The evidence for non-invasive ventilation in the preterm infant

Eduardo Bancalari, Nelson Clauke

Non-invasive ventilation was among the earliest forms of respiratory support used in infants with respiratory failure in the early seventies. Its use in preterm infants, however, subsided to the use of nasal continuous positive airway pressure (N-CPAP). Continuous distending pressure provided by N-CPAP improves oxygenation by stabilising lung volume in infants with respiratory distress syndrome (RDS), reduces apnoea of prematurity and attenuates distortion of the chest wall during inspiration. The use of N-CPAP as a primary mode of respiratory support to avoid invasive ventilation and facilitate weaning from the ventilator has become standard practice. Although successful in a large proportion of infants, N-CPAP is not always effective in avoiding the need for intubation or preventing extubation failure. This is most evident in the more immature infants who are the ones at a higher risk of developing complications associated with invasive mechanical ventilation.

Nasal intermittent positive pressure ventilation (N-IPPV) is being increasingly used in preterm infants with respiratory failure in lieu of or to facilitate removal from invasive mechanical ventilation. N-IPPV consisting of positive pressure cycles delivered on top of the continuous distending pressure delivered by N-CPAP is used as an intermediate mode of respiratory support between N-CPAP and invasive mechanical ventilation.

Several investigations have explored the physiological and clinical effects of N-IPPV in preterm infants. This manuscript describes the evidence provided by these studies and discusses the areas where further research is needed.

PHYSIOLOGICAL EFFECTS

The proposed mechanisms by which N-IPPV may enhance the support provided by N-CPAP include increased ventilation, higher mean airway pressure, washout of the upper airway anatomical dead space and a possible stimulatory effect of intermittent cycling on the respiratory drive.

Although it is difficult to determine what portion of the positive pressure is transmitted to the distal airways during N-IPPV, physiological data from studies involving the use of N-IPPV in preterm infants shortly after extubation showed increased ventilation and reduced PaCO₂. The improved ventilation was accompanied by reductions in breathing effort and frequency.

In more stable infants N-IPPV can unload the respiratory pump without inducing changes in ventilation or gas exchange. The use of N-IPPV in patient triggered modalities such as nasal assist/control, pressure support or synchronised intermittent mandatory ventilation decreased the breathing effort compared with N-CPAP. In these infants who were able to maintain their own ventilation on N-CPAP, N-IPPV did not improve ventilation. However, in infants with a higher baseline PaCO₂, N-IPPV did increase ventilation when compared with N-CPAP. This observation suggests a greater benefit of N-IPPV in infants with some degree of ventilatory failure or those struggling to maintain adequate ventilation on N-CPAP alone.

Distortion of the preterm infant’s soft chest wall during inspiration was attenuated by synchronised N-IPPV compared with N-CPAP. This is most likely the result of the synchronous increase in airway pressure and a decrease in inspiratory effort.

Nasal bi-level positive airway pressure (N-BiPAP) is a form of nasal ventilatory support where airway pressure increases modestly above the basal N-CPAP level intermittently. Depending on the duration of the cycle, frequency and pressure change, N-BiPAP can be considered as providing either two levels of CPAP or N-IPPV. A possible advantage offered by the intermittent increase in airway pressure is better lung recruitment and volume stability while avoiding the side effects of a continuously applied high N-CPAP level. In preterm infants, N-BiPAP produced a decrease in transcutaneous PCO₂ and an increase in oxygenation which was likely the result of lung recruitment due to the higher distending airway pressure.

CLINICAL EFFECTS OF N-IPPV

Apnoea

In short term studies, N-IPPV appears to be more effective than N-CPAP in reducing the occurrence of apnoea among premature infants who present with frequent apnoea spells but less consistent among infants with infrequent spells (table 1). Trials comparing N-IPPV and N-CPAP after extubation describe severe apnoea as a common cause of extubation failure among infants receiving N-CPAP. The findings of these trials are discussed later.

Respiratory distress syndrome

Clinical reports indicate that N-CPAP failure rates and the need for subsequent mechanical ventilation in small preterm infants with RDS ranges from 20 to more than 50%. Consequently, there is considerable interest in the use of N-IPPV in this population during the initial phase of respiratory failure to avoid the use of invasive ventilation.

Randomised controlled trials in infants with mild to moderate RDS have shown that N-IPPV is more effective than N-CPAP in reducing the need for invasive ventilation during the first week after birth (table 2). The relative efficacy of N-IPPV over N-CPAP varied

<table>
<thead>
<tr>
<th>Table 1</th>
<th>N-IPPV versus N-CPAP in apnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Outcome</td>
</tr>
<tr>
<td>Ryan 1989</td>
<td>n=20, GA: ≤32 w</td>
</tr>
<tr>
<td>Lin 1998</td>
<td>n=18, GA: 25–32 w</td>
</tr>
<tr>
<td>Bisceglia 2007</td>
<td>n=38, GA: 28–34 w</td>
</tr>
</tbody>
</table>

Apnoea frequency in spells per hour.
GA, gestational age; N-CPAP, nasal continuous positive airway pressure; N-IPPV, nasal intermittent positive pressure ventilation.
considerably between studies, which may be explained by different entry criteria and other respiratory interventions. These studies enrolled infants of gestational age ranging from 24 to 34 weeks and used different criteria to define RDS severity. Hence, the populations may differ in terms of risk for N-CPAP failure. Some of these studies involved a brief intubation period and administration of surfactant which likely provided a significant benefit to the subjects and also reduced the risk of failure.

In spite of the reduced need for mechanical ventilation, the effects of N-IPPV on respiratory outcome have not been consistent among the different trials in infants with mild or moderate RDS.15–19 (table 2). Some of these trials showed striking reductions in the incidence of bronchopulmonary dysplasia (BPD) with N-IPPV compared with N-CPAP while other studies showed no or small differences. The reasons for these discrepancies are unclear, but they may be related to differences in the populations enrolled in these studies. The impact of N-IPPV in infants with mild RDS who are likely to do well on N-CPAP alone is expected to be smaller than in infants who are failing N-CPAP and therefore have a greater need for invasive ventilation.

The use of N-IPPV to support early extubation after a brief intubation and surfactant administration was shown as effective as continued invasive ventilation with later extubation and better than N-CPAP on the success of early extubation.19 20 In these studies the incidence of BPD was considerably lower.

**Postextubation**

The advantage of N-IPPV compared with N-CPAP in reducing the failure rates after extubation has been consistently shown in multiple randomised trials.21–24 (table 3). In these trials, severe apnoea and increased PaCO₂ were the most common causes of failure in infants receiving N-CPAP and a larger reduction in extubation failure with N-IPPV was observed among the smaller premature infants and those with worse lung mechanics.2 3

The reported rates of BPD in most postextubation trials have been lower in N-IPPV compared with N-CPAP.22–24 However, although well controlled, these studies were not individually powered to detect significant differences in BPD. Nonetheless, their consistency suggests important advantages of N-IPPV over N-CPAP when used after extubation.24

A preliminary report from the largest randomised controlled trial comparing N-IPPV and N-CPAP in the early phase of respiratory failure or after mechanical ventilation was completed recently. The primary outcome, death or BPD, did not differ between the two treatments. In the entire group of infants or between infants enrolled during the first week and those enrolled after extubation.25 Further analyses of these data are likely to provide a better understanding of the effects of N-IPPV and the factors that determine its efficacy.

The clinical evidence provided by the studies mentioned above indicate N-IPPV is as or more effective than N-CPAP in reducing the need for invasive ventilation or achieving successful weaning from the ventilator. Contrary to what was expected, these findings however did not correlate with clear improvements in long term respiratory outcome.

Because most of the N-CPAP failure and the side effects of invasive mechanical ventilation occur in the more premature infants, there is considerable interest in further evaluating the effects of N-IPPV in the smaller and more immature infants with moderate or severe respiratory failure who are at a higher risk of intubation and BPD. N-IPPV is not likely to offer significant advantages to premature infants in whom the support provided by N-CPAP alone is sufficient. There is also a need to further assess if N-IPPV can be as effective and safer than invasive ventilation when used as the primary modality early after birth.

**Table 2** N-IPPV versus N-CPAP in respiratory distress syndrome

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome</th>
<th>N-CPAP</th>
<th>N-IPPV</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kugelman 2007</td>
<td>n=84</td>
<td>Failure</td>
<td>49%</td>
<td>25%</td>
</tr>
<tr>
<td>GA: 24–34 w</td>
<td>BPD</td>
<td>17%</td>
<td>2%</td>
<td>0.04</td>
</tr>
<tr>
<td>Sai Sunil Kishore 2009</td>
<td>n=76</td>
<td>Failure</td>
<td>41%</td>
<td>19%</td>
</tr>
<tr>
<td>GA: 28–34 w</td>
<td>BPD</td>
<td>10%</td>
<td>3%</td>
<td>NS*</td>
</tr>
<tr>
<td>BW: ≥750 g</td>
<td>Death or BPD</td>
<td>31%</td>
<td>16%</td>
<td>NS*</td>
</tr>
<tr>
<td>Lista 2010</td>
<td>n=40</td>
<td>Failure</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>GA: 28–34 w</td>
<td>BPD</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Meneses 2011</td>
<td>n=200</td>
<td>Failure</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td>GA: 26–33 w</td>
<td>BPD</td>
<td>5%</td>
<td>11%</td>
<td>NS*</td>
</tr>
<tr>
<td>GA: 24–33 w</td>
<td>Death or BPD</td>
<td>42%</td>
<td>40%</td>
<td>NS*</td>
</tr>
</tbody>
</table>

BPD: Defined as oxygen supplementation at 36 weeks postmenstrual age; Failure: Defined as need for intubation.

*Estimated from published data.

†Author's personal communication.

BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; N-CPAP, nasal continuous positive airway pressure; N-IPPV, nasal intermittent positive pressure ventilation.

**Table 3** N-IPPV versus N-CPAP postextubation

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome</th>
<th>N-CPAP</th>
<th>N-IPPV</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedlich 1999</td>
<td>n=41</td>
<td>Failure</td>
<td>37%</td>
<td>5%</td>
</tr>
<tr>
<td>BW: 500–1500 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrington 2001</td>
<td>n=54</td>
<td>Failure</td>
<td>44%</td>
<td>15%</td>
</tr>
<tr>
<td>BW: ≤1250 g</td>
<td>BPD</td>
<td>56%</td>
<td>44%</td>
<td>NS</td>
</tr>
<tr>
<td>Khalaf 2001</td>
<td>n=64</td>
<td>Failure</td>
<td>40%</td>
<td>6%</td>
</tr>
<tr>
<td>GA: ≤34 w</td>
<td>BPD</td>
<td>53%</td>
<td>35%</td>
<td>NS</td>
</tr>
<tr>
<td>Moretti 2008</td>
<td>n=63</td>
<td>Failure</td>
<td>39%</td>
<td>6%</td>
</tr>
<tr>
<td>BW: ≤1250 g</td>
<td>BPD</td>
<td>22%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>32%</td>
<td>16%</td>
<td>NS*</td>
<td></td>
</tr>
</tbody>
</table>

BPD: Defined as oxygen supplementation at 36 weeks postmenstrual age; Failure: Defined as need for reintubation.

*Estimated from published data.

BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; N-CPAP, nasal continuous positive airway pressure; N-IPPV, nasal intermittent positive pressure ventilation.
ventilation did not improve with synchronised or non-synchronised N-IPPV, probably reflecting a relatively good basal lung function in the study infants. Synchronised N-IPPV reduced the spontaneous breathing effort whereas non-synchronised N-IPPV did not, as illustrated in figures 1 and 2. These findings suggest pressure transmission during N-IPPV is improved by synchronisation, but additional investigation is required to determine whether synchronisation may offer advantages in sicker infants who struggle to maintain adequate ventilation on N-CPAP.

Most physiological studies and clinical trials describing positive physiological or clinical effects of N-IPPV involved synchronised delivery of the positive pressure. However, the ventilator capable of providing synchronised N-IPPV used in the majority of these trials is no longer available while other synchronised devices are only available in some countries. Conversely, most studies showing less striking effects used non-synchronised N-IPPV. Although this observation does not provide evidence of the benefits of synchronisation, it underlines the need to further explore this issue. Detection of the onset and ending of the spontaneous inspiration with sufficient sensitivity to assure timely delivery of the pressure cycle and sufficient specificity to avoid auto-cycling is important in N-IPPV. The Graseby pressure capsule used in many trials of N-IPPV is a non-invasive method that can provide adequate synchrony when placed properly. Our data indicate more than 90% of N-IPPV cycles were properly synchronised when using this method. In contrast, during non-synchronised N-IPPV only 25% of the cycles are synchronous with the onset of the infant’s inspiration while other investigators have shown that the preterm infant’s breathing frequency does not become entrained with the ventilator frequency during non-synchronised N-IPPV.

Other methods of synchronisation involve detection of the spontaneous inspiratory flow of the infant. This however may be affected by the large and variable gas leaks that are commonly present during N-IPPV. Increased gas leakage mimic spontaneous inspiratory flow and can result in auto-cycling. Although this can be compensated by manual or automatic adjustment of the flow trigger threshold in the ventilator, there are no published data on the efficacy of the compensatory adjustments. Newer technologies are being developed and tested to improve infant-ventilator synchrony during N-IPPV. One of these, neurally adjusted ventilatory assist, uses the electrical activity of the diaphragm to determine the timing and magnitude of the ventilator pressure during N-IPPV.

At present, the most common modality used to provide N-IPPV is non-synchronised. However, there are no data on the most adequate settings of ventilator frequency, pressure and inspiratory time. This is largely due to the lack of monitoring parameters that would indicate the adequacy of ventilation other than visual assessment of chest expansion and blood gases to guide the adjustment of the ventilator settings during N-IPPV. One limiting factor is gas leakage around the nasal interface and through the mouth which prevents accurate estimation of the inspiratory or expiratory tidal volume.

The clinical benefits of N-IPPV and transmission of the positive pressure in individual patients vary considerably. Further investigation is needed to identify the subgroups of infants that may benefit...
more and the conditions that prevent or facilitate transmission of the N-IPPV pressure.

Proper application of N-IPPV can play a significant role in the success of this strategy in the individual infant. At present time, N-IPPV is generally provided by conventional neonatal ventilators with standard tubing and gas conditioning systems and applied to the patient using the same interfaces used for N-CPAP. Conventional ventilators usually maintain the end-expiratory and peak pressure with a user-set constant circulating flow. Increased gas leakage or opening of the mouth can result in pressure loss unless the circuit flow is manually increased. Newer ventilators can adjust the circulating flow to assure the set pressures are achieved.

Another important aspect is the proper conditioning of the inspired gases. Insufficient humidity can lead to damage and obstruction of the air passages by mucus plugs which may render N-IPPV or N-CPAP ineffective. For this reason, frequent verification of the potency of the air passages is critical during any type of nasal support.

An area that needs further improvement is the patient interface. Although the care has markedly improved, it is not uncommon to find nasal injuries due to excessive pressure applied to keep the interface in place or because the interface itself produces torque on the infant’s nasal septum. Development of better interfaces along with smart monitoring methods to detect patient disconnection, large leaks or flow obstruction are needed.

Although there were early concerns of increased risk of gastrointestinal perforation with the use of N-IPPV recent clinical trials have not confirmed these findings or increased risks of pulmonary interstitial emphysema or pneumothorax.

IN SUMMARY

The available evidence on the advantages or disadvantages of non-invasive ventilation in the premature infant indicates important physiological advantages compared with N-CPAP. Evidence from clinical trials indicates non-invasive ventilation is more effective than N-CPAP in infants with apnoea, in reducing the need for intubation in mild to moderate RDS and in improving the success of extubation. In spite of these findings, non-invasive ventilation has not been proven to confer significant advantages with regard to long term respiratory outcome but there is no evidence that N-IPPV is accompanied by increased risk of adverse events.

Further research is needed to determine the advantages of N-IPPV over N-CPAP in a target population that is at a higher risk of intubation and poor respiratory outcome. This should be extended to investigate whether primary use of non-invasive ventilation soon after birth can provide comparable or better results than invasive ventilation. Analysis of existing and future data from clinical trials should be expanded to examine the effects on the incidence of the more severe forms of BPD.

Development and testing of newer technologies to improve patient interfaces, to synchronise the ventilator with the patient and to improve transmission of the positive pressure are also needed. This should be accompanied by further investigation of conditions that increase or limit the efficacy of non-invasive ventilatory support.

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