and cycling on and off CPAP to nasal cannula. Infants weaned from CPAP to room air were exposed to fewer days on CPAP compared with other groups and had a lower rate of BPD (12.5%) when compared with infants cycled from CPAP to room air (42%) and cycled from CPAP to nasal cannula (19%). Infants cycled off CPAP also had a longer length of stay compared with infants weaned to room air.⁹ Although not powered to address this question, infants in the present study were weaned from CPAP on postnatal day 4 and there were no differences in BPD between infants that remained off CPAP compared with those infants exposed to additional CPAP.

The strengths of this study include prospective data collection, case-control design to compare infants successfully weaned from CPAP to infants exposed to prolonged CPAP, similar background characteristics between cases and controls, and adequate power to compare achieved oxygen saturation patterns between cases and controls. In addition, histograms are an available tool on bedside monitors and may be readily used to make CPAP-weaning readiness assessments. A limitation of this study is that standardized criteria were not used to identify infants ready to wean from CPAP. In addition, failure criteria were not used systematically to identify infants that would be restarted on CPAP.

In this case-control study of preterm infants on CPAP, oxygen saturation distributions assessed by bedside histograms differed between infants that successfully weaned from CPAP compared with infants subsequently re-exposed to CPAP. As CPAP-weaning failure rates in RCTs of CPAP discontinuation suggest current criteria for CPAP-weaning readiness may be insufficient, oxygen saturation histograms may help predict infants ready to wean from CPAP support. Future studies using achieved oxygen saturations as a criterion for CPAP-weaning readiness may further support the use of histograms as a tool for this clinical context.

AUTHOR CONTRIBUTIONS

Samuel J. Gentle, MD Dr. Gentle made substantial contributions to the concept and design, analysis, and interpretation of data. Dr. Gentle lead drafting of the manuscript and manuscript revision critically important to intellectual content. Dr. Gentle provided final approval of the version of the manuscript being submitted. Namasivayam Ambalavanan, MD Dr. Ambalavanan made substantial contributions to the concept and design, analysis, and interpretation of data. Dr. Ambalavanan contributed to drafting of the manuscript and manuscript revision critically important to intellectual content. Dr. Ambalavanan provided final approval of the version of the manuscript being submitted. Waldemar A Carlo, MD Dr. Carlo made substantial contributions to the concept and design, analysis, and interpretation of data. Dr. Carlo contributed to drafting of the manuscript and manuscript revision critically important to intellectual content. Dr. Carlo provided final approval of the version of the manuscript being submitted.

ADDITIONAL INFORMATION

The online version of this article (<https://doi.org/10.1038/s41390-020-0772-2>) contains supplementary material, which is available to authorized users.

Competing interests The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

- Finer, N. N. et al. Early CPAP versus surfactant in extremely preterm infants. *N. Engl. J. Med.* **362**, 1970–1979 (2010).
- Bamat, N., Jensen, E. A. & Kirpalani, H. Duration of continuous positive airway pressure in premature infants. *Semin. Fetal Neonatal Med.* **21**, 189–195 (2016).
- Abdel-Hady, H. et al. Hemodynamic changes during weaning from nasal continuous positive airway pressure. *Pediatrics* **122**, e1086–e1090 (2008).
- Morley, C. J. et al. Nasal CPAP or intubation at birth for very preterm infants. *N. Engl. J. Med.* **358**, 700–708 (2008).
- Yong, S. C., Chen, S. J. & Boo, N. Y. 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. *Arch. Dis. Child Fetal Neonatal.* **90**, F480–F483 (2005).
- Mols, G., Priebe, H. J. & Guttman, J. Alveolar recruitment in acute lung injury. *Br. J. Anaesth.* **96**, 156–166 (2006).
- Gentle, S. et al. Oxygen saturation histogram monitoring to reduce death or retinopathy of prematurity: a quality improvement initiative. *J. Perinatol.* **40**, 163–169 (2020).
- Mascoll-Robertson, K. K., Viscardi, R. M. & Woo, H. C. The objective use of pulse oximetry to predict respiratory support transition in preterm infants: an observational pilot study. *Respir. Care* **61**, 416–422 (2016).
- Todd, D. A. et al. Methods of weaning preterm babies <30 weeks gestation off CPAP: a multicentre randomised controlled trial. *Arch. Dis. Child Fetal Neonatal.* **97**, F236–F240 (2012).
- O'Donnell, S. M. et al. The NOFLO trial: low-flow nasal prongs therapy in weaning nasal continuous positive airway pressure in preterm infants. *J. Pediatr.* **163**, 79–83 (2013).
- Rastogi, S. et al. Factors affecting the weaning from nasal CPAP in preterm neonates. *Int. J. Pediatr.* **2012**, 416073 (2012).
- Rastogi, S. et al. Gradual versus sudden weaning from nasal CPAP in preterm infants: a pilot randomized controlled trial. *Respir. Care* **58**, 511–516 (2013).
- 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.* **87**, 205–208 (2011).
- Jensen, C. F. et al. Sudden vs pressure wean from nasal continuous positive airway pressure in infants born before 32 weeks of gestation: a randomized clinical trial. *JAMA Pediatr.* **172**, 824–831 (2018).
- Nair, V. et al. Effect of nasal continuous positive airway pressure (NCPAP) cycling and continuous NCPAP on successful weaning: a randomized controlled trial. *Indian J. Pediatr.* **82**, 787–793 (2015).
- Borenstein-Levin, L., Konikoff, L. & Solimano, A. Clinical quantification of SpO2 instability using a new histogram classification system: a clinical study. *Pediatr. Res.* (2019). <https://doi.org/10.1038/s41390-019-0566-6>. [Epub ahead of print].
- Lam, R. et al. The effect of extended continuous positive airway pressure on changes in lung volumes in stable premature infants: a randomized controlled trial. *J. Pediatr.* (2019). <https://doi.org/10.1016/j.jpeds.2019.07.074>. [Epub ahead of print].