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State of the Art: Neonatal Non-invasive Respiratory Support: Physiological Implications

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Summary

The introduction of assisted ventilation for neonatal pulmonary insufficiency has resulted in the successful treatment of many previously fatal diseases. During the past three decades, refinement of invasive mechanical ventilation techniques has dramatically improved survival of many high-risk neonates. However, as with many advances in medicine, while mortality has been reduced, morbidity has increased in the surviving high-risk neonate. In this regard, introduction of assisted ventilation has been associated with chronic lung injury, also known as bronchopulmonary dysplasia. This disease, unknown prior to the appearance of mechanical ventilation, has produced a population of patients characterized by ventilator or oxygen dependence with serious accompanying pulmonary and neurodevelopmental morbidity. The purpose of this article is to review non-invasive respiratory support methodologies to address the physiologic mechanisms by which these methods may prevent the pathophysiologic effects of invasive mechanical ventilation.

Keywords

CPAP; bubble CPAP; high-flow nasal cannula; NIMV; nitric oxide; oxygen therapy; surfactant therapy

Introduction

The introduction of assisted ventilation for neonatal pulmonary insufficiency has resulted in the successful treatment of many previously fatal diseases. In addition, the refinement of mechanical ventilation during the past three decades has dramatically improved survival of many high-risk neonates. As with many advances in medicine, however, the introduction of assisted ventilation has been associated with chronic lung injury, also known as bronchopulmonary dysplasia (BPD) [1]. This disease, unknown prior to the appearance of mechanical ventilation, has produced a population of patients characterized by ventilator or oxygen dependence with serious accompanying morbidity and mortality [2,3]. The purpose of this review article is to identify methods for eliminating the physiologic and pathophysiologic effects of mechanical ventilation on the lungs by using non-invasive respiratory support.

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Pulmonary physiology and pathophysiology: considerations with respiratory support

Although the design of the lung serves multiple functions, the primary structure and its placement within the thorax establish its main purpose as that of gas exchange. The respiratory system consists of a series of branching tubes that bring fresh gas from the atmosphere to the terminal air spaces while allowing the respiratory metabolic byproducts to flow from the alveoli back into the environment. The diaphragm, the primary muscular force during quiet ventilation, contracts during inspiration, which lowers intrapleural pressure. This contraction results in a pressure gradient that decreases from the mouth to the alveoli and leads to an inward flow of gas. Concomitantly, the increase in intra-abdominal pressure limits inspiratory movement until rising intrathoracic pressure terminates flow. During inspiration, a series of elastic elements—the chest wall muscles, diaphragm, airway connective tissue, pleura, and blood vessels—expand within the thorax. At the end of inspiration, the energy stored in these elastic elements provides a recoil that forces gas out of the lung during expiration. Under normal physiological conditions, expiration is a passive process. When the respiratory workload is increased, however, the accessory respiratory muscles (intercostal and abdominal musculature) are recruited so that both inspiration and expiration may become active. The gas volume in the lungs when inspiration begins to oppose the expiratory recoil forces is called the functional residual capacity (FRC).

In the newborn, neurochemical control of breathing and its influence upon the process is not clearly understood. Furthermore, control of breathing is continuously evolving throughout gestation. In this regard, several features serve to distinguish the neonate from the adult. Brain stem centers of respiratory control are immature and are more susceptible to failure, as seen in apnea of infancy [4]. Chemoreceptor responsiveness also appears to be diminished in the neonate, particularly with respect to hypoxemia [5-7]. Furthermore, a number of reflex responses in very young infants disappear rapidly during the first months and years of life [8]. Finally, sleep state, which influences respiratory control, is different in the newborn infant compared to the adult, with predominance of REM sleep [6, 7].

A number of studies have attempted to establish values for ventilatory volumes in neonates [9]. Although tidal volume and minute ventilation change with growth and development, physiologic dead space (VD/VT) remains relatively constant throughout life in the healthy individual, at about 0.3. Pulmonary function testing, aided by the use of computerized analysis, has produced extensive data on compliance and resistance measurements during states of both health and disease [9]. Compliance refers to the change in lung volume for a given change in pressure. In general, the smaller the lung is, the lower the compliance. Thus, the ratio of compliance to FRC (*specific compliance*) in the healthy newborn is comparable to that in older children and adults. The newborn chest wall contributes little to total lung compliance, especially in preterm infants, since thoracic compliances are relatively high.

The airways of young infants are small caliber, highly distensible, and susceptible to injury during mechanical ventilation [10-14]. Airway resistance is rapidly elevated by any reduction in airway caliber, such as increased secretions, airway edema, or increased collapsibility of the airway (associated with the use of mechanical ventilation in small infants) [15]. Furthermore, assessment of flow-volume and pressure-volume loops provides important information about airway patency and chest-wall distortion [16]. Functional residual capacity measurement, though somewhat more difficult, can also be performed with either a helium dilution method [17] or with the nitrogen washout technique [18]. Finally, the lack of infant cooperation during forced expiratory volumes, an important pulmonary function examination of the airway, has been resolved by the use of an external compression of the thorax [19]. These techniques enable the neonatologist/pulmonologist to understand both normal infant ventilation and the alterations produced during assisted ventilation.

Certain features of the developing lung predispose it to injury during mechanical ventilation. Surface tension is higher in the alveoli for all infants during the first hours of life, with some degree of atelectasis being common until a monomolecular layer of phospholipids and their accompanying proteins (collectively known as surfactant) is deposited at the air-liquid interface. Surfactant is primarily composed of phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, and several other lipid-soluble moieties. It decreases lung biophysical forces and the surface tension in the lung at end-expiration [20-25]. Surfactant reduces the tendency of the lung to collapse from increased surface active forces in the alveoli. Surface tension and structural immaturity appear to be the major factors that lead to respiratory insufficiency in the premature lung and may result in hyaline membrane disease (HMD), also known as respiratory distress syndrome (RDS). Although primarily a disease of prematurity, RDS does occasionally occur in full-term births. When surfactant deficiency and structural immaturity are present, lung compliance in the newborn is reduced and respiratory support is frequently necessary.

A number of studies have suggested that the ventilatory muscles of newborns are more susceptible to fatigue than those of adults—a factor that, in addition to lung immaturity, may contribute to the respiratory problems of preterm neonates [26]. Studies of histochemical and physiologic properties of respiratory muscle fibers have reported age-related differences in both the human and baboon diaphragm [26]. Because of these age differences, the premature diaphragm contracts from progressively shorter lengths and develops less tension.

Other factors, such as the fragility of lung tissue, marginal energy reserves, limited ability to increase cardiac output, and lability of pulmonary perfusion from pulmonary hypertension, also may result in both a greater need for respiratory support and thus the additional problems associated with assisted ventilation.

Non-invasive respiratory support modalities

Several different methods for respiratory support can be applied in the care of individual infants. Each method has both physiologic advantages and disadvantages that must be considered.

Oxygen Therapy—Adequate tissue oxygenation maintenance is one of the primary goals of therapy during respiratory support. The simplest way to achieve adequate oxygenation is to increase the fraction of oxygen in inspired gas. Oxygen must be considered a drug, however, because it has potential harmful side effects, such as retinopathy of prematurity [27-29], oxidative stress, and BPD. Retinopathy is believed to occur, at least in part, from varying oxygen concentrations in the blood that result in vasoconstriction and subsequent proliferation and abnormal vascular growth in the immature infant's retina. Other factors, such as prematurity itself, carbon dioxide levels, apnea, blood pressure, vitamin E levels, and some additional (possibly unknown) factors, also appear to be important in the development of this condition [28]. Genetic tendency may play a role as well.

Oxidative stress is related to the damage from extended oxygen exposure to lung tissue. Human epithelial cells (Calu-3 cells) exposed to graded oxygen concentrations (21, 40, 60, and 80% FiO₂) demonstrated cell dysfunction and inflammation in a dose-dependent manner [30]. Trans-epithelial resistance across the cell monolayer decreased in a dose- and time-dependent manner, and cell viability was reduced at 72 hrs in the all hyperoxic 40, 60, and 80% FiO₂ groups. Interleukin (IL)-6 secretion was elevated in all-hyperoxic groups at 24 hrs, and both IL-6 and IL-8 levels were greater in the 40% FiO₂ group compared with all other groups at 72 hrs. In this model, airway epithelial cells demonstrated profound concentration and time-dependent responses to hyperoxic exposure with respect to cell physiology, viability, histology, and secretion of inflammatory mediators.

Bronchopulmonary dysplasia appears to be a result of prolonged exposure to high inspired-oxygen concentrations and positive-pressure ventilation. This condition may have an underlying inherited tendency in some families [31] and is also multifactorial in etiology. Superoxide anion generation from oxygen may be one of the inflammatory processes that initiates the lung response that later results in BPD. Superoxide dismutase, catalase, glutathione peroxidase, and other enzymes important in the catalytic reduction of these anions are reduced in the premature infant. As a result, the premature lung may be at increased risk from the effects of this oxygen byproduct. Recent studies with superoxide dismutase have suggested a therapeutic role for this agent in preventing BPD.

Because of the substantial morbidity from these conditions, oxygen therapy must be administered cautiously and monitored during the neonatal period. Inspired oxygen concentration and blood oxygen saturation and tension should be frequently assessed.

Hyperoxia leads to major morbidity in the newborn, but hypoxia can produce even greater problems. Hypoxemia, if prolonged, results in a change from aerobic to anaerobic metabolism, increased lactic acid production, and ultimately, cellular and organ demise. Death usually follows soon after. These effects are unquestionably time-related. A shorter duration of hypoxemia, however, may still result in organ injury that can be permanent at times [32]. Effects of hypoxemia on central nervous system function and development are a constant concern for the neonatologist.

New approaches to oxygen delivery show promise in protecting the lungs from oxidative stress. It is possible to better control inspired oxygen by using a computer-assisted controller to regulate inspired oxygen in response to pulse oximetry signals. In a preclinical RDS spontaneously breathing lung injury model [33], it was demonstrated that it was possible to maintain SaO_2 within a $95 \pm 2\%$ range throughout the study protocol with lower inspired oxygen using an adaptive, computer-regulated oxygen blender (Columbia Life Systems, Durham, NC) compared to a conventional manual oxygen weaning protocol (Figure 1). In addition, it was reported that SaO_2 and arterial oxygen tension were similar between groups throughout weaning thus suggesting a reduction in alveolar oxidative stress exposure during supplemental oxygen support therapy.

A further advancement to oxygen therapy is the use of helium (as opposed to nitrogen) as a vehicle to administer oxygen [34-36]. In a neonatal model of acute lung injury, Nawab et al [35] showed that a heliox-gas-breathing group was associated with a more efficient respiratory pattern, increased alveolar recruitment, and lower inspired oxygen requirements than a group of respiratory distressed animals breathing a nitrox gas mixture of the same oxygen concentration. Ultimately, this heliox breathing led to an attenuated inflammatory profile. As such, the role of heliox in the management of acute lung injury in early development has been extended, for the first time, beyond reducing resistive of work of breathing to an affect on the inflammatory and structural profile of the lung.

Continuous positive airway pressure—Since its introduction by Gregory et al [37] in 1971, continuous positive airway pressure (CPAP) has become a standard part of ventilatory care. The full effects of this therapy are not fully understood, and part of the difficulty may be that CPAP may have variable results in different clinical situations. It is believed to progress alveolar recruitment, vary degrees of pressure delivery to the lung, inflate collapsed alveoli [37], and reduce intrapulmonary shunt [38-41].

$$\text{From LaPlace's law, Pressure} = \frac{2 \times \text{tension}}{\text{radius}}$$

One might expect that collapsed alveoli would remain collapsed and that inflated or partially inflated alveoli would become increasingly inflated or overdistended. These findings have never been clearly documented. Some of the effects of CPAP, however, have been measured: CPAP increases gas volume in the lung, including FRC [38]. Initially, as FRC increases, gas exchange improves, PaO_2 increases, and PaCO_2 decreases. With excessive CPAP, however, the volume of the lung increases excessively and the lung becomes overdistended. In such cases, PaO_2 remains high, but PaCO_2 also begins to increase as tidal volume diminishes and physiological dead space increases. Continued excessive CPAP may ultimately lead to very serious consequences, such as air leak syndromes: pneumomediastinum, pneumothorax, or pneumopericardium [42]. It may also increase dead space ventilation, leading to a rise in PaCO_2 . Furthermore, although low levels of CPAP may be useful in decreasing pulmonary edema or left-to-right cardiac shunting, high levels of CPAP can lead to a reduction in cardiac output, reduced pulmonary perfusion, and enhanced ventilation-perfusion (V/Q) mismatching, resulting in a lower PaO_2 [43-45]. Depending on the levels of CPAP applied and lung compliance, pulmonary vascular resistance may be increased with CPAP; although, its use early in the course of RDS may lead to decreased pulmonary vascular resistance [46].

Continuous positive airway pressure has some nonspecific effects on neonatal ventilation as well. Application of CPAP appears to produce a more regular breathing pattern in preterm neonates [47] and has been thought to be mediated through chest-wall stabilization and reduction of thoracic distortion. Continuous positive airway pressure also reduces Obstructive apnea [48], even via nasopharyngeal application. Furthermore, it has been shown that both inspiratory and expiratory times are increased with CPAP. Finally, it is thought that surfactant release may be enhanced by CPAP in RDS.

Intracranial pressure is increased by CPAP and is directly related to the amount of CPAP applied and to the compliance of the lungs [49]. With increased lung compliance, more pressure is transmitted to the cardiovascular system, resulting in a rise in central venous pressure and intracranial pressure. Cerebral perfusion pressure, however, can decrease with end-distending pressure application, since venous pressure rises and arterial pressure decreases initially. Some compensation is likely to occur over time; however, these changes in intracranial pressure may lead to an increased risk of intracranial hemorrhage, especially in the preterm baby [32].

Some effects of CPAP on renal function have been documented [50]. These include decreased glomerular filtration rate (GFR), reduced urinary sodium excretion, and diminished urinary output [51,52]. These findings also appear to be mediated through transmission of pressure to the cardiovascular system with reduction in renal blood flow. As renal blood flow decreases, there may be some redistribution of intra-renal blood flow to the inner renal cortex and outer medulla [53]. Aldosterone appears to increase with CPAP application [54], and antidiuretic hormone (ADH) secretion may increase as well [55]; although, there have been reports of decreased ADH with CPAP. These contradictory findings may again be reflect the fact that CPAP may improve or worsen lung compliance, thereby resulting in either an increase or decrease in intracranial perfusion.

Because there has been little improvement in BPD since the introduction of surfactant, a large study was recently conducted in which infants who were born at 25 to 28 weeks were randomized to either CPAP or intubation and ventilation at 5 min after birth. The investigators assessed outcomes at 28 days of age, at 36 weeks gestational age, and before discharge [56]. They found that early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia in infants born at 25 to 28 weeks of gestation, as compared with intubation. Even though the CPAP group had more incidences of

pneumothorax, fewer infants received oxygen at 28 days, and they had fewer days of ventilation.

Due to the aforementioned issues, there has been a renewed interest in using bubble continuous positive airway pressure (BCPAP) for premature neonates with RDS. Numerous theories have been proposed for the outcome of neonates treated with BCPAP. Literature suggests that BCPAP may mimic high frequency oscillatory ventilation (HFOV). In a series of spontaneously breathing lambs with either CPAP or BCPAP, Pillow et al [57] reported that, compared to continuous CPAP, BCPAP promoted airway patency and improved physiological outcomes in acute respiratory distress. Based on these findings, the authors suggested that BCPAP may offer further protection against lung injury in the neonate. Also in an attempt to support or refute these issues, Blackson et al [58] evaluated BCPAP *in vitro* and *in vivo* to determine a physiological basis for ventilation augmentation. For the *in vitro* studies, tests were conducted with BCPAP, a Michigan test lung, and a hot-wire anemometer (Florian, Acutronic Med. System, Basal, Switzerland). For the *in vivo* parallel studies, neonatal pigs were anesthetized, paralyzed, instrumented, and gas ventilated ($\text{FiO}_2 = 1.0$) through an endotracheal tube using a Servo 900C (Siemens, Los Angeles, CA) in the pressure-control mode (pressure-controlled ventilation; PCV). The ventilator was set during a 10-min stabilization period to produce a pre-CPAP PaCO_2 of 30-50 mm Hg. Pigs were then randomized to receive either BCPAP or conventional CPAP (CCPAP) of 5 cm H_2O for 3 min while paralyzed and apneic. BCPAP was administered using the same *in vitro* circuitry and CPAP was administered using the Servo 900C. Arterial blood gases and vital signs were measured at the end of each pre-CPAP ventilator stabilization period and at the end of each 3-min CPAP trial.

The *in vitro* studies revealed no measurable HFOV effect when monitored with flow rates of 7, 8, and 9 L/min. HFOV effects were measurable using a flow rate of 10 L/min, ($f = 5\text{-}9$ Hz; $V_T = 0.1\text{-}0.3$ ml; $MV = 0.03\text{-}0.16$ L/min and $\text{HFMV} = 0.05\text{-}0.81$ ml²BPM). These levels of ventilation were very low relative to those reported by Sturtz et al [59], who measured the same parameters in RDS infants during HFOV. Furthermore, *in vivo* results demonstrated that ventilation (Figure 2) and oxygenation measured following each CPAP trial were not different between CPAP modes ($P = 0.8$). HFOV during BCPAP produced $f = 8.9 \pm 1.9$ Hz, $V_T = 0.63 \pm 0.04$ ml, $MV = 0.4 \pm 0.1$ L/M, and $\text{HFMV} = 4.65 \pm 1.65$ ml²BPM (Figure 3). Thus, this study showed that BCPAP at 10 L/min provides an HFOV effect that is measurable both *in vitro* and *in vivo*, and the bubble frequency is in the same frequency domain as commercial high frequency oscillatory ventilators. However, the V_T , MV , and HFMV measured during BCPAP both *in vitro* and *in vivo* are lower than previously reported values for HFO ventilators [59]. As compared to CPAP, BCPAP does not produce a significant HFOV effect that could augment ventilation in either an *in vitro* or *in vivo* apneic neonatal model.

High-amplitude BCPAP (HAB-CPAP) provides high-frequency oscillations in the airway with higher amplitude by increasing the angle of gas entry at the water seal. Previous attempts at increasing the amplitude of oscillations by increasing the bias flow did not result in corresponding physiologic changes. Using this device, the authors [60] were able to demonstrate an increase in PaO_2 and a decrease in the work of breathing in an animal model of non-invasive respiratory support. The amplitude of oscillations increased due to the forces generated by the water flow in reverse direction as it reenters the bubbler. At greater angles, the oscillations were predominantly at lower dominant frequencies that allowed more time for volume delivery. The HAB-CPAP device also delivers tidal volumes in a manner similar to high frequency oscillatory ventilation as noted by Sturtz et al [59]. For HAB-CPAP, the authors postulate these mechanisms will improve alveolar recruitment. Further studies are

warranted to demonstrate the safety and efficacy of this mode of ventilation in clinical settings.

Non-invasive mechanical ventilation—Another noninvasive method to maintain FRC and treat apnea of prematurity without endotracheal ventilation is non-invasive mechanical ventilation (NIMV). This method can augment CPAP by administering a “sigh” to the infant through delivery of ventilator breaths via nasal prongs. Each “sigh” can potentially open micro atelectasis and recruit more ventilation units. Several reports have shown that NIMV can superimpose mechanical ventilator cycles on CPAP to assist spontaneous ventilation and avoid intubation and traditional mechanical ventilation [60-62].

Initial studies on NIMV focused on preventing extubation failure. These studies demonstrated a statistically significant benefit for infants extubated to NIMV compared to CPAP to prevent extubation failure after mechanical ventilation and surfactant therapy for RDS treatment [63,64]. A greater reduction in the frequency of apneas has also been demonstrated with NIMV when compared to CPAP [65]. These benefits of NIMV over CPAP were associated with a trend towards lower rates of CLD, but did not reach statistical significance; that was partly related to small sample size and use of rescue NIMV in infants failing CPAP. These trials also showed no increased adverse effects, such as pneumothorax or gastric distension, when compared to CPAP. More recent data suggest that NIMV is also effective in the initial treatment of RDS. It significantly decreased the rate of endotracheal ventilation and the incidence of BPD as compared to CPAP [66,67].

There are two modes of nasal ventilation: non-synchronized and synchronized NIMV (S-NIMV). The mode currently used in most neonatal intensive care units in the United States is non-synchronized NIMV. The physiologic effects of non-synchronized, nasally delivered ventilator breaths are variable. Owen et al [68] demonstrated that in spontaneously breathing preterm infants, NIMV peak pressures resulted in small tidal volume increases only when the pressure peak commenced during spontaneous inspiration, whereas expiratory time was increased when the pressure peak commenced during spontaneous expiration. During apnea, even though pressure peaks resulted in small tidal volumes and occasional chest rise, they were sufficient to ameliorate oxygen desaturations [68].

Based on these findings, one might assume that synchronizing every NIMV peak pressure with spontaneous inspiration would increase its effectiveness. An observational study that addressed this question showed that S-NIMV did not increase tidal volume as compared to NIMV [69]; however, synchronization resulted in significant reduction in the inspiratory work of breathing by respiratory unloading [69,70]. The long-term effects of these short-term benefits are yet unknown. It is important to note that there are several difficulties in achieving synchronization of nasal ventilation due to the open systems and the very small flows and pressures that preterm infants generate. Synchronization for the purpose of clinical research is commonly achieved by a capsule taped on the abdominal wall; however, this is subject to motion artifacts that limit its routine clinical use. Neurally adjusted ventilatory assist (NAVA) is a potential source of improved synchronization. The ventilator responds by sensing the electrical activity of the diaphragm, thus achieving effective synchronization even in the presence of large leaks [71].

In summary, NIMV is an effective mode of non-invasive ventilation for acute RDS and postextubation to wean to spontaneous unsupported breathing. Long-term respiratory and neurological outcomes need to be studied before recommending its routine clinical use.

Finally, nasal high frequency ventilation potentially minimizes lung injury with minimal assisted tidal volume displacement without the need for endotracheal intubation. In a

preterm lamb study [72], it was shown that nasal high frequency ventilation alters mesenchymal cell turnover and improves alveolarization. Thus, nasal ventilation, in this model of infant RDS, preserves the balance between mesenchymal cell apoptosis and proliferation in the distal airspace walls such that alveolarization progresses.

Continuous positive airway pressure and aerosolized surfactant—Attempts to avoid intubation in the treatment of neonatal RDS have led to administering surfactant in a direct, non-invasive approach using the aerosolized form of the drug. To date, four clinical studies have used aerosolized surfactants combined with nasal CPAP for neonatal RDS prevention [73-76], and the results have shown the safety of this approach. Along these lines, in a preliminary study, Wolfson et al [77] compared the effects of CPAP support alone to CPAP plus Aerosurf® (KL₄-surfactant, lucinactant for inhalation; Discovery Laboratories, Warrington, PA) delivered by a novel aerosol generator, in spontaneously breathing preterm lambs. Lucinactant is a novel synthetic surfactant that contains KL₄, a 21-amino acid peptide mimicking the function of surfactant protein B (SP-B) [78,79]. By 4 hrs, and in comparison to controls, lambs treated with CPAP plus aerosolized KL₄ surfactant demonstrated a dose-dependent increase in compliance and decrease in lung IL-8; marked differences occurred with the 20-min dose, and there were little further differences between the 20-, 30-, and 90-min doses. Relative to controls, PaO₂ was greater following the 10-, 20-, and 30-min doses and trended towards control values with the 90-min dose. Independent of the duration of aerosolized surfactant, gross inspection and lung histomorphometry demonstrated greater and more homogenous expansion compared to controls. Based on these preliminary studies, it was concluded that, relative to treatment with CPAP alone, aerosolized KL₄ surfactant improved gas exchange, pulmonary mechanics, lung structure integrity, and reduced lung inflammation in a dose-dependent manner in preterm lambs. These observations provide preliminary guidance for titrating dosing strategies designed to optimize peri-dosing functional responses and lung protective biomarker outcomes for the management of neonatal RDS [77].

High-flow nasal cannula—Nasal cannula (NC) with supplemental oxygen is often used as an initial support modality for neonates requiring oxygen support. In these early cases, gas flow with NC is generally low (at 2 L/min or less). Conventional NC in neonates provides unheated, humidified gas and attempts to deliver warm gas via NC using available systems; it has resulted in an unacceptable amount of condensation in the tubing.

Delivery of unheated gas via NC has several potential adverse consequences. Maintaining normal body temperature during increased convective heat loss when receiving unheated and non-humidified gas may lead to an increased metabolic rate and the conversion of life-sustaining substrates to acidic metabolic byproducts. One study [80] reported increased nasal secretions, mucosal injury, and coagulase-negative staphylococcal sepsis in extremely low-birth-weight infants who were receiving unheated humidified gas via NC. Kopelman [81] also reported two infants who developed upper-airway obstruction secondary to mucosal injury from receiving unheated, humidified gas. In addition, Greenspan et al [82] demonstrated that resuscitation with room-temperature, unhumidified gas in preterm infants resulted in adverse airway responsiveness as compared to warmed, humidified gas resuscitation.

In an attempt to circumvent several of these problems, high-flow nasal cannula (HFNC) have been developed to deliver high-flow, warm, humidified gas. In this regard, Locke et al [83] demonstrated that delivered oxygen and end-distending pressure varied depending on breathing patterns, cannula size, and infant size. They showed that there was unregulated positive end-distending pressure and altered breathing patterns in preterm infants receiving flow rates of 0.5 to 2 L/min via NC. They cautioned the use of high flows when cannula size

and infant nares were not properly matched. Sreenan et al [84] demonstrated that flow rates of 1 to 2.5 L/min via NC generated end-distending pressure similar to CPAP at 6 cm H₂O. The flow needed to generate the end-distending pressure was proportional to the size of the baby.

Recently, Chang et al [85] characterized the effect of gas flow on temperature, humidity, pressure, and resistance profiles of three different respiratory support systems under well-controlled *in vitro* conditions (fixed thermal, humidification, and respiratory load). This *in vitro* model was designed to evaluate the pressure and resistive load delivered by the three devices and the affect of the temperature and humidity load on the airway's milieu at specific flow conditions in a typical neonatal intensive care setting. Gas delivered by HFNC was more humid than that delivered by NC and CPAP. The investigators indicated that it is necessary to match infant airway orifices, cannula size, and flow such that the infant is not given inadvertent end-expiratory pressure and compromised with respect to work of breathing.

In a recent observational study of humidified HFNC compared with nasal continuous positive airway pressure (NCPAP), Lampland et al [86] reported that although mean end-expiratory esophageal pressure (EEEP) in infants on NCPAP+6 cm H₂O and HFNC were similar, massive intra- and inter-patient variation existed and limited the predictability of actual delivered pressure. Additionally, tachypnea developed as flow was diminished. In an animal model of infant RDS, Frizzola et al [87] proposed that HFNC may provide a practical means to wash out nasopharyngeal dead space during spontaneous breathing without the need for intubation. The study was designed to demonstrate this washout effect and the flow dependence of CO₂ elimination and oxygenation during HFNC and CPAP. With HFNC, CO₂ trended downward in a flow-dependent manner independent of gas leak. Oxygenation and tracheal pressures increased in a flow-dependent manner with the greatest effect during double prong HFNC (Figure 4). At 8 L/min, tracheal pressures did not exceed 6 ± 1 cm H₂O. In summary, the study concluded that HFNC improves gas exchange in a flow dependent manner; double prong HFNC had a greater impact on O₂, whereas single prong HFNC had a greater impact on CO₂ elimination.

Thus, a principle mechanism of action for HFNC may be related to the ability to flush the dead space of the nasopharyngeal cavity, making alveolar ventilation a greater fraction of minute ventilation and improving the efficiency of respiration [88]. In this regard, the essential clinical criteria to remain on non-invasive respiratory support modes are effective spontaneous respiratory effort and CO₂ elimination. Hypercapnia and apnea that may be secondary to hypercapnia are the most common reasons for progressing to more invasive forms of ventilatory support. Therefore, if CO₂ retention during conventional non-invasive ventilation can be reduced or eliminated, many infants can avoid potential lung injury and subsequent chronic lung.

Nitric oxide inhalation therapy—Despite many attempts, pharmacological therapy to relieve pulmonary hypertension in newborns has had limited success. Most vasodilators lack pulmonary selectivity, and the response within the pulmonary vasculature is often transient. Nitric oxide (NO) is a gas that can be delivered through a ventilator circuit directly to the lungs. When delivered in this manner, NO, a vasodilator, seems to be effective in reducing pulmonary hypertension and improves oxygenation without causing adverse side effects in selected infants [89,90]. Limitations of this therapy may include potential toxicities of NO and related metabolites as well as reduced efficacy due to other pulmonary pathology. This promising work has stimulated a number of independent and collaborative assessments of inhalational NO. It should be noted that this therapy can be utilized with non-invasive forms of CPAP.

Summary of adjuncts to mechanical ventilation

The care of infants with RDS during the newborn period has been helped immeasurably by a number of additional non-invasive approaches and therapies. These therapeutic interventions include oxygen therapy, CPAP, HFNC, inhaled NO, and synthetic- or natural-surfactant administration.

Pulmonary function testing—which enables the determination of factors such as tidal volume, dynamic or static lung compliance, resistance, work of breathing, FRC, and others—has eliminated much of the guesswork that was once standard in neonatal intensive care units. Furthermore, pulmonary function tests have altered our understanding of the management of some diseases, such as RDS, BPD, and congenital diaphragmatic hernia (CDH) during the neonatal period [91]. Increased use of pulmonary function testing can better define therapy and should be a standard part of newborn intensive care.

Few therapeutic adjuncts have had the impact in the intensive care nursery that surfactant has. Since its widespread introduction, surfactant has significantly decreased the severity and incidence of RDS during the neonatal period and has reduced the likelihood of BPD. Over the next decade, it will be interesting to see the impact of combining non-invasive respiratory support with the administration of surfactant, inhaled NO, and other aerosol interventions.

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Figure 1. Oxygen titration protocol demonstrating FiO₂ associated with manual (solid squares) and adaptive, computer-regulated (open squares) oxygen titration over time. (Adapted from Touch et al. *Pediatr Res* 2003;53:355A). Mean values for 6 animals per group.

Figure 2.

Measured arterial CO₂ PRE and 3-min POST apnea using bubble continuous positive airway pressure (BCPAP) and conventional continuous positive airway pressure (CCPAP). No significant difference in arterial PCO₂ between CPAP groups (n = 5/group).

BCPAP vs. HFOV **Figure 3.**

A comparison of measured minute volume (MV), tidal volume (Vt), and high frequency minute volume (HFMV) during bubble continuous positive airway pressure (BCPAP) and high frequency oscillatory ventilation (HFOV) in neonates (HFOV data modified from Sturtz et al. *Pediatr Crit Care Med* 2008;9:101-104).

Figure 4.

Comparison of PaCO₂ with A) high-flow nasal cannula (HFNC; solid line: low leak; dotted line: high leak) and B) continuous positive airway pressure (CPAP; minimal leak; Modified from Frizzola et al. *Ped Pulmonol* 2011;46:67-74).