REVIEW

Neonatal nasal intermittent positive pressure ventilation: what do we know in 2007?

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Although neonatal nasal intermittent positive pressure ventilation (NIPPV) is widely used today, its place in neonatal respiratory support is yet to be fully defined. Current evidence indicates that NIPPV after extubation of very premature infants reduces the rate of reintubation. However, much is still not known about NIPPV including its mechanisms of action. It may improve pulmonary mechanisms, tidal volume and minute ventilation but more studies are required to confirm these findings. There is some evidence that NIPPV marginally improves gas exchange. More research is needed to establish which device is best, what settings to use or whether to use synchronised rather than non-synchronised NIPPV, and about the way to wean NIPPV. Future studies should enrol sufficient infants to detect uncommon serious complications and include long-term follow up to determine important neurodevelopment and pulmonary outcomes.

Neonatal nasal intermittent positive pressure ventilation (NIPPV) provides non-invasive respiratory support to premature infants who may otherwise require endotracheal intubation and ventilation. NIPPV is the augmentation of continuous positive airway pressure (CPAP) with superimposed inflations, to a set peak pressure. NIPPV may be delivered by nasal mask or prongs, which may be short or long, single or bi-nasal. Some devices attempt to synchronise inflations with the infant's inspiration. The end expiratory pressure, peak pressure, inflation rate and time can all be manipulated. Overlapping terms in the literature include nasopharyngeal-synchronised intermittent mandatory ventilation (NP-SIMV)¹ and nasal bi-level positive airway pressure (N-BiPAP).²

DEVELOPMENT OF NEONATAL NIPPV

Neonatal endotracheal intubation and ventilation are potentially life saving, but they are associated with increased pulmonary morbidity: subglottic stenosis,^{3–4} respiratory infection,⁵ ventilator-induced lung injury^{6–7} and increased risk of chronic lung disease (CLD).^{8–10} Despite use of surfactant, and ventilation techniques, including high-frequency oscillation, patient-triggered ventilation and tidal volume targeting,^{11–12} CLD remains an important cause of neonatal mortality and morbidity.

Neonatal CPAP was first used as an alternative to ventilation in 1971.¹³ Since then it has been

increasingly used to provide respiratory support in place of intubation and ventilation, and it has become established as an effective bridge between ventilation and unsupported breathing.¹⁴ CPAP has been shown to reduce extubation failure,¹⁴ treat respiratory distress syndrome and apnoea of prematurity¹⁴ and reduce rates of CLD.^{14–16} It reduces airways resistance,^{17–18} increases functional residual capacity,^{19–20} stabilises the chest wall,²¹ reduces obstructive apnoea,²² and improves lung volume and oxygenation.^{19–23–25}

Some infants managed with early CPAP develop respiratory failure due to ongoing lung disease,²⁶ apnoea of prematurity²⁷ or progressive atelectasis.²⁸ Studies have shown that in 25–40%^{14–15–29} of low birthweight infants, there is failure to extubate to CPAP. Efforts to reduce these failure rates prompted the use of NIPPV, as it may provide sufficient support to avoid endotracheal intubation in some infants.

The use of NIPPV is well established in many adult^{30–34} and paediatric conditions.^{35–36} In adults with acute exacerbations of chronic obstructive pulmonary disease, kyphoscoliosis and restrictive thoracic disease, NIPPV reportedly improves blood gases, respiratory effort, respiratory rates, tidal volume^{37–38} and ventilatory response to high levels of carbon dioxide. NIPPV is used to aid ventilator weaning and reduce rates of reintubation.^{39–41} In paediatric intensive care, NIPPV has been shown to improve oxygenation and reduce dyspnoea, tachypnoea and tachycardia.³⁵ In these populations NIPPV is given through a tight-fitting mask covering the mouth and nose, or the nose alone, with minimal leak and an in-circuit flow trigger allows synchronisation. For neonatal NIPPV, nasal prongs are used with variable leak via the mouth and nose, and no flow trigger.

Neonatal NIPPV was initially delivered using a face mask (covering the mouth and nose).^{42–44} The technique lost favour following case reports of head moulding and cerebellar haemorrhages.⁴⁵ As very premature infants are now more likely to be extubated early, NIPPV is being used as it might improve respiratory function,^{2–46–47} reduce the rates of reintubation^{1–48–49} and treat apnoea of prematurity.^{50–51}

Abbreviations: CLD, chronic lung disease; CPAP, continuous positive airway pressure; nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PEEP, positive end expiratory pressure; PIP, positive inspiratory pressure; sNIPPV, synchronised nasal intermittent positive pressure ventilation

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HOW DOES NIPPV WORK?

The physiological effects of nasal CPAP (nCPAP) in premature infants with respiratory difficulties are well described,^{52–53} but the mechanism of action of NIPPV remains uncertain. Hypotheses include:

- increasing pharyngeal dilation^{1–49–54–55};
- improving the respiratory drive⁵⁰;
- inducing Head's paradoxical reflex⁵¹;
- increasing mean airway pressure allowing recruitment of alveoli⁴⁹;
- increasing functional residual capacity;
- increasing tidal and minute volume.

EFFECT ON RESPIRATORY PHYSIOLOGY

In a crossover study of very premature infants (<1500 g) after extubation, Moretti *et al*⁴⁶ measured the changes in chest volume with an inflatable jacket, and compared nCPAP with synchronised NIPPV (sNIPPV). The sNIPPV settings were the same as those used during ventilation. They found higher tidal volumes and minute ventilation during sNIPPV. They also found that during sNIPPV transcutaneous carbon dioxide (TcPco₂) was considerably lower and respiratory rate was lower than during nCPAP (TcPco₂ 7.0 kPa *v* 7.3 kPa, respectively; respiratory rate 38/min *v* 44/min, respectively). Migliori *et al*² found that compared with nCPAP, during sNIPPV transcutaneous carbon dioxide (TcPco₂), 20 premature infants (24–31 weeks' gestation) had markedly higher pulse oximeter oxygen saturation (Spo₂ 95.5% *v* 93.4%) and transcutaneous oxygen (TcPo₂ 51.5 mm Hg *v* 49.8 mm Hg), with a slightly lower TcPco₂ (51.1 mm Hg *v* 51.8 mm Hg) and lower respiratory rate (53/min *v* 57.4/min). Previously Ryan *et al*⁵¹ and Lin *et al*⁵⁰ conducted randomised crossover trials comparing NIPPV with nCPAP in infants <32 weeks' gestation with apnoea. Both studies did not find any remarkable changes in blood gases. So NIPPV may lead to a clinically small, but important, improvement in respiratory function in very preterm infants.

EFFECT ON THORACOABDOMINAL SYNCHRONY

Kiciman *et al*⁴⁷ measured thoracoabdominal movement with circumferential strain gauges in 14 premature infants (26–36 weeks' gestation) during sNIPPV. They calculated the phase angle (degree of synchrony) between the chest and abdomen, and showed improved synchronisation during sNIPPV compared with CPAP. They suggested that less chest wall retraction was a reflection of improved pulmonary mechanics during sNIPPV.

NIPPV FOR APNOEA OF PREMATURITY

Two randomised controlled trials have compared NIPPV and nCPAP for the treatment of apnoea.^{50–51} Ryan *et al*⁵¹ randomised 20 premature infants with apnoea, on nCPAP, to a 6-h crossover study of NIPPV or nCPAP. They did not find any differences in number or severity of apnoeas. They noted that during some apnoeas the peak pressure of 20 cm H₂O did not produce chest movement and postulated that these apnoeas were due to upper airway obstruction. In 1998, Lin *et al*⁵⁰ randomised 34 spontaneously breathing infants with apnoea to 4 h of either nCPAP or NIPPV. The NIPPV group had a significant reduction in the severity and number of apnoeas (3.5/h to 0.8/h, compared with 2.6/h to 1.5/h in the CPAP group, *p* = 0.02). However, a meta-analysis of these small trials showed no advantage of NIPPV over CPAP in treating apnoea.⁵⁶

NIPPV AFTER EXTUBATION

Three randomised controlled trials have investigated the effect of sNIPPV and nCPAP after extubation.^{1–48–49} All three studies showed more sNIPPV-treated infants remained extubated at 48 h to 72 h. A pooled analysis of these trials (total 159 infants) showed a significant (*p* < 0.001) absolute risk reduction for extubation failure of 32% using NIPPV,⁵⁶ with a number needed to treat of 3. Some infants randomised to nCPAP, and who fulfilled the reintubation criteria, were not reintubated but were given "rescue" NIPPV. Eight out of nine of these infants remained extubated. The numbers were too small to detect reliable differences in the rate of CLD, days of supplemental oxygen or hospital stay.^{48–49}

NIPPV AS THE PRIMARY MODE OF VENTILATION

Two observational studies in premature infants (mean 31 and 33 weeks' gestation, total *n* = 75) with respiratory distress syndrome indicated that NIPPV may be a feasible alternative to endotracheal intubation.^{55–57} No randomised trials have evaluated NIPPV as the initial mode of respiratory support.

WHAT IS THE BEST DEVICE FOR DELIVERING NIPPV?

Several nasal and nasopharyngeal prongs have been used to deliver NIPPV: Hudson prongs (Hudson-RCI, Temecula, California, USA), Argyle prongs (Sherwood Medical, St Louis, Missouri, USA), 3.0-Fr silicone Bi-nasal Pharyngeal Airway (Vest Inc, Wisconsin, USA), Inca prongs (Ackrad Laboratories, New Jersey, USA), and Infant Flow Prongs (EME, Brighton, UK). No study has compared prong types for NIPPV delivery. In a recent survey of 91 neonatal units in England, all those using NIPPV used short bi-nasal prongs; 50% also used nasal masks (personal communication, L S Owen, C J Morley, P G Davis, 2007). It has been reported that nasopharyngeal tubes may be associated with gastric distension.⁵⁸ No published studies have investigated the efficacy of masks used to deliver NIPPV or CPAP.

IS THERE ANY ADVANTAGE OF NIPPV THAT IS SYNCHRONISED TO THE INFANT'S INSPIRATIONS?

No trials have compared synchronised with non-synchronised NIPPV. Synchronisation, defined as mechanical inflation commencing within 100 ms of the onset of inspiration,⁵⁹ uses a capsule to detect abdominal movement at the start of inspiration. Compared with non-synchronised endotracheal ventilation, synchronised ventilation is associated with reduced work of breathing,⁶⁰ improved pulmonary function,⁶¹ stabilisation of blood pressure⁶² and improved cerebral blood flow patterns.⁶³ These effects have not been investigated in NIPPV, nor are there any published studies on the accuracy of synchronisation devices in NIPPV.

In 1981 Moretti *et al*,⁵⁴ using non-synchronised NIPPV, noted, "the majority of patients became easily adapted and followed the ventilator". In 1999, using synchronised NIPPV, Moretti found higher tidal volumes with synchronised infant-triggered breaths than with inflations triggered by the ventilator in the absence of infant effort (7.9 ml/kg *v* 3.9 ml/kg, respectively).⁴⁶ There have been concerns that non-synchronised NIPPV may deliver high pressure during expiration, with increased risk of raised upper airway pressure and pneumothorax,^{50–64} although there is no evidence to support this. Recently, Jackson *et al*⁵⁸ and Manzar *et al*⁵⁷ introduced non-synchronised NIPPV to their nurseries with apparently good effect, without complications.

WHAT VENTILATOR SETTINGS SHOULD WE USE DURING NIPPV?

The effect of different settings on the success of NIPPV and of changing the settings on clinical status has not been investigated.

Positive end expiratory pressure (PEEP)

In studies published to date, PEEP has ranged from 3 cm H₂O to 6 cm H₂O. No study has investigated the optimal level of PEEP during NIPPV. Meta-analyses of CPAP studies suggest that a pressure of at least 5 cm H₂O is needed to provide benefit over ambient oxygen.¹⁴

Positive inspiratory pressure (PIP)

No studies have investigated optimal PIP during NIPPV. Some NIPPV studies used a PIP similar to that used during ventilation,^{1 46} whereas others used pressures 2–4 cm H₂O higher than pre-extubation PIP.^{49 55 65} One study used enough pressure “to see the chest rise”,⁵⁰ and others chose specific target pressures (16–20 cm H₂O).^{48 51 57} Ryan *et al*⁵¹ noted that despite a set pressure of 20 cm H₂O the pressure generated at the proximal end of the nasal prongs was highly variable (range 8–21 cm H₂O; mean 10 cm H₂O). PIP is limited by some NIPPV devices—for example, SiPAP (Viasys Healthcare, California, USA), which has a maximum pressure of 15 cm H₂O, and Infant Flow Advance (Viasys Healthcare) with a maximum pressure of 11 cm H₂O.

Inflation rate

The optimal rate of inflation during NIPPV has not been investigated. A range of rates have been used, mainly 10–25/min. Two studies reported the use of assist control mode, in which every infant-initiated breath is supported by a ventilator inflation.^{46 55}

Inflation time

Most studies do not mention the inflation time. In those that have done, it was 0.4–0.6 s. Longer inflation times were used because it was thought this might optimise alveolar recruitment,¹ but there was no evidence that this occurred. However, concerns have been raised about the potential for an inflation occurring during spontaneous expiration, potentially inducing high airway pressure with risk of air leak.⁵⁰

Circuit gas flow rate

No studies have investigated the rate of flow to use in the circuit during NIPPV. The circuit flow, and the leak from the device, will influence the PIP achieved during each inflation. Moretti *et al*⁵⁴ suggested that a fast rising pressure wave is necessary to produce successful NIPPV inflations, indicating that flow is important. Studies that have provided details about flow used 8–10 l/min.^{47 50 57} Some devices (Infant Flow Advance and SiPAP, Viasys Healthcare) use variable flows (up to 15 l/min) to generate pressures up to 15 cm H₂O.

WEANING NIPPV

No studies have compared strategies for weaning from NIPPV. In the studies reviewed in this article, infants were weaned according to clinical and blood gas criteria, by reducing rate, pressure and inspired oxygen.

WHAT ARE THE COMPLICATIONS OF NIPPV?

Early in the history of NIPPV concerns were raised about excessive gastrointestinal perforations⁶⁶ and cerebellar haemorrhage with face masks.⁴⁵ These have not been reported in recent studies. Complications of nCPAP are well established and include gastric distension,⁶⁷ nasal trauma^{68–70} and pneumothorax.⁷¹ These effects could reasonably be expected with NIPPV, although none have been formally reported. Some studies suggested using a gastric tube, open to air, to avoid gaseous distension of the stomach during NIPPV,^{1 47} although there is no evidence that this works. Jackson *et al*⁵⁸ described excessive abdominal distension with incorrect nasopharyngeal prong position, until they changed their practice and started using shorter prongs in smaller infants.⁵⁸ Other studies have not reported problems with abdominal distension.

Theoretical complications secondary to high pressure in the nasopharynx include middle ear infection, hearing impairment and chronic mucosal inflammation,¹ although none have been reported. Friedlich *et al* noted a case of epistaxis three days after stopping NIPPV.¹ No other adverse effects of NIPPV have been reported compared with CPAP,^{47–51 55} but none of the studies were powered to look for complications.

WHAT ARE THE LONG-TERM BENEFITS OF NIPPV?

The main focus of studies of NIPPV has been short-term respiratory outcomes. One, small, non-randomised, retrospective case-control study of infants <33 weeks' gestation⁶⁵ compared the effect of sNIPPV (n = 30) and nCPAP (n = 30) after extubation on the incidence of bronchopulmonary dysplasia, nutrition and weight gain. There were significantly fewer infants with bronchopulmonary dysplasia in the sNIPPV group (40% v 73% with nCPAP; p < 0.01). There was no difference between the two groups with regard to weight gain, calorie intake or days of parenteral nutrition. Adequately powered randomised studies are needed to determine the effect of NIPPV on long-term respiratory and neurological health, growth and retinopathy of prematurity.

HOW WIDELY IS NEONATAL NIPPV BEING USED?

In 1986, a survey of 19 tertiary care units in Canada showed more than 50% had tried some form of NIPPV, despite minimal evidence of its efficacy at that time.⁵¹ A recent survey of 91 neonatal units in England showed that 48% of nurseries are currently using NIPPV (personal communication, L S Owen, C J Morley, P G Davis, 2007). The demise of the Infant Star ventilator meant that some units lost the ability to synchronise NIPPV breaths. Recently, new devices designed specifically to synchronise NIPPV with an infant's inspiration may have increased its use. In more current studies the introduction of NIPPV seems to have been well accepted.^{57 58 65}

CONCLUSIONS AND FUTURE WORK

There is evidence that NIPPV, after extubation of very premature infants, reduces the rate of reintubation. There is some evidence for using NIPPV in the treatment of apnoea, but this is inconclusive. There is limited observational evidence that NIPPV may be used as a primary mode of ventilation.

We know little about how NIPPV works. It may improve chest and abdominal synchronisation, tidal volume and minute ventilation. There is limited evidence that NIPPV marginally improves gas exchange. There is no evidence about the best device, what settings to use or whether to use synchronised rather than non-synchronised NIPPV. There is no evidence about the way to wean NIPPV. No RCT has investigated long-term outcomes or was powered to look for uncommon complications.

NIPPV is widely used. However, more research is needed to define its place among techniques of neonatal respiratory support and delineate in exactly what conditions, and by what methods, it provides the most benefit with the least harm.

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IMAGES IN NEONATAL MEDICINE.....

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Newborn with intermittent grunting in the first hours after delivery

Figure 1 Chest x ray before referral to the neonatal intensive care unit. Large amounts of intestines in the left thorax are seen pushing the lung tissue towards the apex and the heart to the right. The stomach is in the abdominal cavity, but few intestinal loops are seen here.

Figure 2 (A) Thoracoscopic view of the abdominal cavity through the diaphragmatic defect. Several intestinal loops are seen in the thorax, and the lung is collapsed. (B) Thoracoscopic closure of the diaphragmatic defect with Ethibond 3×0 non-absorbable sutures.

A newborn baby boy (42 weeks' gestation with good start, Apgar scores 9,10) developed intermittent grunting with slight subcostal retractions in the first hours after birth. At first heart sounds were audible on the left side, but within two hours these shifted to the right side of the chest. The baby's colour changed from pink to pale. A chest x ray (fig 1) showed a left diaphragmatic hernia with displacement of the heart to the right side due to intestinal loops in the left thorax. A thoracoscopy was carried out. There was a small defect in the left posterolateral diaphragm, which was closed primarily without a patch (figs 2 and 3). The baby was rapidly extubated and oral feeding started. A chest x ray taken on the fourth postoperative day showed almost normal findings.

Diaphragmatic hernia has a spectrum of presentations, ranging from non-symptomatic to a life-threatening situation immediately after birth. Symptomatic hernias are treated by surgical closure of the posterolateral defect. With the advent of minimal invasive surgery, in patients with stable cardiorespiratory status, the defect may be closed through a laparoscopic or thoracoscopic approach with or without the use of a patch.^{1 2} In the present case the baby had an envelope-like defect, which was suitable for primary closure. The case illustrates nicely the minimal invasive closure of the diaphragmatic hernia using a thoracoscopic approach.

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