Review Article

Non-Invasive Ventilation in Neonatology

Judith Behnke, Brigitte Lemyre, Christoph Czernik, Klaus-Peter Zimmer, Harald Ehrhardt, and Markus Waitz

Summary

Background: Invasive mechanical ventilation (IMV) has been replaced by early continuous positive airway pressure (CPAP) in the treatment of respiratory distress syndrome (RDS) in preterm infants aiming to reduce the rate of bronchopulmonary dysplasia (BPD). Subsequently, modern non-invasive ventilation strategies (NIV) were introduced into clinical practice with limited evidence of effects on pulmonary and neurodevelopmental outcomes.

Methods: We performed a selective literature search in PubMed including randomized controlled trials (RCT) ($n \geq 200$) and meta-analyses published in the field of NIV in neonatology and follow-up studies focusing on long term pulmonary and neurodevelopmental outcomes.

Results: Individual studies do not show a significant risk reduction for the combined endpoint death or BPD in preterm infants caused by early CPAP in RDS when compared to primary intubation. One meta-analysis comparing four studies found CPAP significantly reduces the risk of BPD or death (relative risk: 0.91; 95% confidence interval [0.84;0.99]). Nasal intermittent positive pressure ventilation (NIPPV) as a primary ventilation strategy reduces the rate of intubations in infants with RDS (RR: 0.78 [0.64;0.94]) when compared to CPAP but does not affect the rate of BPD (RR: 0.78 [0.58;1.06]).

Conclusion: Early CPAP reduces the need for IMV and the risk of BPD or death in preterm infants with RDS. NIPPV may offer advantages over CPAP regarding intubation rates. Networking-based follow-up programs are required to assess the effect of NIV on long term pulmonary and neurodevelopmental outcomes.

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For years, invasive mechanical ventilation (IMV) was the primary treatment of very low birth weight infants (VLBWI) with respiratory distress syndrome (RDS). RDS is caused by a primary surfactant deficiency of the immature lungs and leads to a reduced compliance of the respiratory system and progressive hypoxic respiratory failure if untreated (1). Although life-saving, IMV is an important risk factor in the development of bronchopulmonary dysplasia (BPD) (2). BPD is characterized histologically by impaired alveolar and vascular lung development and clinically defined clinically as the need for oxygen and or respiratory support at 36 weeks postmenstrual age (2, 3). More than 20% of preterm infants with a gestational age (GA) <32 weeks in Germany are affected by the disease (4).

The diagnosis of BPD is associated with neurological sequelae (i.e. cerebral palsy, visual and hearing impairment, mental and motor developmental delay), as well as chronic respiratory problems in childhood and adolescence including asthma-like symptoms and frequent wheezing episodes (5, 6). Affected infants require comprehensive medical follow-up and treatment after hospital discharge with frequent hospital readmissions, visits to the doctor's office, home oxygen therapy, treatment for pulmonary hypertension and specific immunization requirements (7).

Despite advances in neonatal pulmonology, such as antenatal corticosteroids and surfactant administration, the incidence of BPD has not changed significantly over the last decade (e1). To alleviate the harmful effects of IMV on the immature lungs (i.e. volu- and barotrauma, inflammatory mediated alveolar and vascular destruction resulting in progressive impaired gas exchange), nasal CPAP has been introduced as a noninvasive ventilation (NIV) strategy in neonatal care. CPAP significantly reduced the need for IMV, but failure rates of almost 50% have prompted neonatologists to seek more effective NIV modalities (8, 9). Nasal intermittent positive pressure ventilation (NIPPV) and heated humidified high flow nasal cannulae (HHFNC) have emerged and are now used in both pediatrics and adult intensive care medicine (10, 11, e2).

In this review, we discuss and summarize the current evidence of the available NIV modes in neonatology, their indications, mechanisms of action and effects on important short and long term morbidities associated with the use of NIV. The review is based on a selective literature search in PubMed.

Department of General Pediatrics & Neonatology, Center for Pediatrics and Youth Medicine, Justus Liebig University of Giessen: Dr. med. Judith Behnke, MD; Prof. Dr. med. Klaus-Peter Zimmer, MD; PD Dr. med. Harald Ehrhardt, MD; Dr. med. Markus Waitz, MD

Division of Neonatology, Children's Hospital of Eastern Ontario, Ottawa, Canada:
Dr. med. Brigitte Lemyre, MD

Department of Neonatology, Charité—Universitätsmedizin Berlin, Berlin: PD Dr. med. Christoph Czernik, MD

Member of the German Lung Research Center (DZL), Giessen: Dr. med. Judith Behnke, MD;
PD Dr. med. Harald Ehrhardt, MD

Figure 1:
Interfaces for
nCPAP application
1 = endotracheal
2 = short binasal
prongs
3 = nasal mask

Figure 2:
Preterm infant with
nCPAP and binasal
prongs (bonnet)

Effects and Clinical Application of Different NIV Modes in Neonates

Nasal CPAP—nasal continuous positive airway pressure

Since CPAP was first used clinically in preterm infants in 1971 (e3), various effects on respiratory mechanics have been reported with its use (*eBox 1*). Nasal CPAP devices deliver constant positive pressure (PEEP) to the neonatal lungs using different nasal interfaces (*Figures 1 and 2*). PEEP counteracts the collapsing lung properties, maintains functional residual capacity and facilitates gas exchange (1).

Several randomized controlled trials (RCT) assessed the efficacy and safety of early nasal CPAP in VLBWI in the surfactant and antenatal corticosteroid era (*Table 1, eBox 2*). Although the study designs and thresholds for respiratory interventions (i.e. criteria for intubation and surfactant administration) vary among the trials, two basic treatment strategies were compared:

- infants were randomized either to early nasal CPAP (variable set pressure levels of 5–8cmH₂O) with

selective intubation if prespecified CPAP failure criteria were met (i.e. oxygen requirements, apnea and hypoxemic events, respiratory acidosis) or

- were primarily intubated in the delivery room and exposed to a short or a longer course of IMV.

The results of the trials demonstrate that the use of early CPAP significantly reduced the need for IMV and surfactant administration as compared to primary intubation in the delivery room. However, none of the individual trials was able to show a significant reduction in the rate of BPD or death (8, 9, 12–15) (*Table 1*).

A meta-analysis of 4 trials confirmed a small, but significant reduction in the combined outcome of BPD or death (relative risk [RR]: 0.91, 95% confidence interval [0.84;0.99], number needed to treat [NNT]: 25) (16). However, BPD alone (RR 0.91 [0.79;1.04]) and death alone (RR 0.88 [0.68;1.14]) were not significantly affected by the CPAP intervention. The incidence of CPAP failure within the first week of life ranged from 46.0–51.2% (8, 9, 12).

CPAP failure was ultimately linked with some degree of IMV, which may have diminished the possible lung protective treatment effects of CPAP among the trials.

NIPPV—nasal intermittent positive pressure ventilation

NIPPV has emerged as an alternative strategy to nasal CPAP (1, e2, e4). NIPPV delivers time-cycled positive pressure ventilation above a PEEP level in the absence of an endotracheal tube. Currently, two NIPPV delivery systems are available: bilevel-NIPPV and conventional mechanical ventilator-driven NIPPV (CMV-NIPPV). Bilevel-NIPPV provides two alternating PEEP levels on which the infant breathes spontaneously. In contrast, CMV-NIPPV uses higher peak inspiratory pressures and shorter inspiratory times (*eFigure 1*) (17, e5). The interfaces to support NIPPV are identical to those that deliver CPAP (*Figure 1*).

NIPPV can be applied in a synchronized mode with different trigger systems (i.e. pneumatic capsule to detect abdominal movement or flow-trigger). Effects mediated during NIPPV are summarized in *eBox 3*. NIPPV can be used in different clinical scenarios.

- “Primary or early” mode of ventilation refers to its use within the first six hours of life.
- NIPPV as “post extubation” refers to its use after a longer period (usually >24 hours) of IMV.

Evidence for the use of NIPPV mainly derives from small, single-center trials that differ substantially in the ventilators used (bilevel-NIPPV, CMV-NIPPV), the settings (i.e. respiratory rate, pressures, inspiratory times), the patient population and the mode of synchronization, if applied. A recent Cochrane meta-analysis including RCT and quasi RCT found a significantly lower rate of respiratory failure (RR: 0.65 [0.51;0.82]) and need for intubation within the first week of life (RR: 0.78 [0.64;0.94]) in infants treated with primary NIPPV as compared to CPAP (18) (*Table 2*).

NIPPV as post-extubation mode of ventilation resulted in a significantly lower rate of respiratory failure (RR: 0.71 [0.61;0.82]) and reintubation rates (RR: 0.76 [0.65;0.88]) when compared to nasal CPAP in another Cochrane meta-analysis (19). Data on other important outcome measures (BPD, mortality, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity) remained unaffected by the NIPPV intervention in the CPAP and the NIPPV group in both meta-analyses (*Table 2*).

HHHFNC—heated humidified high flow nasal cannula

The function of HHHFNC is to deliver heated and humidified gas at flow rates > 1l/min through small binasal prongs (*eFigure 2*). Several mechanisms of action and clinical effects of this method have been reported (*eBox 4*) (20, e6). Importantly and in contrast to nasal CPAP, HHHFNC creates a flow-related, variable distending pressure that is unmeasurable in clinical practice, delivered to the infants’ upper airway and lungs. Because of the pragmatic setup, easy handling and cost-effectiveness, the use of HHHFNC is rapidly

TABLE 1

Selected RCTs on nCPAP with selective or prophylactic surfactant administration vs. IMV with or without surfactant application (including INSURE)

RCT	Study population	Intervention	Outcomes					Primary outcome	BPD definition
			IMV (Median no. days [IQR] or %)	p-value/95% CI	BPD/death (%)	Surfactant treatment (%)	p-value/95% CI	p-Wert/95%-KI	
Morley et al., 2008 (COIN)(8)	n=610 GA 25+0–28+6	nCPAP + selective surfactant vs. IMV + selective surfactant	3 [0–11] 4 [1–14]	p<0.001	33.9 38.9	OR: 0.80 [0.58; 1.12]	38 77	p<0.001	death or BPD need for oxygen treatment at 36 weeks’ GA
Finer et al., 2010 (SUPPORT) (9)	n=1316 GA 24+0–27+6	nCPAP + selective surfactant vs. IMV + prophylactic surfactant	10 [2–32] 13 [2–36]	p=0.03	47.8 51	RR: 0.95 [0.85; 1.05]	67.1 98.9	p<0.001	physiological definition death or BPD
Sandri et al., 2010 (CURPAP) (13)	n=208 GA 25+0–28+6	nCPAP + selective INSURE vs. prophylactic INSURE	33.0 31.4	RR: 0.95 [0.64; 1.41]	11.7 ¹ 14.3 ¹	RR: 1.22 [0.58; 2.50]	N.A. N.A.		need of IMV within the first 5 days of life moderate to severe BPD in survivors
Dunn et al., 2011 (12)	n=648 GA 26+0–29+6	nCPAP + selective surfactant vs. prophylactic INSURE vs. IMV + prophylactic surfactant	52.3 59.3 95.7	N.A. N.A. N.A.	30.5 28.5 36.5	RR: 0.83 [0.64; 1.09]	14.8 98.6 98.2	N.A. N.A. N.A.	death or BPD moderate to severe BPD at 36 weeks’ GA
Tapia et al., 2012 (14)	n=256 BW 800–1500g	nCPAP + selective INSURE vs. oxygen + selective IMV + selective surfactant	29.8 50.4	RR: 0.59 [0.43; 0.81]	13.7 ² 19.2 ²	RR: 0.72 [0.41; 1.25]	27.5 46.4	RR: 0.59[0.42; 0.83]	any requirement for IMV need for oxygen treatment at 36 weeks’ GA
Rojas et al., 2009 (15)	n=278 GA 27+0–31+6	nCPAP + selective surfactant vs. - prophylactic INSURE	39 26	RR: 0.69 [0.49; 0.97]	59 ¹ 49 ¹	RR: 0.84 [0.66; 1.05]	N.A. N.A.		any requirement for IMV need for oxygen treatment at 36 weeks’ GA

BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; GA, gestational age; IMV, invasive mechanical ventilation; IQR, interquartile range; INSURE, intubate surfactant extubate; N.A., not available; nCPAP, nasal continuous positive airway pressure; no., total number; O₂, oxygen therapy; vs, versus; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk
¹ BPD alone; ² death or BPD

TABLE 2

Results of meta-analyses on NIPPV vs. nCPAP as primary respiratory support and post-extubation

RCT/ Meta-analysis	Study population	Intervention	Outcomes					Primary outcome	BPD definition
			Respiratory failure n/N (%)	95% CI	Intubation n/N (%)	95% CI	BPD/death n/N (%)	95% CI	
Lemire et al., 2016(18) (Cochrane meta-analysis)	n=1061 GA 24+0–36+6 Included trials: 10	Primary NIPPV vs. Primary nCPAP	83/523 (15.9) 128/537 (23.8)	RR: 0.65 [0.51; 0.82]	112/470 (23.8) 143/480 (29.8)	RR: 0.78 [0.64; 0.94]	60/450 (13.3) 77/449 (17.1)	RR: 0.78 [0.58; 1.06]	oxygen require- ment at 36 weeks' GA
Lemire et al., 2017(19) (Cochrane meta-analysis)	n=1431 GA≤37+0 Included trials: 10	Post extubation NIPPV vs. Post extubation nCPAP	195/654 (29.8) 273/647 (42.2)	RR: 0.71 [0.61; 0.82]	194/654 (29.7) 256/647 (39.6)	RR: 0.76 [0.65; 0.88]	193/580 (33.3) 199/560 (35.5)	RR: 0.94 [0.80; 1.10]	oxygen require- ment at 36 weeks' GA

BPD, bronchopulmonary dysplasia; CI, confidence interval; GA, gestational age; IMV, invasive mechanical ventilation; nCPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation; n, number of events; N, total number of participants; RCT, randomized controlled trial; RR, relative risk; vs, versus; *BPD alone

increasing (21). However, evidence for the use of HHHFNC as primary respiratory support for RDS or post-extubation is limited and predominantly restricted to non-inferiority trial settings with nasal CPAP being the comparative measure (Table 3).

Manley et al. randomized preterm infants to HHHFNC or nasal CPAP after extubation (22). The primary outcome “treatment failure within seven days” occurred in 34.2% in the HHHFNC group and in 25.8% of the CPAP group (risk difference: 8.4%, [–1.9; 18.7]). Based on a chosen non-inferiority margin of 20% the authors concluded that HHHFNC is non-inferior to nasal CPAP after extubation. Of note, almost 50% of infants that failed on HHHFNC in this trial were rescued with nasal CPAP, leaving concerns regarding the non-inferiority conclusion. Two recent non-inferiority RCT assessed HHHFNC versus nasal CPAP as primary respiratory support in preterm infants with RDS (GA >28 weeks) defining a more restrictive margin of non-inferiority (5% and 10%, respectively) (23, 24). Enrollment was stopped early in both trials owing to a significant difference in the primary outcome “treatment failure within 72h” between the HHHFNC and the CPAP group (25.5% vs. 13.3%, risk difference: 12.3%, [5.8; 18.7], p<0.001 and 26.3% vs. 7.9%, risk difference: 18.4% [9.7; 27.1], p<0.001), both studies favoring CPAP. While the rate of intubation did not differ between the groups in the intention-to-treat analysis in both studies, respectively 39% and 91% of subjects assigned to the HHHFNC group received rescue CPAP and were subsequently saved from intubation. Another comparable non-inferiority trial, however, found non-significant failure rates between HHHFNC and CPAP/Bilevel-NIPPV when used as primary mode of ventilation (25) (Table 3).

According to a recent meta-analysis, HHHFNC as primary mode or post extubation does not significantly affect the rate of BPD or other short term neonatal morbidities, except for significantly less nasal trauma in comparison to nasal CPAP (e7, e8). However, only few subjects were <28 weeks GA in most of the trials and study results confirm inferiority of HHHFNC compared to nasal CPAP when used as primary mode of ventilation in preterm infants with RDS.

Long Term Pulmonary and Neurodevelopmental Outcomes Associated with NIV

Advances in perinatal care, i.e.

- antenatal corticosteroids,
- improved fetal monitoring,
- caffeine therapy
- surfactant therapy,
- enhanced nutrition,
- and gentle ventilation strategies

have contributed to improved rates of survival, especially in the very immature population between 22+0 and 24+6 weeks GA (survival rate of 30% in 2000–2003 and 36% in 2008–2011, analysis of US data) (26). In Germany, the number of preterm infants

born before 28 weeks GA increased by 65% between 2001 and 2010 (27).

Since the risk of BPD is inversely proportional to GA and birthweight, it is not surprising that the incidence of BPD has increased over time by shifting the demographics to earlier GA (28). Of note, the rates of BPD reported in the NIV studies differ substantially since the definition of BPD and the study population is often diverse (5).

Few prospective long-term follow-up studies on the effect of NIV on pulmonary and neurodevelopmental outcomes in preterm infants have been published. Respiratory follow-up from the SUPPORT study showed fewer episodes of wheezing (28.9% vs. 36.5%, $p<0.05$) and fewer physician visits for breathing problems (68.0 vs. 72.9%, $p<0.05$) in the CPAP group as compared to the IMV + surfactant group at 18–22 months corrected age (29). Doyle and colleagues recently presented 8 year follow-up data on lung function of surviving infants with ≤ 28 weeks GA and compared cohorts with similar baseline demographics from three different time periods (1991–1992 vs. 1997 vs. 2005) (30). Besides a substantial increase in CPAP duration over time the authors found a higher rate of BPD and significantly reduced expiratory flow rates in the 2005 study cohort as compared to the 1991–1992 study population. However, these data should be interpreted with caution. First, the 8-year survival rate of the 1991–1992 cohort was 53% vs. 65% in the 2005 study group, therefore a trade-off effect for the outcome lung function cannot be excluded since the causes of mortality were not reported in the study. Second, the authors found a significant decrease in the use of postnatal steroids (40% in 1991–1992 vs. 23% in 2005), a treatment strategy that reduces the rate of BPD but may also adversely affect neurodevelopmental outcomes (31) (*eBox 5*).

The SUPPORT study group did not find significant differences in the composite outcome of death or neurodevelopmental impairment between the CPAP and the IMV + surfactant group at 18–22 months corrected age (32). Importantly, 10.9 % of infants in the CPAP group and 9.1% in the IMV group had neurodevelopmental impairments (defined as any of the following: a cognitive composite score on the Bayley Scale of Infants and Toddler Development III of less than 70, a Gross Motor Function Classification System score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment).

Lack of systematic follow up data from other representative RCTs (e.g. COIN-trial, CURPAP-study (8, 13) emphasizes the need for an adequate long term neurological and pulmonary follow up and interdisciplinary treatment of these high risk infants.

Trends and Future Perspectives in Neonatal NIV

Acknowledging the evidence for the use of early CPAP, the European Consensus Guidelines currently recommend

TABLE 3

Selected RCTs on HHHFNC vs. CPAP/NIPPV as primary respiratory support or post extubation

RCT	Study population	Intervention	Ergebnisse						Primary outcome	BPD definition
			BPD n/N (%)	p-value/95% CI	Treatment failure n/N (%)	p-value/95% CI	Intubation n/N (%)	p-value/95% CI		
Lavizzari et al., 2016(25)	n=316 GA 29+0–36+6	Primary HHHFNC vs. Primary nCPAP/Bilevel-NIPPV (non-inferiority trial, margin 10%)	7/158 (4.4) 8/158 (5.1)	p=0.79	17/158 (10.7) 15/158 (9.5)	p=0.71	N.A. N.A.		need for IMV within 72 hours from the beginning of respiratory support	need for oxygen and/or respiratory support at 36 weeks' GA
Roberts et al., 2016(23)	n=564 GA 28+0–36+6	Primary HHHFNC vs. Primary nCPAP (non-inferiority trial, margin 10%)	17/278 (12.1) 17/286 (11.4)	RR: 0.7 [-6.7; 8.2]	71/278 (25.5) 38/286 (13.3)	RD: 12.3 [5.8; 18.7]	43/278 (15.5) 33/286 (11.5)	RD: 3.9 [-1.7; 9.6]	treatment failure within 72 hours after randomization	need for oxygen and/or respiratory support at 36 weeks' GA
Manley et al., 2013(22)	n=303 GA $\leq 32+0$	HHFNC post extubation vs. nCPAP post extubation (non-inferiority trial, margin 20%)	47/152 (30.9) 52/151 (34.4)	RR: -3.5 [-14.1; 7.0]	52/152 (34.2) 39/151 (25.8)	RD: 8.4 [-1.9; 18.7]	27/152 (17.8) 38/151 (25.2)	RD: -7.4 [-16.6; 1.8]	treatment failure within 7 days after extubation	oxygen supplementation at 36 weeks' GA
Murki et al., 2018(24)	n=272 GA ≥ 28 and BW > 1000g	Primary HHHFNC vs. Primary nCPAP (non-inferiority trial, margin 5%)	1/133 (0.7) 0/139 (0.0)	p=0.49	35/133 (26.3) 11/139 (7.9)	RD: 18.4 [9.7; 27.1]	9/133 (6.8) 13/139 (9.4)	RD: -2.6 [-9.0; 3.9]	failure of the support mode in the first 72 hours after birth	oxygen supplementation at 36 weeks' GA

Bilevel-NIPPV, bilevel positive airway pressure; BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; GA, gestational age; HHHFNC, humidified highflow nasal cannula; IMV, invasive mechanical ventilation; N, total number of participants; nCPAP, nasal continuous positive airway pressure; RCT, randomized controlled trial; RD, risk difference n, number of events; RR, relative risk.

Key messages

- Invasive mechanical ventilation (IMV) can be a lifesaving procedure in very low birth weight infants (VLBW) with surfactant deficient lungs and risk of hypoxemic respiratory failure
- IMV is a known risk factor for the development of bronchopulmonary dysplasia (BPD)
- Prophylactic nasal CPAP reduces the need for IMV in VLBW in large randomized controlled trials but significant effects on the reduction of BPD or death are only demonstrated in a meta analysis
- Nasal intermittent positive pressure ventilation (NIPPV) reduces the need for intubation or reintubation when compared with nasal CPAP
- Heated humidified high flow nasal cannula (HHFNC) are inferior to nasal CPAP when used as primary respiratory support for VLBW in the delivery room

prophylactic CPAP and early selective surfactant administration over primary intubation in spontaneously breathing preterm infants (33). The results of a survey study in the US (26 participating network centers) suggest a decreasing number of VLBW being on IMV and an increased use of NIPPV modes from 2002 to 2012 (14% to 37%) (34).

There is growing evidence that frequent fluctuations in arterial oxygen saturation are associated with the development of retinopathy of prematurity and a higher risk of late death and neurological disabilities at 18 months corrected age in VLBW (35, 36).

Utility and duration of NIV have been further extended by caregivers to prevent and treat symptoms of apnea of prematurity (e9, e10). This opens further research questions on the effect of prolonged NIV support on neonatal morbidities, as well as the upcoming and challenging questions about the appropriate weaning strategies from NIV (37).

Newer methods, such as neurally adjusted ventilator assist (NAVA) or the use of nasal high frequency oscillatory ventilation (nHFOV) are promising innovations for NIV in preterm infants. To date, only results of small single-center trials are available with promising data on effective synchronization during neurally adjusted NIV and a reduced need for IMV with the use of nHFOV as compared to nasal CPAP in preterm infants with moderate/severe RDS (38, 39).

In the context of initial stabilization on NIV, the role of noninvasive surfactant application becomes more important, especially how its use may further contribute to improved outcomes in VLBW (40).

Conclusion

Based on best evidence, nasal CPAP is the gold standard NIV mode. NIPPV is an alternative to nasal CPAP as primary or post-extubation respiratory support in preterm infants with RDS. With its advantages of easy handling, less nasal trauma and improved infant-parent bonding, HHFNC therapy is now almost universally

employed in neonatal intensive care but may not be suitable in VLBW infants with surfactant-deficiency and severe acute pulmonary dysfunction. Effects of NIV on the rate of BPD are small but promising and warrant ongoing research in the field of NIV. Long-term neurodevelopmental and pulmonary outcomes require a prospective, ideally neonatal network-based follow-up program.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Corresponding author

Dr. med. Markus Waitz, MD
Abteilung Allgemeine Pädiatrie & Neonatologie
Zentrum für Kinderheilkunde und Jugendmedizin
Justus-Liebig-Universität Gießen
Feulgenstr. 10–12
35392 Gießen, Germany
markus.waitz@paediat.med.uni-giessen.de

► Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref1119

eBoxes, eFigures:
www.aerzteblatt-international.de/19m0177

Supplementary material to:

Non-Invasive Ventilation in Neonatology

by Judith Behnke, Brigitte Lemyre, Christoph Czernik, Klaus-Peter Zimmer, Harald Ehrhardt, and Markus Waitz

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eBOX 1

nCPAP- Mechanism of action and potential side effects (e11, e12)

- **Mechanism of action:**

- continuous distending pressure level to maintain functional residual capacity (FRC)
- reduction of airway collapse by decreased airway resistance
- splinting of the pharyngeal airway to avoid obstruction
- keeping surfactant on alveolar surface and reduction of alveolar edema
- reduced work of breathing
- improvement in ventilation-perfusion ratio and decreased intrapulmonary shunting

- **Side effects:**

- nasal trauma
- feeding intolerance, gastric distension, gastroesophageal reflux, gastrointestinal perforation
- air leak syndromes (i.e. pneumothorax, pulmonary interstitial emphysema)

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nCPAP= nasal continuous positive airway pressure

eBOX 2

Effects of antenatal systemic corticosteroids on the preterm lung and side effects (e13–e15)

- **Administration and effects:**

- most effectively if delivery occurs >24h and <7 days after administration
- improve alveolarisation, increase surfactant synthesis and enhance antioxidant status
- Meta-analyses demonstrated a lower risk of neonatal death, RDS, intraventricular hemorrhage, necrotizing enterocolitis and need for IMV
- are associated with lower rate of death or neurodevelopmental disability at corrected age 18–22 months in infants born at 22–25 weeks gestational age

- **Side effects:**

- reduced birth weight and decreased head circumference

IMV, invasive mechanical ventilation; RDS, respiratory distress syndrome; VLBWI, very low birth weight infant

eBox 3

NIPPV- Mechanism of action and potential side effects (e2, e16)

- **Mechanism of action:**
  - splints upper airway
  - improves lung recruitment and maintains FRC
  - equivocal effects on minute ventilation and tidal volumes
  - reduces symptoms of apnea of prematurity
  - decreases work of breathing and chest wall distortion (particularly in synchronized modes)
  - improves thoracoabdominal synchrony
  - potential for less pathologic lung inflammation
- **Side effects:**
  - see nCPAP box

FRC, functional residual capacity; nCPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation

eBOX 4

HHHFNC- Mechanism of action and potential side effects (20, e6)

- **Mechanism of action:**
  - flow-based noninvasive respiratory support with heated and humidified gas flow (delivered up to 8l/min)
  - washout of nasopharyngeal dead space
  - reduces work of breathing
  - improves lung and airway mechanics by eliminating the effects of drying/cooling
  - provides PEEP (pharyngeal pressure is directly related to flow, but inversely related to infant size)
- **Side effects:**
  - air leak syndromes (i.e. pneumothorax, pulmonary interstitial emphysema)

HHHFNC, humidified highflow nasal cannula; PEEP, positive end-expiratory pressure

eBOX 5

Effects of postnatal systemic corticosteroids on the preterm lung and side effects (31, e17, e18)

- **Administration and effects:**
  - early (<8 days postnatally) treatment reduced the incidence of death or BPD at 36 weeks postmenstrual age and extubation failure
  - assessing late treatment (>7 days postnatally) found a reduction in neonatal mortality, reduction in extubation failure, death or BPD at 36 weeks postmenstrual age
  - inhibiting pulmonary inflammatory response in developing or established BPD and reduce pulmonary edema
- **Side effects:**
  - increased risk of gastrointestinal perforation, cardiomyopathy, growth failure and cerebral palsy (early treatment)
  - increased risk of infection, gastrointestinal hemorrhage and a trend towards increased cerebral palsy and abnormal neurological examination at late follow-up (late treatment)

BPD, bronchopulmonary dysplasia

Time and Pressure Cycling during Bilevel-NIPPV versus CMV-NIPPV Different pressure wave types during (A) bilevel-NIPPV and (B) CMV-NIPPV
 PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure
 Adapted from Waitz et al. Clin Perinatol 2016 (e19)

eFigure 2
 Preterm infant with
 HHHFNC