Review article

Weaning preterm infants from continuous positive airway pressure: evidence for best practice

Hesham Abdel-Hady, Basma Shouman, Nehad Nasef
Mansoura, Egypt

Background: **Nasal continuous positive airway pressure (NCPAP) is frequently used in preterm infants. However, there is no consensus on when and how to wean them from NCPAP.**

Data sources: **Based on recent publications, we have reviewed the criteria of readiness-to-wean and factors affecting weaning success. A special focus is placed on the methods of weaning from NCPAP in preterm infants.**

Results: **Practical points of when and how to wean from NCPAP in preterm infants are explained. Preterm infants are ready to be weaned from NCPAP when they are stable on a low NCPAP pressure with no (or minimal) oxygen requirement. Methods used to wean from NCPAP include: sudden weaning of NCPAP, gradual decrease of NCPAP pressure, graded-time-off NCPAP (cycling), weaning to high or low flow nasal cannula, and a combination of these methods. The best strategy for weaning is yet to be determined. Cycling-off NCPAP increases the duration of NCPAP and length of hospital stay without beneficial effect on success of weaning. Gradual decrease of NCPAP pressure is more physiological and better tolerated than cycling-off NCPAP.**

Conclusion: **Further studies are needed to reach a consensus regarding the optimal timing and the best method for weaning from NCPAP in preterm infants.**

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Key words: **continuous positive airway pressure; preterm infant; weaning**

Introduction

Nasal continuous positive airway pressure (NCPAP) is frequently used for treatment of respiratory disorders in preterm infants.[1-4] It improves oxygenation via opening the alveoli, recruiting lung volume, stabilizing the chest wall, improving lung compliance, reducing work of breathing, improving thoracoabdominal synchrony, and improving ventilation-perfusion matching.[5-10] It also splints the upper airways[11] and reduces obstructive and central apnea.[12] Early NCPAP in preterm infants reduces mortality, the need for intubation, and the incidence of bronchopulmonary dysplasia (BPD).[13-16]

NCPAP therapy is associated with complications such as nasal trauma which may lead to nasal deformities, gastric distension, pulmonary air leaks, patient discomfort and excessive secretions requiring more frequent suctioning.[16-24] It can impede systemic and pulmonary blood flow in infants with resolving respiratory distress syndrome (RDS).[25] Moreover, this mode of respiratory therapy requires more intensive nursing care.[19,26] Early weaning of preterm infants is beneficial to reduce the above-mentioned complications. However, weaning from NCPAP too soon may lead to increased frequency of apneas, work of breathing, oxygen requirements and the need to put the infant back on NCPAP or mechanical ventilation. It is also more likely to cause atelectrauma. Despite the widespread use of NCPAP in neonatal intensive care units (NICUs), there is no consensus on when or how to wean preterm infants from this mode of respiratory therapy.[3,4,23]

When to wean from NCPAP

One of the most important questions regarding NCPAP therapy is "How long should infants require therapy?". It is generally considered appropriate to evaluate an infant's readiness to come off NCPAP when they are stable on a minimal end-expiratory pressure with no (or minimal) supplemental oxygen requirement.[27] It is critical that a proactive weaning process is in place and followed. The decision is often arbitrary, and based on

Author Affiliations: Neonatal Intensive Care Unit, Mansoura University Children's Hospital, Mansoura, Egypt (Abdel-Hady H, Shouman B, Nasef N)

Corresponding Author: Hesham Abdel-Hady, Mansoura University Children's Hospital, Gomhoria Street, Mansoura 35516, Egypt (Tel: +20 1114328500; Email: hehady@yahoo.com)

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the "judgement and experience" of the neonatologist.

Different "readiness-to-wean" criteria are used by different investigators (Table 1). Some NICUs wean directly from NCPAP of 5 cm H_2O,[2,28] whereas others wean infants at NCPAP of 3-5 cm H_2O.[29,30] The optimal fractional inspired oxygen (FiO_2) at which the preterm infant is ready for weaning is not well defined. Preterm infants requiring FiO_2 >40% are unlikely to be successfully weaned off NCPAP.[24] Some neonatologists wean NCPAP when FiO_2 requirements are <40%[31] or <30%,[2,28,32] whereas others wean the infants only when they have no oxygen requirements.[3,13,29,30]

Predictors of successful weaning

Before considering NCPAP weaning, some NICUs also include parameters such as weight or corrected gestational age (GA). In one study, neonates were successfully weaned off NCPAP at the mean weight of 1611±432 g and the mean postmenstrual age (PMA) of 32.9±2.4 weeks. The duration on NCPAP decreased by 0.4 week for every week increase in GA and decreased by 0.2 week for every 100 g increase in birth weight. Birth weight significantly affected weaning among both intubated and non-intubated neonates. However, no effect of gender or ethnicity on the PMA at successful NCPAP weaning was observed. Weaning from NCPAP was delayed in the intubated preterm neonates.[29] In neonates who were never intubated, maternal chorioamnionitis, anemia and gastroesophageal reflux may affect the duration of NCPAP. Increased length of time on NCPAP in the non-intubated neonates with maternal chorioamnionitis may be due to inflammatory mediators predisposing to chronic lung disease (CLD).[33,34] Failure to wean off NCPAP in presence of gastroesophageal reflux could be related to increased incidence, severity of apnea and frequent aspiration[35] in addition to a higher incidence of BPD.[36] Thus, identification and management of these comorbid conditions are essential to facilitate early weaning of NCPAP and to decrease the number of weaning failures. Among neonates who were intubated, weaning from NCPAP was not associated with any of the previous factors.[29]

Weaning failure

The criteria for failure of weaning from NCPAP are also not clear.[27] Reported criteria used for assessing the failure of coming off CPAP are shown in Table 2.[23,27,28,30-32,37]

How to wean from NCPAP

There are little data on the best way to wean from NCPAP and the best weaning strategy is not known. Despite the paucity of evidence, the practice of weaning NCPAP is very common in NICUs. A survey of 58 neonatal units in the North of England highlighted the lack of consensus, with only 6% of the responders having a written protocol. Furthermore, there was variability in the methods used to wean infants from NCPAP. Some respondents practised abrupt discontinuation of CPAP, but the majority of units (66%) weaned by "time off", 4% by weaning pressure and 30% indicated no set method.[38] In another survey in Australia, 71% of neonatologists reported using a graded-time-off CPAP weaning strategy and 74% used a weaning strategy involving decreasing airway pressure prior to coming off NCPAP. There was a substantial inter-institutional and inter-provider variability within the same NICU in the weaning practices for NCPAP.[27]

Table 1. Criteria for readiness-to-wean form NCPAP

Receiving NCPAP at a pressure of 3-6 cm H_2O for 24-48 h
FiO_2 <30% to keep SpO_2 ≥87% in the preceding 24 h
Hemodynamically stable
No single apnea requiring bagging
Not more than six episodes of apnea requiring stimulation during the preceding 24 h
Less than 3 episodes of self reverting apneas (<20 sec), and/or bradycardias (<100 BPM) and/or desaturations (≤86%) in 1 h during the previous 6 h
Respiratory rate <60/min
No significant chest recession (sternal/diaphragmatic)
Satisfactory arterial blood gases (pH >7.25, $PaCO_2$ <60 mmHg, and base deficit <8)
Tolerates time off CPAP during nursing cares (up to 15 min)
Not currently treated for patent ductus arteriosus or sepsis

NCPAP: nasal continuous positive airway pressure; FiO_2: fractional inspired oxygen; SpO_2: pulse oximeter oxygen saturation; $PaCO_2$: peripheral arterial carbon dioxide concentration; BPM: breath per minute.

Table 2. Criteria for failure of weaning off NCPAP

Increased inspired oxygen concentrations above baseline by ≥10%-15% or decreased SpO_2 <87% despite increasing FiO_2 to a maximum of 60%
Increased oxygen requirements >25% to maintain SpO_2 >86% and/or PaO_2/transcutaneous PaO_2 >45 mmHg
One apneic episode requiring either moderate stimulation or bag-and-mask ventilation
More than one self-correcting apneic episode per h (defined as a bradycardia <100/min with SpO_2 <85% lasting >20 sec) or increased frequency of apnea and bradycardia (>6 apnea requiring stimulation/24 h)
Increased work of breathing (defined as increased respiratory rate >70 BPM, use of accessory respiratory muscles or expiratory grunting or a score of 6-10 on the Silverman-Anderson Respiratory Scale), indicating moderate to severe respiratory distress
$PaCO_2$ >60 mmHg, pH <7.2

NCPAP: nasal continuous positive airway pressure; FiO_2: fractional inspired oxygen; SpO_2: pulse oximeter oxygen saturation; PaO_2: partial pressure of arterial oxygen; $PaCO_2$: peripheral arterial carbon dioxide concentration; BPM: breath per minute.

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Table 3. Methods of weaning of NCPAP

Sudden weaning of NCPAP
Gradual weaning of NCPAP pressure
Graded-time-off NCPAP "NCPAP cycling"
Weaning to high flow nasal cannula
Weaning to low flow nasal cannula
Combinations of the above methods

NCPAP: nasal continuous positive airway pressure.

A recent Cochrane review on weaning preterm infants from NCPAP also highlighted the lack of information available on the weaning from this mode of respiratory therapy.[23] In the absence of specific protocols, weaning from NCPAP has been highly dependent on the physician's expertise and past experiences. Different methods of weaning from NCPAP are shown in Table 3.

Sudden weaning of NCPAP

CPAP is taken "off" completely once the infant fulfills "readiness-to-wean" criteria (Table 1), and the infant remains in oxyhood or air with intention to stay off CPAP. If the discontinuation of the CPAP fails according to pre-specified failure criteria (Table 2), CPAP is recommenced and continued for at least 24 hours. Then, a new evaluation takes place and if the infant again meets the inclusion criteria again, another attempt of sudden weaning can be undertaken.[23,24]

A multicenter randomized controlled trial (RCT) was conducted in Australia on preterm infants <30 weeks GA who were randomized into one of the three methods of ceasing CPAP: 1) method 1 "CeasIng Cpap At standarD criteriA (CICADA)"; 2) method 2 "cycling off gradually"; 3) method 3 "cycling off gradually with low flow cannula (LFNC) oxygen/air during time off NCPAP". They have shown that the CICADA method was superior to the other 2 methods as it significantly reduced duration of NCPAP therapy, duration of oxygen therapy, CLD and the length of hospital stay.[37] Moreover, the CICADA method reduced the time to reach full feeds and stop caffeine.[39] These authors later reported that the introduction of CICADA for ceasing CPAP in their NICU has significantly reduced time on CPAP in preterm infants <30 weeks GA and may have benefits including earlier breastfeeding and lower hospitalization costs.[40]

Gradual weaning of NCPAP

Gradual weaning of CPAP to the lowest limit that may maintain adequate functional residual capacity is followed by stopping NCPAP completely. NCPAP is reduced by 1 cm H_2O every 8 hours to a minimum of 2-3 cm H_2O. Each time the pressure is to be reduced, the infant needs to be evaluated according to "readiness-to-wean" criteria; only if these are still met, will the pressure be reduced. The infant is maintained on this pressure for 12-24 hours and then the NCPAP is discontinued.[32] Weaning the NCPAP may gradually increase respiratory muscle strength without the associated risk of atelectasis. Weaning by reduction in pressure rather than by time cycling was associated with a shorter duration of weaning, and fewer days on CPAP.[32] Similar findings were also reported by Soe et al[41] in 24-27 weeks GA infants, but not in 28-31 weeks GA infants. To date, no data are available on the benefits of sudden weaning versus gradual weaning of NCPAP.

Graded-time-off NCPAP (cycling-off NCPAP)

There are a number of methods of "cycling" described: coming off NCPAP for a predetermined number of hours each day (this can be a single time period: e.g., 4 hours off, 20 hours on; or a number of smaller time periods, e.g., 1 hour off, 5 hours on)[27] or gradually increasing the amount of time off CPAP each day, while maintaining the same NCPAP until total withdrawal of support is achieved (graded-time-off). Todd et al[37] used a fixed length of time on NCPAP and increased the amount of time off NCPAP in between that time period (e.g., have 6 hours on CPAP and 1 hour off, repeated for 24 hours, and then 6 hours on, 2 hours off the following day, and so on). Once the baby was able to tolerate 16 hours "OFF" CPAP, an attempt was made to stop CPAP at the next period off. Rastogi et al[42] have cycled NCPAP off for 3 hours alternating with 3 hours on for 48 hours. If tolerated, NCPAP was kept off for 6 hours and on for 3 hours for the next 48 hours. If the infant tolerated this for 48 hours, the NCPAP was discontinued.

NCPAP cycling may cause "atelectotrauma" (due to alveolar collapse when off NCPAP and re-recruitment once NCPAP recommences), which may lead to lung trauma and increase the risk for BPD.[37] Having periods of time off NCPAP may reduce the incidence of nasal trauma or possibly lead to increased nasal trauma secondary to the frequent re-application of the prongs.[23]

As discussed earlier, two RCTs demonstrated the benefits of sudden weaning versus cycling off NCPAP in very low-birth-weight (VLBW) infants in terms of weaning success and duration of NCPAP therapy.[32,41] These data were confirmed subsequently in a large multicenter RCT which concluded that sudden weaning off NCPAP reduced the length of weaning time, duration of NCPAP, hospital stay, the incidence of BPD and the time to reach full feeds and stop caffeine therapy.[37,39,40] In a recent RCT, graded-time-off weaning strategy from NCPAP was not significantly different from sudden weaning in terms of success of weaning, infants' weight or PMA at time of successful wean, and the length of hospital stay (Table 4).[42]

A meta-analysis including 3 of the above trials concluded that graded-time-off strategy significantly increased the total time on NCPAP as well as the durations of oxygen therapy and hospital stay, and the authors recommended that future trials should compare strategies of weaning pressure to a predefined level, rather than time off, and to define clear criteria for stability prior to complete discontinuation of NCPAP.[23]

Weaning to heated, humidified, high-flow nasal cannulae (HHHFNC)

Stopping NCPAP and starting HHHFNC (air or oxygen if required) is frequently applied in many NICUs. HHHFNC deliver blended gas at flow rates >1-2 L/min and up to a maximum of 6-8 L/min.[43-46] HHHFNC is frequently used for non-invasive respiratory support in preterm infants.[47] Several studies have demonstrated that HHHFNC is as effective as NCPAP for early stages of RDS,[46] postextubation,[46,48,49] and for apnea of prematurity.[50] A recent study[51] has shown that in spite of the differing mechanisms of pressure generation, the application of NCPAP or HHHFNC resulted in comparable effects in terms of breathing pattern, gas exchange, lung mechanics and work of breathing in preterm infants with mild-moderate RDS, when similar end-expiratory pressures were applied. HHHFNC washout the anatomic and physiologic dead space, making minute ventilation more efficient,[52,53] decreasing the inspiratory work of breathing,[54] improving lung mechanics as conductance, compliance and lung elasticity,[55] and improving secretion mobilization.[56] It probably creates positive end expiratory pressure (PEEP).[50,57-60] However, uncertainty regarding the delivered PEEP has raised concerns regarding the safety of HHHFNC in terms of air leak,[59,61] lung trauma and overdistention from the unmeasured and variable PEEP,[62] subcutaneous scalp emphysema, pneumo-orbitis, and pneumocephalus.[63]

Weaning preterm infants from NCPAP to HHHFNC is a common practice in many NICUs,[31,64-66] although there is insufficient evidence to establish the safety or effectiveness of HHHFNC in preterm infants.[44,62,67,68] HHHFNC are perceived by health caregivers as a gentler way to deliver CPAP and relatively easy to apply, while having smaller, less bulky nasal interface that do not need to be as snugly inserted into the nostrils as NCPAP prongs. This leads to improved patient comfort[69,70] and less nasal trauma[46,48,49] and allows greater access to the baby's face, thus improving developmental care.[45]

To date, three single-center studies evaluated the use of HHHFNC as a method of weaning from NCPAP (Table 4). There is heterogeneity between these studies regarding the population studied, type of HHHFNC device and flow levels used. We have previously reported in a RCT that weaning preterm infants >28 weeks GA from NCPAP to HHHFNC limited to 2 L/min was associated with a longer duration of oxygen and respiratory support compared with infants maintained on NCPAP until weaned

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Table 4. Studies comparing different methods of weaning from NCPAP

Study	Study design	Sample size	Population	Comparison	Main results
Soe[41]	Single center RCT	98	24-31 wk gestation	Pressure weaning versus cycling	No difference between both methods in preterm infants ≥28 wk Pressure weaning is more appropriate in preterm infants <28 wk
Singh et al[32]	Multicenter RCT	112	<1500 g	Pressure reduction versus cycling to LFNC	The gradual reduction in NCPAP pressure may facilitate more rapid respiratory weaning compared with cycling to LFNC
Abdel-Hady et al[28]	Single center RCT	60	Preterm infants ≥28 wk gestation	Sudden weaning versus weaning to HHHFNC	No difference in weaning success Weaning preterm infants from NCPAP to HHHFNC is associated with increased exposure to oxygen and longer duration of respiratory support
Todd et al[37]	Multicenter RCT	154	<30 wk gestation	Sudden weaning versus cycling versus cycling to LFNC	Sudden weaning off CPAP was associated with significantly reduced length of weaning, duration of oxygen therapy, chronic lung disease and length of hospital stay
Rastogi et al[42]	Single center RCT	56	≤32 wk gestation	Sudden weaning versus cycling	No difference in success of weaning from NCPAP No difference in infants' weight and postmenstrual age at the time of successful weaning off NCPAP
O'Donnell et al[30]	Two-center RCT	78	<1500 g	LFNC air versus spontaneous breathing	No benefit in weaning VLBW infants from NCPAP to LFNC. However, the CIs were wide enough to accommodate substantial differences in success of weaning from NCPAP No significant differences in length of time to failure and change in heart rate, respiratory rate, oxygen saturation, and respiratory distress score
Fernandez-Alvarez et al[31]	Matched pair cohort study	79	≤28 wk and <1250 g	Weaning to HHHFNC versus LFNC	HHHFNC shortens NCPAP time without increasing overall length of non-invasive respiratory support in very preterm infants Unlike NCPAP, HHHFNC does not seem to increase the risk of nasal trauma and appears to improve cost effectiveness whilst producing otherwise equal respiratory and non-respiratory outcomes

NCPAP: nasal continuous positive airway pressure; HHHFNC: heated, humidified, high-flow nasal cannula; LFNC: low flow nasal canuula; RCT: randomized controlled trial; CIs: confidence intervals; VLBW: very low-birth-weight.

directly to room air. No differences were found between groups regarding success of weaning from NCPAP.[28] Iranpour et al[71] randomized 70 uncomplicated preterm infants (30-35 weeks GA) with RDS 24 hours after early surfactant treatment and immediate extubation to NCPAP to either continuing NCPAP at 6-8 cm H_2O or switching to HHHFNC until respiratory distress and oxygen requirements improved. There were no differences between the groups with regard to short-term morbidities, duration of hospitalization or duration of oxygen treatment. However, infants in the HHHFNC group had less nasal trauma and the nursing staff perceived HHHFNC application easier than NCPAP. In the third study, Fernandez-Alvarez et al,[31] in a matched-pair cohort analysis, compared the outcome of very preterm infants <28 weeks GA with RDS treated with a combination of NCPAP and HHHFNC (8 L/min) versus NCPAP and LFNC (<0.3 L/min). They demonstrated that the use of HHHFNC did not prolong the time of non-invasive respiratory support. Instead, it shortened the time on NCPAP by 50% while reducing the risk of nasal trauma, maintaining the same risk for BPD, and reducing costs by 33%.

A recent retrospective study showed a reduction in the duration of invasive ventilation and CPAP along with a 6% reduction in CLD rates when HHHFNC was used for weaning NCPAP in preterm infants <32 weeks GA. However, using logistic regression, HHHFNC had no significant effect on rates of CLD or home oxygen.[72]

Weaning to low-flow nasal cannula

Many NICUs use LFNC to wean infants from NCPAP.[31,37,62] This involves stopping NCPAP and starting LFNC (oxygen/air at flow rate <1 L/min). Then LFNC is stopped completely once patients are able to maintain saturations between 85% and 93% (or >93% after day 28 of life) in air for over 24 hours.[31] The use of LFNC to deliver CPAP has not been adequately studied and thus we remain unsure of how much pressure, if any, is delivered through LFNC, when used on the preterm infants. Earlier studies have demonstrated that LFNC can deliver CPAP; however, the amount of pressure delivered was unpredictable and inconsistent.[50,57,59]

A small RCT did not demonstrate any benefit in the use of LFNC air in weaning VLBW infants from NCPAP compared with spontaneous breathing. There were no significant differences in other outcomes such as length of time to failure and change in heart rate, respiratory rate, oxygen saturation, and respiratory distress score. The respiratory rate was significantly lower in those randomized to LFNC.[30] As described previously, Todd et al[37] have shown that preterm infants who were cycled off NCPAP with the use of LFNC required a prolonged duration of NCPAP compared with infants who were taken off NCPAP directly. Additionally, Fernandez-Alvarez et al[31] have demonstrated that weaning preterm infants to HHHFNC did not prolong the time of non-invasive respiratory support requirement, instead, it shortened the time on NCPAP by 50% while reducing the risk of nasal trauma and maintaining the same risk for BPD compared with weaning to LFNC (Table 4).

Combinations of the above strategies

Decreasing CPAP pressure to a predefined level and then discontinuing CPAP for a number of hours each day or decreasing CPAP pressure and cycling to HHHFNC or LFNC.

Other precautions

When preterm infants are weaned off NCPAP, special attention should be paid to upper airway suctioning and to keeping the neck in a neutral position to prevent excessive flexion or extension. The presence of weaning protocols in the NICU and the use of methylxanthines during weaning may increase the success of weaning from NCPAP.

Conclusions

Determining the optimal time and best strategy for successful weaning from NCPAP in preterm infants is crucial to reduce unwarranted complications. There is no consensus on defining the optimal timing for weaning. Moreover, the methods of weaning from the NCPAP have been variable and inconsistent across NICUs. The role of other methods of non-invasive respiratory support such as HHHFNC and LFNC is still under investigation. Development of evidence-based guidelines based on clinical characteristics of the infants may help neonatologists to determine the best timing and method for weaning from NCPAP.

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