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Optimal level of nasal continuous positive airway pressure in severe viral bronchiolitis

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Abstract *Purpose:* To determine the optimal level of nasal continuous positive airway pressure (nCPAP) in infants with severe hypercapnic viral bronchiolitis as assessed by the maximal unloading of the respiratory muscles and improvement of breathing pattern and gas exchange. *Methods:* A prospective physiological study in a tertiary paediatric intensive care unit (PICU). Breathing pattern, gas exchange, intrinsic end expiratory pressure (PEEPi) and respiratory muscle effort were measured in ten infants with severe hypercapnic viral bronchiolitis during spontaneous breathing (SB) and three increasing levels of nCPAP. *Results:* During SB, median PEEPi was 6 cmH_2O (range 3.9–9.2 cmH_2O), median respiratory rate was 78 breaths/min (range 41–96), median inspiratory time/total duty cycle (T_i/T_{tot}) was 0.45 (range 0.40–0.48) and transcutaneous carbon dioxide pressure ($P_{tc}CO_2$) was 61.5 mmHg (range 50–78). In all the infants, an nCPAP level of 7 cmH_2O was associated with the greatest reduction in respiratory effort with a mean reduction in oesophageal and diaphragmatic pressure swings of 48 and 46%, respectively, and of the oesophageal and diaphragmatic pressure time product of 49 and 56%, respectively. During nCPAP, median respiratory rate decreased to 56 breaths/min (range 39–108, $p < 0.05$), median T_i/T_{tot} decreased to 0.40 (range 0.34–0.44, $p < 0.50$) and $P_{tc}CO_2$ decreased to 49 mmHg (range 35–65, $p < 0.05$). Only one infant with associated bacterial pneumonia required intubation and all the infants were discharged alive from the PICU after a median stay of 5.5 (range 3–27 days). *Conclusion:* In infants with hypercapnic respiratory failure due to acute viral bronchiolitis, an nCPAP level of 7 cmH_2O is associated with the greatest unloading of the respiratory muscles and improvement of breathing pattern, as well as a favourable short-term clinical outcome.

Keywords Nasal continuous positive airway pressure · Intrinsic positive end expiratory pressure · Bronchiolitis · Work of breathing · Children

Introduction

Severe viral bronchiolitis is one of the first causes of epidemic lower respiratory tract infection among infants and represents 2–6% of all admissions to the paediatric intensive care unit (PICU) in developed countries [1, 2]. Viral infection triggers airways inflammation and obstruction. Severe bronchiolitis is characterized by a rapid swallow breathing pattern with an increase respiratory rate, a decrease inspiration time (T_i), and an increase in inspiratory to expiratory time ratio. Physiologically, the increases in both respiratory system resistance and lung elastance result in an increased load on respiratory muscles. Because of a reduced proportion of diaphragmatic muscle type-1 fibres, inducing a lower resistance of respiratory muscle to endurance than in adults, infants are more sensitive to respiratory muscle fatigue [3]. When the energy required to overcome the forces opposing ventilation (elastic recoil and airway resistance), namely the work of breathing (WOB), exceeds the capacity of the respiratory muscle to ensure adequate alveolar ventilation, hypercapnic respiratory failure may occur, requiring ventilatory support. Nasal continuous positive airway pressure (nCPAP) is widely recognized as an efficient ventilatory support in severe bronchiolitis by improving alveolar ventilation and clinical outcome [4–8]. However, levels of nCPAP levels used in published studies are mainly determined empirically and based on clinical improvement. The optimal level of nCPAP, defined by the level of continuous positive pressure associated with the greatest unloading of the respiratory muscles, has never been evaluated.

The aim of the present study was thus to determine the optimal nCPAP level in infants with severe hypercapnic viral bronchiolitis and to assess the clinical improvement of the patients with this nCPAP level.

Materials and methods

Patients

This prospective physiological study was performed between October 2006 and December 2008 in a 20-bed tertiary care university PICU. Criteria for enrolment were as follows: PICU admission for viral bronchiolitis as defined by the French consensus [9] and an acute hypercapnic respiratory failure defined as a respiratory rate (RR) in at least the 97th percentile for age associated with a transcutaneous carbon dioxide pressure ($P_{tc}CO_2$) of at least 50 mmHg [10].

Exclusion criteria were an unstable clinical condition leading to emergency endotracheal intubation, such as haemodynamic instability, major acidosis (defined by a pH less than 7.2), refractory apnoea, altered consciousness (paediatric Glasgow coma score less than 12), ineffective cough or enrolment in another research protocol.

The study was approved by the local institutional board (P 02-73) and written informed consent was obtained from all the parents.

Measurements and data analysis

Respiratory rate (RR), heart rate (HR), pulse oximetry (SaO_2) (HP Omnicare M1165/66A, Hewlett Packard, Böblingen, Germany) and $P_{tc}CO_2$ (Tina TCM 4/40, Radiometer Medical ApS, Brønshøj, Denmark) were recorded continuously. Airway pressure (P_{aw}) was measured with a differential pressure transducer (MP 45 model, Validyne, Northridge, CA) on the piece between the nasal prongs and respiratory circuit. Oesophageal (P_{es}) and gastric pressures (P_{ga}) were measured using a 2.1-mm-external-diameter catheter with two integrated pressure transducers, mounted 5 and 25 cm from the distal tip (Gaeltec, Dunvegan, Isle of Skye, UK) inserted orally because of the age of the infants and their predominant nose breathing [11–13]. Adequate P_{ga} transducer positioning was checked by gentle manual pressure on the patient's abdomen to observe P_{ga} fluctuations without effect on the P_{es} trace. Placement of the P_{es} transducer was checked by the presence of a negative deflection during inspiration and an occlusion test as recommended by Baydur et al. [11]. All signals were digitalized at 128 Hz, sampled for analysis using an analogical/numeric acquisition system (MP 100, Biopac Systems, Goletta, CA) and transferred to a computer with Acknowledge software.

Data analysis

PEEPi was assessed as the mean difference between the beginning of P_{es} drop and the 0 cmH_2O level measured on 10 consecutive cycles. Transdiaphragmatic pressure (P_{di}) was obtained by subtracting the P_{es} signal from the P_{ga} signal. The diaphragmatic (PTP_{di}/breath) and oesophageal pressure–time products per breath (PTP_{es}/breath) were obtained by measuring the area under the P_{di} and P_{es} signal between the onset of inspiration, defined as the point at which the deflection occurred on the P_{es} trace, and the end of inspiration defined as the peak of P_{di}. Both PTP_{di} and PTP_{es} were also expressed per minute by multiplying the pressure–time products per breath by the RR (PTP_{di}/min and PTP_{es}/min) [14–16].

Experimental protocol

All measurements were performed in a semi-recumbent position. The oeso-gastric catheter was inserted orally. The study started with a spontaneous breathing (SB) period with additional oxygen, delivered by nasal prongs, to achieve an SaO_2 of at least 94%. After a 15-min period of clinical stabilisation, breathing pattern and respiratory muscle effort were recorded during a 3-min additional period. Then, nCPAP was applied using adapted nasal prongs (Fisher and Paykel Healthcare, Auckland, New Zealand).

nCPAP was delivered via a standard ICU ventilator (Babylog 8000 or Evita 2 dura Neoflow; Dräger, Lübeck, Germany) with an infant ventilator circuit dual heated with MR 290 autofeed chamber (Fisher Paykel, New Zealand). Three different levels of nCPAP were recorded consecutively: 4, 7 and 10 cmH_2O. Each nCPAP level lasted

Table 1 Patient characteristics and outcome

Patient	Age (days)	Weight (g)	Sex	Length of nCPAP (days)	RSV	Intubation	PICU stay (days)
1	34	4,515	M	4	Yes	No	7
2	56	5,000	M	5	Yes	No	19
3	27	4,420	F	3	No	No	6
4	60	3,000	M	3	Yes	No	6
5	27	3,560	M	1.5	Yes	Yes	27
6	42	2,920	F	1.5	Yes	No	4
7	26	4,265	F	1.5	Yes	No	3
8	94	7,100	F	3	Yes	No	5
9	75	5,840	M	3	Yes	No	4
10	48	4,300	F	2.5	Yes	No	5

RSV respiratory syncytial virus, *PICU* Pediatric intensive care unit, *RSV* respiratorysyncytial virus

18 min, with a 15-min period of stabilisation, followed by a 3-min period of recording. Data were measured on 10–20 stable breathing cycles with cycles corresponding to coughing or swallowing being excluded.

Statistical analysis

Data are presented as median with range. Wilcoxon signed-rank test analysis was used to compare continuous variables measured in the four experimental conditions (SB, nCPAP + 4 cmH_2O, nCPAP + 7 cmH_2O and nCPAP + 10 cmH_2O). Correlations were established using the Spearman rank correlation test. A p value less than 0.05 was considered as statistically significant.

Results

Characteristics of the population

During the study period, 171 infants were admitted to the PICU for severe viral bronchiolitis: 37 infants did not require mechanical ventilatory support, 13 were intubated before the PICU admission and 121 received a first-line treatment with nCPAP. Of these 121 infants, 42 received nCPAP for recurrent or sustained apnoea, and 79 for acute hypercapnic respiratory failure. The characteristics of the patients are presented in Table 1. Two infants were born before 37 weeks of gestation age (33 and 36, respectively) and none had chronic lung disease. All 10 infants included in the study tolerated the oeso-gastric catheter insertion and completed the study.

Breathing pattern and respiratory muscle load during spontaneous breathing

During SB, all infants needed nasal oxygen (0.5–4 L/min) to maintain an SaO_2 of at least 94%. Lung segmental atelectasis was present on chest X-ray in six infants before nCPAP initiation.

All the patients had hypercapnic respiratory failure with a median $P_{tc}CO_2$ of 61.5 mmHg (range 50–78) (Table 2). Median PEEPi was 6.05 cmH_2O (range 3.9–9.2 cmH_2O). All the indices assessing respiratory efforts (swing P_{es} and P_{di}, PTP_{es} and PTP_{di}) were markedly increased. No correlation between parameters of respiratory workload and age or weight of infants was found (data not shown).

Table 2 Breathing pattern and respiratory muscle load on spontaneous breathing and nCPAP support in infants with severe viral bronchiolitis

	Spontaneous breathing	nCPAP (+7 cmH_2O)
Breathing pattern		
RR (breath/min)	78 (41–96)	56 (39–108)*
T_i (s)	0.35 (0.25–0.49)	0.41 (0.28–0.67)
T_e (s)	0.42 (0.28–0.73)	0.59 (0.47–0.99)*
T_i/T_{tot}	0.45 (0.4–0.48)	0.40 (0.34–0.44)*
PEEPi (cmH_2O)	6.05 (3.9–9.2)	Not applicable
$P_{tc}CO_2$ (mmHg)	61.5 (50–78)	49 (35–65)*
Respiratory muscle output		
Swing P_{es} (cmH_2O)	18.3 (10.9–40.4)	8.3 (2.8–22.1)*
Swing P_{di} (cmH_2O)	15.7 (12.2–40.4)	8.5 (3.6–25.3)*
PTP_{es}/breath (cmH_2O s)	6.2 (3.1–22)	3.5 (1.3–16.7)*
PTP_{di}/breath (cmH_2O s)	7.2 (3.5–20.7)	3.2 (1.7–14.9)*
PTP_{es}/min (cmH_2O s min^{-1})	478 (297–1,060)	204 (82–601)*
PTP_{di}/min (cmH_2O s min^{-1})	511 (319–995)	221 (103–536)*

Data are presented as median with range in parentheses
nCPAP nasal continuous positive airway pressure, *RR* respiratory rate, T_i inspiratory time, T_e expiratory time, *PEEPi* intrinsic end expiratory pressure, $P_{tc}CO_2$ transcutaneous carbon dioxide pressure, *swing* P_{es} oesophageal pressure swing, *swing* P_{di} diaphragmatic pressure swing, *PTP* oesophageal and diaphragmatic pressure–time product per breath or per minute
* $p < 0.05$

Level of nCPAP and effects on breathing pattern and respiratory muscle load

Nasal CPAP was associated with an immediate improvement in breathing pattern and respiratory muscle effort in all the patients (Figs. 1, 2). All patients had a similar response with a maximum decrease in respiratory muscle effort at nCPAP + 7 cmH_2O (Fig. 2). This improvement was not correlated with the respiratory muscle effort or PEEPi during SB. An nCPAP level of 7 cmH_2O resulted in a statistically significant decrease in RR, $P_{tc}CO_2$ and T_i/T_{tot} ratio (Table 2). A significant correlation was observed between the decrease in $P_{tc}CO_2$ and the PTP_{es}/min ($\rho = 0.79$, $p = 0.01$).

A significant decrease in mean P_{es} and P_{di} swings (−48%, and −46%, respectively) and in mean PTP_{es}/min and PTP_{di}/min (−56% and −54%, respectively) were observed during nCPAP. When nCPAP level was decreased from 7 to 4 cmH_2O, mean PTP_{es}/min and mean PTP_{di}/min increased significantly from 236.8 ± 160 to 431.5 ± 216 cmH_2O s min^{-1} ($p < 0.05$), and from 255 ± 140 to 468.2 ± 171 cmH_2O s min^{-1} ($p < 0.05$), respectively. The increase of the CPAP pressure level from 7 to 10 cmH_2O was associated with an increase in mean PTP_{es}/min and mean PTP_{di}/min from 236.8 ± 160 to 371 ± 183 cmH_2O s min^{-1} ($p < 0.05$), and from 255 ± 140 to 404.3 ± 153 cmH_2O s min^{-1} ($p < 0.05$), respectively.

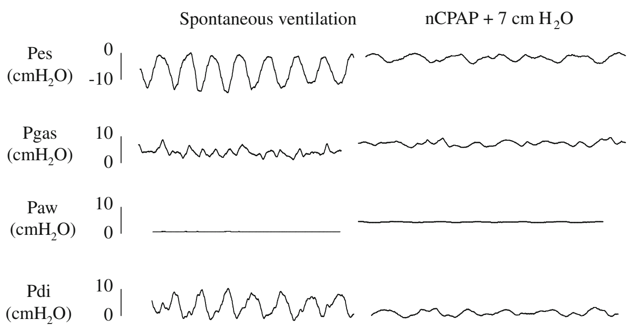
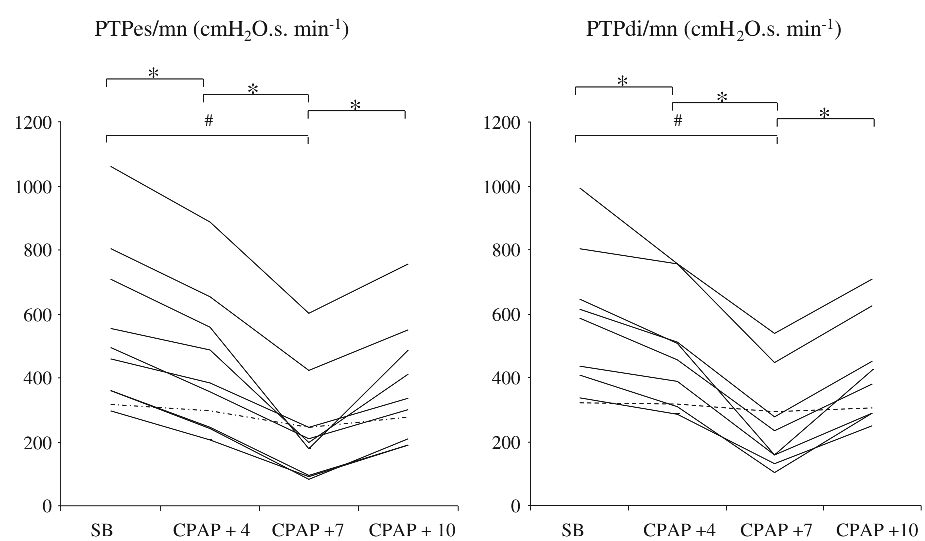


Fig. 1 Inspiratory pressure effort during spontaneous breathing and with nCPAP support. Traces from an infant during spontaneous breathing (SB) (*left panel*) and with nasal continuous pressure support (nCPAP) with a pressure level of 7 cmH_2O (*right panel*). Parameters of respiratory muscle load measured are shown: P_{es}, oesophageal pressure; P_{gas}, gastric pressure; P_{di}, transdiaphragmatic pressure; P_{aw}, airway pressure

Clinical outcome

The median duration of nCPAP was 3 days (range 1.5–5 days) and the median length of stay in the PICU was 5.5 days (range 3–27 days). One infant (patient 5) developed an acute respiratory distress syndrome, with *Haemophilus influenzae* pneumoniae, requiring 18 days of mechanical ventilation, and was discharged from the PICU after 27 days. This patient had the lowest PEEPi (3.9 cmH_2O) and PCO_2 (50 mmHg) during SB and the lowest SaO_2/FiO_2 ratio (160) during nCPAP. This patient did thus not have an exclusive obstructive lung disease but also an associated parenchymal lung disease. No patient died and no adverse effect (pneumothorax, gastric distension or inhalation) occurred during the study. Transient nasal skin irritation was observed in one infant who required 5 days of nCPAP. Haemodynamic tolerance of nCPAP versus SB was good for all patients without any change in heart rate [153 ± 14 vs. 163 ± 17/min, not significant (NS)], systolic arterial pressure (103 ± 10 vs. 101 ± 12 mmHg, NS) and diastolic arterial pressure (60 ± 8 vs. 61 ± 12 mmHg, NS).

Fig. 2 Variations of oesophageal and diaphragmatic load in infants with severe viral bronchiolitis during spontaneous breathing and nCPAP at different pressure levels. Oesophageal pressure–time product per minute (PTP_{es}/min) and diaphragmatic pressure–time product per minute (PTP_{di}/min) of the 10 infants with severe bronchiolitis during spontaneous breathing (SB), and the three consecutive nCPAP levels (+4 cmH_2O, +7 cmH_2O, +10 cmH_2O). Each pressure level was compared to the previous level, *$p < 0.05$. The optimal level (7 cmH_2O) was compared to SB, $^{\#}p < 0.05$



Discussion

Our study shows that severe hypercapnic viral bronchiolitis is an obstructive pathology associated with a high PEEPi. An nCPAP level of 7 cmH_2O was associated with an optimal unloading of the respiratory muscles and an improvement of breathing pattern, gas exchange and clinical outcome in all the infants included in the study.

Bronchiolitis is associated with bronchial smooth muscle constriction, mucosal oedema and plugging of the airways by mucus and cellular debris leading to obstruction of peripheral airways with severe airflow limitation. In the most severe cases, alteration of respiratory mechanisms with an increase in resistance and in lung elastance precipitates severe hypercapnic respiratory failure. Because of this increase in inspiratory load, the infants change their breathing pattern by decreasing their inspiratory pressure and tidal volume and increasing their RR. The main consequence is a decrease in expiratory time length (T_e) with an increase in the T_i/T_{tot} ratio. Because of severe airflow limitation and T_e decrease, the time available for expiration may be insufficient to allow complete volume relaxation, leading to dynamic hyperinflation and PEEPi [17]. In order to initiate inspiratory airflow, respiratory muscles must generate a negative pressure that overcomes PEEPi. PEEPi has therefore been described as an inspiratory threshold load increasing the WOB. In addition, dynamic hyperinflation alters thoracic wall geometry and the muscle length–tension relationship thereby further increasing muscle workload [18]. To our knowledge, this is the first study that measures PEEPi in infants with severe bronchiolitis. nCPAP was associated with a significant increase in T_e and T_i/T_{tot} ratio. These results are in agreement with the "waterfall theory" described by Tobin and Lodato [19], which stipulates that if PEEPi is the result of expiratory airflow limitation, the application of extrinsic PEEP should decrease the pressure gradient between the mouth and alveoli at end expiration, and thus the inspiratory threshold load. This is also in accordance with Gauthier et al. [20] who clearly showed in six infants intubated for severe bronchiolitis that PEEP is able to decrease respiratory impedance in cases of expiratory flow limitation.

Quantification of the respiratory muscle load can be achieved either by measuring the mechanical force developed by the diaphragm during inspiration, the transdiaphragmatic pressure (P_{di}) and the PTP_{di}, which are correlated with the oxygen consumption of the respiratory muscles [21–23], or by measuring the electrical activity of the diaphragm (EMG_{di}) [24]. In our study, inspiratory muscle load was measured using P_{es} and P_{di} and their pressure–time products.

During SB, all infants had a high level of P_{es} swings and PTP_{es} and PTP_{di}. The increased respiratory muscle load observed in our patients was comparable to that previously reported by Stokes et al. [25]. In their study, a sixfold increase of the WOB was observed in 26 infants with acute bronchiolitis but no correlation with clinical parameters was found. Recently, Cambonie et al. [8] observed a mean P_{es} exceeding 25 cmH_2O in 12 infants with RSV-bronchiolitis. They also showed that nCPAP decreased P_{es} swings and PTP_{es}. We confirmed these data and further observed that nCPAP + 7 cmH_2O was the optimal CPAP level in all the infants. This level is explained by the level of PEEPi that has to be overcome at the onset of inspiration. Moreover, we observed a significant positive correlation between $P_{tc}CO_2$ and PTP_{es}/min.

With a higher level of CPAP (10 cmH_2O), we observed a decrease in physiological parameters, with increases of PTP_{es} and PTP_{di}/min. Our hypothesis is that evolution is related to an increase in respiratory muscle activity especially an increase in gastric pressure in order to overcome the high pressure applied.

Our study has two limitations. First, a series effect of the three consecutive levels of nCPAP cannot be excluded. However, respiratory parameters were recorded only after a 15-min period of stabilisation between each level to reduce this possible effect. Of note, all the infants had the same evolution with an initial but not optimal improvement at 4 cmH_2O and the greatest decrease of muscle load at 7 cmH_2O which is clinically relevant. Second, airflow could not be recorded during SB because of the severity of the respiratory distress and during nCPAP because of air leaks.

In conclusion, an nCPAP level of 7 cmH_2O is able to significantly unload respiratory muscles in infants with hypercapnic bronchiolitis with concomitant significant improvement in respiratory distress and clinical outcome.

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