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Chapter 5

Non-Invasive Ventilation of the Neonate

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Abstract

The use of mechanical ventilation in the past few decades has greatly contributed to the survival of critically ill neonates, both preterm and term. With this, however, has come an accompanied rise in certain complications and neonatal co-morbidities. Avoiding mechanical ventilation, or at least minimizing the time a neonate is intubated, is considered a critical goal in the care of these patients. Different modes of non-invasive ventilation have developed over the course of the time to help address these issues.

Keywords: non-invasive ventilation, neonate, preterm, prematurity, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula (HFNC)

1. Introduction

Survival of premature infants has improved steadily since neonatal care became a national focus in the 1960's. A key component in this improvement is improved respiratory care, especially mechanical ventilation. Increased survival of vulnerable infants, however, is associated with complications and co-morbidities, some of which are directly caused by invasive ventilation. Therefore, minimizing exposure to mechanical ventilation is critical to the care of these babies. Gregory et al., in 1971, first described the use of continuous positive airway pressure (CPAP) to treat neonates afflicted with respiratory distress syndrome (RDS), which transformed respiratory care of neonates [1]. Subsequently, the use of CPAP and other forms of non-invasive ventilation have become the standard of care and have saved countless lives.

Non-invasive ventilation refers to any mode of respiratory support provided via the nasal airway of infants to support spontaneous breathing, without placement of an endotracheal tube. The most common non-invasive modes include nasal continuous positive airway

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pressure (NCPAP), non-invasive intermittent mandatory ventilation (NIMV), and humidified high-flow nasal cannula (HHFNC). The ultimate goal of each of these devices is to prevent barotrauma, volutrauma, and atelectotrauma, all of which contribute to lung injury and long-term complications. Proposed mechanisms of lung protection due to non-invasive ventilation include mitigation of shear-type injury by maintenance of optimal end-expiratory lung volumes and prevention of cyclical collapse and over-distention of alveoli. Other potential benefits include lung-recruitment, improved gas exchange, and decreased work of breathing [2].

In this chapter, we will first explore historical aspects of the development of non-invasive ventilation in neonates. Then we will focus on specific respiratory mechanics unique to neonates and post-uterine adaptation. Finally, we will discuss specific non-invasive modalities.

2. Historical perspectives

Improved perinatal care, the advent of parenteral nutrition, advances in thermoregulation, and aggressive neonatal resuscitation have all contributed enormously to improved outcomes for neonates. Perhaps the most significant change, however, is a marked improvement in our ability to provide aggressive and sophisticated respiratory care and support to ever-smaller infants. In this section, we will focus on the historical development of innovative approaches to non-invasive ventilation in tiny premature infants.

Although Gregory et al. published the first modern description of the use of CPAP to treat RDS, a similar device was first described in 1914 by Professor August Ritter von Reuss [2]. This device resembled bubble CPAP, and consisted of an oxygen tank with tubing attached to the equivalent of a mask-and-bag device, with a simple valve to regulate oxygen flow. Unfortunately, it took almost six decades for this concept to gain acceptance. Prior to Gregory's description of CPAP, there was very little respiratory support that could be provided to neonates. In the 1940s and 1950s, the provision of supplemental oxygen was the sole therapeutic option for ill neonates [3]. It was during this time that two seminal discoveries were made. The first was the discovery that supplemental oxygen provided benefit to ill neonates, but that exposure to high concentrations led to blindness due to retinopathy of prematurity (ROP) [3]. The second was a report by Avery and Mead in 1959 describing increased surface tension in lung fluid recovered from preterm babies that had died from respiratory distress syndrome, and the observation that preterm infants lacked some sort of "surface-active agent" that could alleviate these forces [4].

Neonatology was still a relatively new field in the latter part of the 20th century, and 1963 was a pivotal year in its development. President John F. Kennedy's son, Patrick Bouvier Kennedy, was born 6 weeks prematurely and died from complications of respiratory distress syndrome on the third day of life [3]. This inspired rapid innovation in the development of new technologies geared towards critically ill neonates. Infant ventilators, blood gas machines, umbilical vascular catheterization and the development of the first true neonatal intensive care units all occurred in the late 1960s. As the field improved, survival rates for neonates with respiratory compromise began to improve as well, mainly due to the widespread use of infant ventilators.

Unfortunately, these advances were also associated with complications and many of these neonates were left with a form of chronic lung disease. This was first described in 1967 by Northway et al., who noted that prolonged exposure to mechanical ventilation and supplemental oxygen were likely to blame [5].

Subsequently, in 1971, Gregory et al., described the use of CPAP to treat neonates with respiratory distress syndrome, using either an endotracheal tube or a head box [2]. This use of CPAP represented an intermediate step that was more supportive than supplemental oxygen alone, was relatively easy to use, and seemed to avoid exposure to the injury associated with mechanical ventilation. The introduction of CPAP in neonates was not the only milestone that this decade produced; in 1972, Liggins and Howie published the results of a randomized controlled trial of antenatal steroids in mothers expected to delivery premature infants. They demonstrated that steroids accelerated fetal lung maturation and decreased the risk of respiratory distress syndrome and death by as much as half [3].

Despite the successes associated with CPAP and antenatal steroids, there were substantial concerns about risks. Specifically, some observers suggested that air leaks and pneumothoraces were more common with CPAP than mechanical ventilation. In addition, CPAP seemed to lead to gastric and abdominal distention of unclear clinical significance. Finally, there were fears that the devices themselves would predispose infants to neurological and cosmetic injury [2]. For these among other reasons, intermittent mandatory ventilation using an endotracheal tube was widely adopted, and quickly overtook CPAP as the standard of respiratory care for critically ill neonates. In addition, for about two decades, CPAP was largely replaced by non-invasive intermittent mandatory ventilation (NIMV). It involved using time-cycled, pressure-controlled breaths delivered by a mechanical ventilator via an oronasal mask or prongs [2].

In the late 1980s, there was renewed interest in CPAP and non-invasive ventilation, sparked by the seminal report in 1987 by Avery et al. which concluded that, among eight NICUs observed, the center with the most aggressive use of NCPAP had the lowest rates of chronic lung disease [6]. Coupled with the fact that the landscape of chronic lung disease, as originally described in 1967, was changing in both a clinical and histological sense due to prolonged exposure to mechanical ventilation, it was no surprise that non-invasive ventilation was resurgent. While CPAP was originally designed for the premature baby with respiratory distress syndrome, today it has multiple uses in neonates of varying ages and conditions. It is used to successfully treat transient tachypnea of the newborn, congenital pneumonia, meconium aspiration syndrome, primary pulmonary hypertension, as well as central apnea of prematurity and certain congenital upper airway lesions [2]. While the technology has certainly evolved quite a bit since Professor von Reuss' initial apparatus in 1914, CPAP and other forms of non-invasive ventilation have become the cornerstones of neonatal respiratory care.

3. Neonatal pulmonary mechanics

It is important to understand the core concepts of fetal and neonatal lung development, as well as basic pulmonary mechanics, to better understand the most appropriate respiratory

support modality. Fundamentally, the respiratory system is designed for the conduction and humidification of air into the lungs, uptake of oxygen from the ambient environment, and the removal of waste product in the form of carbon dioxide. All of this ensures that normal aerobic cellular metabolism is supported and that acid–base homeostasis is maintained.

The respiratory system develops through five distinct, yet overlapping phases: *embryonic*, *pseudoglandular*, *canalicular*, *saccular*, and *alveolar* [7]. While a full review of the embryology is not necessary for the understanding of neonatal respiratory care, it is important to note that each particular phase leads to unique respiratory difficulties and opportunities. Lung growth begins in the third week of gestation during the *embryonic* phase, with a small growth of diverticulum from the ventral wall of the foregut. This is often referred to as the primitive respiratory diverticulum or primitive lung bud [7]. Three rounds of branching and division also occur during this phase, leading to a left & right half as well as the formation of multiple tertiary bronchi. The vascular components of the respiratory system also begin their development during this phase. The *pseudoglandular* phase occurs from weeks 5–17, and this time period is notable for the completion of all bronchial divisions as well as formation of cilia and cartilage [8]. After this phase, any further lung growth is simply by the elongation, widening and hypertrophy of existing tissue. The *canalicular* phase is particularly important, as it encompasses 16–26 weeks of development and includes neonates of periviable gestational ages (ie, around 23 weeks gestation). Here, the earliest capillary beds begin to form, and areas of gas exchange start to develop. Many of the overlying epithelial cells also begin to thin out and improve the air-blood interface, further enhancing regions of gas exchange. More importantly, these cells also start to differentiate into type I pneumocytes that help form and stabilize the alveoli. Type II pneumocytes also start to appear, and these cells are vitally important in the production of endogenous surfactant [7, 8]. The canalicular stage is the earliest gestational age at which interventions can be provided. The *saccular* phase occurs from weeks 24–38 and leads to further development of alveolar ducts and conducting airways. Mucous and cilated cell growth also increases. Surfactant synthesis continues to improve, but overall production compared to full-term infants remains low [9]. This time period encompasses the bulk of premature infants, including those that are "late preterm." The relative structural immaturity coupled with insufficient (and often ineffective) surfactant production explains the need for respiratory support in this age group, even in infants born beyond 34 weeks gestation. Finally, the *alveolar* phase occurs from about 36 weeks – 8 years of age. This final stage is mainly characterized by further development of alveolar units, thinning of the air-blood interface, increased surface area for gas exchange, and increased numbers of type II pneumocytes, leading to enhanced synthesis of surfactant [7].

Throughout fetal development, fetal lung fluid is vital in the growth of normal lung structure. Fetal lung fluid is an isotonic fluid secreted by epithelial cells that helps promote growth and development. It is low in protein and high in chloride ions. Combined with contractions of fetal airway smooth muscle and fetal breathing in utero, these processes help promote the normal developmental process of lung growth. Fluid clearance is a process initiated by various labor mechanisms, and this also presents an area for maladaptation and one etiology of respiratory distress after birth [10].

Lung function in neonates, especially those born prematurely, is altered for a number of reasons. Structural issues include poorly developed lung parenchyma, airways and a highly elastic chest wall, and surfactant deficiency complicates these issues. This results in dramatic changes in normal lung mechanics and physiology, manifested by an overall state of abnormally decreased compliance, low functional residual capacity (FRC), and increased respiratory effort by the neonate [8]. This is further compounded by deranged gas exchange. If undertreated, each of these mechanisms may combine to cause respiratory failure. Antenatal steroids improve some of the structural and biochemical derangements, but post-natally the clinician must provide the correct level of respiratory support and surfactant when appropriate. The goal, as we will discuss, is resolve the skewed lung mechanics towards a more normal physiologic state by re-establishing FRC and decreasing work of breathing.

Functional residual capacity (FRC) is defined as the volume of air remaining in the lungs after a normal passive exhalation [8]. In most term, healthy neonates, this figure is typically about 20–30 mL/kg. To understand the significance of FRC in the management of neonatal respiratory care, it is important to understand normal transitional events in early postnatal life. During gestation, the developing fetus is entirely dependent on the placenta for gas exchange. This in-utero circulatory pattern consists of very limited pulmonary blood flow with intracardiac shunts in place to allow for adequate flow of blood to vital organs. The approximate oxygen saturation in a term fetus prior to delivery is about 60% [2]. When labor is initiated, epithelial lung cells halt their production of fetal lung fluid and begin to actively absorb it back into circulation. This process is triggered by thyroid hormone, glucocorticoids and epinephrine working in combination to change epithelial cells from chloride secreting to sodium reabsorption [11]. With the neonate's first spontaneous breaths, the lungs inflate and there is an increase in pulmonary arterial pO2 as well as activation of stretch receptors. This process, in conjunction with production of endogenous nitric oxide, dramatically reduces pulmonary vascular resistance [2]. As pulmonary vascular resistance continues to decrease, more pulmonary blood flow is established and oxygen saturations steadily increase to normal postnatal levels. The intra-cardiac shunts at the level of the ductus arteriosus and foramen ovale close due to increasing arterial oxygen content and increasing systemic vascular resistance from clamping of the umbilical cord, respectively. This process results in physiologic changes that can be witnessed in real time, as most healthy term neonates will obtain oxygen saturations greater than 90% by about 10 minutes of life.

For gas exchange to properly occur after birth, there must be an immediate interface between environmental oxygen and pulmonary blood flow at the alveolar-capillary level. Ventilation (V) and perfusion (Q) ratios reflect this physiologic state, and there are a number of ways that this process can be deranged. To allow for a normal VQ matching, there must be both an adequate alveolar gas volume and normal FRC [7]. If adequately sustained, either due to spontaneous respirations or assisted ventilation, FRC serves as an intrapulmonary pool of oxygen. Preterm infants and ill term infants are prone to a low FRC. This may lead to decreased compliance, increased airway resistance, increased work of breathing, increased pulmonary vascular resistance, hypoxemia, atelectasis, and impaired gas exchange [8]. Conversely, too much FRC from overinflation can also have negative effects and may lead to lung injury, air leaks and decreased cardiac output. Positive distending

pressure is therefore critical in recruiting collapsed alveoli and establishing optimal FRC in neonates that cannot achieve it spontaneously (**Figure 1**).

Specific mechanical and physical properties of the lung also play an important role in neonatal respiratory care. The elasticity of a system refers to the property of matter such that a system will tend to return to its original position when all external forces are abated [8]. In the neonate, the elastic properties of the lung refer to not just the parenchyma, but also the air exchange spaces, muscle, connective tissue and vasculature. In addition, there is also a recoil effect from surface tension in the alveoli, which is artificially increased with impaired surfactant production. Lastly, there are opposing elastic forces that may be provide by the chest wall to assist with lung expansion and air entry. All of these elastic forces form a complex, interdependent balance that may determine FRC [8].

The pressure required to inflate a lung is directly proportional to the volume of inflation – this is often referred to as Hooke's Law [7]. While this relationship is often seen as an extension of the elastic properties of the lung, it brings us to our next biophysical property of respiratory physiology. The compliance of a lung is strictly defined as the change in lung volume due to a change in distending pressure during normal breathing, expressed as a ratio [8]. This is an extension of Hooke's Law. Compliance may be further divided into static and dynamic compliance. Static compliance refers to the tendency of the lung to recoil to its original dimensions after a known volume of pressure is applied and then removed [2]. Dynamic compliance, on the other hand, is measured during spontaneous breathing and refers to the change in pressure from the end of exhalation to the end of inspiration for a given volume. It reflects both the intrinsic elastic and resistive properties of the lung [2]. The compliance of a given respiratory system includes both the lung and the chest wall. In neonates, the chest wall is primarily made up of cartilage and thus is a high compliance system. Conversely, the compliance of the

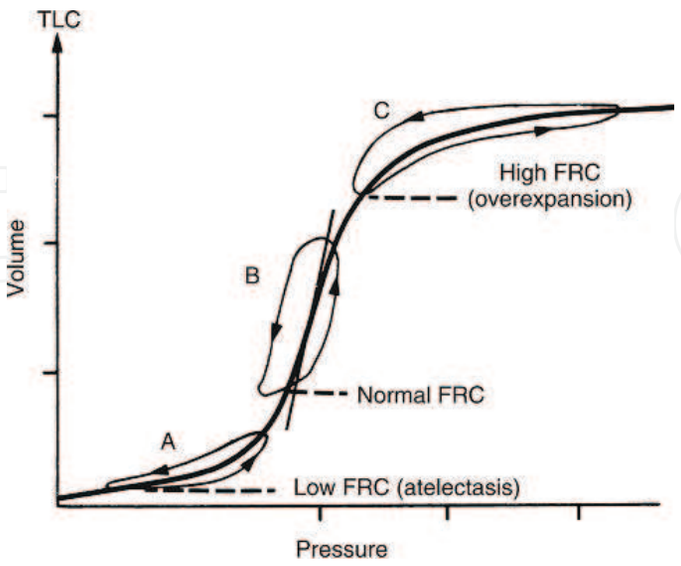


Figure 1. Compliance curve demonstrating different states of FRC. Area A represents poor lung volumes or collapse, where area C represents over distension of the lung. Area B demonstrates optimal lung volumes in which normal physiological FRC is maintained. Image used with permission by Elsevier Books, Inc.

lung is relatively low given surfactant deficiency and decreased alveolar radius, especially in premature infants [7]. This is a problematic scenario, as the balance of forces thereby is tilted towards lung collapse. This also negatively impacts FRC. Neonates respond by augmenting their FRC by increasing expiratory resistance through laryngeal abduction, clinically manifested as "grunting" [7]. Additionally, the higher respiratory rates seen in infants in low-compliant states creates relative gas trapping that helps slightly improve FRC [2]. The definitive treatment, however, is to deliver optimal PEEP via CPAP or another non-invasive modality to avoid atelectotrauma and to re-establish and sustain FRC (**Figure 2**).

The resistance to gas flow in a closed respiratory system is an important determinant of respiratory mechanics in neonates. Resistance is the direct result of friction, and can be defined as either viscous or airway resistance [2]. Viscous resistance refers to the resistance encountered by tissue elements as they touch and move past one another. Airway resistance refers to the resistance that occurs between moving gas molecules and between these molecules and the walls of the respiratory system [2]. Airway resistance makes up the majority of total resistance in a neonate. It is determined by the relationship between the velocity of gas flow, length of the airways, viscosity of the gas, and the diameter of the conducting airways. For laminar flow where all gas molecules move in an orderly fashion perfectly parallel to the walls of the airway, resistance is described by Poiseuille's law. This states that resistance is directly proportional to the product of the tube length and gas viscosity, and inversely proportional the airway radius to the fourth power [2]. Thus airway diameter is the critical determinant

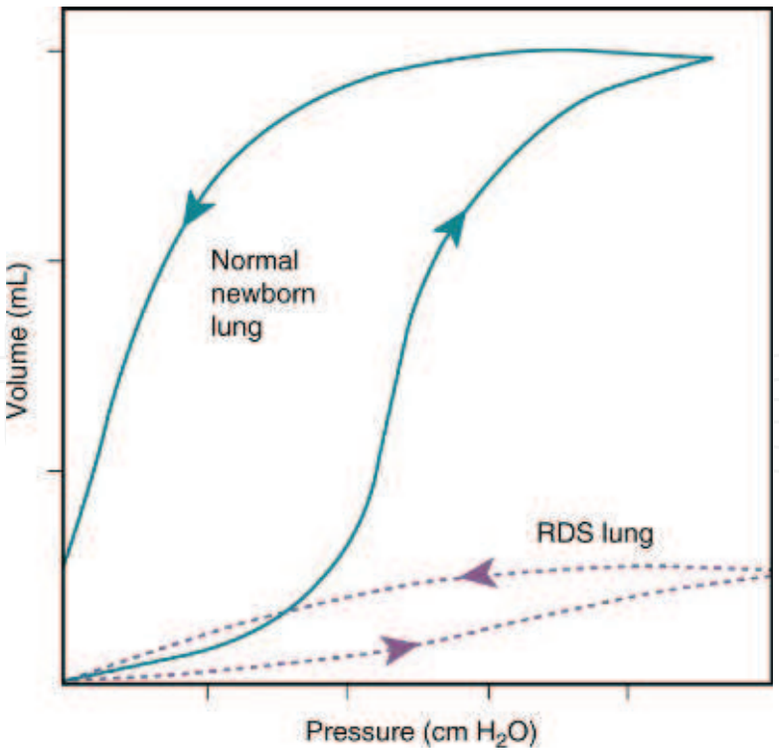


Figure 2. Comparison of compliance curves between a normal neonate (solid line) versus that of a neonate with RDS (dotted line). Note the very little volume change for an applied pressure seen in the infant with RDS due to the lack of surfactant and poor alveolar stabilization. Image used with permission by Elsevier Books, Inc.

of airway resistance, as even small changes in airway radius will have exponential effects on resistance. This effect in neonates is especially exaggerated as they have narrow airways relative to adults.

There is an inverse, nonlinear relationship between airway resistance and lung volume. This is due to the fact that airway size increases as FRC increases, therefore decreasing the total resistance of the system [2]. The converse is also true: any pathologic state in which low lung volumes occur will increase the airway resistance of that system. This is another lung mechanical property that is affected by the FRC. That is, application of adequate PEEP via non-invasive ventilation will establish optimal FRC, increase airway size, and decrease airway resistance [2].

One final concept to explore is work of breathing. Clinically, this term refers to the signs of respiratory distress exhibited by a patient. This can be manifested by tachypnea, grunting, intercostal retractions, or nasal flaring. Mathematically, work of breathing can be quantified as the energy needed to overcome the existing elastic and resistive forces. More specifically, this can be defined as the product of the force exerted and the volume of air displaced [2]. About two-thirds of this energy expenditure is used to overcome the elastic forces of the respiratory system, while one-third is used to overcome resistance [2]. While most clinicians recognize that a neonate exhibiting increased work of breathing is at risk for respiratory deterioration, it is important to realize that increased energy expenditure also results in increased oxygen consumption [8]. It is apparent that work of breathing can be decreased by the application of positive pressure via CPAP or some other non-invasive modality – but how? Of all the respiratory muscles, the diaphragm carries the majority of the workload. Like most skeletal muscles, its ability to generate optimal force is related to its initial relaxed position and the length of muscle fibers at the beginning of contraction [2]. Delivering PEEP via CPAP will not only help better inflate the lungs, but move the diaphragm into a more optimal position for contraction. In addition, PEEP may prevent atelectasis and move the neonate to a more ideal position on the pressure-volume curve where either extreme in atelectasis or over-distended are avoided, and instead optimal FRC is achieved [2, 12]. Lastly, one major role of the nasopharynx and lining of the upper airway is to provide warmth and moisture to inspired air. Non-invasive ventilation replaces the warming and humidification process required by the neonate, and in turn this may reduce metabolic demand [13].

4. Interface devices for providing non-invasive ventilation

Since Gregory's initial description of CPAP *via* a head-box, the technology used to provide continuous distending pressure to neonates has greatly evolved, first with the introduction of binasal prongs. Subsequently, both Kattwinkel et al. and Caliumi-Pellegrini et al. described non-invasive devices in which binasal prongs were connected to a ventilator to provide both flow and pressure [2]. This approach remained standard for a number of years. While the latter parts of this chapter will focus on each of the specific non-invasive modalities themselves, there is a considerable amount of overlap in terms of using the interface devices.

Devices such as "head boxes" or negative pressure boxes are purely of historical interest and are no longer in clinical practice. Facial masks can be used to provide CPAP provided that the mask is attached to a flow-inflating bag or a T-piece resuscitator (for more precise pressures generated). This is a commonly used approach in the delivery room for initial stabilization of neonates, but rarely used in a prolonged manner. Nasal masks, on the other hand, are often used to provide long-term support to neonates receiving non-invasive ventilation. This is typically with variable-flow devices or SiPAP [8]. Nasal prongs, however, are the most popular and effective way to provide non-invasive ventilation. Neonates are obligate nasal breathers so prongs provide the most reliable way of delivering consistent distending pressure [8]. If the infant's mouth is open, however, a large leak of pressure may occur and the neonate will not receive prescribed distending pressure. This may be addressed by using a chin strap or pacifier to keep the mouth closed. One other area where leak and loss of pressure can occur is at the nares; it is vital for nasal prongs to be large enough to fill the space within the nares to prevent this, but at the same time not so wide that they injure the surrounding mucosa and tissues [2, 8]. Long, thin prongs are generally avoided as they may increase the resistance in the system and even minor secretions can lead to significant obstruction and increased work of breathing. Endotracheal tubes are sometimes cut and used as "nasopharyngeal prongs." This practice is less common given all the previously described advantages of shorter binasal prongs. In addition, a recent Cochrane review also suggested that binasal prongs are simply more effective [14]. While we will explore some of the complications associated with non-invasive ventilation later in the chapter, skin and nasal trauma is perhaps the most commonly encountered issue. Adequate skin care requires assiduous nursing care, and often skin barriers are applied.

The pressure delivered by CPAP is typically *via* a continuous or variable flow device. Continuous flow was the method originally used in the 1970s and 1980s, and historically relied on gas flow generated from a ventilator [2]. Continuous-flow CPAP is still used today, typically *via* bubble or water-seal CPAP; this will be described in detail later in this chapter. Two of the most commonly used binasal prongs in continuous-flow CPAP are the Hudson (Hudson Respiratory Care, Inc., Arlington Heights, Illinois, USA) and Inca (Ackrad Laboratories, Inc., Cranford, New Jersey, USA) prongs. Argyle prongs are also occasionally used, but have fallen out of favor [14]. Many of these binasal prongs are interchangeable with different modes of non-invasive support, including CPAP, SiPAP/BiPAP or even nasal intermittent positive pressure ventilation (NIPPV) via a ventilator [15]. There are scant comparative studies in the literature comparing one prong type to another [2] (**Figure 3**).

Nasal masks are another avenue of providing non-invasive ventilation. The mask itself is connected to the pressure generator, typically a variable-flow device. Many units alternate the use of nasal masks with prongs to help prevent nasal and mucosal trauma. As with prongs, leaks can decrease the amount of pressure delivered to the patient. Therefore a proper seal around the nose must be maintained at all times. Very little data exists about the safety and efficacy of nasal masks versus prongs, and there are currently no reported studies of using NIPPV via nasal mask [2, 15] (**Figure 4**).

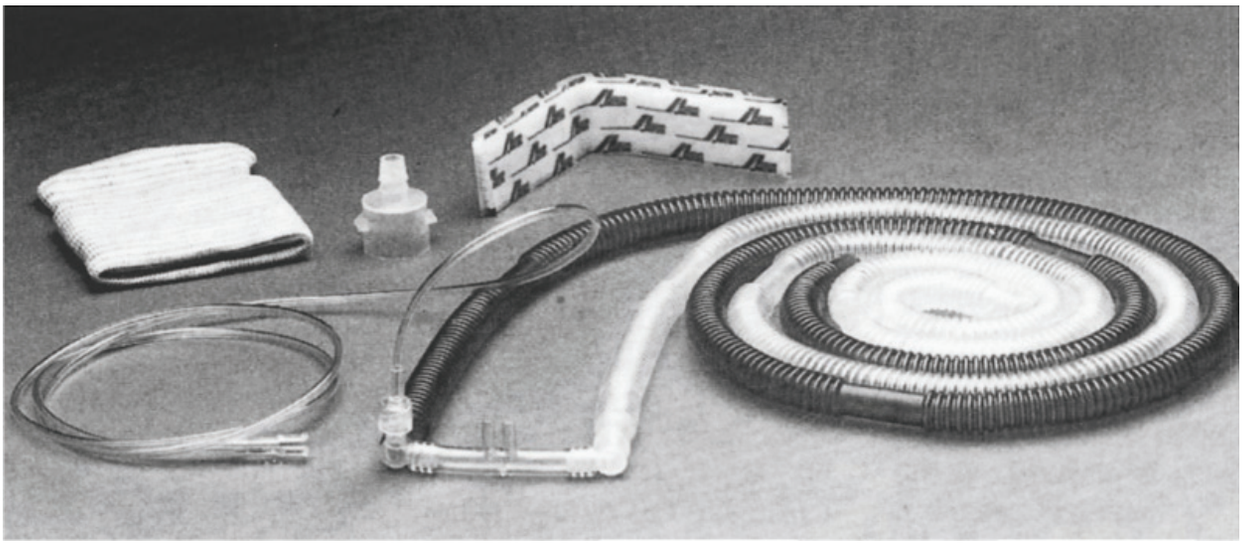


Figure 3. The Hudson NCPAP equipment very commonly used in many NICUs. Image used with permission by Elsevier Books, Inc.

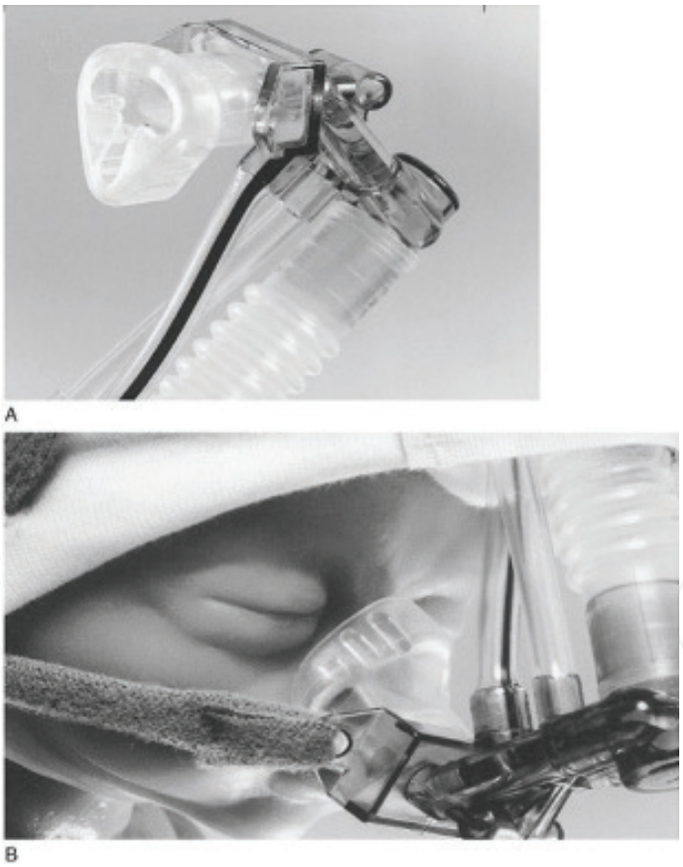


Figure 4. An example of a typical nasal mask used to deliver NCPAP with the infant flow driver device. Image used with permission by Elsevier Books, Inc.

While nasal cannulae (NC) are routinely used to provide supplemental oxygen, some distending pressure can be generated. The rate of gas flow, size of the cannulae, and degree of leak around the nares determine the amount of pressure generated [2]. Higher flow rates

delivered with relatively large sized nasal cannulae is termed "high flow nasal cannulae" (HFNC). Often heated and humidified, the physiology of respiratory support provided by HFNC is different than CPAP. The primary concern with a HFNC system is that depending on the flow rate and degree of leak, very high, uncontrolled positive pressure may be delivered. Not all HFNC devices contain "pop-off" valves to prevent this. These concepts will be explored later in this chapter. Finally, the RAM Nasal Cannula (Neotech, Valencia, California, USA) was originally designed to provide supplemental oxygen, but is a versatile interface device [2]. It has been used in various forms of CPAP as well as NIPPV *via* a ventilator. While at its core it is essentially another short binasal prong, it is designed with larger bore tubing to help reduce resistance and dead space. It has gained widespread use in many NICUs for its relative ease of use [2]. Early anecdotal reports also suggested lower rates nasal trauma. Concerns regarding the RAM Nasal Cannula have to do with the long segment of narrow tubing from the circuit connector to the prongs, creating a great deal of resistance. This can potentially lead to a sizeable drop in pressure and also raises concern about whether the clinician can accurately assess if the patient is receiving the desired distending pressure. It is important to also note that the use of the RAM Nasal Cannula in providing non-invasive ventilation is currently considered off-label use, as it is only approved for providing supplemental oxygen at this time.

5. Nasal continuous positive airway pressure (NCPAP)

Continuous positive airway pressure (CPAP) is positive pressure applied to the airways of spontaneously breathing neonates. As previously discussed, the primary function of the respiratory system is to move ambient air into the lungs for gas exchange. Any factor that limits this basic physiology will predispose the neonate to respiratory failure [8]. The inability to establish and maintain adequate lung volumes is perhaps the biggest risk factor for compromise. Low lung volumes and the resulting atelectasis may result in ventilation-perfusion mismatch and intrapulmonary shunting of blood. Oxygenation is typically affected the most, and while carbon dioxide can generally diffuse across biological membranes easily, its removal can be hampered by a low lung-volume state. Other mechanisms that contribute to respiratory distress in neonates include: retained lung fluid and pulmonary edema, suboptimal FRC, unstable chest wall with high compliance, upper airway more prone to collapse, poor laryngeal tone, and surfactant deficiency [8].

5.1. Physiological benefits of CPAP

CPAP alleviates many of physiologic derangements by increasing mean airway pressure and distending the airways to establish and maintain optimal FRC. By stabilizing and opening terminal alveoli, surface area for gas exchange is enhanced, and ventilation-perfusion mismatching is reduced. CPAP also improves diaphragmatic contractility. In addition, CPAP decreases the range of different opening pressure gradients between different areas of the lung and helps homogenize the total delivered tidal ventilations [8]. By better distending the individual alveolar units, CPAP also reduces the pressure needed to overcome surface tension. Surfactant is better preserved on the alveolar surface, further preventing atelectasis

and the resulting atelectotrauma. In addition, CPAP has been shown to reduce upper airway occlusion by increasing pharyngeal cross-sectional area and decreasing upper airway resistance [8]. Coupled with stabilization of the chest wall and improved compliance, CPAP also reduces work of breathing. Apnea of prematurity is a common issue for many neonates born before 35 weeks gestation. It is manifested by various episodes of apnea, bradycardia and oxygenation desaturation, or some combination of the three. While there is very limited evidence of CPAP being an effective treatment for apnea of prematurity, it is often clinically used in such a manner [2].

5.2. Methods of CPAP delivery

The pressure delivered via CPAP is either via a continuous flow or variable flow device. One of the most common methods of providing continuous-flow CPAP is what is referred to as bubble or water-seal CPAP [2]. Blended gas is first heated and humidified, then delivered to the neonate, typically *via* binasal prongs or a nasal mask. The distal end of the expiratory tubing is submerged in either 0.25% acetic acid or sterile water to a specific depth; this depth determines the level of CPAP generated [2]. The bubbles from the exhalation limb produce observable chest vibrations that could potentially enhance gas exchange. Furthermore, the applied gas flow rate to the CPAP device affects the degree of bubbling, suggesting that there may be a low-amplitude, high-frequency oscillatory effect to the lungs [13]. Initial studies that reported these findings, however, were using bubble CPAP delivered via a nasopharyngeal tube and not binasal prongs [2]. More studies are needed to determine if there exists an oscillatory waveform that enhances ventilation while on bubble CPAP.

Variable-flow CPAP has been in use since 1995 and was originally developed by Moa et al. to help reduce neonatal work of breathing [2]. These devices use dual injector jets directed towards each nasal prong to establish a constant airway pressure. In addition, when the neonate makes a spontaneous expiration, there is a "fluidic flip" in which the flow of gas is reversed and allowed to exit via the expiratory limb of the device. This phenomenon is enhanced due to the Coanda effect, in which gas tends to follow a curved surface [2]. The two most common variable-flow devices currently available are the Infant Flow (Cardinal Health, Dublin, Ohio, USA) and the Arabella system (Hamilton Medical, Reno, Nevada, USA). Some studies have indeed demonstrated less work of breathing and better synchrony in neonates on variable-flow devices compared to bubble CPAP. Others have found similar rates of extubation failure after randomization to either bubble CPAP or variable-flow CPAP following extubation from mechanical ventilation [2]. Despite these differences in the literature, there is no definitive evidence to suggest one mode of CPAP is superior. Many of these studies were done with neonates of various gestational ages and weights, which may confound the results further. Clearly, the clinician must be familiar with the device(s) available to them in their particular units and to be comfortable with their management.

5.3. Clinical management of CPAP

Determining the optimal CPAP level should be individualized to each neonate's underlying pathophysiology and should be aimed to obtain optimal without over-distention. This target

may change based on the neonate's disease course and postnatal age. The use of correctly sized binasal prongs with a chinstrap or pacifier to keep the mouth closed (if needed) is important to minimize any loss of pressure. Immediately after birth, most neonates of all gestational are started on a level of 5 or 6 cm H_2O, with escalation to 8–10 cm H_2O as needed [2, 8]. There is limited evidence, however, to suggest a singular approach to initiating or changing the CPAP level. Again, these decisions should be driven by the underlying pathophysiology and supported by clinical and laboratory measures when necessary. Many institutions have their own specific guidelines and goals, especially when caring for the very low birthweight or extremely low birthweight infant. In general, the CPAP level is deemed appropriate when the neonate's oxygenation and ventilation are satisfactory, the chest radiograph is optimally inflated, work of breathing is minimal, and the neonate is otherwise hemodynamically stable. When the CPAP level is too high, one may see signs of over-distention on the chest radiograph manifested by a flattened diaphragm or small heart size. Gas exchange may be worsened and, in severe cases, over-distention can reduce cardiac output leading to tachycardia and hypotension [8].

Weaning the neonate off CPAP is another area that should be driven by the underlying physiology and any continued need for respiratory support. This is typically possible when the neonate is requiring little to no supplemental oxygen, work of breathing is negligible, and there are few episodes of apnea, bradycardia, and desaturation [8]. While some institutions wean the CPAP level during this time, other institutions do not. An alternative method of weaning CPAP consists of "sprinting" the neonate off CPAP support for a period of time, which gradually increases until off entirely. This is not well studied and this method of "sprinting" may actually lead to CPAP weaning failure and may prolong the length of time ultimately spent on CPAP [8]. Additional questions include at what postnatal age to consider removal of CPAP, and what level of support (if any) should the neonate be transitioned to. The duration of CPAP is often driven by the neonate's gestational age even in the absence of significant lung disease, as very preterm infants often benefit from longer use of CPAP while their chest walls mature and offset the elastic recoil of the lungs [8]. While this may vary from one institution to another, typical goals for removing an extremely preterm neonate from CPAP are around 32–34 weeks postmenstrual age, when appropriate goals are achieved (ie, no work of breathing and/or minimal supplemental oxygen requirement, etc). When discontinuing CPAP, the neonate can either be taken directly to room air or transitioned to a lesser mode of support (typically some form of nasal cannula). Again, much of this decision-making is driven by the current lung disease (if any) being treated at the time, as well as any other factors that may predispose the neonate to continued need for respiratory support. For example, the neonate that is otherwise stable on a fairly low CPAP level, has no oxygen requirement, and is growing well can reasonably be taken to room air as the initial attempt at discontinuing CPAP. The neonate that still has a minimal oxygen requirement but otherwise meets other criteria for coming off CPAP can be taken to a nasal cannula.

5.4. BiPAP and SiPAP

Bilevel CPAP (BiPAP) or sigh intermittent positive airway pressure (SiPAP) has been marketed as a means of delivering alternating levels of distending pressure. Both are typically

used with the Infant Flow driver and can alternate between a lower and higher CPAP pressure throughout the respiratory cycle; some ventilators can provide this mode as well [2]. This method of support is not synchronized (synchrony is currently only available in Europe and Canada), and the neonate breathes spontaneously at both levels of support. This potentially creates two distinct FRCs [16]. The CPAP levels cycle at a specific rate. The higher pressure level is delivered during "inspiration", with typical values of 8–10 cm H_2O, but sometimes as high as 15 cm H_2O if using a patient triggered BiPAP device. Most SiPAP devices, on the other hand, will have a "sigh" pop-off that will prevent inspiratory PEEP from exceeding 10 cm H_2O. During "expiration", the neonate will breathe the lower pressure level, with typical values set at 4–6 cm H_2O. A higher "inspiratory time" is typically used, with some authors suggested as high as 1 second [8]. Lista et al. compared outcomes in preterm neonates with RDS that were initially supported with CPAP versus SiPAP [16]. They found that infants supported with SiPAP had a shorter duration of mechanical ventilation overall, needed less oxygen, and were discharged home sooner. A caveat of these studies is that it can be difficult to compare the actually distending mean airway pressure delivered between CPAP and BiPAP/SiPAP. The latter, with alternating levels of pressure, will typically generate a pressure that is 2–3 cm H_2O higher than CPAP [2]. It is quite possible that it is this higher overall level of pressure in addition to the cyclical tidal volumes delivered that result in benefit to the infant. A recent study in 2016 by Victor et al. aimed to compare the use of CPAP and BiPAP in infants born before 30 weeks' gestation and less than two weeks old using equivalent mean airway pressures [17]. They did not find any difference in extubation failures between the two groups, nor did they find any difference in total duration of mechanical ventilation, oxygen requirement at 28 days & 36 weeks corrected, or length of hospitalization.

6. Humidified high flow nasal cannula (HHFNC)

HHFNC use rapidly expanded in NICUs since 2005. The two major commercially available devices are Vapotherm (Exeter, New Hampshire, USA) and Fisher & Paykel (Auckland, New Zealand) [2]. While most clinicians refer to this technology as "HFNC," the delivered air undergoes a heating and humidification process. Traditional nasal cannula was limited to flow rates of 2 lpm of either 100% or blended oxygen for neaontes [13]. Higher rates of flow often caused significant drying of the airway mucosa, leading to irritation and mucosal trauma. The new HFNC systems create nearly 100%, allowing clinicians to use higher flow rates. This can vary from one institution to another. Some centers will use flow rates of up to 4 lpm, while others use rates as high as 8 lpm. Many of the same physiological benefits seen with the use of CPAP can be extrapolated to the use of HHFNC, as the higher flow rates has been shown in some studies to provide comparable distending pressure [2]. These benefits include improved pharyngeal tone, nasopharyngeal deadspace washout, decreased work of breathing, and maintenance of FRC [13]. The primary concern with the use of HHFNC is that it can potentially deliver unpredictable, uncontrolled and widely variable levels of distending pressure. Some studies using esophageal probes have measured the pressure delivered by HHFNC; this level is a determined not only by the flow rate delivered, but also the weight of the neonate and the size of the cannulae [2]. Neither of the two commercially available HHFNC

devices are capable of measuring the level of pressure provided. They do, however, have an internal pressure-limiting mechanism as a safety measure to prevent excessive pressures from reaching the patient [8]. Ultimately, though, there currently is no reliable way to calculate how much distending pressure is delivered. For that reason, it is vital that the nasal prongs selected allow for some leak around the nares so that extremely high pressures are avoided.

6.1. Clinical use of HHFNC

HHFNC has been tried in various domains of neonatal respiratory management, including as a means of avoiding extubation failure in premature neonates. There have been a handful of recent studies to look at this, and the general consensus seems to be that HHFNC was non-inferior to CPAP in terms of extubation failures [8]. The additional finding of less nasal and mucosal trauma was consistent across most of these studies. Overall, however, there is still insufficient evidence to suggest that HHFNC is equal or superior to CPAP in preventing extubation failure. Much of this has to do with wide variations in the previously mentioned study designs, use of different devices, and unknown severity of respiratory distress in enrolled patients [8]. These data are even more limited for extremely low birthweight infants or those born less than 28 weeks' gestation [13].

HHFNC has also been studied for treatment of apnea of prematurity and work of breathing. Saslow et al. (2006) evaluated the effects of CPAP and Vapotherm HFNC on work of breathing patterns in a crossover study of preterm infants requiring either support modality and weighing <2.0 kg at birth. They did not find any significant differences between the two groups [8]. Sreenan et al. (2011) also looked at stable premature infants in a crossover study of CPAP and HHFNC. They did not find any differences between the two modalities with respect to apnea, bradycardia, or desaturation events, oxygen requirement, or work of breathing [8]. This remains an area where success with HHFNC can certainly be achieved, but it is important to note that no definitive evidence exists to prove it is equally efficacious as CPAP.

6.2. Current best evidence regarding HHFNC use

In June 2015, an international group of experts met in Oxford, England to discuss the use of nasal high-flow therapy in neonatology. The goal of the meeting was to reach consensus among clinicians on how to best use and study HHFNC in neonates and to try to establish guidelines for its management [13]. At the time of their meeting, their review encompassed four current RCTs that involved over 1100 preterm infants [13]. The following is summary of the group's findings.

The Oxford group recommended that in general, HHFNC can be *considered* for most neonates in which CPAP would be used. This includes preterm infants with respiratory distress, increased work of breathing, or an oxygen requirement. Special consideration should be given to neonates with significant nasal trauma from CPAP use, as switching to HHFNC may allow the nares to heal [13]. The same level of monitoring and nursing care provided to a neonate on CPAP should be applied to a neonate on HHFNC [13].

As previously mentioned, one of the major differences at the level of the nasal prongs between CPAP and HHFNC is the desired amount of leak. With HHFNC, there must be a moderate

amount of leak around the nares to allow gas egress and to ensure that unpredictably high pressures do not occur. The group concluded that the prong dimensions be no greater than 50% of the diameter of the nares, and that the gas flow via HHFNC be heated between 34 and 37 degrees C [13]. Furthermore, the actual cannulae used should be per manufacturer recommendations, and components from different systems should not be mixed.

Individual institutions may have their own particular guidelines, but the Oxford meeting recommends starting with flows of 4–6 lpm for most preterm infants. Lower flow rates of 2–3 lpm may be acceptable for larger neonates closer to or at term [13]. A maximum flow rate of 8 lpm is recommended, and only in response to increased work of breathing or higher oxygen requirements. Escalation from HHFNC to a different support modality should be considered in cases of increased work of breathing, increased apnea, or oxygen requirements greater than 50% [13]. Weaning the flow rate can be considered once the neonate is stable for about 24 hours and on 30% or less oxygen, with one recommended approach of weaning the flow rate by 1 lpm every 12 hours as tolerated. Again, institutions may have their own weaning protocols. Discontinuing HHFNC can be considered once flow rates of 2–4 lpm are achieved, as 2 lpm is actually the lowest most devices will sustain, and the benefits of rates less than 3 lpm are actually unclear at this point [13].

6.3. Summary

A growing body of evidence seems to suggest that HHFNC is fairly safe and efficacious in supporting many preterm infants, however no definitive evidence exists. Flow rates of 2–8 lpm are generally acceptable, with careful attention to prong size and adherence to all manufacturer recommendations. Clearly, however, more research is needed. Specifically, more studies are needed to evaluate the use of HHFNC in extremely low birth weight infants and those born less than 27 weeks' gestation, as well as the potential use of HHFNC in delivery room resuscitation and during neonatal transport [13]. *This is one specific age group in which the evidence still overwhelmingly supports the use of CPAP as the initial mode of support*. More studies are also needed to compare different HHFNC devices, types of cannulas, and true flow rate recommendations based on weight and gestational age. Finally, the Oxford group strongly recommends that each institution devise and adhere to their own agreed-upon guidelines so that a standardized approach to the use of HHFNC can be applied and subsequently studied.

7. Nasal intermittent positive pressure ventilation (NIPPV)

Nasal intermittent mandatory ventilation (NIMV), also known as nasal intermittent positive pressure ventilation (NIPPV), refers to ventilation provided via a conventional ventilator in a non-invasive fashion. This is usually administered *via* short binasal prongs, the RAM Nasal Cannula, or a nasal mask [2, 8]. Depending on the type of ventilator and settings used, NIPPV is designed to deliver positive pressure throughout the respiratory cycle with defined, intermittent increases in pressure, often in synchrony with respiratory efforts [8]. This method of respiratory support was initially described in the early 1970s when *via* time-cycled inflations

using a ventilator with an oronasal mask [2]. In the 1980s, more than 50% of the level III NICUs in Canada were consistently using this method of respiratory support. Shortly after, it fell out of favor due to reports of facial neurological injuries and gastrointestinal perforations; subsequent studies regarding the use of NIPPV in neonates have not reported higher rates of these complications [2, 13]. Of note, nasal high-frequency ventilation (NHFV) is also described in the literature and is increasingly common in some centers in Europe. Given its relative new nature and lack of extensive comparative studies, it will not be discussed here.

7.1. Benefits of NIPPV

The physiological benefits of NIPPV are similar to other modes of positive pressure delivery. Specifically, NIPPV will expand the lung and recruit terminal alveoli, increase FRC, prevent atelectasis and atelectotrauma, and improve ventilation-perfusion mismatches [8, 18]. In addition, the positive pressure delivered helps splint the upper airways, improves laryngeal tone, and stabilizes the highly compliant neonatal chest wall. Synchronized NIPPV, or sNIPPV, has been shown in several studies to deliver higher tidal volumes than CPAP or non-synchronized NIPPV [13, 18]. In addition, all forms of NIPPV deliver additional positive pressure breaths, further increasing mean airway pressure. This in turn helps to further improve tidal volumes and reduces thoraco-abdominal asynchrony (especially true with sNIPPV), which has may reduce work of breathing and improve pulmonary mechanics [8]. Animal studies have also shown that the intermittent distending pressure above PEEP that NIPPV provides can more effectively recruit the lung than CPAP alone, leading to further improvements in FRC [13].

NIPPV has been studied in three major domains: preventing extubation failures, treating apnea of prematurity, and as the primary mode of treating respiratory distress in premature neonates. As of 2015, there have been ten randomized controlled trials comparing NIPPV with CPAP after extubation in premature infants. Friedlich et al. were the first to publish a study comparing CPAP with sNIPPV, and demonstrated that sNIPPV reduced extubation failures significantly [19]. In 2017, a Cochrane meta-analysis of these trials demonstrated a reduction in extubation failure (NNT = 4), but the studies included various NIPPV devices with a mix of synchrony versus asynchrony [8]. Furthermore, there was variability in the definition of extubation success. Despite these *caveats*, the conclusion from the review was that NIPPV may reduce extubation failure within 48 hours to one week after extubation more effectively than CPAP. No effect, however, was seen on chronic lung disease or mortality [18].

For treatment of apnea of prematurity, there are three studies comparing CPAP with NIPPV. The evidence is conflicting and there is no current recommendation whether NIPPV is superior to CPAP [8, 13]. A total of eight studies with 850 patients have looked at NIPPV as the primary mode of initial ventilation in premature neonates with respiratory distress syndrome, with the primary outcome being failure of non-invasive support and the need for intubation. The studies included different devices with mixed populations. Furthermore, some studies allowed the use of surfactant while others did not. As one might imagine, the results were mixed, with six of the trials essentially finding no difference between the two respiratory modalities [8]. As mentioned above, the strongest evidence in this area as demonstrated by

the 2017 Cochrane review appears to be the use of NIPPV to prevent extubation failure when used immediately after extubation [18].

7.2. Typical NIPPV settings

As with every mode of respiratory support, the settings applied to any particular neonate should be based on the particular device used and the underlying pathophysiology. Initial settings on NIPPV are typically similar to those of a mechanical ventilator, with two exceptions, applied peak inspiratory pressure (PIP) and inspiratory time (Ti). Higher PIP is often necessary as pressure is delivered via a nasal interface and pressure is attenuated prior to delivery to the lungs. Therefore, NIPPV PIP is typically started about 2–4 cm H_2O higher than that normally used for mechanical ventilation *via* an endotracheal tube [8]. This is then adjusted based on adequate chest rise and blood gas measurements. For similar reasons, slightly higher inspiratory times of 0.4–0.5 seconds are also typical, as breaths delivered nasally have more resistance to overcome versus those delivered via an endotracheal tube.

Weaning from conventional ventilator to NIPPV should be done according to the same general recommendations as for any other mode. The goal should be well inflated lungs with an adequate FRC and minimal work of breathing. Settings on NIPPV are typically similar to prior settings on mechanical ventilation at the time of extubation. While this will differ from one institution to the next, this typically consists of rates below 25 breaths/min, a PIP of less than 20 cm H_2O, and an oxygen requirement of less than 30–35%. PEEP can be variable depending on oxygen requirement and need for lung expansion, but ideally will be 6 cm H_2O or less [8].

8. Summary

Although the means of delivering non-invasive respiratory support are widely variable, with numerous interfaces, devices and modes, the underlying goal is the same for all. Each baby's physiology should be assessed and non-invasive respiratory support must be tailored to resolve the most important underlying pathophysiology. When properly supported, babies should be well oxygenated, with minimal work of breathing, infrequent apnea, and a stable respiratory status.

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References

[1] Gregory GA et al. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. The New England Journal of Medicine. 1971;**284**:1333-1340

[2] Goldsmith Jay P, Karotkin E, Keszler M, Suresh G, editors. Assisted Ventilation of the Neonate: An Evidence-Based Approach to Newborn Respiratory Care. 6th ed. Philadelphia: Elsevier; 2017 500 p

[3] Berger TM, Fontana M, Stocker M. The journey towards lung protective respiratory support in preterm neonates. Neonatology. 2013;**104**:265-274. DOI: 10.1159/000354419

[4] Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child. 1959;**97**:517-523

[5] Northway WH, Rosan R, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: Bronchopulmonary dysplasia. The New England Journal of Medicine. 1967;**276**:357-368

[6] Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al. Is chronic lung disease in low birth weight infants preventable? Pediatrics. 1987;**79**:26-30

[7] Davis RP, Mychaliska GB. Neonatal pulmonary physiology. Seminars in Pediatric Surgery. 2013 Nov;**22**(4):179-184. DOI: 10.1053/j.sempedsurg.2013.10.005

[8] Donn SM, Sinha SK, editors. Manual of Neonatal Respiratory Care. 4th ed. Cham, Switzerland: Springer International Publishing AG; 2017. 820 p. DOI: 10.1007/978-3-319-39839-6

[9] McBride W. Congenital lesions of the lung. NeoReviews. 2016;**17**(5):e263-e270. DOI: 10.1542/neo.17-5-e263

[10] Cullen AB, Wolfson MR, Shaffer TH. The maturation of airway structure and function. NeoReviews. 2002;**3**:e125-e130. DOI: 10.1542/neo.3-7-e125

[11] Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. Seminars in Perinatology. 2006 Feb;**30**(1):34-43. DOI: 10.1053/j.semperi.2006.01.006

[12] Alexiou S, Panitch HB. Physiology of non-invasive respiratory support. Seminars in Fetal & Neonatal Medicine. 2016 Jun;**21**(3):174-180. DOI: 10.1016/j.siny.2016.02.007

[13] Yoder BA, Kirpalani H, editors. Non-Invasive Ventilation, an Issue of. Clinics in Perinatology. 1st ed. Philadelpha, PA: Elsevier; 2016 200 p

[14] De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database of Systematic Reviews. 2008 Jan;**23**(1):CD002977. DOI: 10.1002/14651858.CD002977.pub2

[15] Owen LS, Manley BJ. Nasal intermittent positive pressure ventilation in preterm infants: Equipment, evidence, and synchronization. Seminars in Fetal & Neonatal Medicine. 2016 Jun;**21**(3):146-153. DOI: 10.1016/j.siny.2016.01.003

[16] Salvo V, Lista G, et al. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: An RCT. Pediatrics. 2015 Mar;**135**(3):444-451. DOI: 10.1542/peds.2014-0895

[17] Victor S, Roberts SA, et al. Biphasic positive airway pressure of continuous positive airway pressure: A randomized trial. Pediatrics. 2016;**138**(2). DOI: 10.1542/peds.2015-4095

[18] Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database of Systematic Reviews. 2017 Feb:1-75. DOI: 10.1002/14651858.CD003212.pub3

[19] Ramanathan R. Nasal respiratory support through the nares: Its time has come. Journal of Perinatology. 2010 Oct;**30**:S67-S72. DOI: 10.1038/jp.2010.99

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