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6 cmH₂O Continuous Positive Airway Pressure Versus Conventional Oxygen Therapy in Severe Viral Bronchiolitis: A Randomized Trial

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Summary. Objective: To compare the effects of nasal continuous positive airway pressure (nCPAP) and conventional oxygen therapy on the clinical signs of respiratory distress and the respiratory muscle workload in acute viral bronchiolitis. Design: Prospective, randomized, monocentric study carried out in the pediatric intensive care unit (PICU) of a university hospital. Patients: Infants <6 months old, admitted to the PICU with severe respiratory syncytial virus bronchiolitis. Intervention: The patients were randomized into two groups for 6 hr. The nCPAP group (n = 10) received 6 cmH₂O pressure support delivered by a jet flow generator and the control group (n = 9) received an air/oxygen mixture from a heated humidifier. Respiratory distress was assessed by the modified Wood's clinical asthma score (m-WCAS), and inspiratory muscle work was evaluated by calculating the pressure-time product per breath (PTP_{insp}/breath) and per minute (PTP_{insp}/min) from the esophageal pressure (Pes) recordings. Measurements and Main Results: Compared with control condition, nCPAP decreased m-WCAS [-2.4 (1.05) vs. -0.5 (1.3), *P* = 0.03], PTP_{insp}/breath [-9.7 (5.7) vs. -1.4 (8.2), *P* = 0.04], PTP_{insp}/min [-666 (402) vs. -116 (352), *P* = 0.015], and FiO₂ [-7 (10) vs. +5 (15), *P* = 0.05]. Significant worsening of m-WCAS was only observed in the control group (4/9 vs. 0/10, *P* = 0.03). Conclusions: nCPAP rapidly decreased inspiratory work in young infants with acute bronchiolitis. Improvement in the respiratory distress score at 6 hr was proportional to the initial clinical severity, suggesting the importance of rapid nCPAP initiation in the more severe forms of the disease.

Key words: acute viral bronchiolitis; continuous positive airway pressure; infant; randomized control trial; respiratory syncytial virus infections.

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INTRODUCTION

In infants under 1-year-old, severe respiratory syncytial virus (RSV) bronchiolitis is the major cause of acute respiratory distress.¹ However, few prospective randomized studies have been performed, making it difficult to formulate clear-cut recommendations for the management of these patients.²⁻⁴

Several clinical studies have suggested that continuous positive airway pressure (CPAP) is beneficial in cases of acute viral bronchiolitis.⁵⁻¹¹ In this disease, the critical narrowing in the peripheral airways results in severe obstruction, with markedly increased respiratory system resistance.¹² During the expiratory phase of respiration, dynamic collapse of the airways produces a disproportionate decrease in airflow, leading to dynamic hyperinflation and intrinsic end-expiratory pressure (PEEPi).¹³ PEEPi not only decreases compliance, but it

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Conflict of interest: None.

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also adversely affects the work required to initiate inspiration to overcome the difference between alveolar and upstream pressures at end-expiration.¹⁴ Hyperinflation generates an extra elastic load from the chest wall and forces respiratory muscles to operate in unfavorable biomechanical conditions, thereby altering the efficiency of force generation by the respiratory muscles.¹⁵ A sixfold increase in the total work of breathing or the inspiratory effort is commonly reported in severe bronchiolitis.^{13,16,17} In response to this higher inspiratory load, the respiratory pattern is modified, with increased breathing frequency and T_i/T_{tot} ratio. The main consequence of this ventilatory adaptation is a decrease in expiratory time and resulting air trapping.^{13,17}

Two recent works observed consistent increases in expiratory time (T_e) and a 50% reduction in inspiratory work immediately following CPAP initiation.^{13,17} The demonstration of increased PEEP_i during spontaneous ventilation and the change in breathing pattern with this pressure support suggested that nCPAP improves the work of breathing mainly by offsetting the patient's inspiratory effort to overcome PEEP_i. This leads to a decrease in the dynamic collapse of the very compliant upper and lower airways, which is particularly amplified under forceful respirations in this age group.¹⁸ Ultimately, this airway recruitment helps to empty the lung during expiration, thereby decreasing hyperinflation and the work of breathing.

The methodologies used in these studies of CPAP to treat severe bronchiolitis have been descriptive or retrospective, which has limited the impact of the findings.¹⁹ Recently, Thia et al. conducted a randomized, cross-over study in 29 infants with moderately severe bronchiolitis that demonstrated the effectiveness of CPAP in reducing capillary PCO_2 compared with oxygen therapy. However, very young infants were not included in this trial and the physiological data were limited to blood gases and respiratory and heart rates, potentially explaining the absence of clinical improvement.¹⁰

On the basis of a pilot study, we designed a prospective and randomized study and hypothesized that CPAP would have a beneficial clinical effect on infants with severe RSV bronchiolitis. Our objective was to assess and compare the effects of nasal CPAP and conventional oxygen therapy on the clinical signs of respiratory distress and the respiratory muscle workload in infants <6 months old presenting severe acute RSV bronchiolitis.

MATERIAL AND METHODS

Patients

Infants <6 months old and hospitalized in our pediatric intensive care unit (PICU) with the clinical

diagnosis of bronchiolitis were eligible for this study. The inclusion criteria were the following: (1) RSV bronchiolitis confirmed by nasopharyngeal enzyme immunoassay; (2) severe respiratory distress defined by a modified Wood's clinical asthma score (m-WCAS) >4; (3) no invasive or noninvasive ventilation, including nasal continuous positive airway pressure (nCPAP), prior to PICU admission; (4) no underlying cardiopulmonary or neuromuscular disease and no pneumothorax on chest radiograph; and (5) signed authorization by the parents.

Study Protocol

This prospective, randomized, controlled study was performed during three consecutive RSV epidemic periods, from November 2006 to March 2009. Cardiorespiratory monitoring was started in eligible infants and included pulse oximetry (SpO_2) and oscillometric measurement of arterial blood pressure (IntelliVue MP70, Philips Medical Systems, Eindhoven, the Netherlands). Transcutaneous (T_c) PCO_2 was continuously recorded using a TCM4 (Radiometer, Copenhagen, Denmark).

Initial management consisted of aspiration of secretions, if necessary, and delivery of a humidified air/oxygen blend from a heating base in order to reach an SpO_2 of 94–98%. A 120 ml/kg venous perfusion with a binary parenteral nutrition preparation was started. Corticosteroid and bronchodilator administration were stopped on admission, and no enteral nutrition was given during the protocol. Chest X rays and capillary blood gas measurements were taken, and the infant was then maintained in a quiet environment for at least 1 hr.

Once the diagnosis of RSV-positive bronchiolitis was confirmed by enzyme immunoassay, respiratory distress was quantified using the m-WCAS.^{17,20–22} Then, the inspiratory work was assessed by measuring esophageal pressure (P_{es}). After these baseline evaluations, the patients were randomized into one of two groups, nCPAP or control, using sequentially numbered, opaque sealed envelopes from the Department of Medical Information of the institution.

nCPAP was generated with the Infant Flow Ventilator (Electro Medical Equipment, Brighton, UK). The flow was adjusted to deliver positive continuous pressure of 6 cmH_2O via a mask connected to a twin injector nozzle fixed to the patient by a specially designed bonnet. The esophageal catheter was left in place.

Infants in the control group continued to receive a heated and humidified air/oxygen mixture delivered through a nasal cannula, which allowed a maximum gas flow of 2.5 L/min (MR 850 and RT094, Fisher and Paykel, Villebon, France). In both groups, the air/oxygen blend was adjusted in order to reach an SpO_2 of 94–98%.

The protocol lasted 6 hr after the allocated treatment was begun. In both groups, m-WCAS was assessed hourly and Pes was measured 1 and 6 hr after the start of the procedure. At any moment during this study, an increase of more than 30% in m-WCAS justified a switch to the other treatment group.

Clinical Score and Esophageal Pressure Measurement

A detailed description of the data acquisition and analysis has been reported elsewhere.^{17,22} A single observer, who was not involved in patient care or pressure recordings, quantified the respiratory distress using m-WCAS, with the help of a visual analog scale to standardize the scoring of accessory muscle use and wheezing. An investigator who was unaware of this scoring was designated to measure Pes using an esophageal balloon catheter (Marquat, Boissy-Saint-Léger, France) connected to a differential pressure transducer system. The catheter (with an external diameter of 1.9 mm) was inserted orally and placed in the middle portion of the esophagus to estimate intrapleural pressure from the esophageal pressure (Pes). The catheter position was adjusted by continuous online Pes monitoring until a clear oscillating signal with negative deflection was obtained during inspiration. The inspiratory work was estimated from the pressure–time product (PTP) per breath and per minute, defined as the area under the pressure–time curve.²³ The inspiratory muscle pressure–time product per breath (PTPes_{insp}/breath) was calculated by measuring the mean area under the Pes signal between the onset of the inspiratory effort and the end of inspiration ($\int \text{Pes dt}$) of 30 consecutive and regular respiratory cycles. PTPes_{insp} per minute was obtained by multiplying the pressure–time products per breath by the breathing frequency (PTPes_{insp}/min = $\int \text{Pes dt} \times \text{breathing frequency}$).

Data Analysis

Based on a pilot study,¹⁷ we assumed that 15 patients would have to be included to demonstrate a twofold greater decrease in m-WCAS in the nCPAP group, with an alpha risk of 5% and a power of 80%. In order to overcome the uncertainty of the calculation related to the small sample in the preliminary study, we planned to include 20 patients.

The intention-to-treat analysis was conducted using the last-observation-carried-forward (LOCF) method. Variations in the outcome measures between baseline (H0) and 6 hr (H6) for each group and between groups were assessed using Student's *t*-test or a nonparametric test (Mann–Whitney, Wilcoxon, or Kruskal–Wallis). In a second step, the changes in the outcome measures were compared between the two groups using a linear

mixed model for longitudinal data. The model included intercept and random slope effects. Fixed back in the model were time, the arm of randomization, and the interaction between time and the randomized arm. A multivariate analysis of the primary endpoint was achieved by adjusting the results of clinical characteristics when the initial value differed by more than 15% between the two groups.

Qualitative variables were compared with the chi-square test, or Fischer's exact test when appropriate. The Spearman correlation coefficient was calculated to assess the correlation between continuous variables.

Data are expressed as mean (SE) or absolute frequencies (%). The significance level was set at 0.05. Statistical analysis was conducted with the SAS software package, version 9 (SAS Institute, Cary, NC).

Ethical Considerations

Informed written consent was obtained from the parents of all infants. The study protocol was approved by the Human Protection Committee of Montpellier, France. This clinical trial was recorded on the National Library of Medicine registry (number NCT00513890).

RESULTS

Population

From November 2006 to April 2009, 58 infants presenting RSV bronchiolitis were admitted to the PICU. Thirty-seven of them were not eligible: 25 presented an m-WCAS <4, six were older than 6 months, six had been intubated by the ambulance crew before admission, and three had already been treated by nCPAP.

Of the 21 eligible infants, two were not included because the parents declined to sign a consent form. The 19 included infants were 7.5 (1) weeks old, weighed 4.3 (0.2) kg, and had a clinical risk index for babies (CRIB) score of 2.2 (0.2).

Baseline Characteristics

At enrollment, the mean baselines values were as follows: m-WCAS: 4.8 (0.2), respiratory rate: 50 (2) breaths/min, FiO₂: 0.3 (0.01), SpO₂: 95 (1)%, and PCO₂: 56 (2) torr. The pressure–time products, per breath, and per minute, were respectively 14.6 (2) cmH₂O/s and 949 (104) cmH₂O/s/min (Table 1).

Ten infants were randomly assigned to the nCPAP group and nine to the control group. The two groups were comparable for anthropometric parameters, severity scores, criteria of respiratory distress severity, and hemodynamic values. Four infants had been born prematurely, one in the nCPAP group and three in the control group, with a mean gestational age of 33 (0.5)

TABLE 1—Baseline Characteristics of the Population Randomized Into the Nasal Continuous Positive Airway Pressure (n-CPAP) and Control Groups

	nCPAP, n = 10	Controls, n = 9	P-value
Age (week)	6.8 (0.9)	8.2 (1.7)	0.47
Weight (kg)	4.5 (0.5)	4.1 (0.2)	0.4
CRIB	1.9 (0.2)	2.4 (0.5)	0.93
m-WCAS	5 (0.2)	4.7 (0.2)	0.24
RR (breaths/min)	51 (4.5)	49 (3.5)	0.94
SpO ₂ (%)	97 (1)	95 (1.6)	0.42
FiO ₂ (%)	33 (2)	32 (1.6)	0.59
HR (beats/min)	165 (3)	162 (4)	0.56
MAP (mmHg)	66 (6)	68 (8)	0.83
PCO ₂ (torr)	55 (2)	57 (4)	0.58
PTPes _{insp} /breath (cmH ₂ O/s)	14.6 (0.9)	14.6 (1)	0.99
PTPes _{insp} /min (cmH ₂ O/s/min)	975 (169)	918 (172)	0.81

CRIB, clinical risk index for babies; m-WCAS, modified Wood's clinical asthma score; RR, respiratory rate; SpO₂, pulse oximetry; FiO₂, fraction of inspired oxygen; HR, heart rate; MAP, mean arterial blood pressure; PCO₂, partial pressure of carbon dioxide measured on capillary blood gas sampling; PTPes_{insp}, inspiratory muscle pressure–time product.

Values are expressed as mean (SEM).

weeks and a mean birth weight of 2,170 (120) g; none had chronic lung disease.

Four infants in each group had received a nebulized β -adrenergic agent 4–6 hr before study enrollment. Corticosteroid treatment had been administered to three infants of the nCPAP group and two infants of the control group. These treatments had been stopped on admission to the PICU. The times between admission and enrollment in the nCPAP group and the control group were, respectively, 100 (33) and 200 (110) min; $P = 0.7$.

Comparison of the nCPAP and Control Groups

Clinical Improvement

The m-WCAS decreased in the nCPAP group, whereas it remained unchanged in the control group. The linear model confirmed the variation in m-WCAS between H0 and H6 only in the nCPAP group [-2.4 (1.05) vs. -0.5 (1.3), $P = 0.03$, Fig. 1A]. The decline in m-WCAS between H0 and H6 in the nCPAP group was correlated with the m-WCAS value at H0, with a Spearman correlation coefficient of 0.64 ($P = 0.04$). In the control arm, we observed an inverse correlation between the m-WCAS value at H0 and the difference

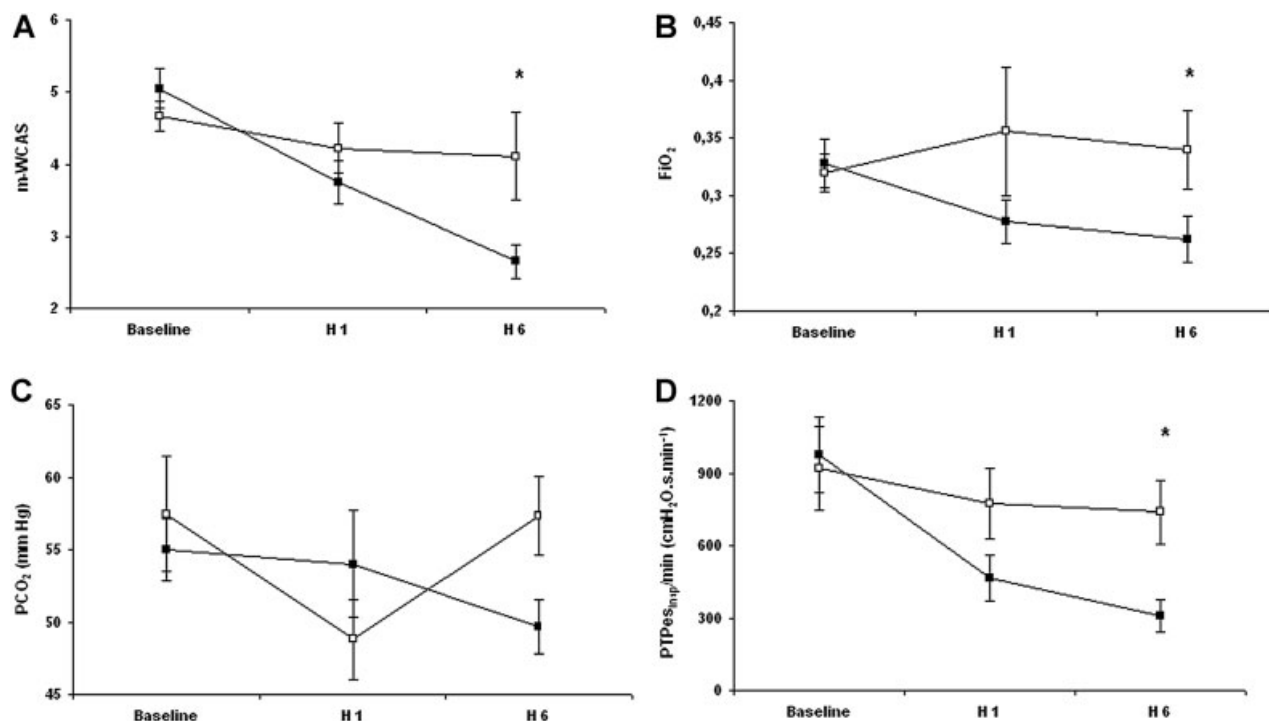


Fig. 1. Respiratory distress parameters at baseline (H0), 1 (H1), and 6 (H6) hr in the nasal continuous positive airway pressure (nCPAP, black squares) and control (white squares) groups. A: Change in respiratory distress as assessed by the modified Wood's clinical asthma score (m-WCAS). **B,C:** Change in the fraction of inspired oxygen (FiO₂) and transcutaneous PCO₂. **D:** Change in an index of respiratory work, the inspiratory muscle pressure–time product per minute (PTPes_{insp}/min). Values are expressed as mean (SEM). * $P < 0.05$ using a linear mixed model for longitudinal data.

between m-WCAS at H0 and H6, with a Spearman correlation coefficient of -0.76 ($P = 0.02$; Fig. 2; Table 2).

At H6, the respiratory rate in the nCPAP and control groups did not differ from the baseline values. The FiO_2 required to maintain SpO_2 within the target range remained stable from H0 to H6 in the two groups. However, the linear model revealed a significant difference in FiO_2 variation during the study period between the groups [-7 (10) in the nCPAP group vs. $+5$ (15) in the control group, $P = 0.049$, Fig. 1B].

Heart rate and mean arterial pressure showed no variation in either group.

Gas Exchanges

PCO_2 decreased in the nCPAP group, from 55 (2) torr at H0 to 49 torr (2) at H6; $P = 0.047$. In the control group, PCO_2 remained comparable (Fig. 1C). However, no inter-group difference was revealed in the linear model.

Esophageal Pressure Measurements

Placement of the neonatal esophageal balloon catheter was not possible in one patient because it induced excessive agitation. In three other patients, the recordings could not be interpreted, probably because of unsatisfactory positioning. Thus, the recordings were analyzed in 15 patients, eight in the nCPAP group and seven controls.

At H6, we observed a decrease in $PTP_{es}/breath$ and PTP_{es}/min in the nCPAP group as compared with baseline values. In the control group, the variables at H0 and H6 did not differ. The linear model confirmed the greater reductions in $PTP_{es,insp}/breath$ [-9.7 (5.7) vs.

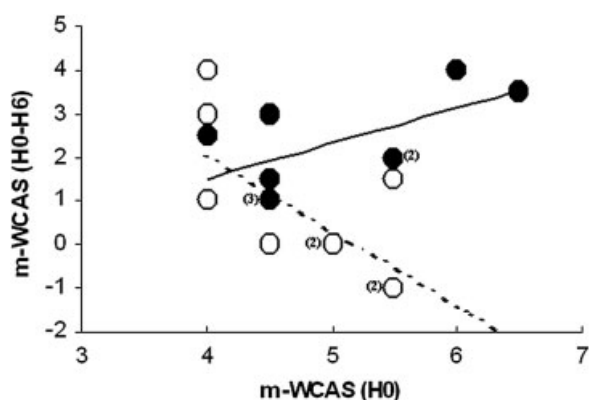


Fig. 2. Relationship between the baseline respiratory distress score using the modified Wood's clinical asthma score [m-WCAS (H0)] and its change after 6 hr [m-WCAS (H0-H6)] in the nasal continuous positive airway pressure (nCPAP, black circles) and control (white circles) groups. The correlation was significant in both groups, positive in nCPAP (solid line) and inverse in controls (dashed line).

TABLE 2—Change in Respiratory Distress in the Nasal Continuous Positive Airway Pressure (n-CPAP) and Control Groups, Assessed by the Difference in Clinical, Gas Exchange, and Esophageal Pressure Measurements Between Baseline (H0) and After 6 hr (H6)

H0-H6	nCPAP, n = 10	Controls, n = 9
m-WCAS	2.4 (0.4) ^a	0.5 (0.4) ^b
RR (breaths/min)	7 (4)	1.3 (4)
SpO_2 (%)	0.7 (1)	2.4 (3)
FiO_2 (%)	7 (3)	-5 (5) ^b
HR (beats/min)	9 (7)	2 (4)
MAP (mmHg)	-4 (6)	-4 (5)
PCO_2 (torr)	6 (2) ^a	4 (4)
$PTP_{es,insp}/breath$ (cmH ₂ O/s)	10 (2) ^a	1.4 (3) ^b
$PTP_{es,insp}/min$ (cmH ₂ O/s/min)	666 (134) ^a	116 (117) ^b

m-WCAS, modified Wood's clinical asthma score; RR, respiratory rate; SpO_2 , pulse oximetry; FiO_2 , fraction of inspired oxygen; HR, heart rate; MAP, mean arterial blood pressure; PCO_2 , partial pressure of carbon dioxide measured on capillary blood gas sampling; $PTP_{es,insp}$, inspiratory muscle pressure-time product.

Values are expressed as mean (SEM).

^a $P < 0.05$ versus H0.

^b $P < 0.05$ versus nCPAP.

-1.4 (8.2); $P = 0.04$] and $PTP_{es,insp}/min$ [-666 (402) vs. -116 (352); $P = 0.015$] in the nCPAP group between H0 and H6 (Fig. 1D).

Switching a Patient From One Group to the Other

A switch to the other treatment group for a worsening clinical score $>30\%$ concerned only the patients initially included in the control group: 4/9 versus 0/10 ($P = 0.032$). The change in group of the four patients occurred 1, 3, 4, and 5 hr after the protocol had begun. After nCPAP was started in these infants, m-WCAS improved from 5.8 (1) to 2.5 (1.5); $P = 0.039$. An illustration of the favorable effect of nCPAP on Pes swings is given in Figure 3. The severity of respiratory distress at admission and the anthropometric characteristics of this patient subgroup were not different from those of the rest of the cohort.

Patient Outcomes

None of the infants had to be intubated and none presented pneumothorax. In the nCPAP group, nCPAP lasted 72 (11) hr and hospital stay was 5 (0.5) days. In the control group, nCPAP lasted 112 (12) hr for the four patients that changed groups during the study. The hospital stay for the control group was 5 (0.5) days.

DISCUSSION

This randomized, controlled study demonstrated that nasal CPAP reduced the clinical respiratory distress

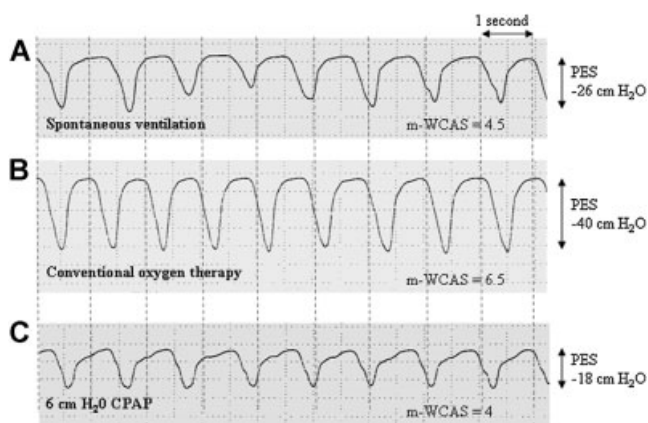


Fig. 3. Esophageal pressure (Pes) swings and concomitant respiratory distress score (m-WCAS) in an infant switched from oxygen therapy to nasal continuous positive airway pressure (nCPAP). At baseline, m-WCAS was 4.5 and Pes swings reached 26 cmH₂O during inspiration (A). The infant was randomized into the control group and received conventional oxygen therapy. After 1 hr, m-WCAS increased to 6.5 and a new recording of Pes swings showed a dramatic increase to nearly 40 cmH₂O (B). Delivery of +6 cmH₂O nCPAP for 1 hr induced decreases in both Pes swings (18 cmH₂O) and the respiratory distress score (C).

score, the need for oxygen, and the respiratory muscle load in <6-month-old infants presenting acute severe RSV bronchiolitis. We observed that the higher the initial m-WCAS was, the greater the decrease in score when the infant was treated by nCPAP. Conversely, in infants who did not benefit from this ventilatory support, the higher the initial m-WCAS score was, the greater the tendency toward aggravation.

What this Study Adds

The current literature offers little justification for CPAP use except in cases of acute viral bronchiolitis with apnea.^{7,24} However, in the first randomized, control trial, Thia et al.¹⁰ confirmed the reduction in CO₂ under CPAP. Although in our study we observed a similar drop in CO₂ after 6 hr of nCPAP, the dispersion in the values did not allow us to confirm a significantly different change compared with the group treated by oxygen therapy. Our study is original because it demonstrates an improvement in the clinical signs of respiratory distress that can objectively be attributed to the reduced inspiratory work under nCPAP.

Practical CPAP Use in Acute Viral Bronchiolitis

The standard pressure for first-intention CPAP in infants is between 4.5 and 6 cmH₂O.^{5,8,9,11} We used a predetermined pressure of 6 cmH₂O because it

appeared both effective and safe in our pilot study.¹⁷ The effect of three increasing levels of nCPAP on breathing pattern, gas exchange, PEEPi and respiratory muscle work was recently reported.¹³ In this study, the use of an nCPAP level of 7 cmH₂O was associated with the greatest reduction in respiratory work, as assessed by esophageal and diaphragmatic pressure–time product per minute. However, the increase in CPAP pressure from 7 to 10 cmH₂O produced a further rise in respiratory muscle activity to overcome the high pressure applied. Precise adjustment of the pressure level to the individual PEEPi is not easy to achieve at the bedside of infants with acute bronchiolitis, because it requires combining esophageal and gastric pressure measurement with airflow monitoring.²⁵

Study Limitations

Esophageal pressures were assessed using an orally inserted catheter with an external diameter of 1.9 mm. In these conditions, the effect of this probe on inspiratory muscle work was probably modest,²⁶ but this was not specifically evaluated. The difference in equipment used in the two groups precluded a blind study, and the small sample and short evaluation period were also limitations. Several authors, ourselves included, have reported that CPAP failure in the infant with acute respiratory distress occurs very early on, and always within the first 6 hr of management.^{27–30} Our principal criterion, the change in m-WCAS, was not as powerful as the need for intubation, which generally serves as a reference in cases of acute respiratory distress. With our study design, we were unable to determine whether the infants switched to the nCPAP group would have eventually been intubated if they had remained under oxygen therapy.

Perspectives

Although the “CPAP effect” seems favorable for managing severe bronchiolitis, the problem of choosing the optimal interface has not been resolved. Several interfaces have been suggested, like the nasal mask^{7,11} and the bi-nasal cannula used in this study.^{5,8,9,17,21} Other interfaces seem promising, especially the helmet, which seems to be an effective and well-tolerated solution for this age and weight category.^{30–32} Also, the high-flow nasal cannula (HFNC) is very easy to put into place and is relatively inexpensive.^{33,34}

A meta-analysis recently underlined the benefits of a mixture of air and helium, heliox, for signs of respiratory distress.² These works open new perspectives for research to determine whether the combined use of CPAP and heliox can be validated for treatment of severe acute bronchiolitis in the young infant.²¹

CONCLUSION

nCPAP rapidly decreased the inspiratory muscle work in young infants with acute bronchiolitis. Improvement in the respiratory distress score at 6 hr was proportional to the initial clinical severity, suggesting the importance of rapid initiation of nCPAP in the more severe forms of the disease.

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