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Nasal high-frequency oscillatory ventilation and CO_2 removal: A randomized controlled crossover trial

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Abstract

Objective: To compare short-term application of nasal high-frequency oscillatory ventilation (nHFOV) with nasal continuous positive airway pressure (nCPAP).

Working Hypothesis: nHFOV improves CO_2 removal with respect to nCPAP in preterm infants needing noninvasive respiratory support and persistent oxygen supply after the first 72 h of life.

Study Design: Multicenter non-blinded prospective randomized crossover study.

Patient Selection: Thirty premature infants from eight tertiary neonatal intensive care units, of mean ± SD 26.4 ± 1.8 weeks of gestational age and 921 ± 177 g of birth weight.

Methodology: Infants were randomly allocated in a 1:1 ratio to receive a starting treatment mode of either nCPAP or nHFOV delivered by the ventilator CNO (Medin, Germany), using short binasal prongs of appropriate size. A crossover design with

four 1-h treatment periods was used, such that each infant received both treatments twice. The primary outcome was the mean transcutaneous partial pressure of CO_2 ($TcCO_2$) value during the 2-h cumulative period of nHFOV compared with the 2-h cumulative period of nCPAP.

Results: Significantly lower $TcCO_2$ values were observed during nHFOV compared with nCPAP: 47.5 ± 7.6 versus 49.9 ± 7.2 mmHg, respectively, $P = 0.0007$. A different $TcCO_2$ behavior was found according to the random sequence: in patients starting on nCPAP, $TcCO_2$ significantly decreased from 50.0 ± 8.0 to 46.6 ± 7.5 mmHg during nHFOV ($P = 0.001$). In patients starting on nHFOV, $TcCO_2$ slightly increased from 48.5 ± 7.8 to 49.9 ± 6.7 mmHg during nCPAP ($P = 0.13$).

Conclusions: nHFOV delivered through nasal prongs is more effective than nCPAP in improving the elimination of CO_2.

KEYWORDS

nasal continuous positive airway pressure, nasal high-frequency oscillatory ventilation, preterm infants

1 | INTRODUCTION

Very low birth weight (VLBW) infants usually develop respiratory distress syndrome (RDS) due to lung immaturity, surfactant deficiency, and immature respiratory control mechanisms.[1] Even though mechanical ventilation is frequently lifesaving, complications are common[2]: tracheal intubation and mechanical ventilation are associated with ventilator-induced lung injury (VILI) and airway inflammation, leading to bronchopulmonary dysplasia (BPD). The mechanisms of this injury involve alveolar over distension, the presence of shear forces, and the release of pro-inflammatory cytokines,[3] moreover prolonged duration of intubation and mechanical ventilation is associated with an increased risk of death or survival with neurologic impairment.[4] In an effort to reduce VILI and consequently BPD in premature infants, there has been a trend toward increased use of noninvasive forms of respiratory support: nasal continuous positive airway pressure (nCPAP), nasal intermittent positive-pressure ventilation (nIPPV), high-flow nasal cannula (HFNC), nasal high-frequency oscillatory ventilation (nHFOV).[1,2,5–9] In this sense, nCPAP is an alternative to intubation and a meta-analysis focused on the use of early nCPAP versus intubation and ventilation showed that nCPAP reduces the risk of BPD.[10] Nonetheless, use of nCPAP in the delivery room may fail in extremely low birth weight infants, with 34-83% of such infants requiring subsequent intubation. Furthermore, post-extubation support with nCPAP in these infants is associated with a 16-40% failure rate at 1 week.[4–7] High-frequency oscillatory ventilation (HFOV) in intubated neonates is frequently used in neonatal intensive critical care. The experience in the use of invasive HFOV and the recommended noninvasive approach has somehow pushed clinicians to combine both concepts: noninvasive HFOV should provide the advantages of HFOV (no need for synchronization, high CO_2 removal, less volutrauma/barotrauma)*[11] and nCPAP (noninvasive interface, increase in functional residual capacity allowing oxygenation to improve). Thus, nHFOV could be useful to avoid invasive ventilation and its complications. Moreover, given the HFOV physical characteristics, nHFOV could hypothetically be more efficient than other types of noninvasive respiratory support in certain clinical conditions.[12,13] In fact, nCPAP stabilizes the surfactant deficient alveoli and improves oxygenation, but does not necessarily improve alveolar ventilation or partial pressure of carbon dioxide elimination.[2]

Objective of this study is to evaluate whether short-term application of nHFOV compared with nCPAP in preterm infants needing noninvasive respiratory support and persistent oxygen supply after the first 72 h of life and despite surfactant replacement therapy would improve CO_2 removal.

2 | MATERIALS AND METHODS

We designed a Multicenter non-blinded prospective randomized crossover study, conducted from January 2016 until April 2017 in eight tertiary neonatal intensive care units (NICUs) of Italy (*n* 7) and Lithuania (*n* 1). This study was registered at http://www.clinicaltrials.gov (ID:NCT 02772835) and approved by the Ethics Committee of each participating center. Written parental consent was obtained prior to study entry.

Eligible patients were preterm infants with birth weight (BW) <1500 g and/or gestational age (GA) <32 weeks, who still needed nasal CPAP (4-8 cm H_2O) with fraction of inspired oxygen (FiO_2) more than 0.21 to keep oxygen saturation (SpO_2) 90-95%, after the first 72 h of life and despite surfactant replacement therapy. A loading dose of intravenous caffeine citrate (20 mg/kg) was given immediately after admission to the NICU, followed by a daily maintenance dose of 5-10 mg/kg.

Exclusion criteria included active medical treatment for patent ductus arteriosus (PDA) or culture proven sepsis, major congenital malformations, genetic syndromes, or postoperative recovery period of <24 h.

Infants were randomly allocated in a 1:1 ratio to receive a starting treatment mode of either nCPAP (4-8 cm H_2O, with the same CPAP level used prior to entering into the study) or nHFOV with the following starting parameters: mean airway pressure level: 4-8 cm H_2O (at the same CPAP level used prior to entering into the study); Flow: 7-10 L/min (providing the desired mean airway pressure level); Frequency: 10 Hz, Amplitude: set interval 10, I:E:1:1. All respiratory support was delivered by the ventilator CNO (Medin, Olching, Germany), using short binasal prongs of appropriate size (Size: xsmall, small, medium, large; Diameter: 3.0, 3.5, 4.1, 4.7 mm, respectively; Medin). FiO_2 was adjusted by an investigating physician to obtain a targeted SpO_2 of 90-95%. Randomly permuted blocks were used. The random allocation sequence was generated using ralloc.ado version 3.2.5 in Stata 13 (Stata-Corp, College Station, TX). We used a crossover design with four 1-h treatment periods, such that each infant received both treatments twice.

The primary outcome was the mean transcutaneous partial pressure of CO_2 ($TcCO_2$) during the 2-h period of nHFOV compared with the 2-h period of nCPAP.

All the infants were studied in the supine position, were maintained in the incubator throughout the study, and received the standard routine care by the primary care team.

Vital signs of each enrolled infant were monitored by pneumocardiogram and pulse oximeter. Moreover, at study initiation, a transcutaneous carbon dioxide and oxygen monitor (TCM4 shuttle, Radiometer, Copenhagen, Denmark) was placed on each studied infant. Cerebral (cer-rSO_2) and renal (ren-rSO_2) tissue oxygenation was measured by near-infrared spectroscopy (NIRS; INVOS 5100C cerebral/somatic oximeter, Covidien, Boulder, CO) as additional variable during the study period, based on the instrument availability in each participating center. Apnoeic episodes were defined as absence of thoracic impedance change for a minimum of 20 s. Bradycardic episodes were defined as persistent heart rate <80 beats per minute for a minimum of 10 s. Significant desaturation episodes were defined as persistent SpO_2 values <80% for a minimum of 10 s. Noninvasive blood pressure was detected with appropriate sized neonatal blood pressure cuff, 30 min after the beginning of the second treatment block either on nCPAP and nHFOV.

An investigating physician was dedicated to record on a respiratory sheet continuously at 1-min intervals directly from the monitor $TcCO_2$, transcutaneous partial pressure of O_2 (TcO_2), heart rate, respiratory rate, SpO_2, FiO_2, cer-rSO_2, ren-rSO_2, CPAP, and amplitude levels (in cm H_2O) as displayed on the CNO screen, episodes of apnea, bradycardia, and significant desaturation. Respiratory frequency was measured by electrodes placed on the chest. In particular, the physician ensured the accuracy of the spontaneous respiratory rate measurements checking the correspondence between the numbers displayed on the monitor and patients' chest movements. Pain and discomfort were assessed hourly by the nursing staff using the neonatal pain, agitation, and sedation scale.[14]

Immediately before entering the study, a capillary blood gas analysis was performed in order to test the reliability of the $TcPCO_2$ data. The study would have been terminated earlier if the patient had developed any signs of intolerance, including an increase of >50% in the number of episodes of apnea or bradycardia compared with the pre-study baseline noted 1 h preceding study entry, or increased supplemental $FiO_2 > 0.3$ from pre-study baseline for at least 15 min.

The physiological, respiratory, and hemodynamics variables have been compared between the two treatment groups (nCPAP and nHFOV) considering the cumulative periods (2 h of nCPAP vs 2 h of nHFOV), by paired *t* test. To allow equilibration, we grouped and analyzed data points from the last 20 min of each treatment block, as previously described in a similar four-period crossover study comparing Bi-level CPAP versus CPAP alone.[5]

A sample size of 30 has been calculated to detect a mean difference of 2 mmHg $TcCO_2$ based on a two-tailed *P* value of 0.05, power of 0.9, and a within-patient SD of 3 mmHg. Clinical characteristics of the studied infants, physiological, respiratory, and hemodynamics variables have been described using mean values and standard deviation. Data were analyzed using Stata software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and commercial statistical software (GraphPad Prism V.5.0a; Chicago, IL). Paired two-tailed *t* tests were employed, and *P* values <0.05 were considered statistically significant.

3 | RESULTS

During the study period, 62 VLBW infants were screened; 30 of them were enrolled and were randomized to receive a starting treatment mode of either nCPAP or nHFOV (Table 1 and Figure 1). All recruited newborns have completed the study because they have not developed any sign of intolerance. There were no episodes of apnea during the study period and no significant differences in

TABLE 1 Baseline data of infants at the study entry

	Mean ± SD
Gestational age, weeks	26.4 ± 1.8
Birth weight, g	921 ± 177
Postnatal age at the study entry, days	26.6 ± 15.2
Weight at the study entry, g	1168 ± 344
CPAP pre-study, cm H_2O	6.0 ± 1.2
FiO_2 pre-study	0.29 ± 0.04
$TcCO_2$ pre-study, mmHg	50.6 ± 8.0
TcO_2 pre-study, mmHg	54.7 ± 8.1
O_2 saturation pre-study (%)	92.2 ± 2.2

CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; $TcCO_2$, transcutaneous partial pressure of CO_2; TcO_2, transcutaneous partial pressure of O_2.

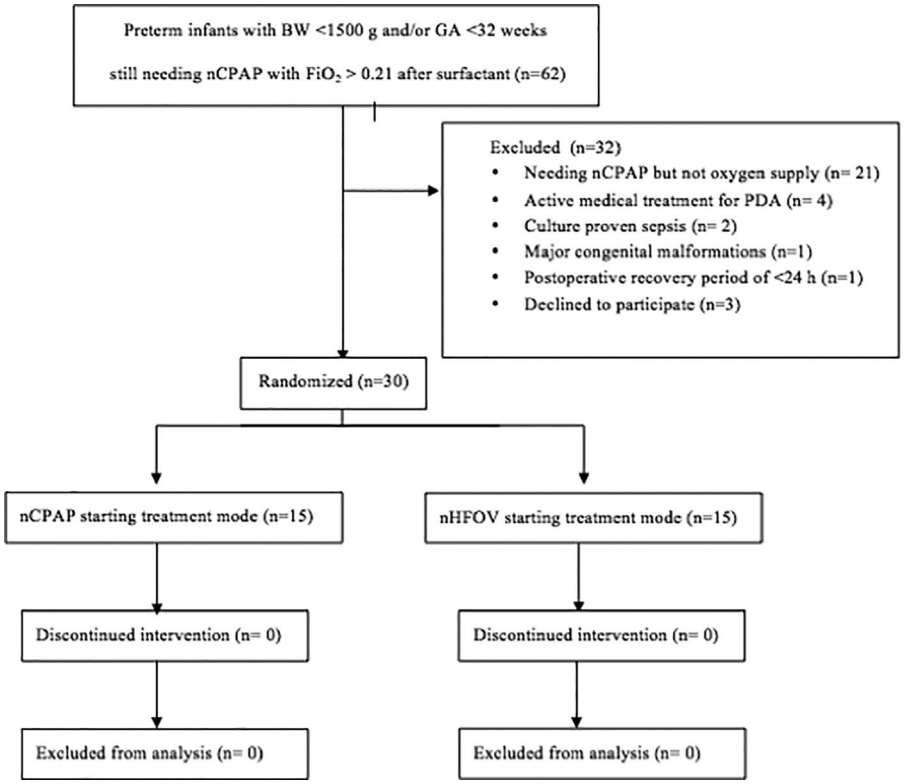

FIGURE 1 Participant's CONSORT flow diagram

desaturation or bradycardia events between the two treatment groups (Table 2). The capillary blood gas analysis performed before the beginning of the study confirmed the reliability of the $TcPCO_2$ data in all studied infants.

Significantly lower $TcCO_2$ values as well as a trend for higher values of TcO_2 and SpO_2 were observed during nHFOV compared to nCPAP (Table 2 and Figure 2). Significantly lower $TcCO_2$ values during nHFOV period (48.1 ± 7.1 mmHg) with respect to nCPAP period (49.4 ± 7.0 mmHg, $P = 0.002$) were observed even without considering the four extreme outliers (ie, the subjects showing a difference ≥8 mmHg between the two treatment blocks).

A different $TcCO_2$ behavior was found according to the random sequence: in patients starting on nCPAP, $TcCO_2$ significantly decreased from 50.0 ± 8.0 mmHg to 46.6 ± 7.5 mmHg during nHFOV ($P = 0.001$). In patients starting on nHFOV, $TcCO_2$ slightly increased from 48.5 ± 7.8 mmHg to 49.9 ± 6.7 mmHg during nCPAP ($P = 0.13$) (Figure 3).

Other physiological and hemodynamic variables, including heart rate, respiratory rate, and blood pressure were similar among treatment groups, as well as FiO_2 and mean airway pressure as displayed on the ventilator screen (Table 2). Cer-rSO_2 and ren-rSO_2 tissue oxygenation were available for nine patients only: a trend for higher values of ren-rSO_2 was observed in nHFOV treatment group compared to nCPAP (Table 2). The starting parameters during nHFOV periods (Frequency: 10 Hz, Amplitude: 10) remained unchanged throughout the 2 h. The mean corresponding ΔP values shown on the ventilator screen were 7.7 ± 1.0 cm H_2O.

4 | DISCUSSION

This short-term crossover study was designed to test a simple physiological hypothesis, that is, that nHFOV would improve ventilation and lower CO_2, as reflected in $TcCO_2$ values, when compared to nCPAP in premature infants needing noninvasive respiratory support and persistent oxygen supply after the first 72 h of life and despite surfactant replacement therapy. The results showed improved ventilation during nHFOV since $TcCO_2$ values were significantly lower than during nCPAP. High-frequency oscillatory pulses have been shown to stimulate respiratory effort in adult patients with central apnea when delivered to the upper airway by a nasal mask.[13] We did not observe differences in the spontaneous respiratory rate between the two treatment blocks. Since CO_2 elimination under nHFOV is also provided in the upper airway,[15] a possible mechanism responsible for the significantly lower $TcCO_2$ values during nHFOV was the washout of the upper airway dead space. However, we have to keep in mind that the mean postnatal age at study entry was 26.6 ± 15.2 days and all infants had additional oxygen requirements. Some of the infants might reflect an "incoming BPD group," this aspect being particularly relevant since pressure transmission and oscillatory dumping during high frequency ventilation mainly depends on stiffness of the interface and the lung disease (restrictive vs emphysematous). Other than the washout of the upper airway dead space, different physiologic effects according to the present lung disease state cannot be excluded in explaining the improved ventilation during nHFOV.

TABLE 2 Summary of vital signs, respiratory, hemodynamics, and discomfort parameters

	nCPAP (*n* 30)	nHFOV (*n* 30)	*P* value
$TcCO_2$, mmHg	49.9 ± 7.2	47.5 ± 7.6	0.0007
TcO_2, mmHg	55.2 ± 13.6	56.3 ± 11.0	0.55
Respiratory rate, brpm	59.4 ± 8.8	59.9 ± 7.4	0.70
Heart rate, bpm	162.7 ± 10.7	163.5 ± 12.1	0.57
Mean airway pressure (cm H_2O)	5.6 ± 0.7	5.7 ± 0.7	0.10
FiO_2	0.29 ± 0.04	0.29 ± 0.04	0.84
O_2 saturation (%)	92.0 ± 2.4	92.8 ± 1.9	0.08
Desaturation episodes	0.5 ± 1.4	0.3 ± 0.5	0.40
Bradycardia episodes	0.1 ± 0.2	0.1 ± 0.2	0.57
Systolic blood pressure, mmHg	65.3 ± 6.9	65.9 ± 7.7	0.73
Diastolic blood pressure, mmHg	39.6 ± 6.3	39.9 ± 8.9	0.87
Mean blood pressure, mmHg	47.6 ± 5.4	47.8 ± 8.6	0.93
Cer-rSO_2 % (*n* 9)	71.5 ± 6.0	71.8 ± 5.5	0.53
Ren-rSO_2 % (*n* 9)	63.7 ± 9.3	65.5 ± 7.5	0.11
N-PASS	2.3 ± 0.9	2.6 ± 1.2	0.14

bpm, beats per minute; brpm, breaths per minute; Cer-rSO_2, cerebral tissue oxygenation; FiO_2, fraction of inspired oxygen; nCPAP, nasal continuous positive airway pressure; nHFOV, nasal high-frequency oscillatory ventilation; N-PASS, neonatal pain, agitation, and sedation scale; Ren-rSO_2, renal tissue oxygenation; $TcCO_2$, transcutaneous partial pressure of CO_2; TcO_2, transcutaneous partial pressure of O_2.

Even though nHFOV may provide a higher mean airway pressure due to the additional oscillatory delta pressure, potentially resulting in a better and longer lasting lung recruitment and explaining the difference in $TcCO_2$ behavior according to the random sequence, no significant differences in the values of mean airway pressure were found between nCPAP and nHFOV periods, as shown in Table 2. We also found no effects of nHFOV on heart rate, blood pressure or oxygenation. There were no episodes or apnea during the study period and no significant differences in desaturation or bradycardia events between the two treatment groups.

Most of previous studies used a single nasopharyngeal tube as the interface to deliver nHFOV: Colazay et al[1] reported their experience in 14 VLBW infants with respiratory failure and showing that this technique can lower pCO_2. Van der Hoeven et al[16] investigated the efficacy of nHFOV in an heterogeneous group of 21 infants with moderate respiratory insufficiency and they showed it was effective in reducing pCO_2. The use of nHFOV is currently steadily increasing in NICUs, especially in Europe[8] and Canada[12] even though no clear evidence exists about its clinical usefulness.

Recently the efficacy of nHFOV versus nCPAP[17] or bi-phasic nCPAP has been evaluated by using different interfaces, that is, binasal prongs or nasal masks in VLBW infants: Mukerji et al[17] aimed to assess the feasibility of a larger trial comparing failures rates when using nHFOV versus bi-phasic-CPAP as rescue non invasive respiratory support in preterm infants requiring escalation from CPAP. Failure of assigned noninvasive respiratory support mode was lower with nHFOV, although not statistically significant. Moreover there was no significant drop in pCO_2 levels before and after rescue

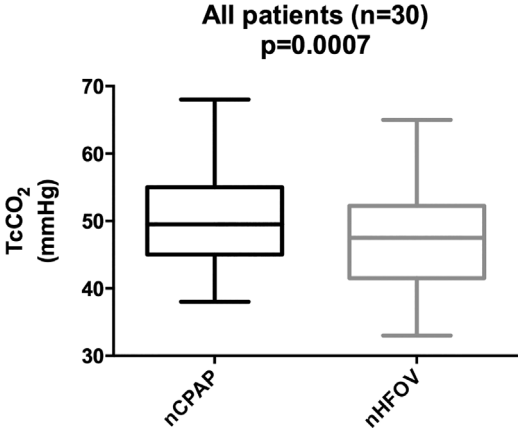

FIGURE 2 Box and whisker plot of $TcCO_2$ in the 2 h of nCPAP or nHFOV in all patients

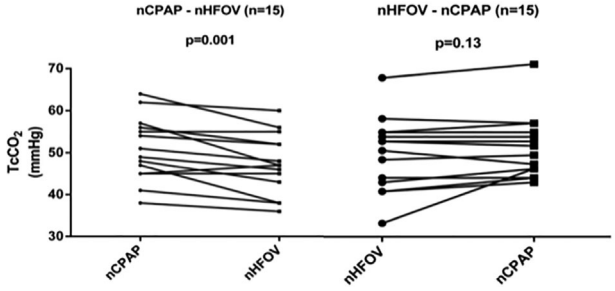

FIGURE 3 $TcCO_2$ in the 2 h of nCPAP or nHFOV in each sequence

nHFOV.[18] In a recent randomized controlled study, nHFOV significantly reduced the need for invasive mechanical ventilation as compared with nCPAP in preterm infants with moderate-severe RDS after surfactant administration via INSURE method, although no data on pCO_2 behavior are reported.[19]

Regarding the respiratory setting adopted in our experience, amplitude and frequency adjustments were not made during the study period. There are no standard parameters for nHFOV in vivo at the moment: in fact most of the studies report the use of nHFOV delivered by different machines for invasive HFOV. In our study we used CNO, a machine designed to deliver noninvasive respiratory support specifically. The CNO ventilator is limited in the maximum amplitude it can generate, which in turn limits the tidal volume delivered: we decided to use the maximum power of amplitude, that is, 10 in order to overcome the high resistance of the upper airways. The mean corresponding ΔP value measured in our study was limited (7.7 ± 1.0 cm H_2O), compared to the ΔP values reported in other experiences and provided by different ventilators, that is, Infant Star[1] or VN500.[18] Frequency has been set at 10 Hz, instead of 15 Hz, to increase the duration of inspiratory time, and then the corresponding tidal volume delivery. Interestingly, this is the same value of frequency set by Zhu et al[19] in their recent study comparing the effect of nHFOV delivered by CNO with nCPAP. Another randomized crossover trial did not demonstrate an increased efficacy of nHFOV compared with nCPAP for CO_2 clearance in premature infants. Moreover the Authors found a high failure rate for nHFOV as noninvasive respiratory support.[20] Nevertheless, significant differences exist between this latter study and our experience: a) the age at enrolment: the first week of life vs three weeks of life; b) the machine used to generate nHFOV: different neonatal ventilators (Sophie, Stephan, Gaggenbach, Germany, and Leoni plus, Heinen + Lowenstein, Bad Ems, Germany) versus just one ventilator able to deliver noninvasive respiratory modes only (CNO Medin, Germany) and producing high-frequency oscillation by flow interruption with cyclic opening-closure of the end expiratory valve; c) the interface adopted in the studied patients: bi-nasal prongs or nasal masks versus only bi-nasal prongs of right size; and d) the modality of obtaining the primary outcome (pCO_2 behavior): through arterial or arterialized blood gas analysis versus $TcCO_2$ data. This is an important aspect to consider: the decrease in pCO_2 in the study by Colaizy et al[1] was not corroborated by $TcCO_2$ levels, which do not show a similar decrease. It is possible that the heel prick itself may have increased respiratory drive and led to some transient hyperventilation causing a decrease in the blood PCO_2 level. Even though in a crossover design both periods are equally affected, we have chosen a more robust parameter such as $TcCO_2$ monitoring instead of blood pCO_2 levels to evaluate the efficacy of nHFOV in increasing ventilation.

Interestingly, even though a significant decrease of $TcCO_2$ was observed during nHFOV with respect to nCPAP in all patients, a different behavior was found according to the random sequence: in the patients starting on nCPAP, $TcCO_2$ significantly decreased during nHFOV while in patients starting on nHFOV, $TcCO_2$ slightly increased during nCPAP. This time-dependent effect might be related to a "long-acting" effect of nHFOV on pCO_2 levels. Although we only considered the last 20 min of each 1-h period for the final analysis of the data (just to allow for equilibration), it is possible that the effect of lowering pCO_2 during 1 h of nHFOV is partly maintained also during the following 1 h of nCPAP.

Our study's strengths include a rigorous protocol. We exposed the subjects to a uniform intervention for a standardized period of time and all the data have been observed directly by an experienced neonatologist and manually recorded on a respiratory sheet. The 2-h exposure to nHFOV was well tolerated by all our patients without any adverse effects and was effective in reducing $TcCO_2$. The results of this study demonstrate that nHFOV delivered through nasal prongs is more effective than nCPAP in improving CO_2 elimination in premature infants who still require noninvasive respiratory support, in a short period of time.

Major limitations of our study are its small sample size and its short study time. The analysis of only short-term physiological effects in stable premature infants does not consent any conclusions about important long-term outcomes. Future studies of long-term nHFOV should be undertaken to test the ability of this technique to decrease the noninvasive respiratory support failure during both the acute phase of RDS and/or the post-extubation period, as compared to nCPAP alone and/or to other forms of noninvasive respiratory support.

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DECLARATIONS

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CONFLICTS OF INTEREST

None declared.

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