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REVIEW

Clinical practice

Noninvasive respiratory support in newborns

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Abstract The most important goal of introducing noninvasive ventilation (NIV) has been to decrease the need for intubation and, therefore, mechanical ventilation in newborns. As a result, this technique may reduce the incidence of bronchopulmonary dysplasia (BPD). In addition to nasal CPAP, improvements in sensors and flow delivery systems have resulted in the introduction of a variety of other types of NIV. For the optimal application of these novelties, a thorough physiological knowledge of mechanics of the respiratory system is necessary. In this overview, the modern insights of noninvasive respiratory therapy in newborns are discussed. These aspects include respiratory support in the delivery room; conventional and modern nCPAP; humidified, heated, and high-flow nasal cannula ventilation; and nasal intermittent positive pressure ventilation. Finally, an algorithm is presented describing common practice in taking care of respiratory distress in prematurely born infants.

Keywords Noninvasive ventilation · Neonatology · CPAP · Humidified high-flow nasal cannula · Neopuff · Resuscitator · Nasal intermittent positive pressure ventilation

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Abbreviations

BPD	Bronchopulmonary dysplasia
EEV	End-expiratory lung volume
GA	Gestational age
HHFNC	Humidified high-flow nasal cannula
INSURE	Intubation Surfactant Extubation
nCPAP	Nasally delivered continuous positive airway pressure
nIPPV	Nasal intermittent positive pressure ventilation
NIV	Noninvasive ventilation
PEEP	Positive-end expiratory pressure
PIP	Peak inspiratory pressure
SIMV	Synchronized intermittent mandatory ventilation
Surfactant	Surface active agent

Introduction

One of the most critical events in life is the switch from dependence on placental gas exchange in utero to air breathing at birth. In utero several processes take place to ensure an effective transition. However, full respiratory adaptation to extra uterine life takes weeks to complete. The primary function of the lungs is to arterialize mixed venous blood. This is achieved by pulmonary gas exchange and involves three important processes: ventilation, diffusion, and perfusion. When the newborn child is suffering from an incomplete transition due to, e.g., asphyxia, persistent pulmonary hypertension, infection, or prematurity, acute respiratory problems develop soon after birth. Pulmonary disorders represent one the most common diagnoses in infants admitted to neonatal units. In the previous decades, it was common practice to start endotracheal intubation and mechanical ventilation in case of moderate to severe respiratory distress. Nowadays, it is well known that these lifesaving actions may lead to adverse effects on the respiratory system. For example, there is a risk for bronchopulmonary dysplasia (BPD) to develop. The pathogenesis of BPD is mainly linked to the use of mechanical ventilation in the immature lung [5]. The main factor underlying chronic lung disease of the newborn is immaturity of the respiratory system. Other factors involved in the development of BPD are related to changes in delivered volume (volutrauma), delivered pressure (barotrauma), and intubation (endotrauma) [20, 24]. The aspect of traumatic exposure related to increased risk of airway colonization and infection with pathogens after intubation (biotrauma) is becoming more relevant. Although there is little evidence to support the hypothesis that prevention of intubation decreases the incidence of BPD, it is widely accepted that when endotracheal intubation is required, it should be as brief as possible [14]. Minimizing lung injury could lower the incidence of BPD. New modern aspects show that trauma to the respiratory system can be prevented by starting gentle respiratory support as soon as possible after birth. The ultimate objective of non-intubated or noninvasive ventilation (NIV) is to prevent intubations and invasive mechanical ventilation [8, 11, 12, 14, 15, 28] (Table 1). In the past years, improvements in sensors and flow delivery systems have resulted in the introduction of a variety of other types of NIV in addition to well-known nasal CPAP. For the best possible application of these innovations, a thorough physiological knowledge of the mechanism of the respiratory system in the newborn is a must [15]. This will be explained below. Furthermore, the modern insights of noninvasive respiratory therapy in newborns are being discussed in this general overview.

Physiological background of noninvasive ventilation

Lung volume depends largely on two important mechanical units: the resistive and the elastic properties of the respiratory system (lungs and airways). Compliance multiplied by resistance results in a factor called time constant, the rate by which the respiratory system fills and/or empties. High resistance and/or high compliance result in a long time constant; it takes longer before the lung is completely filled and/or emptied. The finally achieved balance between compliance of the lungs and the chest determines the static lung volume of the lung.

Postnatal lung compliance depends on the presence of an alveolar lining layer with properties that permit a decrease in surface tension at end-expiration and an increase in surface tension on lung expansion. This surface active agent (surfactant) prevents atelectasis at the end of expiration and confers mechanical stability on the alveolar structure. Almost all neonatal respiratory distress disorders are related to the disruption of the surfactant monolayer in a quantitative and/or qualitative manner.

The newborn child has a major disadvantage due to the high compliance of the chest resulting in an abnormal low volume resulting in a low oxygen store. Every clinician should be aware of the neonate's reflexes in order to gain the optimal end-expiratory volume (EEV), even more in case of prematurity. Extreme low gestational age neonates are born at the end of the canicular and beginning of the saccular stage of lung development. The saccules have a reduced gas exchange surface. Together with the poor presence of the type-II alveolar cells, the extreme compliant thorax, and the lack of surfactant results in a limited thoracic expansion. Also, the elasticity is reduced, and the establishment of functional residual capacity may be hindered. Alveolar collapse (atelectasis) during expiration can be provoked [32].

The newborn child applies three mechanisms to adjust for alveolar collapse: post-inspiratory diaphragmatic muscle activity (during the expiration, the inspiratory muscle tone persists, Fig. 1), premature inspiration (initiation of inspiration before the end of expiration, Fig. 1), and laryngeal adduction during expiration (increase resistance). The last

Table 1 Noninvasive or non-intubated ventilation in newborns

Delivery room; Neopuff®
Non-cycled respiratory support
Low-flow therapy (<2 L/min)
High-flow therapy (>2 L/min)
nCPAP; conventional and modern
Cycled respiratory support
Noninvasive nasopharyngeal positive pressure ventilation

nCPAP nasal continuous positive airway pressure

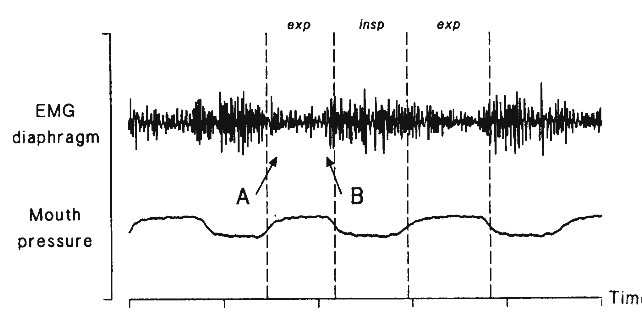

Fig. 1 Electromyography tracings of the diaphragm obtained from surface electrodes and mouth pressure in a 1-day-old healthy newborn. *Arrow A* points to post-inspiratory diaphragm activity at the start of expiration. *Arrow B* points to the early start of the next inspiration (*insp*) at the end of the same expiration (*exp*)

step is expiratory braking, clinically apparent as grunting, resulting in a higher EEV.

An important aspect of noninvasive ventilation in the newborn is preventing failure of expiratory braking and, therefore, respiratory failure. This can be reached by giving enough oxygen for the strenuous task of respiratory muscles and/or enough positive-end expiratory pressures (PEEP) to overcome respiratory braking. NIV stabilizes the respiratory system and should prevent a collapse of the respiratory system.

Delivery room respiratory support

The optimal neonatal respiratory support starts immediately after birth. Depending on the vital condition of the newborn during the resuscitation period, maximal effort should be made to minimize damage to the fragile respiratory system. The rather old fashioned but still practiced technique of neonatal resuscitation consists of using 100% cold and dry oxygen delivered with devices that provide variable and unmeasured volumes and pressures. This procedure may damage the premature lung [3, 16, 29]. At birth, the lungs are filled with fluid, and aeration must occur to establish lung volume. Current guidelines advocate the use of positive pressure ventilation for newborns with inadequate or gasping respirations with or without associated bradycardia [16, 17]. The use of self-inflating and flow-inflating bags is extensively described. All devices should deliver peak inspiratory pressure (PIP) and PEEP, measured by means of a barometer in the circuit. Initially, the first five breaths should be sustained with slow and prolonged inflations. The widespread use of T pieces attached to the face mask or tube is much easier to use especially by inexperienced operators. The Neopuff® Infant Resuscitator is a modified T piece with an adjustable PEEP valve and PIP control. The PEEP is constantly present in the system, and the PIP is delivered by manual occlusions at the T piece. Unfortunately, no clinical trials have yet shown the superiority of this T-piece resuscitation [32]. Theoretically, this system produces more stable pressure waves and more regular cycles. Some anxiety remains whether a higher tidal volume might cause volutrauma in the smallest newborns [3, 4, 15].

It has been demonstrated that neonates who receive sustained inflations followed by early nasally delivered continuous positive airway pressure (nCPAP) through a nasopharyngeal tube and started in the delivery room had shorter ventilatory support times and less need for intubation and surfactant [26–28]. The most important factors which seem to prevent pulmonary sequelae are fine tuning the start of the ventilatory support and the PEEP pressures delivered during the procedure (approximately 5 cm H_2O) [16, 17, 29]. Early administration of surfactant during a brief intubation and an immediate extubation followed by nCPAP has shown to be successful. This Danish technique called Intubation Surfactant Extubation (INSURE) significantly reduces the need for mechanical ventilation, air leaks, and probably BPD [9, 17, 18, 20, 28]. Nowadays, this technique is rarely used in the delivery rooms but mostly at the NICU.

nCPAP: conventional and modern

The non-intubated application of continuous pressure throughout the whole respiratory cycle (nCPAP) can be provided by several different techniques ranging from a simple bubble system (conventional nCPAP) to sophisticated (modern nCPAP) mechanical systems. nCPAP pressure is generated by two possible mechanisms: varying the flow rate or providing a constant flow and varying pressure by other mechanisms. Bubble CPAP is characterized by variations in the pressure generated by rapid gas bubbling underwater. Currently, there are no studies which compare the different devices and show a better clinical outcome of the modern systems. Optimal and effective use of nCPAP requires team effort and experience with the chosen device. To maintain an infant on nCPAP demands more nursing time and knowledge of the mechanism than keeping the child on a mechanical ventilator [5, 7, 9, 11, 15, 19, 23].

The application of positive pressure results in a number of important physiological benefits, including stabilization of the airways, increased lung volume, decreased airway resistance, and breathing work [2, 4] (Table 2). However, with excessive PEEP levels $PaCO_2$ may increase as tidal volume decreases and dead space increases. The increased lung volume will also reduce lung compliance and cause a potential problem: air leak syndromes. Pediatricians should also be aware of depressed cardiac output caused by an increasing intrathoracic pressure. Furthermore, several reports have shown that the CPAP devices may produce skin excoriation and nasal damage [9, 11].

nCPAP has been tested not only in several trials as an alternative to mechanical ventilation for respiratory failure but also in prophylactic studies with or without surfactant treatment [5, 14]. Some studies suggest that surfactant replacement therapy coupled with nCPAP in the early stage of RDS is more effective than nCPAP alone.

Since the original work [18], nCPAP has been primarily used to treat premature infants with RDS. Several aspects in respiratory handling of these infants have been investigated: treating RDS, prevention of extubation failure, and treating apnoea. In the treatment of RDS, nCPAP has become a popular alternative for intubation and ventilation.

Early treatment with nCPAP could induce development of alveoli and restore long volume, thus preventing

Table 2 Beneficial effects of noninvasive ventilation in newborns

Improved respiratory mechanics	Increased lung volume
	Increased compliance
	Decreased resistance
Improved respiratory timing	Decreased thoracoabdominal asynchrony
	Decreased obstructive and mixed apnoea
	Improved respiratory timing
Improved oxygenation	Decreased pulmonary vascular resistance
	Decreased intrapulmonary shunting
	Increased alveolar volume and less collapse

mechanical intubation [8]. nCPAP delivered by binasal prongs is more effective than single prongs and can prevent post-extubation failure. The optimum pressure that should be used is under study, but for nCPAP pressures between 5 and 7 cm H_2O probably represent a reasonable range [14, 25].

Studies at early nCPAP showed significantly lower incidence of BPD in the follow-up of very low birth weight neonates after a gestational age of 25 weeks [3, 27]. Using the INSURE technique followed by nCPAP for moderate or severe RDS improves the oxygenation and reduces the need for mechanical ventilation [23].

Presently, more state-of-the-art ventilators are available that not only can produce a stable PEEP level but also deliver PIP values for the delivering of nasal intermittent pressures. The future might bring aerosolized surfactants that might help to prevent INSURE procedures and show therapeutic effects on the respiratory system without causing trauma [6, 22]. To date, only a few small clinical studies in this interesting field have been performed [22]. More studies are needed to confirm the dose, particle size, and the best delivery system and to invent the right surfactant formulation that maintains its activity once aerosolized.

High-flow therapy

Flow delivered to the newborn by means of nasal cannula has been used for several decades. Until the development of modern devices, the provision of nasal cannula gas at a flow rate of more than about 2 l/min and the humidification of the air were not recommended in newborns [21]. Both recommendations were based on very limited evidence.

A new technique already in use for adults was introduced: humidified high-flow nasal cannula (HHFNC). HHFNC therapy in adults is nowadays widely used and increasingly popular in the USA. One of the most used definitions for HHFNC in neonates is that humidified and optimally warmed respiratory gases are given by nasal cannula at flow rates between 2 and 8 L/min [13]. Theoretically, HHFNC should prevent airway water loss, airway cooling, thickened secretions, and nasal irritation [10, 13]. The interface is lighter and easier to apply and might lessen nasal septal damage compared with the CPAP systems. The theoretical aspects have been tested in the laboratory; trials have shown neither positive nor negative effects on the newborn respiratory system. It has been shown that HHFNC indeed produces some kind of positive airway pressure. Before introducing HHFNC on neonatal wards and even before starting randomized trials, there are several obstacles that have to be taken; the PEEP pressure is very variable and relatively unpredictable. Besides that, the positive airway pressure is unregulated. Clinical effects and/or changes in pulmonary function should be measured carefully.

Noninvasive intermittent positive pressure ventilation

Nasal intermittent positive pressure ventilation (nIPPV) is another approach of noninvasive respiratory assistance combining nCPAP with superimposed ventilator breaths. With this mode, the nasal intermittent positive pressure ventilation is given via nasal prongs and, therefore, creates intermittently elevated pharyngeal pressures. Theoretically, this may improve the patency of the upper airway [1, 20]. By initiating inspiratory reflexes, the respiratory drive is activated [4, 30]. It was concluded that nIPPV for optimal support remains a complicated art [4]. Furthermore, research showed that, compared to nCPAP, the addition of ventilator delivered PIP decreased the work of breathing in premature infants [1, 2]. When the nIPPV is synchronized, tidal and minute volumes are improved what makes nIPPV preferable to nCPAP alone [23]. A recent meta-analysis showed the superiority of nIPPV to nCPAP in preventing extubation failure [5]. Lower incidence of BPD in preterm infants treated with nIPPV is seen, but not significantly proven yet. Current studies are focused on preterm infants treated with surfactant for RDS, to determine whether rapid extubation to nIPPV would be a more successful approach than continued endotracheal SIMV [25]. Although nIPPV is emerging as an effective noninvasive alternative for the treatment of RDS, controlled studies have not yet been published [31].

Example of an algorithm for the noninvasive treatment of RDS in prematurely born infants

Hundreds of studies have discussed the (dis)advantages of more than a dozen different techniques in optimal respiratory management of premature infants from the first minutes of life up to several days. The conclusion is that the optimal strategy is related to the gestational age. The premature infant below 28 weeks of gestational age probably needs more prophylactic treatments like CPAP and surfactant. In the Netherlands, the policy is that all infants below 32 weeks of gestational age are transported in utero to one of eight neonatal intensive care units. Nasal flow and nCPAP can be started in infants born after 32 weeks of gestational age, depending on the severity of RDS, and can be continued in the majority of the general hospitals. A potential algorithm is displayed in Fig. 2. It is common practice to start low flow followed by nCPAP in premature infants born after 32 weeks of gestational age. If RDS worsens, PEEP level is increased in order to obtain a FiO_2 below 0.4. With increasing respiratory distress, intubation is started, and if needed, surfactant is given after transportation to a neonatal intensive care unit. Usually, nCPAP is started very soon or even immediately after birth in infants born before 32 weeks. Depending on the severity of respiratory distress, intubation and extubation is performed within 1 day. The INSURE procedure can only be applied to the smallest premature infants born at a neonatal intensive care unit in university hospitals. The experience depends largely on locally available conditions.

Practical conclusions

NIV is a modern instrument for the pediatrician and is nowadays widely available. With increasing availability of instruments, the scientific evidence is unfortunately decreasing. Several methods need a thorough research before application in newborn children can be justified. nCPAP and nIPPV are not without important risks. HHFNC needs a thorough investigation before this type of NIV can be applied in trials.

Important practical conclusions for applying NIV in newborns with respiratory distress:

- A physiological background is needed to understand NIV
- NIV can be used to avoid mechanical ventilation
- Adjustable and measured PEEP should be used immediately after birth
- PEEP levels should remain around +5 cm H_2O or higher
- nCPAP appears to be a satisfactory alternative to endotracheal intubation
- Without available scientific evidence, it seems potentially harmful to use HHFNC in newborns.

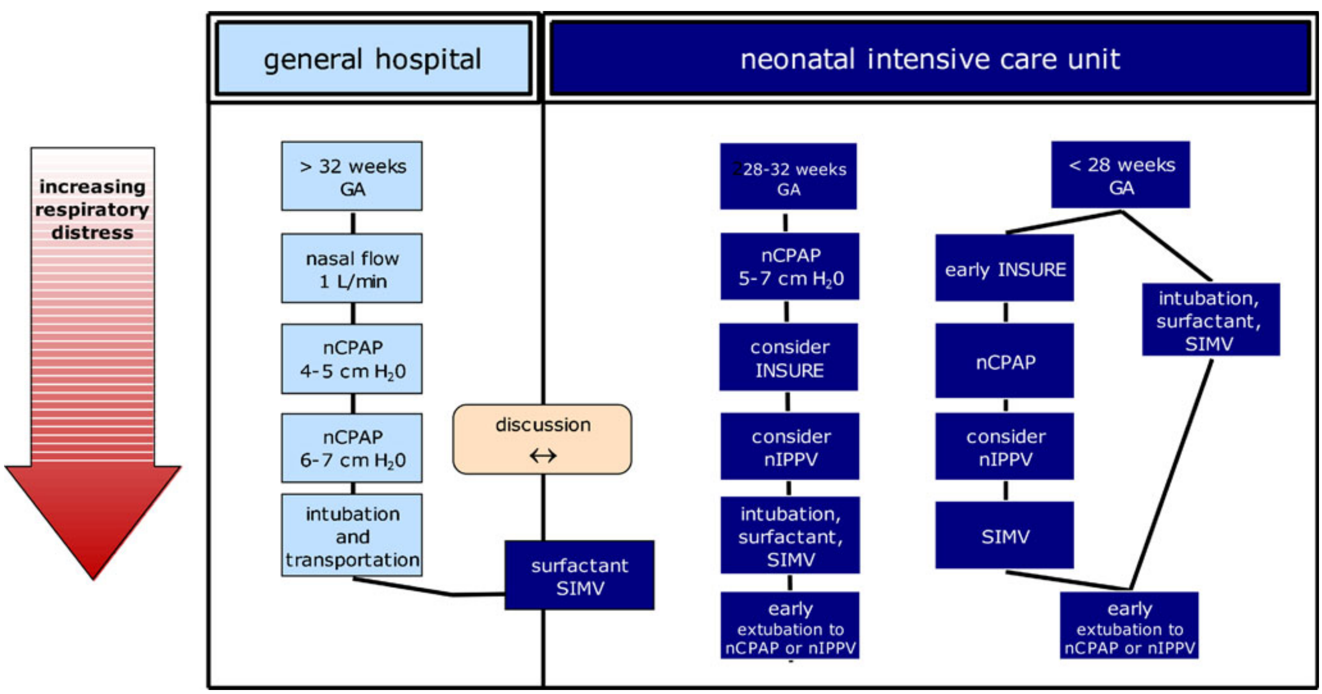

Fig. 2 Proposed algorithm for the treatment of RDS using noninvasive ventilation in premature infants with increasing respiratory distress syndrome. *GA* gestational age; *INSURE* Intubation Surfactant Extubation; *nCPAP* nasally delivered continuous positive airway pressure; *nIPPV* nasal intermittent positive pressure ventilation; *SIMV* synchronized intermittent mandatory ventilation

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