

Neonatal Non-Invasive Respiratory Support: Synchronised NIPPV, Non-Synchronised NIPPV or Bi-Level CPAP: What Is the Evidence in 2013?

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Key Words

Newborns · Respiratory distress syndrome · Ventilation · Non-invasive respiratory support · Non-synchronised nasal intermittent positive pressure · Bi-level positive airway pressure

Abstract

Nasal continuous positive airway pressure (NCPAP) has proven to be an effective mode of non-invasive respiratory support in preterm infants; however, many infants still require endotracheal ventilation, placing them at an increased risk of morbidities such as bronchopulmonary dysplasia. Several other modes of non-invasive respiratory support beyond NCPAP, including synchronised and non-synchronised nasal intermittent positive pressure ventilation (SNIPPV and nsNIPPV) and bi-level positive airway pressure (BiPAP) are now also available. These techniques require different approaches, and the exact mechanisms by which they act remain unclear. SNIPPV has been shown to reduce the rate of reintubation in comparison to NCPAP when used as post-extubation support, but the evidence for nsNIPPV and BiPAP in this context is less convincing. There is some evidence that NIPPV (whether synchronised or non-synchronised) used as primary respiratory support is beneficial, but the variation in study methodology makes this hard to translate confidently into clinical practice. There is currently no evidence to sug-

gest a reduction in mortality or important morbidities such as bronchopulmonary dysplasia, with NIPPV or BiPAP in comparison to NCPAP, and there is a lack of appropriately designed studies in this area. This review discusses the different approaches and proposed mechanisms of action of SNIPPV, nsNIPPV and BiPAP, the challenges of applying the available evidence for these distinct modalities of non-invasive respiratory support to clinical practice, and possible areas of future research.

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Introduction

Endotracheal ventilation is a life-saving treatment for many preterm infants. However, it is associated with increased mortality and morbidity, including bronchopulmonary dysplasia (BPD) [1, 2]. Despite therapeutic advances such as antenatal steroids, surfactant replacement, high-frequency [3], patient-triggered [4] and volume-targeted ventilation [5], more than 40% of infants born below 28 weeks' gestation still develop BPD [6], and in some centres this figure is rising [7].

Although some infants born below 29 weeks' gestation (46–83%) receive endotracheal ventilation [7–9], many others at these gestations can be successfully managed non-invasively from birth, with nasal continuous

positive airway pressure (NCPAP). This observation has led to efforts to find better methods of non-invasive support for those infants who cannot manage with NCPAP alone.

Nasal intermittent positive pressure ventilation (NIPPV) is one such technique, which has been used in several forms. NIPPV may be synchronised with the infant's inspiration or delivered independently of the infant's breathing efforts, and is usually delivered at pressures similar to those used during conventional ventilation. Different modes of ventilation may be applied non-invasively, leading to varying NIPPV terminology such as N-SIMV [10], N-IMV [11] and NI-PSV [12].

In contrast, two alternating levels of NCPAP may be used, described variously as bi-level positive airway pressure (BiPAP) [13, 14], bi-level NCPAP [15] and biphasic NCPAP [16].

This review aims to summarise the evidence for the available methods of non-invasive support, contrasting synchronised NIPPV (SNIPPV) with non-synchronised NIPPV (nsNIPPV) and BiPAP.

Generators and Settings

The majority of studies used conventional ventilators to deliver NIPPV, and delivered NIPPV at pressures similar to or higher than those used prior to extubation (peak pressure 14–24 cm H₂O, positive end expiratory pressure 3–6 cm H₂O) [11, 17–21]. Ventilator-generated NIPPV is used almost exclusively in some parts of the world [22], whereas in the UK in 2007 only 11% of neonatal units using NIPPV did so using a ventilator [23].

NCPAP flow drivers, such as SiPAP (Care Fusion, Yorba Linda, Calif., USA), and its predecessor, the Infant Flow Driver advance (IFDa), can deliver both NIPPV and BiPAP. These are the most commonly used devices in UK and Irish nurseries [23, 24], although there are few studies assessing their clinical effectiveness [13–16]. Flow drivers are limited by the maximum deliverable pressure (11 cm H₂O for the IFDa, and 11–15 cm H₂O for the SiPAP, depending on its operating mode), although chosen set pressures are often well below these maximums [23].

NIPPV and BiPAP use different strategies. In NIPPV the aim is to mimic invasive ventilation, using short inflation times (0.3–0.5 s), variable inflation rates of 10–60/min [11, 17–21, 25–27], with peak pressures and positive end expiratory pressure similar to those used with endotracheal ventilation. In contrast, BiPAP aims to provide two NCPAP levels, over which the infant breathes inde-

pendently. Published studies of BiPAP thus differ from NIPPV in their use of longer high NCPAP times (0.5–1.0 s), lower cycle rates (10–30/min) and ≤ 4 cm H₂O difference between high and low NCPAP levels [13–16].

Interfaces

Short binasal prongs are the most commonly used interface [23, 24] for NIPPV and BiPAP. Short binasal prongs have been shown to reduce rates of reintubation during NCPAP, in comparison to single nasal prongs [28], which have high resistance and greater loss of delivered pressure [29]. Long nasopharyngeal prongs have been used to deliver NIPPV in some studies [18, 21, 30], although abdominal distension has been reported [31]. Nasal masks are also used to deliver NIPPV [23, 24], although no published studies have evaluated them. During NCPAP, masks are sometimes used in the belief that they reduce nasal trauma [32]. However, studies of NCPAP have shown that trauma rates are similar with masks and prongs, but that the sites of trauma are slightly different [32]. Recent trials comparing the efficacy of nasal masks to binasal prongs for NCPAP had conflicting results [33, 34]. With both interfaces, there are frequent leaks from the nose or mouth, which may limit the delivery of NIPPV/BiPAP pressure changes

Use of Synchronisation

Most randomised studies evaluating SNIPPV used a pneumatic capsule to detect abdominal movement [17–19, 30]. A recent crossover study showed that this type of capsule correctly detected inspiration 88% of the time [35]. However, the ventilators using these capsules are no longer commercially available.

The SiPAP device offers synchronisation using a similar abdominal capsule, although this is not approved for use within the United States. Bench top data [36] suggest that at higher breath rates the SiPAP module may not respond to all detected breaths with a pressure peak.

Another form of synchronisation, the use of a pneumotachograph (flow-trigger) to detect inspiratory flow, has been reported by one group [37]. However, flow triggering during non-invasive respiratory support in neonates is affected by leaks at the mouth and nose [38], and others have reported difficulties with this method [39]. Another group used a ventilator's inbuilt pressure trigger to attempt synchronisation [11] and two authors have

synchronised NIPPV using respiratory inductance plethysmography [12, 40].

Recently, a device that synchronises ventilation using a diaphragmatic electromyogram has been marketed. Neurally adjusted ventilator assist offers the attractive possibility of providing not only synchronisation timed with the patient's inspiratory effort, but also providing pressure support proportional to the infant's inspiratory effort [41]. However, it has the disadvantage of being invasive and costly, and to date there are little data on clinical outcomes.

Mechanisms of Action

Pressure Delivery

There appears to be wide variation in delivered pressures during NIPPV [42, 43]. Peak pressure in the prongs is typically substantially below the set peak pressure, with greater differences between set and delivered pressures at higher peak pressures [42, 43]. This may be related to leak around the prongs. Although delivered pressures are below the set peak pressure, they are still above positive end expiratory pressure, thereby increasing mean airway pressure (MAP). It is unclear whether the advantage provided by NIPPV in clinical studies was due to the pressure changes, or simply the provision of a higher mean airway pressure than with NCPAP [43, 44]. These studies measured intra-prong pressure, not intra-thoracic pressure, which may be even lower. NIPPV pressure peaks may not effectively reach the lungs; an observational study in preterm infants found that 5% of NIPPV pressure peaks delivered during central apnoea resulted in chest inflation, and that these inflations produced a tidal volume 27% of that produced during spontaneous breathing [45]. It is possible that this may still be sufficient to assist with 'sigh' breaths.

It has been suggested that NIPPV pressure changes recruit alveoli and may improve and maintain functional residual capacity [1, 19, 46], but there are no clinical trials to support this theory.

Minute Ventilation and Tidal Volume

A short-term study of SNIPPV showed that in comparison to NCPAP of 3 cm H₂O, SNIPPV resulted in significantly higher tidal and minute volumes [47]. However, subsequent studies [12, 35, 40] have failed to replicate these findings.

One of these studies also compared SNIPPV with nsNIPPV [35] and found no difference in tidal or minute volume between NIPPV modes, despite the fact that almost

90% of NIPPV pressure peaks during SNIPPV were delivered in synchrony with spontaneous inspiration (compared with 21–23% of pressure peaks during nsNIPPV).

Work of Breathing

Several studies have demonstrated decreased work of breathing during SNIPPV compared with NCPAP [12, 40, 47]. Additionally, Kiciman et al. [10] demonstrated improved thoraco-abdominal synchrony during SNIPPV compared with both endotracheal CPAP and NCPAP, suggesting more effective chest wall stabilisation during SNIPPV. A crossover study in 16 infants who received both SNIPPV and nsNIPPV described improved thoraco-abdominal synchrony and reduced work of breathing during SNIPPV, compared with nsNIPPV and NCPAP [35].

Gas Exchange

Studies of the effects of NIPPV on oxygen and carbon dioxide levels have produced conflicting results. Two studies reported no differences in oxygenation or CO₂ levels [12, 35] between NCPAP and SNIPPV. One reported better oxygenation with NCPAP [48], whilst a fourth reported better oxygenation and carbon dioxide during SNIPPV, compared with NCPAP [47]. One study of nsNIPPV found lower CO₂ levels but no difference in O₂ levels compared to CPAP [49]. Migliori et al. [14] compared BiPAP with NCPAP and found better oxygenation, respiratory rates and CO₂ levels during BiPAP. These small differences may not be clinically important, or it may be that NIPPV and BiPAP simply allow infants to achieve adequate gas exchange with less work of breathing in comparison to NCPAP. Infants included in these studies were stable on NCPAP prior to study entry, potentially limiting any differences that could be demonstrated from the additional support offered by NIPPV.

Inflammatory Response

Lista et al. [15] conducted a randomised controlled trial (RCT) comparing the effects of BiPAP and NCPAP on pro-inflammatory cytokines, as a marker of bronchopulmonary inflammation, but found no differences between groups.

Use of Non-Invasive Respiratory Support in Specific Clinical Circumstances

Treatment of Apnoea of Prematurity

Two RCTs have compared NIPPV with NCPAP for the treatment of apnoea of prematurity, both using

nsNIPPV. Ryan et al. [42] found no benefit of nsNIPPV in 20 infants <32 weeks' gestation, whereas Lin et al. [25] assessed 34 aminophylline-treated, premature infants and found a significantly greater reduction in apnoeic events in the nsNIPPV group. Four other RCTs have reported apnoea as a secondary outcome measure; two citing reduced apnoeas during NIPPV [17, 49] (one SNIPPV, one nsNIPPV) and the other two studies finding no difference [19, 50] (one SNIPPV, one nsNIPPV). The clinical significance of these contrasting findings is unclear. A crossover study comparing two modes of nsNIPPV (ventilator and IFDa) with two modes of NCPAP (IFDa and 'bubble CPAP') in 16 preterm infants also found no difference in apnoea number between modes [48]. A Cochrane review including the studies by Lin and Ryan concluded that NIPPV may augment the effects of NCPAP in apnoea that is frequent or severe, but only short-term effects were studied, and more data are required before NIPPV could be recommended as a therapy for apnoea [51].

Primary Respiratory Support

SNIPPV as Primary Respiratory Support

An RCT by Kugelman et al. [11] (n = 84) evaluated SNIPPV, compared with NCPAP, as a mode of primary respiratory support. This study used the ventilator's pressure sensor to attempt synchronisation, although the authors acknowledged that they could not verify that synchronisation was achieved. They found significantly lower intubation rates in the SNIPPV group (25 vs. 49%, $p = 0.04$).

nsNIPPV as Primary Respiratory Support

Three trials have compared nsNIPPV with NCPAP as the primary mode of respiratory support after birth [20, 21, 49]. In one study (n = 76), some infants received INSURE (Intubation-SURfactant-Extubation), whilst others did not. 'Failure of treatment' within 48 h occurred in fewer of the nsNIPPV group (13.5 vs. 35.9%, $p = 0.024$) [21]. Two other studies found no difference in intubation rates, one at 4 h of age (n = 88) [49], the other at 72 h of age (n = 200) [20]. If Kugelman's study in fact provided nsNIPPV, this may suggest that NIPPV is beneficial as primary support without the need for synchronisation. A recent meta-analysis combined this 'SNIPPV' study with two nsNIPPV studies [20, 21] and demonstrated a relative risk reduction for intubation in the first 72 h in the NIPPV group compared to NCPAP (RR 0.60, 95% CI 0.43, 0.83) [52].

Biphasic CPAP as Primary Respiratory Support

There are no published RCTs comparing BiPAP with NCPAP as primary respiratory support in which respiratory outcomes were the primary outcome. Secondary outcomes from an RCT investigating inflammatory responses to BiPAP demonstrated that preterm infants with RDS, receiving primary support from BiPAP, had fewer days of respiratory support and supplemental oxygen than those receiving NCPAP [15].

In summary, there is a suggestion that NIPPV (synchronised or unsynchronised) may be advantageous over NCPAP as primary support, but the evidence is not conclusive. BiPAP has not been shown to convey any additional benefit.

Respiratory Support Post-Extubation

SNIPPV Post-Extubation

Four RCTs have compared SNIPPV with NCPAP post-extubation, and all show reduced extubation failure rates in preterm infants [17–19, 37]. Meta-analysis [53] of three studies, which used a pneumatic capsule for synchronisation, showed a clinically important advantage of SNIPPV over NCPAP in preventing extubation failure, RR 0.21 (95% CI 0.10, 0.45) and number needed to treat of three (95% CI 2, 5). A further RCT used an inspiratory flow sensor as a means of synchronising NIPPV and also demonstrated lower re-intubation rates in the SNIPPV group (6 vs. 39%, $p = 0.005$) [37].

nsNIPPV Post-Extubation

Two RCTs have compared nsNIPPV with NCPAP post-extubation. Khorana et al. [50] reported no difference in re-intubation rates at 7 days; however, the groups had significant demographic differences. Ramanathan et al. [26] reported a significant decrease in infants requiring mechanical ventilation at 7 days of age in the nsNIPPV group (17 vs. 42%, OR 3.6, CI 1.5, 8.7, $p = 0.005$). However, in this study the comparison group, by design, received longer duration of initial mechanical ventilation. It is therefore unclear if there is benefit of nsNIPPV over NCPAP, as a post-extubation therapy.

Biphasic CPAP Post-Extubation

One RCT compared BiPAP with NCPAP post-extubation. O'Brien et al. [16] randomised 136 infants <1,250 g (BiPAP settings: upper NCPAP pressure 3 cm H₂O > lower pressure of at least 5 cm H₂O, 20 one-second cycles/min). They found no difference in successful extubation at 7 days; however, the study was underpowered as the trial was stopped early.

In summary, SNIPPV has been shown to reduce extubation failure compared to NCPAP, but trials of nsNIPPV and BiPAP have all had limitations, and these modes have no clear benefit as post-extubation support.

Later Outcomes following NIPPV

Data on in-hospital outcomes in babies receiving NIPPV of any form are limited; few studies have been powered to examine long-term outcomes.

Comparisons with Endotracheal Ventilation

One study randomised 41 surfactant-treated infants of <32 weeks' gestation to either early extubation to SNIPPV (within 90 min), or ongoing mechanical ventilation [30], although very unwell infants were excluded. The primary outcome of death or BPD was significantly lower in the SNIPPV group (20 vs. 52%, $p = 0.03$).

Comparisons with NCPAP

While there are some encouraging non-randomised data [54], RCTs comparing NIPPV or BiPAP with NCPAP have failed to show a convincing effect on BPD. Although nine RCTs have included BPD as a secondary outcome, none of these trials were powered to detect differences in BPD rates. Of these trials, three compared nsNIPPV with NCPAP; two reported no difference in BPD rates [20, 21], and one [26] reported less BPD in the nsNIPPV group (although the comparison group, by design, received longer duration of mechanical ventilation prior to receiving NCPAP). Of four trials comparing SNIPPV with NCPAP, three reported similar BPD rates between groups [17, 19, 37], and the fourth [11] reported a lower rate of BPD during SNIPPV (2 vs. 17%, $p = 0.04$). Neither systematic review including combinations of these trials showed a reduction of BPD with NIPPV [52, 53]. A review by Meneses et al. [52] questioned whether the practice of weaning from NIPPV to NCPAP after the primary outcome period might have limited the long-term benefits, although it could conversely be argued that the risk of BPD would have predominantly been determined by the greater exposure to early mechanical ventilation in the NCPAP group. The two RCTs that compared BiPAP [15, 16] with NCPAP found no difference in BPD rates between groups.

Summary, Conclusions and Future Research

The mechanism of action of NIPPV remains unclear. It is likely that it reduces work of breathing, but the majority of studies have shown little or no effect on ventilation. The infants included in physiological studies have been stable on NCPAP prior to study, and studies of smaller, more preterm, or more symptomatic infants might produce different results.

It seems clear that synchronised NIPPV confers an advantage over NCPAP as a mode of post-extubation respiratory support, but the evidence is less convincing for nsNIPPV and BiPAP. There is some evidence to suggest that NIPPV (synchronised or non-synchronised) may be useful as a mode of primary respiratory support, but the varying approaches in these studies make this difficult to confidently translate into clinical practice. A recently completed trial using the SiPAP device, at the manufacturer's recommended settings, as synchronised primary respiratory support in preterm infants, demonstrated no reduction in intubation rate at 72 h of age compared to NCPAP [55]. BiPAP has not been shown to provide benefit over NCPAP as primary or post-extubation therapy. There is no clear benefit for the use of NIPPV or BiPAP in treating apnoea of prematurity.

While it is helpful, in assessing the evidence, to separate studies by the indication for non-invasive respiratory support, in clinical practice infants will often fulfil more than one of these criteria.

At present, as few neonatal units have access to ventilators, or flow drivers, capable of delivering synchronised NIPPV, most clinicians have no option but to use nsNIPPV. Several ventilator manufacturers are developing synchronisation systems for NIPPV, and new technologies, such as neurally adjusted ventilator assist, may also provide effective synchronisation, but further evidence of efficacy and safety are needed.

Nasal high-frequency ventilation is a concept that has thus far been restricted to a few pilot studies [56–58]. It has the attractive property of obviating the need for synchronisation entirely, and will likely be the subject of future research.

Based on our current knowledge, there is no clear advantage to NIPPV or BiPAP over NCPAP in reducing mortality or important morbidities such as BPD. An update to the Cochrane review, presented recently as an abstract, concluded that there was no advantage in death, or BPD rates, for NIPPV versus NCPAP as post-extubation support [59]. A large international RCT including 1,009 extremely low-birth-weight infants has been completed,

comparing both primary and post-extubation use of NIPPV and/or BiPAP with NCPAP, with a composite primary outcome of death or BPD at 36 weeks' postmenstrual age. Preliminary results indicate that there was no additional benefit or risk conferred by NIPPV/BiPAP in comparison to NCPAP [60]. However, the heterogeneous modes of non-invasive support used and varying experience levels with NIPPV in participating centres mean that these findings will need to be interpreted with caution.

Further adequately designed studies examining later outcomes of NIPPV and BiPAP use are needed. It is clear that non-invasive respiratory support is preferable to prolonged mechanical ventilation when possible [1, 2, 8, 9, 30]. Future work should focus on investigating how available techniques can be best integrated into a complete strategy to prevent BPD, particularly in the most at-risk neonates, soon after birth, when they are most vulnerable to the effects of lung injury [61].

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