Noninvasive respiratory support (NRS) is becoming increasingly more popular as a method of respiratory support in sick newborn infants. NRS refers to respiratory support provided without use of an endotracheal tube. This support consists of continuous positive airway pressure (CPAP), continuous negative expiratory pressure (CNEP), and noninvasive positive-pressure ventilation (NIPPV). Oxyhoods and nasal cannulae may also provide NRS and are briefly discussed in this chapter as well.

Confusing terminology has evolved as this rapidly developing field has expanded, resulting in a veritable alphabet soup of acronyms used to describe various methods of NRS. Unfortunately, such variations can result in confusion among readers of the neonatology literature. In Table 8-1 we have compiled the diverse group of acronyms we have encountered that relate to this topic. In Table 8-2 we list the acronyms we prefer, which are used throughout this chapter. These reflect what we believe to be the most commonly applied terms.

Continuous distending pressure (CDP) is a general term defined as the maintenance of an increased transpulmonary pressure during the expiratory phase of respiration. CPAP, PEEP, and CNEP are each types of CDP. The basic goal when one treats with any form of CDP is to help provide distension of the lungs, thereby preventing collapse of the alveoli and terminal airways during expiration.

The acronym CPAP reflects a positive pressure applied throughout the respiratory cycle to the airways of a spontaneously breathing baby. Positive end-expiratory pressure (PEEP) refers to the positive pressure applied during the expiratory phase of respiration to a mechanically ventilated neonate. Continuous negative expiratory pressure (CNEP) may also be applied transthoracically to similarly distend distal airways. However, it is a technique rarely used in infants during the past four decades. A variety of CDP devices available today allow “breaths” to be delivered above the baseline CPAP pressure; such breaths may be synchronized or nonsynchronized to the infant’s own breaths. The goal of these devices is to enhance CO₂ removal and stimulate breathing. Various CDP devices provide an adjunct to weaning infants off mechanical ventilation after they have been extubated and also help manage apnea of prematurity. They are used for a variety of other respiratory conditions associated with (1) decreased functional residual capacity; (2) atelectasis; (3) right-to-left cardiac or intrapulmonary shunting; (4) ventilation-perfusion mismatch; (5) alveolar edema; (6) aspiration of noxious substances; (7) increased airway resistance; (8) chest wall and airway instability; and (9) obstructive apnea.

In this chapter, we have attempted to present a broad overview of the current status of NRS. As part of this review, we refer to relevant Cochrane Collaboration reviews. For readers unfamiliar with the Cochrane Collaboration, it is an organization in which members perform systematic reviews of randomized, controlled trials in order to produce unbiased and precise estimates of the effect of a treatment on outcomes of clinical importance. A number of such reviews have been completed concerning NRS. Readers interested in the various reviews concerning neonates may go to the following website to peruse the topics: http://www.nichd.nih.gov/cochrane/cochrane.htm. This website is provided for free by the National Institute of Child Health and Human Development, a division of the National Institutes of Health (NIH).

## Background and Historical Aspects

The history of NRS is largely the history of CPAP. Although many neonatologists believe this technique to be a relatively recent innovation, it was described for use in newborn infants almost a century ago. In his 1914 textbook on diseases of the newborn infant, Professor August Ritter von Reuss describes an apparatus (Fig. 8-1, A) that is virtually equivalent to the “bubble CPAP” that is used today (Fig. 8-1, B). We are uncertain why this concept was abandoned from the care of neonates during the ensuing 60 years. The application of positive airway pressure in the clinical management of adult patients with lung disorders dates back to the 1930s. Poulton and Oxon, Bullowa, and Barach et al. described use of positive pressure via face masks for acute respiratory insufficiency, pneumonia, and pulmonary edema, respectively.

During the 1940s, positive pressure was introduced for high altitude flying. Because of the recognition of potential complications of CDP caused by its effects on major blood vessels, the ensuing two decades it was used, but only sporadically in clinical practice. In 1967 PEEP was added to mechanical ventilation in conjunction with peak inspiratory pressure to treat hypoxemia in adults with acute respiratory distress syndrome (ARDS). In neonates that were mechanically ventilated during the 1960s, it was a common practice to allow the positive pressure at end-expiration to fall to 0 cm H₂O.
A landmark report in 1971, Gregory and colleagues recognized that the grunt was produced by the partially closed glottis produced the audible grunt. In an attempt to increase pressure in the airways and maintain dilatation of their alveoli. Limited air escaping through the partially closed glottis during expiration. Widespread alveolar collapse is the predominant pathophysiology of that disorder. Harrison and colleagues described the initial clinical use of CPAP to maintain alveolar stability (via either an endotracheal tube or a head box) in premature infants with RDS. During this decade a simple approach to providing CPAP was widely used, application via binasal prongs, known as nasal CPAP (NCPAP). Alternative methods of providing CPAP were occasionally described (see subsequent section on delivery of CPAP). During the 1970s, it was commonly believed that air leaks (such as pneumothoraces) were more common with CPAP than with mechanical ventilation. Gastric distension during CPAP was frequently observed too. The hard nasal prongs often were not tolerated by neonates. In addition, intermittent mandatory ventilation (IMV), first described in the early 1970s, quickly became the standard of care for supporting the lungs of sick newborn infants, and remained so for three decades. For these reasons the use of CPAP fell out of favor during this period.

Exogenous surfactant therapy has clearly decreased the morality rate of very-low-birth-weight (VLBW) neonates with less than 1500 g birth weight. Other chapters in this textbook describe additional ways of ventilating infants that were developed during the 1980s and 1990s, such as high-frequency ventilation and patient-triggered ventilation, in an attempt to further improve pulmonary outcomes. To date, however, none of these techniques have substantially improved either morbidity (e.g., air leaks and chronic lung disease) or mortality. Over the past 15 years, there has been a resurgence of interest in CPAP as a gentle way of maintaining patency of alveoli and allowing sufficient gas exchange.

Atelectotrauma is both a cause and consequence of lung injury. It is a process of individual lung units collapsing and then requiring higher pressures to reopen. Unfortunately, some areas of the lungs may remain collapsed, whereas others become overventilated. The collapse of some lung units, as well as the overexpansion of others, may injure lung parenchymal elements and the alveoli themselves. The process of closing and reopening, particularly when there is excess alveolar distension, may lead to inflammation and the release of cytokines. This process has been termed biotrauma.

Volutrauma is regional overdistension of the lungs resulting from large tidal volume breathing. Such breaths may damage the pulmonary capillary endothelium and the basement membranes. As a consequence, fluid, protein, and blood may leak into the airways and alveoli. This

A classic clinical finding in nonintubated premature infants with respiratory distress syndrome (RDS) is an expiratory grunt. Widespread alveolar collapse is the predominant pathophysiology of that disorder. Harrison and colleagues recognized that the grunt was produced by the infants who would close their glottises during expiration in an attempt to increase pressure in the airways and maintain dilatation of their alveoli. Limited air escaping through the partially closed glottis produced the audible grunt. In a landmark report in 1971, Gregory and colleagues described the initial clinical use of CPAP to maintain alveolar stability (via either an endotracheal tube or a head box) in premature infants with RDS.

Use of CPAP in neonates during the 1970s was welcomed with enthusiasm as the “missing link” between supplemental oxygen and mechanical ventilation to treat RDS. During this decade a simple approach to providing CPAP was widely used, application via binasal prongs, known as nasal CPAP (NCPAP). Alternative methods of providing CPAP were occasionally described (see subsequent section on delivery of CPAP). During the 1970s, it was commonly believed that air leaks (such as pneumothoraces) were more common with CPAP than with mechanical ventilation. Gastric distension during CPAP was frequently observed too. The hard nasal prongs often were not tolerated by neonates. In addition, intermittent mandatory ventilation (IMV), first described in the early 1970s, quickly became the standard of care for supporting the lungs of sick newborn infants, and remained so for three decades. For these reasons the use of CPAP fell out of favor during this period.

Exogenous surfactant therapy has clearly decreased the mortality rate of very-low-birth-weight (VLBW) neonates with less than 1500 g birth weight. Other chapters in this textbook describe additional ways of ventilating infants that were developed during the 1980s and 1990s, such as high-frequency ventilation and patient-triggered ventilation, in an attempt to further improve pulmonary outcomes. To date, however, none of these techniques have substantially improved either morbidity (e.g., air leaks and chronic lung disease) or mortality. Over the past 15 years, there has been a resurgence of interest in CPAP as a gentle way of maintaining patency of alveoli and allowing sufficient gas exchange.

Atelectotrauma is both a cause and consequence of lung injury. It is a process of individual lung units collapsing and then requiring higher pressures to reopen. Unfortunately, some areas of the lungs may remain collapsed, whereas others become overventilated. The collapse of some lung units, as well as the overexpansion of others, may injure lung parenchymal elements and the alveoli themselves. The process of closing and reopening, particularly when there is excess alveolar distension, may lead to inflammation and the release of cytokines. This process has been termed biotrauma.

Volutrauma is regional overdistension of the lungs resulting from large tidal volume breathing. Such breaths may damage the pulmonary capillary endothelium and the basement membranes. As a consequence, fluid, protein, and blood may leak into the airways and alveoli. This

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIPAP</td>
<td>Bi-level positive airway pressure</td>
</tr>
<tr>
<td>CDP</td>
<td>Continuous distending pressure</td>
</tr>
<tr>
<td>CNEP</td>
<td>Continuous negative expiratory pressure</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Noninvasive positive pressure ventilation</td>
</tr>
<tr>
<td>NP-CPAP</td>
<td>Nasopharyngeal continuous positive airway pressure</td>
</tr>
<tr>
<td>NP-SIMV</td>
<td>Nasopharyngeal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NP-SIMV</td>
<td>Nasopharyngeal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NSIMV</td>
<td>Nasal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NSIPPV</td>
<td>Nasal synchronized positive-pressure ventilation</td>
</tr>
<tr>
<td>NV</td>
<td>Nasal ventilation</td>
</tr>
<tr>
<td>PDP</td>
<td>Positive distending pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>SNIPPV</td>
<td>Synchronized nasal intermittent positive-pressure ventilation</td>
</tr>
</tbody>
</table>

*Note that different acronyms are used to mean the same thing, and sometimes the same acronym is used to mean different things.

**TABLE 8-1** Confusing Status of Acronyms Concerning Continuous Distending Pressure*

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIPAP</td>
<td>Bi-level positive airway pressure</td>
</tr>
<tr>
<td>CDN</td>
<td>Continuous distending pressure</td>
</tr>
<tr>
<td>CNEP</td>
<td>Continuous negative expiratory pressure</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>DPAP</td>
<td>Directional positive airway pressure</td>
</tr>
<tr>
<td>ETCPAP</td>
<td>Endotracheal tube continuous positive airway pressure</td>
</tr>
<tr>
<td>HFNC</td>
<td>High flow nasal cannulae</td>
</tr>
<tr>
<td>IFD</td>
<td>Infant flow driver</td>
</tr>
<tr>
<td>NC</td>
<td>Nasal cannulae</td>
</tr>
<tr>
<td>NCPAP</td>
<td>Nasal continuous positive airway pressure</td>
</tr>
<tr>
<td>NC-CPAP</td>
<td>Nasal continuous positive airway pressure</td>
</tr>
<tr>
<td>n-CPAP</td>
<td>Nasal continuous positive airway pressure</td>
</tr>
<tr>
<td>NEEP</td>
<td>Negative end-expiratory pressure</td>
</tr>
<tr>
<td>NHFV</td>
<td>Nasal high frequency ventilation</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Noninvasive positive pressure ventilation</td>
</tr>
<tr>
<td>NPPV</td>
<td>Noninvasive positive pressure ventilation</td>
</tr>
<tr>
<td>NPSIMV</td>
<td>Nasopharyngeal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NP-SIMV</td>
<td>Nasopharyngeal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NSIMV</td>
<td>Nasal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NSIPPV</td>
<td>Nasal synchronized positive-pressure ventilation</td>
</tr>
<tr>
<td>NV</td>
<td>Nasal ventilation</td>
</tr>
<tr>
<td>PDP</td>
<td>Positive distending pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>SNIPPV</td>
<td>Synchronized nasal intermittent positive-pressure ventilation</td>
</tr>
</tbody>
</table>

*Acronyms presented in this table are used in this chapter.

**TABLE 8-2** Preferred Acronyms Concerning Continuous Distending Pressure*

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIPAP</td>
<td>Bilevel positive airway pressure</td>
</tr>
<tr>
<td>CDP</td>
<td>Continuous distending pressure</td>
</tr>
<tr>
<td>CNEP</td>
<td>Continuous negative expiratory pressure</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>HHNC</td>
<td>High-flow nasal cannulae</td>
</tr>
<tr>
<td>HIFV</td>
<td>Infant Flow system (variable flow nasal CPAP)</td>
</tr>
<tr>
<td>NC</td>
<td>Nasal cannulae</td>
</tr>
<tr>
<td>NCPAP</td>
<td>Nasal continuous positive airway pressure</td>
</tr>
<tr>
<td>NHFV</td>
<td>Nasal high frequency ventilation</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Nasal intermittent positive-pressure ventilation</td>
</tr>
<tr>
<td>NPPV</td>
<td>Nasopharyngeal continuous positive airway pressure</td>
</tr>
<tr>
<td>NSIMV</td>
<td>Nasopharyngeal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NRS</td>
<td>Noninvasive respiratory support</td>
</tr>
<tr>
<td>NSIMV</td>
<td>Nasal synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>NV</td>
<td>Nasal ventilation</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>VFD</td>
<td>Variable flow driver</td>
</tr>
</tbody>
</table>

*Acronyms presented in this table are used in this chapter.
process also promotes lung inflammation. It does not take much to initiate the cascade of lung injury. In preterm animals, as few as six manual tidal ventilations of 35 to 40 mL/kg administered to preterm lambs before surfactant treatment resulted in lung injury and decreased response to exogenous surfactant.  

The term barotrauma refers to purported injury from the pressure used to inflate the lungs. Although barotrauma was once thought to be a major factor in producing lung injury, atelectotrauma, volutrauma, and biotrauma are currently believed to be the key elements. An extensive discussion of the pathophysiology of chronic lung disease can be found in Chapter 23.

Optimal lung inflation is defined as the lung volume at which the recruitable lung is open but not overinflated.  

The art of medicine in the newborn intensive care unit (NICU) is to achieve optimal lung volume in neonates with respiratory disorders. CPAP is one method many clinicians believe best achieves optimal lung inflation with resultant good oxygenation and ventilation, without the
use of an endotracheal tube. Using CPAP, care must be taken not to decrease the distending pressure below the closing pressure of the majority of the alveoli, but instead to achieve the lowest possible pressure that will maintain open alveoli without overdistension.

Reviews of NCPAP over the past two decades will refer to the 1987 publication of Avery et al., who surveyed eight NICUs to assess the incidence of chronic lung disease (CLD). The frequency of CLD in that report was lowest at Babies and Children’s Hospital, Columbia University, New York. That center reportedly used NCPAP considerably more often than the other seven NICUs. Many clinicians have been influenced by the “Columbia” approach in which “bubble CPAP” is used early in the course of respiratory distress of both premature and term-gestation infants.

As part of this strategy, clinicians often accept hypercapnia with \( \text{Paco}_2 \) levels up to 65 mm Hg (8.7 kPa) or higher, \( \text{Pao}_2 \) levels as low or lower than 50 mm Hg (6.7 kPa), and pH values as low as 7.20. This general approach has been used in that institution for more than 30 years. Despite the promulgation and widespread acceptance of this approach, to date there are no published randomized, controlled trials (RCTs) that validate its superiority over any other management strategy or technology. There are no long-term outcome studies comparing neurologic, pulmonary, and other findings among infants treated in this manner with others who are managed differently. Additionally, clinicians should be concerned about the potentially deleterious effects of “permissive hypercapnia” on cerebral autoregulation and the developing brain.

Van Marter and colleagues assessed the differences in outcomes between the Columbia NICU and two NICUs in Boston. Although CLD was less common at Columbia, this review has been criticized because of differences in patient populations, indications for mechanical ventilation, and other treatment strategies, as well as the definition of CLD that was used. Much of the apparent success of the Columbia approach has been attributed to the diligent management of sick neonates by a single senior clinician. A rigorously designed, randomized, controlled trial (RCT) is sorely needed to assess whether or not bubble CPAP will truly prevent or mitigate CLD. Nevertheless, knowledge of the Columbia experience has contributed to the flurry of research concerning CPAP over the past 20 years.

### Methods of Generating Continuous Distending Pressure

Following Gregory’s initial publication demonstrating success using CPAP in premature infants, efforts were made to simplify the manner in which CPAP was generated, as well as the mode of delivery. Kattwinkel et al., as well as Caliuni-Pellegrini and colleagues, described devices in which binasal prongs were used for delivery. These methods were standard for a number of years. In the subsequent section, various methods of CPAP delivery (prongs, mask, and others) are described later in this chapter.

The gas mixture delivered via CPAP is derived from either a continuous flow or variable flow source. From the 1970s through the 1980s, only continuous flow was used. Continuous flow CPAP consisted of gas flow generated at a source and directed against the resistance of the expiratory limb of a circuit. In ventilator-derived CPAP, a variable resistance in a valve is adjusted to provide this resistance to flow.

As part of this strategy, clinicians often accept hypercapnia with \( \text{Paco}_2 \) levels up to 65 mm Hg (8.7 kPa) or higher, \( \text{Pao}_2 \) levels as low or lower than 50 mm Hg (6.7 kPa), and pH values as low as 7.20. This general approach has been used in that institution for more than 30 years. Despite the promulgation and widespread acceptance of this approach, to date there are no published randomized, controlled trials (RCTs) that validate its superiority over any other management strategy or technology. There are no long-term outcome studies comparing neurologic, pulmonary, and other findings among infants treated in this manner with others who are managed differently. Additionally, clinicians should be concerned about the potentially deleterious effects of “permissive hypercapnia” on cerebral autoregulation and the developing brain.

A second method of continuous flow CPAP is the so-called “bubble” or water-seal CPAP (see Fig. 8-1, B), the method advocated at the Columbia University NICU. With bubble CPAP, blended gas flows to the infant after being heated and humidified. Typically, nasal prong cannulae are secured in the infant’s nares, such as with the Hudson® prongs (Hudson Respiratory Care, Inc., Temecah, Calif) (Fig. 8-2) or Inca® prongs (Ackrad Laboratories, Inc., Cranford, NJ). The distal end of the expiratory tubing is immersed under either 0.25% acetic acid or sterile water to a specific depth to provide the approximate level of CPAP desired. Clinicians must be cautious when using this method, however, because the level of CPAP is always higher than the submerged depth of the expiratory tubing and is flow dependent.

---

**Figure 8-2** A representation of the positioning and appearance of Hudson nasal prongs, which are commonly used for NCPAP. (From Arch Dis Child Fetal Neonatal Ed 85:F82-F85, 2001; used with permission.)
The device consists of two coaxially positioned tubes connected by a ring (Fig. 8-3). The device then is connected to a single nasal prong or to binasal prongs. The device works via the Venturi principle to generate pressure and is a continuous-flow CPAP system. The Benveniste gas-jet valve is typically connected to a blended gas source and then to the patient (Fig. 8-4).

Over the past 15 years, variable-flow CPAP has come into widespread use. The technique was developed by Moa et al. to reduce the patient’s work of breathing. CPAP is generated by varying the flow delivered to the infant’s nares and a specially constructed nosepiece is employed. These devices use the Bernoulli effect and gas entrainment via dual injector jets directed toward each nasal prong to maintain a constant pressure (Figs. 8-5 to 8-10). With the variable-flow system, when the infant makes a spontaneous expiratory breathing effort, there is a so-called fluidic flip, which causes the flow of gas going toward the nares.

Lee and colleagues observed vibrations of infants’ chests during bubble CPAP at frequencies similar to those used with high-frequency ventilation when compared to ventilator-derived CPAP. Lee’s group found bubble CPAP to result in decreased minute ventilation and respiratory rate. These authors speculated that the observed vibrations enhanced gas exchange. Pillow et al. described similar findings in the lamb model. However, in both of these studies, bubble CPAP was delivered via an endotracheal tube, not nasal prongs. Data obtained using a NCPAP model suggest that these oscillations are quite minimal and unlikely to contribute in a significant way to ventilation. Morley et al. assessed bubble CPAP in a randomized, crossover trial. The bubbles were generated at various rates, from “slow” to “vigorous.” These investigators found that bubbling rates had no effect on carbon dioxide, oxygenation, or respiratory rate. The gas-exchange mechanisms of the bubble CPAP set-up must be further explored to elucidate whether there is a to-and-fro oscillatory waveform that truly augments ventilation.

The Benveniste gas-jet valve (Dameca, Copenhagen, Denmark) has been used extensively in Scandinavia. The device consists of two coaxially positioned tubes connected by a ring (Fig. 8-3). The device then is connected to a single nasal prong or to binasal prongs. The device works via the Venturi principle to generate pressure and is a continuous-flow CPAP system. The Benveniste gas-jet valve is typically connected to a blended gas source and then to the patient (Fig. 8-4).

Lee and colleagues observed vibrations of infants’ chests during bubble CPAP at frequencies similar to those used with high-frequency ventilation when compared to ventilator-derived CPAP. Lee’s group found bubble CPAP to result in decreased minute ventilation and respiratory rate. These authors speculated that the observed vibrations enhanced gas exchange. Pillow et al. described similar findings in the lamb model. However, in both of these studies, bubble CPAP was delivered via an endotracheal tube, not nasal prongs. Data obtained using a NCPAP model suggest that these oscillations are quite minimal and unlikely to contribute in a significant way to ventilation. Morley et al. assessed bubble CPAP in a randomized, crossover trial. The bubbles were generated at various rates, from “slow” to “vigorous.” These investigators found that bubbling rates had no effect on carbon dioxide, oxygenation, or respiratory rate. The gas-exchange mechanisms of the bubble CPAP set-up must be further explored to elucidate whether there is a to-and-fro oscillatory waveform that truly augments ventilation.

The Benveniste gas-jet valve (Dameca, Copenhagen, Denmark) has been used extensively in Scandinavia. The device consists of two coaxially positioned tubes connected by a ring (Fig. 8-3). The device then is connected to a single nasal prong or to binasal prongs. The device works via the Venturi principle to generate pressure and is a continuous-flow CPAP system. The Benveniste gas-jet valve is typically connected to a blended gas source and then to the patient (Fig. 8-4).

Over the past 15 years, variable-flow CPAP has come into widespread use. The technique was developed by Moa et al. to reduce the patient’s work of breathing. CPAP is generated by varying the flow delivered to the infant’s nares and a specially constructed nosepiece is employed. These devices use the Bernoulli effect and gas entrainment via dual injector jets directed toward each nasal prong to maintain a constant pressure (Figs. 8-5 to 8-10). With the variable-flow system, when the infant makes a spontaneous expiratory breathing effort, there is a so-called fluidic flip, which causes the flow of gas going toward the nares.
Figure 8-6  Attachment of nasal prongs to the Infant Flow Driver prior to insertion in an infant’s nares. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

Figure 8-7  Placement of the nasal prongs and Infant Flow Driver pressure generator in a mannequin’s nares. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)
Figure 8-8  Lateral view of a mannequin on which the Infant Flow Driver is attached. Note the proper fixation of the device. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

Figure 8-9  Schematic representations of the “fluid flip” of the variable-flow CPAP device, the Infant Flow Driver. A, During the child’s inspiration, the Bernoulli effect directs gas flow toward each nostril to maintain a constant pressure. B, During the child’s exhalation, the Coanda effect causes inspiratory flow to “flip” and leave the generator chamber via the expiratory limb. As such, the child does not have to exhale against high inspiratory flow, and work of breathing is decreased compared to continuous-flow CPAP. The residual gas pressure enables stable levels of CPAP to be delivered to the child. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)
either short (6-15 mm) or long (40-90 mm). It is probably more accurate to refer to the former as nasal prongs and to the latter as nasopharyngeal prongs. The acronym for nasal CPAP (NCPAP) is often used in reference to both. A single nasopharyngeal prong is sometimes used to transmit CPAP, and typically consists of an endotracheal tube that has been cut and shortened and then inserted through one of the nares into the nasopharynx.

There are multiple types of binasal prongs. Two examples are noted in Figures 8-10 and 8-11. The nasal prongs used with the Infant Flow Driver are depicted in Figures 8-6 and 8-7. Unfortunately, little comparative data is available to guide clinicians in choosing one type of prong over another. Some prongs, such as those used with the IFS, are specific to the device (Fig. 8-12). Prongs may vary in the type of material, length, configuration, and diameters (both inner and outer). These aspects will affect the resistance to flow in a particular device and, as a result, the pressure entering the device may differ considerably from that entering the child’s nares or nasopharynx. DePaoli et al. compared the pressure drop for five different CPAP devices at various rates of gas flow. These authors found great variation between devices in the pressure drop. Although the least amount of drop-off occurred with the Infant Flow system, these authors cautioned that their findings do not establish clinical superiority of one mode of NCPAP or nasopharyngeal CPAP (NPCPAP) over any other. DePaoli and colleagues have published a more in-depth appraisal in their Cochrane review characterizing NCPAP devices and pressure sources.

Currently two variable-flow CPAP systems are commercially available. The Infant Flow has been the most extensively evaluated and is marketed by Cardinal Health (Dublin, Ohio). The Arabella® system (Hamilton Medical, Reno, Nev.) has a flow-generating chamber that varies slightly from the IFS, although the same principles (Venturi, Bernoulli, and Coanda) apply. These two systems appear to function similarly. Several investigators have assessed whether differences exist among the various methods of delivering NCPAP. Liptsen et al. compared work of breathing in bubble vs. variable-flow CPAP in 18 premature infants. These investigators found more labored and asynchronous breathing with bubble NCPAP compared to variable-flow NCPAP. Boumed and colleagues compared variable-flow NCPAP with ventilator-driven, continuous-flow NCPAP. They described increased tidal volume and improved breathing synchrony with the variable-flow device compared to the ventilator-driven NCPAP.

**Devices Through Which CPAP Is Provided**

Multiple nasal devices are available through which continuous-flow CPAP may be delivered. The devices may be to “flip” around and to leave the generator chamber via the expiratory limb (Figs. 8-9, A and B), thus assisting exhalation. This phenomenon is due to the Coanda effect, which describes the tendency of a fluid or gas to follow a curved surface. A residual gas pressure is provided by the constant gas flow, enabling stable CPAP delivery at a particular pressure during the entire respiratory cycle.

A extensive description of the physiology of variable-flow CPAP can be found elsewhere. Klausner et al. used a simulated breathing apparatus and found the work of breathing via nasal prongs to be one-fourth that of continuous-flow CPAP. Pandit et al. assessed work of breathing in premature infants treated with either continuous-flow or variable-flow NCPAP. They found the work of breathing to be significantly less with variable-flow NCPAP. Additionally, the variable-flow devices appear to be able to maintain a more uniform pressure level compared to continuous-flow CPAP. This may be the reason for the improved lung recruitment seen with variable-flow CPAP of this type.

Currently two variable-flow CPAP systems are commercially available. The Infant Flow has been the most extensively evaluated and is marketed by Cardinal Health (Dublin, Ohio). The Arabella® system (Hamilton Medical, Reno, Nev.) has a flow-generating chamber that varies slightly from the IFS, although the same principles (Venturi, Bernoulli, and Coanda) apply. These two systems appear to function similarly.

Several investigators have assessed whether differences exist among the various methods of delivering NCPAP. Liptsen et al. compared work of breathing in bubble vs. variable-flow CPAP in 18 premature infants. These investigators found more labored and asynchronous breathing with bubble NCPAP compared to variable-flow NCPAP. Boumed and colleagues compared variable-flow NCPAP with ventilator-driven, continuous-flow NCPAP. They described increased tidal volume and improved breathing synchrony with the variable-flow device compared to the ventilator-driven NCPAP.
associated with complications (e.g., trauma from the tube, vagal response, infection).

The head chamber (head box) and face chamber, although noninvasive, never gained wide acceptance because of technical difficulties and mechanical disadvantages. The head chamber is a closed system that permits use of low flows. The chamber seals around the infant’s neck, thus limiting access to the child’s face. It is difficult to administer in infants weighing less than 1500 g. The devices are very noisy and have been associated with complications such as hydrocephalus, nerve palsies, and local neck ulceration from mechanical compression by the neck seal. The face chamber was originally described by Alhstrom et al. and consists of the application of CPAP via a mask covering the entire face. The mask is held in place by negative pressure. This system is simple, effective, and there are no reported patient complications or mechanical problems such as loss of pressure during administration. There is reported success in using the face chamber for treating RDS and in weaning infants. The major limitations are lack of access to the infant’s face and the cumbersome method of administration.

The face mask is another simple, effective mode for administering continuous distending pressure in the treatment of RDS in preterm infants and is associated with relatively less work of breathing compared to nasal prong CPAP. The mask must cover both nose and mouth and be securely placed with a good seal to prevent loss of pressure. However, severe gastric distension may be produced. An orogastric tube could relieve this distension, but loss of pressure may occur because the tube must pass under the edge of the face mask. Other reported pressure-induced effects include trauma to the facial skin and the eyes, as well as the occurrence of intracerebellar hemorrhage and gastric rupture. Hypercapnia due to excessive CO₂ retention from increased dead space of the mask may result if the infant cannot compensate by increasing ventilation. For all of the reasons stated above, CPAP is seldom applied...
Nasal cannulae (NC) are typically used to provide supplemental oxygen (Fig. 8-14). However, depending on the flow rate, size of the NC, degree of leak, and size of the nares, these devices may also provide distending pressure. As no pop-off valve is present on currently available NC, pressure generated is uncontrolled and may be substantial. Cannulae can also be easily dislodged; it is not unusual to pass by a child being treated with NC and to note that the cannulae are not in the nares but on the cheek or in the mouth or elsewhere. NC and humidified high-flow are discussed further later in this chapter.

Nasal and nasopharyngeal prongs remain the most common methods of administering CPAP in neonates. Because infants are generally obligate nose breathers, CPAP may be facilitated when delivered directly into the nose. The most common complications with these devices are obstruction by secretions and kinking of nasopharyngeal prongs in the pharynx. Infants may lose pressure through today with a head chamber, face chamber, or face mask.

Nasal masks are a relatively recent innovation available with the variable-flow systems. A small, soft mask is attached to the pressure generator (Figs. 8-13, A and B). Such masks are markedly smaller than face masks; hence there is little additional dead space. Nasal masks may be useful when the infant’s nares are too small to accept the nasal prongs. Some units also use them in conjunction with nasal prongs, alternating several hours on and off each device to minimize the pressure effects on the nares of the prongs. However, a good seal must be present to prevent pressure loss with the nasal mask. There are no published data concerning the safety and efficacy of nasal masks.

Figure 8-13  A and B, The nasal mask used with the Infant Flow Driver continuous-flow NCPAP system. The mask is attached to the pressure chamber in the same location as nasal prongs. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)
The Benveniste gas-jet valve’s use in neonates was first described in 1968. Jacobsen and colleagues described the “minitouch” approach in which very-low-birth-weight (VLBW) infants (neonates less than 1500 g birth weight) were managed with minimal handling and early use of NCPAP via the Benveniste valve. They compared their experience over 1 year with that of a previous 2-year-long period in which most VLBW infants with respiratory failure were intubated and treated with mechanical ventilation. Gitterman et al. compared outcomes of VLBW infants during two periods: (1) 1990: most infants were not treated with NCPAP and (2) 1993: generalized use of NCPAP was implemented. These authors used Hudson prongs. The method of pressure generation was not stated. They found that during the second epoch fewer infants required mechanical ventilation. There were no differences in CLD or mortality.

Lindner and colleagues similarly addressed management of extremely low-birth-weight (ELBW) infants (birth weight less than 1000 g) during two different epochs. In 1994, ELBW infants were generally intubated and ventilated immediately after delivery once initial resuscitation was accomplished with a mask and bag. By 1996, however, management had changed. During the latter period, ELBW infants had a nasopharyngeal tube placed in the delivery room and initial continuous pressure of 20 to 25 cm H₂O was applied for 15 to 20 seconds. The infants were then managed with NPCPAP at 4 to 6 cm H₂O. This group occasionally received ventilator breaths via the NP tube until there was sufficient respiratory effort achieved by the child. The authors reported that during the latter period (1996), the percentage of babies never needing intubation and mechanical ventilation was 25%, compared with 7% during 1994. Moreover, the infants born in 1996 had lower frequencies of CLD and intracranial hemorrhages (ICHs), as well as shorter hospital stays. There were no differences in mortality.

DeKlerk and DeKlerk also performed a historical comparison of two groups of infants, birth weight 1000 to their open mouths while undergoing NCPAP or NPCPAP. Thus many clinicians actively try to prevent pressure loss by means such as placing a pacifier in the child’s mouth or by using a strap under the infant’s chin to close the mouth (Fig. 8-15). Fortunately, when NCPAP and NPCPAP are applied, there is often enough downward pressure on the palate that it is frequently contiguous to the tongue, providing a natural seal with minimal to no pressure loss through the mouth.

**Clinical Use of CPAP: Anecdotal Experiences**

Much of the literature describing CPAP use in neonates consists of anecdotal experiences: case reports, case series, and cohort-comparison studies (concurrent or historical). Few randomized, controlled trials (RCTs) have been performed. The former carry considerably less strength than RCTs in validating the safety and effectiveness of a therapy. Nevertheless, to present a comprehensive review of CPAP, available literature, including anecdotal experiences, is summarized here.
1499 g, over a 5-year period. During the first part of that period, early intubation and ventilation were frequently performed, whereas during the latter part of the period, infants were routinely placed on NCPAP when they demonstrated respiratory distress. The DeKlerks used bubble CPAP delivered via Hudson nasal prongs. These authors reported that during the second epoch, fewer infants required mechanical ventilation or exogenous surfactant. However, they did not find differences in mortality or CLD.

Kavvidia and colleagues assessed a group of 36 infants managed postextubation with (1) NCPAP via the Infant Flow device (IFD); (2) NCPAP via a single nasal prong; or (3) no CPAP. There were no differences in lung function after 24 hours. The nasal prong group had a significant reduction in supplementary oxygen concentration after 24 hours. Kurz assessed the effect of NPCPAP on breathing pattern and incidence of apneas in preterm infants. Thirteen preterm infants who were weaning from single-prong NPCPAP were evaluated for 2 hours on NCPAP and for 2 hours off any CPAP. During NPCPAP, the respiratory rate was significantly lower. Additionally, there were fewer obstructive apnea periods, less severe apnea-associated desaturation episodes, and more central apnea events. During NPCPAP, infants spent significantly more time in a state of quiet breathing.

Clinical Use of CPAP: Randomized, Controlled Trials

Several randomized, controlled trials (RCTs) have been performed assessing CPAP for resuscitation or early management in the delivery room, for early management of respiratory distress syndrome (RDS), as treatment for apnea of prematurity, and for postextubation management after mechanical ventilation. The trials essentially consist of comparisons of CPAP with a standard therapy or comparisons of different types of CPAP.

Effects of CPAP or PEEP

Finer et al. conducted a feasibility trial addressing the effects of CPAP or PEEP in premature infants less than 28 weeks’ gestation from initial resuscitation in the delivery room; 104 infants were randomized to either no CPAP and 100% oxygen or to CPAP/PEEP using a T-piece resuscitator (NeoPuff™ Infant Resuscitator, Fisher & Paykel, Auckland, New Zealand). Overall mean birth weight of subjects was approximately 775 g and mean gestational age was approximately 25 weeks. Delivery room intubation was needed for 49% of the CPAP/PEEP group vs. 41% of controls. Intubation at some point during hospitalization was required in 78% of the CPAP/PEEP group vs. 82% of controls (not symptomatic [NS]). Death was more likely in the CPAP/PEEP group (27% vs. 13%, \( P = 0.07 \)), as was the incidence of pneumothoraces (13% vs. 9%, NS). The incidence of chronic lung disease was not assessed. Although this was a feasibility trial, the numbers enrolled were more than in the majority of CPAP studies. No positive benefits were noted from early delivery room management with CPAP/PEEP, and the complications of death and pneumothoraces were more common among infants receiving this therapy.

CPAP vs. Intubation and Ventilation

Morley and colleagues randomized 610 premature infants (25-28 weeks’ gestation) in the delivery room at 5 minutes after birth to CPAP or to intubation and ventilation. The CPAP infants were initially treated with either a short single nasal prong or binaural prongs at a pressure of 8 cm H2O. The primary outcome was the combined endpoint of death or bronchopulmonary dysplasia (BPD), defined as the need for oxygen at 36 weeks’ postmenstrual age. Although there was a trend for CPAP babies to have less death/BPD (34% vs. 39%), this difference was not statistically significant. There was a 50% decrease in the use of surfactant in CPAP-treated neonates (\( P < 0.001 \)). Although there was a significant decrease in the number of ventilator days in the CPAP group, this difference was only 1 day. Of note, the CPAP-treated infants were significantly more likely to develop pneumothoraces (9% vs. 3%, \( P < 0.001 \)).

Value of Nasopharyngeal CPAP

A number of investigators have assessed the value of nasal or nasopharyngeal CPAP as primary therapy for premature infants with RDS. Verder and colleagues randomized premature infants with moderate to severe RDS to either NCPAP alone (\( n = 33 \)) or to NCPAP plus surfactant (\( n = 35 \)). They used the Benveniste gas-jet valve to provide NCPAP in both groups. In the surfactant group, infants were transiently intubated and given Curosurf® (Chiesi Farmaceutici, Parma, Italy) followed by several minutes of mechanical ventilation. These infants were then extubated and placed on NCPAP. The NCPAP plus surfactant group was significantly less likely to subsequently require mechanical ventilation (15/35, 43%) compared to the NCPAP-only group (28/33 [85%], \( P = 0.003 \)). Nevertheless, there were no differences at 28 days of life in mortality, grade 3 or 4 intracranial hemorrhage or periventricular leukomalacia (PVL), or need for oxygen. Verder et al. subsequently performed a second small trial to assess whether “early” administration of Curosurf (median age 5.2 hours) was better than “late” administration of this surfactant when infant’s respiratory status had worsened (median age 9.9 hours). This was not a prophylaxis versus rescue surfactant trial. The Benveniste gas-jet valve was the method of NCPAP. The neonates who received surfactant earlier were significantly less likely to require mechanical ventilation prior to discharge (8/33 [24%] vs. 17/27 [63%], \( P = 0.005 \)).

In a group of 36 premature infants with RDS, Marazza et al. randomized subjects to either the IFS or to bubble NCPAP delivered via a single nasal prong. Although IFS-managed infants had more rapid declines in oxygen requirement and respiratory rate, there were no differences between groups in the need for mechanical ventilation or the total duration of respiratory support.

Sandri and colleagues randomized 230 premature infants (28-31 weeks’ gestation) to either prophylactic use of NCPAP (started within 30 minutes of birth) or to “rescue” NCPAP (applied once the infants required an \( F IO_2 \) greater than 0.40 to maintain oxygen saturation levels...
greater than 93%). NCPAP was administered with the IFS in all infants. There were no significant differences between groups in the need for exogenous surfactant (23.8% vs. 22%) or in the need for mechanical ventilation (12% in both groups).

Thompson et al.\textsuperscript{58} randomized 237 neonates of 27 to 29 weeks’ gestation to one of four groups: (1) early NCPAP with prophylactic surfactant; (2) early NCPAP with rescue surfactant if needed; (3) early mechanical ventilation with prophylactic surfactant; or (4) early mechanical ventilation with rescue surfactant if needed. NCPAP was given via the IFS, whereas Curosurf was the surfactant used in this trial. There was significantly less need for mechanical ventilation in the two NCPAP groups during the first 5 days of life. Nevertheless, there were no significant differences among the groups in either mortality or oxygen dependency (at either 28 days of life or at 36 weeks’ postmenstrual age). Although this trial was fairly large and the results have been frequently quoted since 2001, we are disappointed that there has never been a published manuscript concerning the study in a peer-reviewed medical journal.

In an interesting variation, Goldstein et al.\textsuperscript{59} randomized seven mature infants (35 or more weeks’ gestational age) to either ventilator-generated NCPAP \((n = 3)\) or to negative end-expiratory pressure (NEEP) \((n = 4)\) via the Emerson negative pressure chamber (J.H. Emerson Co., Cambridge, Mass.). The NCPAP infants were placed at 4 cm H\(_2\)O, whereas the initial pressure in the NEEP group was −4 cm H\(_2\)O. Infants in the NEEP group were weaned to room air significantly faster than the NCPAP infants \((P < 0.05)\).

**INSURE Approach**

The “INSURE” approach to VLBW infants has been described. Basically, this consists of Intubation, surfactant administration, and rapid extubation to NCPAP. The original Verder trial\textsuperscript{24} used this approach. Dani and colleagues\textsuperscript{60} randomized 27 total infants with RDS in a nonblinded fashion to either INSURE or to surfactant/mechanical ventilation. Their infants were approximately 29 weeks’ gestation. These researchers found the INSURE approach resulted in a decreased need for mechanical ventilation, decreased duration of oxygen use and ventilation, and decreased surfactant use. They found no differences in BPD/CLD. The Texas Neonatal Research Group\textsuperscript{61} enrolled 132 infants with RDS (mean gestational age 32.7 weeks) to INSURE vs. standard management (surfactant or ventilation, as needed). They found no differences in need for mechanical ventilation or in BPD. Reininger et al.\textsuperscript{62} similarly randomized infants with RDS (mean gestational age 32.5 weeks) to either INSURE or to NCPAP alone. They did not find differences in the need for mechanical ventilation or BPD. Most recently, Sandri and colleagues\textsuperscript{63} assessed very premature infants (25–28 weeks’ gestational age) randomized to either INSURE or NCPAP alone soon after birth. They found no differences in the need for mechanical ventilation, mortality, or CLD. Alarming, the INSURE group had significantly more pneumothoraces.

Finally, several unpublished RCTs were performed in the years 2000 to 2002 that evaluated the INSURE approach.\textsuperscript{58,64,65} Although there were trends in the latter trials for the INSURE approach to result in a decreased need for mechanical ventilation, no differences in mortality or chronic lung disease were found. It has been 7 to 8 years since the latter three trials were completed and no publications have resulted from any of them. The authors of this chapter are intrigued by the INSURE approach to surfactant use and NCPAP. We believe the published data indicate that fewer premature infants of 29 to 34 weeks’ gestation treated in this manner will require mechanical ventilation. However, infants of 28 or fewer weeks’ gestation are unlikely to benefit from this approach. Most importantly, we do not believe the data indicate that management with the INSURE protocol will decrease the key outcomes of mortality and chronic lung disease.

**Apnea of Prematurity**

Apnea of prematurity (AOP) is a common disorder in premature infants born before 34 weeks’ gestation. These infants exhibit various combinations of apnea, bradycardia, and oxygen desaturation. Apnea may be classified as obstructive, central, or mixed. Methylxanthines are effective in treating AOP (see Chapter 3). The sole trial comparing CPAP with methylxanthine therapy was performed more than 25 years ago.\textsuperscript{66} In that trial, face mask CPAP at levels of 2 to 3 cm H\(_2\)O was compared with theophylline in 32 infants of 25 to 32 weeks’ gestation. The investigation found theophylline to be more effective than face mask CPAP in (1) reducing prolonged apnea episodes; (2) the need for intubation and ventilation because of worsening AOP; and (3) reducing the number of bradycardia spells. The Cochrane review regarding CPAP use for AOP concludes that this topic needs additional evaluation.\textsuperscript{67} We are aware there is widespread use of NCPAP and NCPAP for management of AOP despite the dearth of supportive evidence. Indeed, since the early 1990s caffeine has been used considerably more commonly than is theophylline. Yet, to date there have been no published trials comparing caffeine with NCPAP for treatment of AOP.

Premature infants being extubated after a period of mechanical ventilation via an endotracheal tube are at risk for developing respiratory failure that may manifest as increased frequency or severity of apnea, CO\(_2\) retention, diffuse atelectasis, increased work of breathing, increased oxygen requirement, or need for reintubation and mechanical ventilation. All of these findings are typically included in “treatment failure” criteria in the various trials that have assessed whether CPAP may be a good therapy for infants postextubation. Davis and Henderson-Smart\textsuperscript{68} reviewed the literature to assess whether direct extubation of mechanically ventilated preterm infants would be as successful as extubation after a short period of endotracheal tube CPAP (ETCPAP). After identifying three appropriate clinical trials addressing this question in their review, these authors concluded that a trial of ETCPAP prior to extubation did not provide any advantages. In fact, there was a trend toward an increased number of apnea episodes in ETCPAP-treated infants.

**Oxyhood vs. NCPAP**

Engleke and colleagues\textsuperscript{69} randomized 18 premature neonates recovering from RDS to either oxygen delivered via an oxyhood or to NCPAP. During the 24 hours of the study, the NCPAP group of infants had lower respiratory
rates, better oxygenation, lower \( \text{Paco}_2 \) values, higher pH values, and less radiographic atelectasis. Higgins et al.\textsuperscript{70} similarly randomized 58 infants of less than 1000 g birth weight to either NCPAP or headbox oxygen at the time of extubation. They found 22 of 29 (79\%) of NCPAP babies remained successfully extubated compared to 6 of 29 (21\%) of the headbox babies (\( P < 0.0001 \)). Chan and Greenough\textsuperscript{71} performed a trial in which ventilated infants with both relatively acute (less than 14 days of age) and chronic (14 days or more of age) disease were randomized to either NCPAP at 3 \( \text{cm H}_2\text{O} \) or to headbox oxygen. These authors did not find any differences in extubation failure rates in either group (NCPAP vs. headbox oxygen) or in acute versus chronic respiratory distress. One should note, however, that 3 \( \text{cm H}_2\text{O} \) is a relatively low amount of distending pressure. Annibale et al.\textsuperscript{72} randomized 124 preterm infants meeting extubation criteria to either (1) a long course of NCPAP (until lung disease was resolved); (2) a 6-hour course of NCPAP; or (3) oxyhood. These investigators found no differences among groups in the extubation success rate. So and colleagues\textsuperscript{73} randomized 50 VLBW infants in an extubation protocol to either NCPAP or oxyhood. Successful extubation was achieved in 21 of 25 (84\%) of NCPAP subjects compared to 12 of 25 (48\%) of the oxyhood group (\( P = 0.01 \)). Tapia et al.\textsuperscript{74} assigned 87 preterm neonates to either oxygen alone, endotracheal tube CPAP for 12 to 24 hours with subsequent extubation, or to NCPAP. They found no differences in extubation failure rates among groups.

Davis and colleagues\textsuperscript{75} randomized 92 ventilated preterm infants ready for extubation to either NCPAP or headbox oxygen. Thirty-one of 47 (66\%) were successfully extubated in the NCPAP group compared to 18 of 45 (40\%) in the headbox oxygen group (\( P = 0.013 \)). Robertson and Hamilton\textsuperscript{76} performed a variation of the preceding trials. They randomized 58 preterm infants after extubation to either immediate NCPAP for 72 hours or to headbox oxygen with “rescue” NCPAP as an option if necessary. These authors found no differences between groups in successful extubation up to 2 weeks after enrollment. Dimitriou et al.\textsuperscript{77} performed a RCT in premature infants (24-34 weeks’ gestation) that were thought to be ready for extubation. The infants were randomized to either headbox oxygen or to NCPAP via either single or binasal prongs. There were no differences between groups in extubation failure. Because there could have been outcome differences between the two types of NCPAP (unfortunately no subgroup analysis was presented), we do not think the Dimitriou study adequately assessed the use of either type of NCPAP for extubation. The Cochrane collaboration analysis\textsuperscript{78} of NCPAP use immediately after extubation concludes that it is an effective therapy in preventing failure of extubation. Nevertheless, the latter evaluation stresses the need for further studies to determine the gestational age and birth weight groups that would benefit most. The Cochrane review also stresses the need for further trials to determine optimal levels of NCPAP and optimal methods of administering NCPAP.

**Comparison of Different Types of NCPAP**

Several investigators have compared different types of NCPAP to see if one method would be more effective than another after extubation of mechanically ventilated preterm infants. Davis et al.\textsuperscript{79} compared ventilator-generated CPAP via either single or binasal prongs. Their population consisted of 87 premature infants of less than 1000 g birth weight. Single-prong NCPAP was delivered via a short-ended endotracheal tube inserted 2.5 cm into one nostril, whereas binasal NCPAP was given through Hudson prongs. Significantly more infants, 26 of 46 (57\%), randomized to the single-prong NCPAP met failure criteria compared to 10 of 41 (24\%) of those managed with binasal NCPAP (\( P = 0.005 \)). Stefanescu et al.\textsuperscript{80} enrolled 162 ELBW (less than 1000 g birth weight) infants into a postextubation RCT. In this trial neonates were randomized to either the IFS or NCPAP administered with binasal prongs. These authors were unable to demonstrate any differences between groups in extubation success rates. Nevertheless, the IFS-managed group had significantly fewer days on supplemental oxygen (66 vs. 77 days, \( P = 0.03 \)) and a significantly shorter duration of hospitalization (74 vs. 86 days, \( P = 0.02 \)).

Sun and Tien\textsuperscript{81} compared the Infant Flow system (IFS) to “conventional” binasal NCPAP that was ventilator generated. Their population consisted of 73 ventilated premature infants of 30 weeks’ or less gestational age and 1250 g or less birth weight who met extubation criteria. Sun and Tien found 19 of 35 (54\%) of the “conventional” group met failure criteria compared to 6 of 38 (16\%) of the IFS-managed neonates (\( P < 0.001 \)). Similarly, Roukema and colleagues\textsuperscript{82} randomized 93 VLBW infants to either IFS or to NCPAP. The NCPAP group was significantly more likely to fail extubation compared with the IFD group (60\% vs. 38\%, \( P = 0.0006 \)). Of note, these latter two trials were presented in abstract form only a decade ago.

**Conclusions**

Cochrane collaborative reviews have addressed diverse CPAP RCTs. To date the following conclusions have been made: (1) there is insufficient evidence to assess the benefits and risks of prophylactic NCPAP in the preterm infant;\textsuperscript{83} (2) early use of CPAP may reduce the need for mechanical ventilation;\textsuperscript{84} and (3) early therapy with surfactant and NCPAP may be of benefit.\textsuperscript{85} Concerning overall CPAP use, there are no definitive conclusions in the Cochrane evaluations. All of the reviews stress the need for further large, prospective RCTs.

**Nasal Ventilation**

Nasal ventilation (NV) is an intriguing concept that has gained popularity with limited medical evidence. The concept is attractive: provision of positive pressure breaths noninvasively. Potentially, NV would avoid potential complications of prolonged ventilatory support via an endotracheal tube (volutrauma, subglottic stenosis, infections). Moreover, NV may have advantages over NCPAP or NCPAP in stabilizing a borderline functional residual capacity, reducing dead space, preventing atelectasis, and improving lung mechanics.\textsuperscript{86,87} The practice was performed in the United States during the mid-1970s (Steven M. Donn, personal communication), as well as in Canada during the mid-1980s, with more than half of the level III
NICUs in that country using the technique. In general, NV has been studied to determine its potential usefulness in (1) preventing extubation failure; (2) treating apnea of prematurity; and (3) as a primary mode of treating respiratory disorders.

Friedlich et al. randomized 41 premature infants to either nasopharyngeal CPAP (NPCPAP) or nasopharyngeal synchronized intermittent mandatory ventilation (NPSIMV) to be used after extubation. These authors used the Infant Star® ventilator (Infrasonics, Inc., San Diego, Calif.) with the “StarSync” abdominal capsule-triggering device (Graesby capsule, Infrasonics, Inc., San Diego, Calif.) for synchronization. Binasal nasopharyngeal prongs were used in both groups. Treatment failure was defined as one of multiple parameters: (1) pH of 7.25 or less; (2) increased Paco₂; (3) increased FiO₂ requirement; (4) need for a NPSIMV rate greater than 20/min; (5) need for a peak inspiratory pressure (PIP) on NPSIMV of 20 cm H₂O or more; or (6) severe apnea. Friedlich and colleagues reported significantly fewer extubation “failures” with NPSIMV (1/22, 5%) compared to NPCPAP (7/19, 37%) (P = 0.016). Barrington et al. randomized 54 VLBW infants to NPCPAP or NSIMV after extubation. They used bimal Hudson prongs with the Infant Star ventilator as the generating source for both groups, as well as the StarSync triggering device. Extubation failure criteria were similar to those of Friedlich. Barrington and colleagues found the NSIMV group to have a lower incidence of failed extubation (4/27, 15%) compared with the NPCPAP group (12/27, 44%) (P < 0.05). Khalaf et al. randomized 64 premature infants to either NSIMV or NPCPAP after extubation using either the Bear Cub Model BP 2001 (Bear Medical Systems, Inc., Riverside, Calif.) or the Star Sync ventilator with the StarSync triggering device, and Argyle nasal prongs. Failure criteria were similar to those of Barrington and colleagues. Six of the 21 neonates had only 21 neonates had a single nasopharyngeal tube in 21 neonates of both preterm and term gestation. NSIMV was provided by the Infant Star high-frequency flow interrupter. Six of the 21 neonates had previously received mechanical ventilation, whereas in the other 15 infants, NSIMV was used early in the course of their respiratory disease. The authors reported a decline in Paco₂ levels after initiation of NSIMV.

In 1985 Garland and colleagues performed an RCT comparing synchronized NV after an initial dose of surfactant with mechanical ventilation after surfactant administration. They found significantly less BPD in the NSIMV group. This was a small trial with 41 total babies enrolled. Kugelman and colleagues randomized 84 premature infants to NIPPV or to NPCPAP. These authors reported a decreased need for mechanical ventilation in the NIPPV group, as well as significantly less BPD.

In a novel application, van der Hoeven et al. reported use of nasal high-frequency ventilation (NHFV) in which high-frequency breaths were delivered via a single nasopharyngeal tube in 21 neonates of both preterm and term gestation. NHFV was provided by the Infant Star high-frequency flow interrupter. Six of the 21 neonates had previously received mechanical ventilation, whereas in the other 15 infants, NHFV was used early in the course of their respiratory disease. The authors reported a decline in Paco₂ levels after initiation of NHFV.

Recently one company has marketed bilevel NPCPAP as an alternative to constant NPCPAP (SiPAP, Viasys, Inc., Conshohocken, Pa.). Using the technology of the Infant Flow driver, these devices can alternate between a lower and higher CPAP pressure. Synchronization using the Graesby capsule is available in Europe and Canada. Whether this device offers any advantage over standard single-pressure NPCPAP is not known at this time, though several RCTs are underway.

Much of the preceding NV data have come from trials assessing efficacy of synchronized NV using the StarSync triggering device and Graesby capsule. Neither of these are currently available for use in the United States. The conclusion of the Cochrane collaboration review is that NV may be useful in augmenting NPCPAP in preterm infants with apnea that is frequent or severe. However, additional safety and efficacy data are required before recommending NV as standard therapy for apnea. The Cochrane collaboration review assessing NV postextubation concluded that NV may augment the beneficial effects of NPCPAP in preterm infants.

Other Applications of CPAP in Neonates

We have mainly concentrated on describing the three primary uses of CPAP, particularly NPCPAP, in newborn infants: (1) postextubation management; (2) treatment of apnea of prematurity; and (3) primary therapy for respiratory distress syndrome. Nonetheless, CPAP has been applied in a variety of other conditions (Box 8-1). There are, however, even less data supporting CPAP use in these other conditions. With use in infants with congenital heart disease postoperatively, CPAP improved pulmonary mechanics and oxygenation. Additionally, CPAP may...
Complications of CPAP

Malpositioned Nasal Cannulae

A major difficulty with the use of nasal cannulae (NC) or nasal prongs is keeping them in proper position. One may walk through most neonatal intensive care units (NICUs) at any given time and note infants with malpositioned or displaced cannulae and prongs. It should be noted that with the variable-flow CPAP systems (the Infant Flow Driver, SiPAP™, and Arabella devices), meticulous attention has to be paid to ensure proper fixation of the nasal prongs. Airway obstruction by secretions, particularly mucus, is a common finding in babies managed with CPAP. Optimal gas humidification, as well as frequent irrigation with saline followed by suctioning, should mitigate airway obstruction. Although nasopharyngeal prongs (single or binausal) may be less likely to be displaced, they are more easily blocked by secretions or can kink and may not be as effective as the shorter prongs. Local irritation to the nares and oral cavity may also occur with CPAP. Some clinicians use steroid and antibiotic ointments on the outer surfaces of the CPAP devices to minimize the effects of this irritation. We have found success in using an inert product, Ayr Gel™. Good oral hygiene (e.g., with lemon glycerin swabs or saline) should be considered to prevent drying and cracking.

Inadvertent PEEP

A number of adverse side effects and complications of CPAP, PEEP, and nasal ventilation have been described. One is the development of inadvertent PEEP—a problem that may occur in ventilated babies, primarily those ventilated via endotracheal tubes. Conceivably, inadvertent PEEP could occur with nasal ventilation. The mechanism is related to fast ventilatory rates and inadequate (too short) expiratory times. Inadvertent PEEP may occur in babies with minimal to no lung disease (such as postoperative patients) or in those with sick lungs. Healthy lungs have longer time constants. Hence passive exhalation requires a greater amount of time. Inadvertent PEEP results in air trapping. Clinically, this may appear as hyperexpanded lungs on chest roentgenograms. Air trapping may clinically manifest as hypoxemia and hypercapnia. Clinicians should be suspicious of this entity when oxygenation deteriorates as inspiratory pressure is increased. Air trapping contributes to the development of air leaks. Additionally, air leaks (pneumothorax, pneumomediastinum, and pulmonary interstitial emphysema [PIE]) may be a direct complication of CPAP/PEEP. The mechanism may be related to overdistension of the more compliant areas of the lung. The recent COIN trial highlights this potential complication. As a generalization, pneumothoraces appear to be a problem with babies in whom CPAP was the primary ventilatory therapy for RDS. We are unaware of any reported increased risk for air leaks when CPAP is used for postextubation respiratory management or as therapy for apnea of prematurity. Moreover, there is no apparent increased risk among infants that are nasally ventilated. In any future trials in which CPAP is compared to mechanical ventilation or to other therapies, air leaks remain an important outcome parameter that should be followed and reported.
Carbon Dioxide Retention
Retention of carbon dioxide (CO₂) has been noted with higher levels of CPAP, particularly at levels above 8 cm H₂O. Alveolar overdistension, as well as inadequate expiratory times, may lead to reduced tidal volumes and cause the CO₂ retention. Other manifestations of lung overdistension include increased work of breathing, impaired systemic venous return, decreased cardiac output, and increased pulmonary vascular resistance. In addition, mechanical ventilation with PEEP may produce a decrease in glomerular filtration rate and a decrease in urine output. Renal effects of CPAP in preterm infants are notable at higher levels of pressure. These effects on the kidney may be due to decreased cardiac output and thus decreased perfusion to the organs. In addition, CPAP and PEEP are known to increase intracranial pressure. Nevertheless, with the widespread use of screening ultrasonography over the past two decades, we are unaware of any direct links between CPAP/PEEP and adverse brain injury in premature or term-gestation neonates.

Decreased Gastrointestinal Blood Flow
Gastrointestinal blood flow may decrease with the application of CPAP. Additionally, marked bowel distension (“CPAP belly”) is frequently recognized in infants treated with this therapy. With NCPAP, administered gas can easily pass into the esophagus. Infants may swallow a considerable volume of gas and present with bulging flanks, increased abdominal girth, and visibly dilated intestinal loops. There may be upward pressure placed on the diaphragm and compromise of the child’s respiratory status. Unquestionably, routine placement of an orogastric tube should take place whenever CPAP is used. The orogastric tube should prevent or alleviate “CPAP belly.” We are unaware of any direct linkage between CPAP and necrotizing enterocolitis (NEC). Although Garland et al. have reported an increased risk of gastric perforation with nasally ventilated neonates, virtually all recent investigations of nasal ventilation have not confirmed this association. Moreover, NCPAP alone has not been reported to cause gastric perforation.

Skin Trauma
Nasal prongs may cause trauma to the nose that can be mild (edema or erythema) or severe. Robertson and colleagues have reported a series of cases of severe trauma, including nasal snubbing (Fig. 8-16), flaring of the nostrils (Fig. 8-17) and columella necrosis (Fig. 8-18, A and B). Nasal deformities may occur with different types of nasal prongs and NCPAP devices. Lubrication of the nares with various substances has been used in an attempt to mitigate the contact trauma between the prongs and the internal surfaces of the nose, including antibiotic ointments, steroids ointments and creams, and Ayr gel™. We are unaware, however, of any clinical trials assessing such therapy. It is of paramount importance that meticulous attention be paid to appropriate positioning of the nasal prongs, with frequent examinations to assess the possibility of developing injury. With variable-flow devices, some clinicians alternate use of nasal prongs with nasal masks in an attempt to obviate trauma. No trials to date have assessed such management. Lastly, attempts have been made to use barrier material to protect the nares. One such material is the Cannulaide™ (Beevers Manufacturing Incorporated, McMinnville, Ore.). It comes in multiple sizes that can be used for varying sizes of preterm infants. Figure 8-19, A shows a baby with the Cannulaide in place. Other clinicians have used alternative material such as DuoDerm® (hydrocolloid gel) or Mepilex® (soft silicone) to similarly cushion the nares. There are limited clinical data that assess the effect of any of the aforementioned materials in preventing nasal trauma.

Other rare complications have been described in single case reports. Peck et al. described the dislodgement of a single nasal prong that slipped into the child’s stomach and ultimately needed endoscopic retrieval. Additionally, a preterm infant developed a pneumatocele approximately 24 hours after CPAP was instituted. Wong and colleagues described an infant being managed on NCPAP who developed bilateral tension pneumothoraces and extensive vascular air embolism.

Contraindications to CPAP
There are several contraindications to CPAP. These include the following:
- Infants who have progressive respiratory failure and are unable to maintain oxygenation, \( \text{PaCO}_2 \) levels greater than 60 mm Hg (8 kPa), and/or pH levels of 7.25 or less
- Certain congenital malformations: congenital diaphragmatic hernia, tracheoesophageal fistula, choanal atresia, cleft palate, gastroschisis
- Infants with severe cardiovascular instability (hypotension, poor ventricular function)
- Neonates with poor or unstable respiratory drive (frequent apnea, bradycardia, and/or oxygenation desaturation) that is not improved by CPAP

**Determining Optimal Levels of CPAP and PEEP**

What is the best level of CPAP or PEEP? We believe it is the level at which oxygenation and ventilation occur in acceptable ranges without evidence of atelectasis or overdistension and no adverse side effects. Unfortunately, no simple and reliable methods exist to find the most advantageous pressure.\(^9\),\(^11\),\(^12\) Clearly, each baby’s support needs at any given moment cannot be extrapolated to all neonates with similar problems. Some investigators have used esophageal pressures or changes in the inspiratory limbs of pressure-volume curves to guide their efforts to find the elusive pressure level. However, these techniques are not generally available at the bedsides of most clinicians.
saturation monitoring, will further assist in the assessment of appropriate CPAP level.

As a general rule, we perform blood gas analysis within 30 to 60 minutes after any changes in pressure. If oxygenation worsens or CO₂ levels increase after increases in the pressure, the lungs may be overdistended. Many of the current mechanical ventilators have graphic monitors available on which pulmonary mechanics are displayed. If one uses ventilator-generated CPAP or PEEP via an endotracheal tube with such a device, these monitors may be useful in determining the optimal pressures.

**Weaning from CPAP**

Once a child is being treated with NCPAP, there are no magic guidelines as to when the child can be weaned off. As we are decreasing the pressures, we assess the baby’s oxygen saturation levels, occurrence of apnea and/or bradycardia, and work of breathing. Hopefully, we have been able to lower the FIO₂ to a relatively low amount. In general, infants who require an FIO₂ greater than 0.40 or are clinically unstable are unlikely to be successfully weaned off NCPAP. Generally, we prefer to decrease pressures down to a relatively low level (≈5 cm H₂O). Once the CPAP is at this level without increasing work of breathing and the baby does not have substantial apnea, bradycardia, or oxygen desaturation levels, we attempt to discontinue NCPAP. Infants without oxygen requirement may be trialed off NCPAP with no additional support. Infants still requiring oxygen may require a nasal cannula. The baby’s subsequent clinical findings and oxygen requirement will guide the clinician as to whether NCPAP needs to be reinstituted.

**Nasal Cannula, Including Humidified High-Flow Nasal Cannula**

Nasal cannulae (NC) are mainly used to deliver supplemental oxygen. Locke et al. demonstrated that NC could deliver continuous distending pressure to infants and alter breathing patterns. However, they advised against its use. Subsequently, Sreenan et al. compared the use of nasal cannulae at flows of up to 2.5 L/min with NCPAP generated by a ventilator using Argyle prongs (Argyle-Sherwood Medical Company, St. Louis, Mo.) in premature infants already being treated with NCPAP for apnea of prematurity. This was a crossover design study in which all infants initially started on NCPAP. After 6 hours, the infants were changed to NC for another 6-hour period. The authors assessed delivered airway pressure by measuring esophageal pressures. Sreenan’s group found that comparable continuous distending pressure could be generated by the NC. The amount of flow required to generate comparable pressures depended upon the infant’s weight. There were no differences between the two systems in the frequency and duration of apnea, bradycardia, or desaturation episodes. Typical flow rates that are used for nonhumidified NC are 0.5 to 2 L/min. Because the gases used are nonhumidified, low-flow NC may have a drying effect on nasal...
secretions that could lead to obstruction or to localized bleeding.

Widespread use of humidified, high-flow nasal cannula (HHFNC) (Fig. 8-20) has become common in NICUs over the past decade. These devices represent one of the least-tested major therapies currently in vogue. The premise is that gases at flow rates greater than 2 L/min are humidified to prevent the adverse effects of dry gas. The higher flow rates are used clinically to provide respiratory support in neonates in lieu of NCPAP or oxygen hoods. Although not specifically approved as devices for generating positive pressure, clinicians generally use HHFNC in the hope that it will be a less invasive form of continuous distending pressure that will prevent some of the complications of NCPAP (nares injury) and low-flow, unhumidified NC (thickened secretions, nasal bleeding). The two major commercial devices that are available are produced by Vapotherm, Inc. (Stevensville, Md.) and by Fisher & Paykel Healthcare (Auckland, New Zealand).

The limited literature concerning HHFNC is mainly in abstract form. Clinicians are unable to continuously measure the pressures generated by HHFNC. Widely variable, extremely high pressures have been noted among infants treated with this therapy. The pressure that is generated is unregulated and unpredictable. Moreover, the Vapotherm® was temporarily removed from the market for approximately 1 year because of the recovery of a bacterium (Ralstonia sp.) in infants who were treated with the device. It has since been marketed again with new guidelines on cleaning. There have also been isolated reports of facial burns, a perforated ear drum, and subcutaneous lines on cleaning. There have also been isolated reports of device. It has since been marketed again with new guidance (approximately 1 year because of the recovery of a bacterium (Ralstonia sp.) in infants who were treated with the device. It has since been marketed again with new guidelines on cleaning. There have also been isolated reports of facial burns, a perforated ear drum, and subcutaneous lines on cleaning. There have also been isolated reports of device.

With so little data, potential for adverse effects and comparability to NCPAP, the question is why are clinicians using HHFNC so frequently? The major reasons appear to be its ease of use with noncumbersome tubing that seems to be better tolerated by the patient. The indications for its use are nonspecific. However, clinicians have used HHFNC as a primary therapy for RDS, as a substitute for NCPAP after extubation, and for treatment of apnea. We and others are concerned about the widespread use of what we consider to be a minimally studied therapy that has potential safety concerns.

Summary

The use of noninvasive respiratory support (NRS), such as CPAP, is not a new concept. Apparent benefits were first noted more than three decades ago. For a 20-year-long period, however, treatment with NRS, as well as research concerning the technology, waned. Renewed interest in these therapies came about in the mid-1990s. With advances in obstetric and neonatal care, survival of increasingly smaller and less mature neonates has become possible. The hope is that CPAP and other forms of noninvasive respiratory support could lessen iatrogenic injury to newborn infants, particularly those of very low birth weight. However, the history of neonatology is replete with widespread enthusiastic acceptance of diverse therapies with a modicum of supportive evidence.

We must carefully evaluate use of CPAP and other forms of NRS so that we may understand the potential benefits and potential disadvantages. The major areas in which these therapies are being used are for postextubation management, for apnea of prematurity, and for primary treatment of RDS. There is some supportive data for NCPAP use postextubation. However, NCPAP use for apnea of prematurity is currently unfounded. There is some evidence that early NCPAP use, often after exogenous surfactant therapy, may reduce the need for mechanical ventilation in premature babies with RDS. There is minimal evidence at this time that early NCPAP will prevent chronic lung disease or mortality. Air leaks may increase with CPAP use. Although CPAP use in the delivery room makes good physiologic sense for infants prone to atelectasis, clinical trials demonstrating benefit are lacking. A similar lack of evidence does not permit us to definitively define a role for nasal ventilation in infants at this time. Simple questions have yet to be answered:

- Does CPAP use increase (or decrease) caloric expenditure?
- What are the long-term pulmonary and neurodevelopmental outcomes among infants that are primarily managed with CPAP or other types of NRS?
- What are acceptable ranges of pH, PaO₂, and PaCO₂ among infants receiving NRS?
- Does early use of NCPAP delay timely administration of exogenous surfactant or does it obviate the need for surfactant therapy?
- Is humidified, high-flow nasal cannulae (HHFNC) therapy a safe and effective form of NRS?
- What forms of NRS are most effective? Safest?

Figure 8-20  Humidified, high-flow nasal cannula being used in a 36-week gestational age infant who had a pneumothorax.
References


47. Sreenan C, Lemark RP, Hudson-Mason A, Osiovich H: High-flow nasal cannulae in the management of apnea of prematurity: a com-
86. Moretti C, Gizzi C, Papoff P: Comparing the effects of nasal synchronized intermittent positive pressure ventilation (nSIPPV) and nasal continuous positive airway pressure (nCPAP) after extubation in very low birth weight infants. Early Hum Dev 56:167-177, 1999.


