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Mini-Symposium: What is new in the NICU in 2022 (Part 1)

Non-invasive respiratory support in preterm infants

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Educational aims

The reader will come to:

- Understand the basis and scope of non-invasive respiratory support for preterm infants.
- Appreciate the availability of a wide range of choices and modes for non-invasive ventilation.
- Understand the mechanisms of action of the various modes.
- Review the clinical evidence supporting the use of non-invasive ventilation in preterm infants.
- Be aware of the newer modes and future directions.

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ABSTRACT

Survival of preterm infants has increased steadily over recent decades, primarily due to improved outcomes for those born before 28 weeks of gestation. However, this has not been matched by similar improvements in longer-term morbidity. One of the key long-term sequelae of preterm birth remains bronchopulmonary dysplasia (also called chronic lung disease of prematurity), contributed primarily by the effect of early pulmonary inflammation superimposed on immature lungs. Non-invasive modes of respiratory support have been rapidly introduced providing modest success in reducing the incidence of bronchopulmonary dysplasia when compared with invasive mechanical ventilation, and improved clinical practice has been reported from population-based studies. We present a comprehensive review of the key modes of non-invasive respiratory support currently used in preterm infants, including their mechanisms of action and evidence of benefit from clinical trials.

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INTRODUCTION

Preterm birth (before 37 weeks of gestation) affects a variable proportion of pregnancies ranging between 5% and 18% [1] and seems to be rising in many countries [2]. Although survival of preterm infants has improved over the last few decades, especially for those infants born before 28 weeks gestation, the incidence of long-term morbidities in the population of surviving preterm infants remains substantial [3]. Respiratory failure due to pulmonary immaturity is one of the commonest immediate morbidities among preterm infants, many of whom develop long-term complications of bronchopulmonary dysplasia (BPD, also called chronic lung disease of prematurity, CLD) [4]. Early and ongoing pulmonary inflammation has been implicated in the development of BPD, which is contributed by invasive positive-pressure ventilation and exposure to supplemental oxygen [4]. The use of non-invasive ventilation (NIV) for respiratory support of preterm infants has been associated with a modest reduction in the incidence of BPD [5] and large population-based longitudinal cohort studies suggest a reduction in the use of invasive mechanical ventilation accompanied by an increase in the use of NIV for respiratory support of preterm infants [6,7].

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MODES OF NON-INVASIVE RESPIRATORY SUPPORT

Currently, there is a wide range of NIV options available for the respiratory support of preterm infants [8]. In this review paper, we discuss the following modes in detail, including their mechanism of action and clinical outcomes.

- Nasal continuous positive airway pressure (nCPAP)
- Nasal intermittent positive pressure ventilation (nIPPV)
- Nasal high-frequency oscillatory ventilation (nHFOV)
- Heated humidified high-flow nasal cannula (HHHFNC)
- Low-flow oxygen therapy

NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP)

Mode

Nasal continuous positive airway pressure (nCPAP) is a non-invasive method that provides distending pressure into the airways throughout the respiratory cycle [5,8]. CPAP can be generated by a mechanical ventilator, underwater bubble CPAP, or variable flow CPAP through a flow-driver.

Mechanisms of action

The continuous distending pressure provided by nCPAP helps to support the infant's own effort to increase functional residual capacity. This results in a reduction of work of breathing and atelectasis, improved ventilation-perfusion mismatch, better gas exchange and conservation of surfactant [5,9]. However, the optimal pressure levels for nCPAP in preterm infants remain unclear. A Cochrane review compared 'low' ($\leq$5 cm H_2O) versus 'moderate-high' (>5 cm H_2O) nCPAP pressures and suggested potential benefits from using 'moderate-high' nCPAP pressures [10].

nCPAP also splints the upper airway by increasing the cross-sectional area and reducing the collapse of the lateral pharyngeal walls. This reduces supraglottic airway resistance and decreases obstructive apnoea [9,11]. nCPAP may enhance the Hering-Breuer reflex, leading to improved respiratory drive and more regular breathing [12].

Evidence supporting the use of nCPAP in newborns

Primary mode of respiratory support: A Cochrane review, comparing the use of nCPAP and supplemental oxygen, showed reduced treatment failure (death or need for assisted ventilation), lower use of mechanical ventilation and lower mortality in the nCPAP group but a higher incidence of pneumothorax. No difference was noted for oxygen duration, BPD at 28 days, length of treatment or stay. Because most of the studies included in this review were carried out in the 1970s, this Cochrane review is only of historical importance [12].

nCPAP has the potential to reduce lung damage, prevent progression to respiratory distress syndrome (RDS) and conserve surfactant, particularly if started prophylactically before atelectasis has manifested [5,13]. Based on a small trial, there is uncertainty about the benefits of early nCPAP (at trial entry) on the need for mechanical ventilation, mortality, and incidence of air leak when compared to delayed nCPAP [13]. A 2021 Cochrane review that included 3201 preterm infants compared prophylactic or very early nCPAP with supportive care or mechanical ventilation. Compared to supportive care, prophylactic or very early nCPAP reduced the need for mechanical ventilation and the use of surfactant; no difference in mortality or other clinical outcomes was observed. Prophylactic or very early nCPAP was associated with lower mortality, less BPD at 36 weeks, less treatment failure (need for mechanical ventilation) and less use of surfactant compared to mechanical ventilation. The only trial comparing prophylactic nCPAP with very early nCPAP showed a decreased need for surfactant in the prophylactic nCPAP group. There was insufficient evidence about the effect on BPD, long term neurodevelopmental outcomes or death [5], so the safety of this strategy is yet to be established.

Post extubation: The use of nCPAP post-extubation was compared to supplemental oxygen in a 2003 Cochrane review that included nine trials. nCPAP resulted in decreased respiratory failure and the need for additional mechanical ventilation compared to supplemental oxygen only. It was estimated that six infants needed to be treated with nCPAP after extubation to prevent one extubation failure. When nCPAP was used as rescue therapy in infants given supplemental oxygen, there was a trend towards less need for re-intubation. The use of nCPAP did not result in a significant difference in supplemental oxygen dependency at 28 days [11].

nCPAP and surfactant administration: A Cochrane review suggests that the combination of early nCPAP and surfactant administration might further prevent nCPAP failure [5], although most of the infants included in this review were >28 weeks gestation. Similar results were reported by Miao et al. since the publication of the Cochrane review [14]. The OPTIMIST-A study, an international multicentre randomised controlled trial including 485 infants (recruitment target was 606 infants) born at 25–28 weeks gestation with RDS, compared nCPAP plus minimally invasive surfactant administration with nCPAP only. The study did not show a reduction in death or BPD at 36 weeks gestation (composite primary outcome) in the nCPAP plus minimally invasive surfactant administration group compared to the nCPAP only group [15], although the study terminated before the recruitment was reached.

Weaning off nCPAP

Different strategies for weaning off nCPAP have been described and vary considerably between neonatal units. Strategies include stopping nCPAP completely regardless of the pressure level (sudden wean), gradually decreasing nCPAP pressure before stopping (gradual wean), taking the infant off nCPAP for several hours each day (interval weaning), switching from nCPAP to HHHFNC or low flow oxygen (stepdown weaning), or a combination of these methods [16,17].

A Cochrane review, which included data from 3 studies, suggested that gradual weaning results in a shorter time on nCPAP, oxygen therapy and length of stay compared to interval weaning [17]. A recent systematic review and meta-analysis of 15 trials including 1547 preterm infants [16] suggested that gradual weaning, compared to sudden weaning, may increase the chances of successful weaning at the first attempt but the process took longer, resulting in infants spending longer on nCPAP. Stepdown weaning, compared to sudden weaning, significantly shortened the duration on nCPAP and facilitated earlier discharge but was associated with a longer duration on supplemental oxygen. No benefits were reported for interval weaning. Importantly, none of the weaning strategies was reported to affect the development of BPD at 36 weeks corrected age [16].

Complications of nCPAP

nCPAP interfaces can cause nasal trauma because of excessive pressure exerted on the nasal septum (prongs) or philtrum and glabella (masks), and this remains a major problem in the use of non-invasive respiratory support. It is not clear which interface causes

the most nasal trauma, but infants of lower gestational age are at higher risk. Incorrect application, or infrequent monitoring, are the main risk factors [12,18]. A recent trial suggests that using bi-nasal cannulae (as for high-flow therapy) with a tighter seal may be an alternative to bi-nasal prongs for the delivery of nCPAP [19] and may result in less nasal trauma.

High nCPAP pressures can lead to overdistension and injury to the terminal airways which can result in air-leaks. Infants treated with nCPAP have a higher incidence of pneumothorax compared to infants treated with supplemental oxygen alone, but this effect seems to be less prominent when infants are treated with nCPAP and surfactant [12,14].

Summary

nCPAP is an established mode of NIV for preterm infants with an extensive body of evidence supporting its clinical use. It is recommended for use in all clinical situations where NIV is considered, although some unanswered questions remain on appropriate strategies for weaning from nCPAP.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION (NIPPV)

Mode

Nasal intermittent positive pressure ventilation (nIPPV) provides two levels of pressure: a constant positive end-expiratory pressure (PEEP) and a higher positive inspiratory pressure (PIP). The rate and inspiratory time for the PIP is set, making this a time-cycled pressure limited mode of NIV, mimicking invasive mechanical ventilation [20].

Mechanisms of action

nIPPV provides positive airway pressure throughout the respiratory cycle; the addition of an intermittent higher pressure possibly results in increased mean airway pressure and reopening of partially collapsed airways which further increases tidal volumes, minute volume and functional residual capacity. A backup rate can reduce the frequency of apnoeas and oxygen desaturation episodes [21]. Some devices synchronise the delivery of peak pressure with the infant's drive [20]. Theoretical implications of the advantages of nIPPV are that it provides positive pressure to the lower airways and may result in an augmented inspiratory reflex (Head's paradoxical reflex) [22]. There is significant variation in the settings used to deliver nIPPV, with peak pressure between 10 and 25 cmH_2O, but can vary as much as 10–60 cmH_2O, inspiratory-time between 0.3 and 0.5 s [22].

Evidence supporting the use of nIPPV in newborns

Primary mode of respiratory support: A 2016 Cochrane review compared nIPPV with nCPAP for preterm infants (<37 weeks gestation) as primary management strategy in the first few hours of life. The review included 1061 infants with gestation from 24 to 35 weeks at birth. A significant reduction in respiratory failure and need for mechanical ventilation was noted for infants receiving nIPPV when compared to nCPAP [23]. However, the use of nIPPV did not decrease BPD, except in one study in which the infants had received surfactant before randomization [23].

A more recent systematic review included 35 studies of 4078 neonates with a mean gestational age of 31 weeks. In five studies, infants had received surfactant before randomisation. The review also noted that nIPPV was more effective in decreasing the need for mechanical ventilation and had less treatment failure than nCPAP or the increasingly utilised method of High Flow Nasal Cannula respectively [24]. Interestingly, the authors reported lower BPD rates and death for nIPPV when compared to nCPAP, concluding that nIPPV could be the most effective method to manage respiratory disease in preterm neonates [24].

Post extubation: A Cochrane review including 10 trials with a total of 1431 infants comparing the use of nIPPV versus nCPAP post-extubation from mechanical ventilation reported a reduction of respiratory failure within 48 hours to seven days post-extubation with the use of nIPPV. No significant effects on BPD or mortality were reported when comparing these modes [25]. A recent meta-analysis of 33 studies including 4080 infants with a mean gestational age of 29.2 weeks on the use of nIPPV as a post-extubation mode concluded that the use of both synchronised and non-synchronised nIPPV resulted in greater risk reduction of reintubation in the 7 days following extubation, but suggested that synchronised nIPPV was preferable to prevent reintubation [26].

Adverse effects

The main potential adverse effects of using nIPPV are related to the use of high pressures. However, the latest Cochrane review did not suggest increased gastrointestinal concerns but demonstrated reduced pulmonary air leaks with nIPPV when compared to nCPAP [21].

Non-Invasive neurally adjusted ventilator assist (NIV-NAVA)

In most current ventilators, synchronisation during nIPPV uses a pressure sensor as the leak in the circuit prevents the effective use of a flow sensor. A newer mode of ventilation called NIV-NAVA, which can be used invasively and non-invasively, uses electrical signals from the diaphragm to trigger breaths and provide synchronised assisted support from the ventilator. By doing so the infant determines respiratory rate, inspiratory pressure and inspiratory & expiratory time for each breath [27].

NIV-NAVA has been proposed for use as a primary mode of respiratory support, post-extubation, as an escalation strategy from other modes of NIV and as nCPAP therapy with backup to treat apneas [27]. A recent Cochrane review, which included two cross-over studies comparing NIV-NAVA with nIPPV, was unable to conclude if NIV-NAVA is effective or safe in preventing respiratory failure in preterm infants due to limited data [27]. A randomised controlled trial of 123 very low birth weight infants with RDS did not find clinical differences in outcomes when comparing nCPAP with NIV-NAVA [28].

The use of NIV-NAVA is reported to result in significantly fewer apneas when compared to nCPAP [29] and significantly fewer bradycardic events per day compared to nIPPV [30]. Further adequately-powered clinical trials are needed to establish the efficacy and safety of NIV-NAVA as a mode of respiratory support for preterm infants.

Summary

nIPPV seems to be an effective mode of NIV for respiratory support of preterm infants. Recent evidence suggests that its clinical efficacy may be superior to nCPAP, which may be enhanced by use of more effective synchronisation methods such as NIV-NAVA but more adequately powered studies are needed to establish its place in clinical practice.

NASAL HIGH-FREQUENCY OSCILLATORY VENTILATION (NHFOV)

Nasal high-frequency oscillatory ventilation (nHFOV) combines a continuous distending pressure through a non-invasive interface, similar to nCPAP, with interposed high-frequency oscillations. Physiological mechanisms of action of nHFOV in neonates are limited [31]. Currently, there is no consensus to standardise settings on nHFOV and a wide range of mean airway pressure (6–10 cmH_2O) and frequency (10–35 Hz) for delivering nHFOV have been used when starting nHFOV[32].

nHFOV has mostly been used as a rescue mode for patients failing nCPAP to avoid invasive modes of ventilation, but less so as a primary mode of respiratory support. Initial reports from clinical trials on nHFOV have been encouraging [32,33] and a meta-analysis of five trials showed nHFOV was associated with better carbon dioxide (CO_2) removal and lower risk of intubation with no significant difference in mortality between the two modes. These results were more pronounced in larger babies (>1000 g and >28 weeks gestation), but also with smaller babies when used for post-extubation support [34]. The experience of this relatively new mode is limited compared to the other modes of NIV [35]. More studies are required to establish its place in clinical practice.

HEATED HUMIDIFIED HIGH FLOW NASAL CANNULA (HHHFNC) THERAPY

Introduction

HHHFNC is a recent mode of respiratory support for newborn infants, although it has been available for almost two decades. The use of HHHFNC in neonates became popular [36] before robust clinical efficacy had occurred [37] due to easier access to the infant for staff and parents, easier training and set-up of the system, and better comfort and tolerance in more mature infants [36].

Mode

Currently, devices that can deliver HHHFNC therapy for neonates can be standalone or incorporated into neonatal ventilators. For the delivery of HHHFNC, manufacturers typically recommend cannula sizes that do not exceed more than 50% of the infant's nare size, to allow adequate leak. A comparison between different systems to prevent extubation failure concluded that there were no significant differences in efficacy between the different devices [38].

Mechanisms of action

HHHFNC uses heated humidifiers with all devices. A comparison of different devices demonstrated that at lower flow rates, heating and humidification achieved recommended standards; however, variability was noted at higher flow rates of 8 L/min [39]. As suggested in animal experiments [40] and adults [41], a crossover study in preterm infants confirmed a reduction in pharyngeal end-expiratory CO_2 with increasing flow [42], confirming the effect of dead-space washout with HHHFNC.

In stable preterm infants, HHHFNC is associated with a modest decrease in respiratory rate [43] and a decrease in minute volume with improved peripheral oxygen saturation without alteration in tidal volume [42]. Importantly, in preterm infants, work of breathing was comparable between HHHFNC and nCPAP groups [44,45]. Together with CO_2 washout, changes in respiratory physiology during HHHFNC may reduce metabolic rates and generation of CO_2 in patients, providing additional secondary benefits.

Studies using in vitro newborn airway models showed that HHHFNC generates low distending pressures in the nasal cavity, which increase with increasing prong size (reducing the leak around the prongs) [46] although this was disputed by a recent crossover study [42]. However, distending pressure from HHHFNC remains a controversial topic in neonates with conflicting results from multiple studies [47], partly due to variability in the site of measurement (nasopharynx, oropharynx, pharynx) and the experimental setup (in vitro models or human infants). This is compounded by the lack of proximal pressure measurements on high-flow circuits. On balance, HHHFNC most likely generates clinically significant distending pressures in the neonatal airways.

Evidence supporting the use of HHHFNC in newborns

Although the use of HHHFNC became popular in neonatal units before robust scientific evidence on its efficacy and safety, several research studies have followed since, providing the evidence base for its clinical use.

Primary Mode of Respiratory Support: The Cochrane Neonatal group published a detailed review of HHHFNC in 2016 summarising clinical data from published studies [48]. Five studies comparing HHHFNC with nCPAP/nIPPV for primary support of preterm infants were identified. Almost all of the recruited infants were >28 weeks gestation at birth; thus, there is a lack of data for using HHHFNC in extremely preterm infants as primary support after birth. No statistically significant differences were observed in the clinical outcomes between the infants receiving HHHFNC or nCPAP at birth including for death, BPD, need for intubation within 7-days after randomisation, duration of respiratory support or hospitalisation, pneumothorax, sepsis and nasal trauma.

Since the completion of the Cochrane review [48], several other trials comparing the efficacy of HHHFNC to other modes of NIV as primary respiratory support for preterm infants have been published. The majority of infants were born after 28 weeks of gestational age and little data were available for extremely preterm infants. Two large trials from Australia and one from India concluded that HHHFNC resulted in significantly higher treatment failure within 72-hours compared to nCPAP [49–51]. In contrast, in a single-centre Italian study involving 316 preterm infants between 29–36 weeks of gestation at birth, HHHFNC was found to be non-inferior to nCPAP/BiPAP for the need for mechanical ventilation within 72-hours [52]. An update of the Cochrane review is awaited to pool together results from all of the above studies to provide further guidance on the use of HHHFNC as primary respiratory support in preterm infants.

Respiratory Support after Extubation: The Cochrane review [48] also included six studies comparing HHHFNC with nCPAP after extubation from mechanical ventilation to compare the efficacy in preventing extubation failure. Included infants had a wide range of gestation at birth, and data by gestational groups were reported. No differences were observed for the studied clinical outcomes in the overall results or the subgroup analysis. However, HHHFNC resulted in a significantly lower incidence of nasal trauma compared to nCPAP.

Since this review, a large study conducted in Japan, which included 372 infants born before 34 weeks of gestation, concluded that HHHFNC was inferior to nCPAP in preventing extubation failure within 7-days of extubation [53], while several other smaller published trials concluded that HHHFNC is comparable to nCPAP after extubation. Of interest, one trial from Qatar included 60 infants born between 24 and 28 weeks of gestation and found comparable results up to 5-days after extubation when they were randomised to HHHFNC or nCPAP [54].

HHHFNC for weaning from Respiratory Support: A Cochrane review failed to identify any randomised study looking at strategies for weaning from HHHFNC therapy in preterm infants [55]. Since then, two small studies used HHHFNC as step-down weaning from nCPAP [56,57]. Although the results were comparable between the groups, further evidence will be needed to recommend the use of HHHFNC as a weaning mode of respiratory support from nCPAP.

Summary

HHHFNC has become a popular mode of respiratory support for preterm infants in neonatal units, especially as post-extubation support for moderately preterm infants. Caution is recommended regarding the use of HHHFNC as a primary mode of ventilation in preterm infants, with limited data available for extreme preterm gestations.

LOW FLOW OXYGEN THERAPY

Low flow oxygen is most commonly used as a "step-down" in weaning from respiratory support [58]. Supplemental oxygen is used to maintain acceptable saturation, reduce pulmonary hypertension, prevent periods of desaturation and promote growth. Several factors affect the concentration of oxygen the patient receives, including nasal cannulae size, tidal volume of the infant, respiratory rate, and body weight [58]. Risks associated with using this system are dislodgement of the cannulae, trauma to the face from tape required to keep prongs in place, kinking of tubing or accidental disconnection [59].

The mainstay of monitoring oxygen supplementation is through pulse oximetry, although debate remains regarding target saturations for infants of term age [60,61]. Sleep studies that record heart rate and saturations over a prolonged period are now widely used to manage flow rates for babies requiring low flow oxygen. However, their use is complicated by discordance concerning the interpretation of the results [62]. Polysomnography may be useful; however, its use is not yet widespread, possibly due to the practicalities involved for families and the requirement for specialist equipment and staff. Currently, local guidance appears to be the main reference for the interpretation of oximetry studies. This will be relevant to the individual as it will be specific to the equipment and software used in the local unit to perform and analyse oximetry studies.

A considerable advantage of low flow oxygen is that infants can be managed in low care settings, including at home. Since its introduction, home oxygen has been highly beneficial to family wellbeing and has reduced demands on in-patient services and related costs of admission [63]. National Institute of Clinical Excellence (NICE) guidance (2021) outlines the standard of care for neonates going home on oxygen particularly, emphasising that its use should be led by an outreach or specialist nurse with an overseeing medical lead [64].

Low flow oxygen is a relatively simple and well-established system of supporting oxygen-dependent neonates. However, developments in the monitoring of the delivery of oxygen and oxygen saturations are more likely as we move towards technology that gives greater accuracy and control via monitoring systems.

CONCLUSIONS, FUTURE DIRECTIONS AND RESEARCH PRIORITIES

NIV has assumed a key role in the respiratory support of preterm infants. While invasive mechanical ventilation will continue to have a role in the management of some preterm infants, a significant change in practice has already occurred with a shift away from invasive ventilation toward increasing the use of NIV modes. Newer modes including NIV-NAVA and nHFOV have the potential to benefit preterm infants but additional studies are required to firmly establish their potential by conducting adequately powered clinical trials.

DIRECTIONS FOR FUTURE RESEARCH

- Explore respiratory benefits of the combination of NIV with less-invasive surfactant replacement therapy in preterm infants, including assessing longer term neurodevelopmental outcomes.
- Assess respiratory benefits of newer modes of NIV including NIV-NAVA and nHFOV in adequately-powered randomised clinical trials.
- Clinical trials to identify optimal weaning strategies from various forms of NIV.

CONFLICT OF INTEREST

No conflict of interest.

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