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ORIGINAL ARTICLE



# Comparison of three non-invasive ventilation strategies (NSIPPV/BiPAP/NCPAP) for RDS in VLBW infants

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**ABSTRACT**

**Background:** Non-invasive ventilation (NIV) significantly changed the management of respiratory distress syndrome (RDS) in preterm infants. Further perspectives for neonatologists regard the assessment of different NIV strategies in terms of availability, effectiveness, and failure.

**Objective:** The aim of the present study is to evaluate the effectiveness of three different NIV strategies: nasal continuous positive airway pressure (N-CPAP), nasal synchronized intermittent positive pressure ventilation (N-SIPPV), and nasal bilevel-CPAP (BiPAP), as first intention treatment for RDS in very low birth-weight infants (VLBW).

**Methods:** A multicenter retrospective study was conducted in three neonatal intensive care unit (NICUs) that enrolled 191 VLBW infants complicated by RDS, who received, as first intention treatment for RDS, three different NIV approaches (N-CPAP: $n = 66$; N-SIPPV: $n = 62$, BiPAP: $n = 63$). We evaluated the performance of different NIV strategies by primary (failure within the first 5 d of life) and some selected secondary end-points.

**Results:** The incidence of NIV failure was significantly higher in the N-CPAP group (22/66) versus N-SIPPV/BiPAP groups (11/62; 11/63) ($p < .05$ for both), while no difference was observed between N-SIPPV and BiPAP groups. Moreover, no differences were found between the three groups regarding secondary outcomes.

**Conclusions:** The present study shows that first intention N-SIPPV/BiPAP, as NIV support, augment the beneficial effects of N-CPAP contributing to a reduced risk of failure in VLBW infants complicated by RDS. Data open up to further RCTs on a wider population to evaluate NIV effectiveness on long-term outcomes.

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**KEYWORDS**
BiLevel-CPAP; nasal synchronized intermittent positive pressure ventilation (NSIPPV); nCPAP; NIV; RDS



## Introduction

There is growing evidence that a non-invasive ventilation (NIV) strategy should be the first choice of respiratory support in very low birth-weight infants (VLBW) affected by respiratory distress syndrome (RDS). The changes in RDS management, allowing to minimize the use of mechanical ventilation (MV), have several explanations: (i) antenatal steroid prophylaxis; (ii) accurate delivery room and respiratory management with early nasal-continuous positive airway pressure (N-CPAP) support, (iii) surfactant replacement in the early phase of RDS, and (iv) the increased use of NIV [1–4].

Thanks to technological improvements, today there are different modalities, devices and interfaces to deliver NIV support and the main key-points for the neonatologist is the choice between different NIV strategies, related to their availability, effectiveness, and limits.

Literature data and meta-analysis reported that NIV strategies, synchronized or not, nasal intermittent positive pressure ventilation (N-IPPV) and bilevel-NCPAP (BiPAP), when used as first intention, had a better respiratory outcomes than N-CPAP [4–7]. Conversely a very large RCT showed no difference for bronchopulmonary dysplasia (BPD) and death at 28 d between CPAP and NIV strategies [8]. Of note, retrospective and RCT observations showed no difference between first intention N-IPPV (synchronized or not) and BiPAP [9–11]. Hence, data comparing the effectiveness of N-CPAP versus N-SIPPV or BiPAP, as best respiratory strategy for early RDS treatment, are still controversial and matter of debate.

The present multicenter retrospective study compares the effectiveness of three different NIV supports

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used as primary treatment for RDS: (i) N-CPAP providing, by a variable flow system, (ii) BiPAP, providing by a flow-driver device, that delivers two different levels of CPAP (higher and lower CPAP), alternating for a preset period, in which the babies can breath spontaneously, with the expiratory way always open, and (iii) N-SIPPV that utilizes a conventional modality of ventilation delivered through nasal interface, in which there is a synchronization of the inspiratory mandatory pressure. Different NIV performances were assessed in terms of failure within 5 d postnatal life and by some selected secondary outcomes.

## Materials and methods

We conducted a multicenter retrospective study in 191 VLBW infants, born at less than 32 weeks of gestational age (wGA), with a birth-weight (BW) less than 1500 g, affected by RDS and admitted at our Neonatal Intensive Care Units (NICU) (C. Arrigo, Children's Hospital, Alessandria, Italy; V. Buzzi, Children's Hospital, Milan, Italy; Maastricht University Medical Center, The Netherlands) from January 2013 to December 2015. The study was approved by local ethical committees.

Respiratory management for RDS was similar in the three NICUs. In the delivery room (DR), all VLBW infants were supported with N-CPAP (positive end expiratory pressure (PEEP): 5 $cmH_2O$) or with sustained lung inflation (SLI) (peak inspiratory pressure (PIP): 25 $cmH_2O$ for 15 s) followed by a PEEP set at 5 $cmH_2O$ [12,13]. All infants were admitted to the NICU on N-CPAP (5–6 cm $H_2O$).

Once admitted in the NICU, the newborns were supported by three different NIV devices (N-CPAP: $n = 66$; N-SIPPV: $n = 62$, BiPAP: $n = 63$) as primary treatment for RDS.

Apneic or severely depressed newborns, requiring MV, were excluded from the study and supported by MV or high-frequency oscillatory ventilation (HFOV) according to local protocols [14]. Furthermore, we excluded all newborns who started NIV after 6-h from birth or complicated by perinatal asphyxia, hemodynamic instability, congenital malformations, or metabolic disease. Another exclusion criterion was the crossover among the three groups, to limit a possible bias.

### N-CPAP

The N-CPAP support was delivered using the Infant Flow-driver device that, through a variable flow system, generates a continuous positive airway pressure, applied through the short binasal prongs as interface (CareFusion, Yorba Linda, USA). The respiratory parameter settings were a CPAP of 4–8 $cmH_2O$.

### BiPAP

For the BiPAP support we used the same flow-driver device and interfaces to the CPAP method (CareFusion, Yorba Linda, USA). The respiratory parameters setting were lower and higher CPAP-levels of 4–7 cm $H_2O$ and 7–10 cm $H_2O$, respectively, a time high of 0.7–1.4 s and a pressure exchange rate of CPAP 10–30/min. Respiratory settings were adjusted to guarantee blood gas analysis within normal ranges.

### N-SIPPV

The N-SIPPV support was delivered by using a conventional ventilator device (Giulia, Ginevri, Rome, Italy), equipped with a specific nasal flow sensor, positioned proximally to the patient (in which it inserts nasal interface) that detects the inspiratory effort by means of a pneumotachograph equipped with a fixed orifice (diameter 2 mm). The inspiratory flow was detected as a pressure change across the resistance. This is a conventional strategy of synchronized ventilation provided by nasal interface, with the short binasal prongs. The initial ventilator parameters were PEEP: 4–6 cm $H_2O$; PIP: 15–20 cm $H_2O$; inspiratory time 0.3–0.4 s; flow rate 6–10 L/min; respiratory rate (RR) 30–40 breaths/min. Respiratory settings (PIP max 25 cm $H_2O$, PEEP max 7 cm $H_2O$, RR max 60 breaths/min) were adjusted to guarantee blood gas analysis within normal ranges.

In all three methods, the lowest $FiO_2$ was adjusted in order to maintain a $SaO_2$ of 90–95%.

### Failure criteria

NIV failure was defined when one or more of the following criteria were present: (a) hypoxia ($FiO_2$ requirement $>0.40$), (b) acidosis and hypercarbia (pH $<7.20$; $pCO_2 > 65$ mmHg, respectively), (c) apnea as $\geq 4$ episodes per hour or the need of mask ventilation $\geq 2$ times per hour. Additional criteria were the occurrence of necrotizing enterocolitis (NEC) or bowel perforation [15]. Newborns who need intubation and MV were included for further analysis.

### Surfactant administration

The protocol for surfactant administration was the same for the three NICUs and provided, if $FiO_2$ requirement was $>0.3$, the first dose of surfactant of 200 mg/kg (Curosurf, Chiesi, Parma, Italy). Additional doses of

**Table 1.** Perinatal characteristics of preterm infants supported by different NIV strategies: continuous positive airway pressure (N-CPAP), bilevel-NCPAP (BiPAP) and synchronized intermittent positive pressure ventilation (N-SIPPV).

| | NCPAP ($N = 66$) | BiPAP ($N = 63$) | NSIPPV ($N = 62$) | $p$ |
|---|---|---|---|---|
| BW (g) | 1104 ± 245 | 1164 ± 275 | 1117 ± 269 | .15 |
| GA (weeks) | 29.3 ± 2 | 29.2 ± 2 | 28.9 ± 2 | .48 |
| GA ≤26 weeks (*n*/total) | 6/66 | 9/63 | 10/62 | .51 |
| GA >26 and ≤29 weeks (*n*/total) | 37/66 | 31/63 | 34/62 | .75 |
| GA >29 weeks (*n*/total) | 23/66 | 23/63 | 18/62 | .72 |
| Male/female | 24/42 | 33/30 | 26/36 | .11 |
| pPROM (*n*/total) | 18/66 | 22/63 | 17/62 | .29 |
| Chorioamnionitis (*n*/total) | 18/66 | 12/63 | 11/62 | .28 |
| PIH requiring antihypertensive drugs (*n*/total) | 18/66 | 22/63 | 20/62 | .29 |
| Twins (*n*/total) | 21/66 | 19/63 | 20/62 | .84 |
| Prenatal steroids completed course (*n*/total) | 56/66 | 55/63 | 55/62 | .94 |
| SLI in the delivery room | 37/66 | 31/63 | 34/62 | .75 |
| APGAR score at 1 min | 7 ± 1 | 7 ± 1 | 7 ± 1 | 1.00 |
| APGAR score at 5 min | 8 ± 1 | 8 ± 1 | 8 ± 1 | 1.00 |
| $SaO_2$ at study entry | 93 ± 3.2 | 92 ± 3.2 | 93 ± 3.5 | .55 |
| $FiO_2$ at study entry | 0.29 ± 0.09 | 0.27 ± 0.06 | 0.29 ± 0.06 | .52 |
| MAP with NIV mode, at study entry ($cmH_2O$) | 5.3 ± 0,7 | 7.0 ± 0.9 | 9.8 ± 1.3 | <.05* |

Values are given as mean ± SD. BW: birth-weight; GA: gestational age; pPROM: preterm premature rupture of membrane; PIH: pregnancy induced hypertension; SLI: sustained lung inflation; $SaO_2$: arterial oxygen saturation; $FiO_2$: fraction of inspired oxygen; MAP: mean airway pressure; NIV: non-invasive ventilation.
*$p < 0.5$ for NCPAP vs BiPAP, for NCPAP vs NSIPPV and for BiPAP vs NSIPPV.

surfactant were given at 100 mg/kg, at least 12-h after previous administration, for a maximum of three doses. Following INtubation, SURfactant extubation (INSURE) newborns received the same NIV support as before.

### End-points

The primary end-point was the rate of NIV failure in the first 5 d of life. Secondary end-points were several pulmonary and extrapulmonary outcomes. Moderate/severe BPD was defined according to the classification of Jobe and Bancalari [16]. Intraventricular hemorrhage (IVH) was classified according to Papile [17] and retinopathy of prematurity (ROP) was graded according to the criteria established by the international committee for ROP [18].

### Statistical analysis

For the calculation of the sample size, we used the rate of NIV failure as the main primary outcome. We assumed a difference of 20% in the failure rate among different NIV strategies [2–5,19–21]. We used a confidence level $\alpha = 0.05$; the power level desired was 0.80 and consequently we needed 60 patients for each group. The sample size was calculated using the formula for the Chi-square test of equal proportions in three groups [22].

Data were reported as means and SD for continuous variables, while absolute and relative frequencies were used for categorical variables. Parameters of the three groups were compared using ANOVA one-way test for continuous variables with Dunn's correction. Chi-square test was performed for categorical variables. A $p < .05$ was considered statistically significant, and all $p$ values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, IL).

## Results

The perinatal characteristics of the studied groups are reported in Table 1. No significant differences ($p > .05$, for all) were found between the three studied groups regarding BW; wGA; gender; the incidence of premature rupture of membranes, of chorioamnionitis, of pregnancy hypertension requiring antihypertensive drugs, of multiple pregnancies, of prenatal glucocorticoids prophylaxis, SLI in the DR and APGAR scores at 1–5 min. No differences ($p > .05$, for both) have been shown regarding $SaO_2$ and $FiO_2$. The mean airway pressure (MAP) at study entry (related to the specific using pressure settings of the respective NIV modes) was significantly higher in the N-SIPPV group when compared with N-CPAP and BiPAP groups ($p < .05$, for both). Moreover, MAP in the BiPAP group was significantly higher than the N-CPAP group ($p < .05$).

In Table 2, primary and secondary outcome results are reported. In detail, the incidence of NIV failure was significantly higher in the N-CPAP group versus N-SIPPV/BiPAP groups ($p < .05$, for both), while no difference ($p > .05$) was observed between BiPAP and N-SIPPV groups. Moreover, there were no significant differences ($p > .05$, for all) for the secondary end-points. Of note, pneumothorax (PNX) ($n = 9$) accounted as a cause of NIV failure in five out nine infants in whom a PNX occurred (N-CPAP: $n = 2$; BiPAP: $n = 1$; N-SIPPV: $n = 2$).

**Table 2.** Primary and secondary outcomes in preterm infants supported by different NIV strategies: continuous positive airway pressure (NCPAP), bilevel-NCPAP (BiPAP) and synchronized intermittent positive pressure ventilation (NSIPPV).

| | NCPAP ($n = 66$) | BiPAP ($n = 63$) | NSIPPV ($n = 62$) | $p$ |
|---|---|---|---|---|
| Primary outcomes | | | | |
| NIV failure (*n*/total) | 22/66 | 11/63 | 11/62 | $p < .05^{\S}$ |
| Secondary outcomes | | | | |
| Surfactant treatment | 31/66 | 30/63 | 29/62 | .99 |
| Multiple surfactant doses (*n*/total) | 24/66 | 20/63 | 26/62 | .50 |
| PDA requiring pharmacological treatment (*n*/total) | 14/66 | 15/63 | 17/62 | .70 |
| BPD (*n*/total) | 11/63 | 10/61 | 12/60 | .95 |
| PNX (*n*/total) | 3/66 | 4/63 | 2/62 | .68 |
| IVH $>2^{\circ}$ (*n*/total) | 6/63 | 4/61 | 4/60 | .67 |
| ROP $>2^{\circ}$ (*n*/total) | 4/63 | 2/61 | 4/60 | .60 |
| NEC (*n*/total) | 3/66 | 2/63 | 2/62 | .84 |
| LOS (*n*/total) | 25/63 | 20/61 | 24/60 | .58 |
| Death (*n*/total) | 3/66 | 2/63 | 2/62 | .86 |

NIV: non-invasive ventilation; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; PNX: pneumothorax; IVH: intraventricular hemorrhage; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; LOS: late onset sepsis.
$^{\S}p < .05$ for NCPAP vs BiPAP and for NCPAP vs NSIPPV. (BiPAP vs NSIPPV $p > .05$).

**Table 3.** Characteristics, timing, and causes of failure of preterm infants who failed support by different NIV strategies: continuous positive airway pressure (NCPAP), bilevel-NCPAP (BiPAP) and synchronized intermittent positive pressure ventilation (NSIPPV). NIV failure rate was significantly higher ($p < .05$, for both) in NCPAP when compared with BiPAP and NSIPPV supports.

| | NCPAP ($N = 22$) | BiPAP ($N = 11$) | NSIPPV ($N = 11$) | $p$ |
|---|---|---|---|---|
| BW (g) | 1045 ± 246 | 1227 ± 243 | 1135 ± 373 | .27 |
| GA (weeks) | 28.6 ± 1.9 | 29.9 ± 1.7 | 29.2 ± 1.8 | .18 |
| GA $\leq$26 weeks (*n*/total of GA subgroup) | 4/6 | 3/9 | 3/10 | .60 |
| GA $>26 \leq 29$ weeks (*n*/total of GA subgroup) | 12/37 | 3/31 | 4/34 | $p < .05^{\S}$ |
| GA $>$29 weeks (*n*/total of GA subgroup) | 6/23 | 5/23 | 4/18 | .89 |
| Prenatal steroids completed course (*n*/total) | 16/20 | 7/11 | 7/11 | .59 |
| Timing of failure (median, 25°–75° centile) (h) | 32 (18–66) | 34 (19–65) | 36 (17–72) | .32 |
| EOS (*n*/total) | 6/22 | 5/11 | 6/11 | .34 |
| Hypoxemia (*n*/total) | 10/22 | 6/11 | 6/11 | .83 |
| Hypercapnia and hypoxemia (*n*/total) | 8/22 | 5/11 | 3/11 | .21 |
| PNX (*n*/total) | 2/22 | 1/11 | 2/11 | .77 |
| NEC (*n*/total) | 2/22 | 2/11 | 2/11 | .71 |

BW: birth-weight; GA: gestational age; EOS: early onset sepsis; PNX: pneumothorax; NEC: necrotizing enterocolitis.
$^{\S}p < .05$ for NCPAP vs BiPAP and for NCPAP vs NSIPPV. (BiPAP vs NSIPPV $p > .05$).

NIV failure occurred in 44 out of 191 infants (N-CPAP: $n = 22$; BiPAP: $n = 11$; N-SIPPV $n = 11$). The causes were early onset sepsis (EOS) (N-CPAP: $n = 6$; BiPAP: $n = 5$; N-SIPPV: $n = 6$); hypoxia and hypercapnia (N-CPAP: $n = 8$; BiPAP: $n = 5$; N-SIPPV: $n = 3$), hypoxia (N-CPAP: $n = 10$; BiPAP: $n = 6$; N-SIPPV: $n = 6$); NEC (N-CPAP: $n = 2$; BiPAP: $n = 2$; N-SIPPV: $n = 2$). The timing of NIV failure did not differ ($p > .05$, for all) among studied groups as shown in Table 3. The NIV failure rate was significantly higher ($p < .05$, for all) in the N-CPAP group, at 26–29 wGA, when subgroups of different wGA were considered. No differences ($p > .05$, for all) were observed in the failure rate among the three NIV groups at wGA $\leq$26 weeks or $>$29 weeks, respectively. No significant differences, in the monitoring parameters recorded at study entry, were shown between infants in whom NIV failed or not.

## Discussion

In the recent years, it is attempted to use NIV techniques to reduce the need of MV and its pulmonary adverse outcome. There is growing evidence that N-CPAP, the most commonly used NIV support for RDS, does not consistently improve ventilation and does not work in infants with poor respiratory drive, with a 30–50% failure rate [23]. In this context, the use of different NIV techniques, with an increased respiratory support, such as N-IPPV or BiPAP, has been proposed.

In the present study, we found that BiPAP and N-SIPPV, used as first intention for RDS treatment of VLBW, had a lower failure rate than N-CPAP. Of note, BiPAP and N-SIPPV strategies did not differ in primary and secondary outcomes. Results are consistent and offer additional support to previous observations that showed the benefit of N-IPPV versus N-CPAP, in preterm infants with RDS, with a significant reduction in the need for intubation and MV, in particular within the first 72 h of life [4–6].

The RCTs that have compared BiPAP versus N-CPAP, as first intention strategy for RDS treatment, showed discrepancies in obtained results. Lista and Zhou [7,24] observed that the BiPAP group had less need of MV,

with a better gas exchange in Zhou's study; while Aguiar et al. did not find an advantage of BiPAP overall, but in the infants with a gestational age (GA) of 30–32 wGA there was a tendency towards better results using BiPAP [25].

Conversely, Kirpalani et al. [8] in a very large multicenter trial, in which 1099 preterm infants <30 wGA were randomly assigned to the NIV group (including different modalities of NIV: NIPPV, delivered neither with ventilator driven or flow driver devices, synchronized or not synchronized, and BiLevel-CPAP, with different setting parameters) or N-CPAP group (including all methods of N-CPAP), did not showed any difference in the rate of survival and BPD between the two groups. Although this is a very important RCT, the heterogeneous modes of NIV used and the different degrees of experience in the participating centers could represent a confounding factors.

In agreement with the aforementioned findings, no differences were observed between N-SIPPV and BiPAP groups [9–11]. In the present study, we also found that BiPAP and N-SIPPV, although acted through different strategies, have superimposable or superior effects compare with N-CPAP. The main explanations reside in their theoretical benefits. In N-SIPPV, the intermittent increase in nasal pressure transmitted to the lower airways increases tidal volume ($V_t$), minute ventilation ($V_m$), and decrease the work of breathing (WOB); moreover, the higher MAP resulted in a better alveolar recruitment with an improvement of the functional residual capacity (FRC) [26]. Nonetheless, BiPAP through a different ventilation mode generates two alternative CPAP levels (higher and lower pressure), and the newborns can inspire and expire spontaneously at both pressures (the expire way is always open) producing two different FRCs; the increase of the MAP improves oxygenation by recruiting collapsed alveoli, instead FRC switching could generate a $V_t$ and reduces the WOB [26]. Additional NIV advantage resides in the stimulation of spontaneous breathing, thanks to the pressure variation in the pharynx, thus reducing failure risk due to apneas [27].

In the present retrospectives observation, despite limitations due to a small sample size, we found in the 26–29 wGA subgroup, a higher failure rate in infants supported by N-CPAP versus N-SIPPV/BiPAP and no differences at <26 wGA or >29 wGA. This latter finding may be explained by the fact that at <26 wGA NIV failure is due to the severe lung immaturity, to the grade of RDS and to the reduced respiratory drive with very poor energy reserves to cope the high WOB to maintain FRC and adequate gas exchanges. Conversely, at 26–29 wGA, at a stage of increased lung maturity, N-SIPPV/BiPAP are more able to amplify the existing respiratory drive than N-CPAP, thus obtaining a sufficient FRC with physiological gas exchanges and a reduced risk of apneas. Finally, data on failure rate at >29 wGA can mainly be explained by several non-respiratory causes (early-onset sepsis, patent ductus arteriosus (PDA), PPHN, etc.), which can play a relevant role in NIV failure. Overall, we observed a low rate of failure for all NIV support used (N-CPAP 33%; BiPAP 17%; N-SIPPV 18%), supporting the notion that perinatal treatments (i.e. antenatal glucocorticoid prophylaxis >88% for our population), improvements in DR management (i.e. early started of N-CPAP support and SLI) can facilitate the neonatal transition and allow an early FRC [2–13].

To date, it is very difficult to judge the effectiveness of the various synchronization systems for NIV in newborns (Graseby's capsule or flow trigger). Therefore, the absence of any difference between N-SIPPV (synchronized) and BiPAP (not synchronized), as found in our study, offers additional matter of debate [4,26,28]. Further studies are necessary to answer the question, including other systems of synchronization that seem to be promising, such as Neurally Adjusted Ventilatory Assist.

In the present series, we found no differences in secondary outcomes among different NIV strategies. The explanation may reside in the small sample size that does not allow to draw definite conclusions, especially for BPD that requires a wider study-population eligible for statistical analysis [29]. However, the absence of any differences among different NIV strategies in other secondary outcomes (i.e. PNX, NEC, etc.) offer additional support to their safety.

Finally, high-risk infants require experienced nurses and very high levels of care. These conditions are fundamental to ensure effective airflow, maintaining adequate pressure from the nostrils to the distal airways, to increase the comfort of the newborns, to improve the performance and for successful of nasal ventilation and to prevent trauma of the nostrils [30].

The limitations of the study are: (i) is retrospective and not randomized, although the protocols were very similar and standardized in our NICUs; (ii) the small sample size; (iii) the choice made by the treating physician to use one or another NIV support that although depends on device availability, we cannot exclude different attitudes of the neonatologists to use a specific NIV modality.

In conclusion, these data suggest that N-SIPPV/BiPAP augments the beneficial effects of NCPAP and contributes to a NIV successful for RDS treatment. It is reasonable to suggest the use of N-SIPPV or BiPAP, in

ELBW/VLBW infants, as primary mode of respiratory support for RDS, or when N-CPAP fails. However, there is a need for further multicenter RCTs in a wider population.

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