Effect of Randomisation of Nasal High Flow Rate in Preterm Infants

Journal:	*Pediatric Pulmonology*
Manuscript ID	PPUL-19-0207.R2
Wiley - Manuscript type:	Original Article: Neonatal Lung Disease
Date Submitted by the Author:	n/a
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Keywords:	Neonatal Pulmonary Medicine, Respiratory Technology, Oxygenation and Therapy
Other Keywords:	Electrical impedance tomography, respiratory inductance plethysmography, ventilation distribution, CPAP, high flow nasal cannula
Abstract:	Objective: To assess the effect of nasal high flow cannula (NHF) on end expiratory lung volume (EEL), continuous distending pressure (CDP) and regional ventilation distribution in preterm infants. Design: Prospective observational clinical study with randomly applied NHF rates. Patients and Setting: Preterm infants requiring continuous positive airway pressure (CPAP) respiratory support in a Neonatal Intensive Care Unit. Interventions: Infants were measured on randomly applied flow rates at 2, 4 and 6 L/min of NHF and compared with bubble CPAP (BCPAP). Measurements and Results: Regional ventilation distribution and EEL were measured using electrical impedance tomography (EIT) and respiratory inductance plethysmography (RIP) in 24 preterm infants (31.19±1.17 weeks corrected age). Changes in CDP were measured from the oesophagus via the nasogastric (NG) tube. Physiological variables were also recorded. There were no differences in ventilation distribution, EEL or CDP between CPAP and NHF ($p>0.05$). However, the physiological variables of FiO_2 ($p=0.01$) and SpO_2/FiO_2 ($p<0.01$) were improved on CPAP compared with NHF. Conclusion: NHF applied in random order with flow rates between 2-6 L/min was equally as good as CPAP in maintaining EEL and ventilation distribution in stable preterm infants. Overall oxygenation was better on

	CPAP compared to NHF.

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Key Words: Electrical impedance tomography; respiratory inductance plethysmography; ventilation distribution; CPAP; high flow nasal cannula

ABSTRACT

Objective: To assess the effect of nasal high flow cannula (NHF) on end expiratory lung volume (EEL), continuous distending pressure (CDP) and regional ventilation distribution in preterm infants.

Design: Prospective observational clinical study with randomly applied NHF rates.

Patients and Setting: Preterm infants requiring continuous positive airway pressure (CPAP) respiratory support in a Neonatal Intensive Care Unit.

Interventions: Infants were measured on randomly applied flow rates at 2, 4 and 6 L/min of NHF and compared with bubble CPAP (BCPAP).

Measurements and Results: Regional ventilation distribution and EEL were measured using electrical impedance tomography (EIT) and respiratory inductance plethysmography (RIP) in 24 preterm infants (31.19±1.17 weeks corrected age). Changes in CDP were measured from the oesophagus via the nasogastric (NG) tube. Physiological variables were also recorded. There were no differences in ventilation distribution, EEL or CDP between CPAP and NHF ($p>0.05$). However, the physiological variables of FiO_2 ($p=0.01$) and SpO_2/FiO_2 ($p<0.01$) were improved on CPAP compared with NHF.

Conclusion: NHF applied in random order with flow rates between 2-6 L/min was equally as good as CPAP in maintaining EEL and ventilation distribution in stable preterm infants. Overall oxygenation was better on CPAP compared to NHF.

Background

Respiratory support is fundamental to the care of the preterm infant, with continuous positive airways pressure (CPAP) the most commonly used respiratory support mode.[1] It is used to decrease the work of breathing, improve functional residual capacity, and reduce regional atelectasis associated with respiratory distress syndrome.[2]

Notwithstanding the acknowledged clinical usefulness of CPAP, respiratory therapy using nasal high flow (NHF) has gained acceptance in many neonatal units as an alternative mode of respiratory support.[3] Perceived benefits of NHF are; ease of application and maintenance,[4] apparent infant comfort,[3] and nurse and parent preference.[5] Heated and humidified gas delivered at high flows (>1L/min), may promote airway mucosa integrity and secretion quality,[6] prevent heat loss and drying of respiratory mucosa,[7,8] and create a flow dependant positive airway pressure.[4,9-14] Washout of nasopharyngeal dead-space has also been proposed as an important mechanism of action.[15,16]

Although randomised controlled trials have demonstrated equal clinical benefit using NHF post extubation compared to CPAP, [17-19] the evidence for the use of NHF as a weaning mode off CPAP is contradictory.[20] Also, significant concerns remain regarding starting flow rate choice; the absence of direct measurement and regulation of the pressure delivered by NHF, and the lack of evidence available on the effect of NHF on ventilation distribution.

Consequently, the purpose of this study was to determine the relationship of randomly applied rates of NHF, on airway pressures, end expiratory level (EEL), regional ventilation distribution and respiratory physiological variables in preterm infants compared with bubble CPAP (BCPAP).

Methods

Study design

In this prospective interventional study, stable preterm neonates requiring respiratory support were measured, initially on BCPAP and then on randomly applied NHF flow rates, to determine the effect of flow rate on lung function.

Subjects

Premature neonates were recruited from a tertiary Neonatal Critical Care Unit (NCCU). Inclusion criteria were; preterm infants aged 28–36 weeks corrected gestational ages, on BCPAP, $FiO_2 \leq 0.25$, nasogastric (NG) feeding tube, and deemed stable by treating medical staff. Exclusion criteria were; lung or cardiovascular anomalies that would substantially affect oxygenation, poor skin integrity, greater than 2 episodes within the last hour of apnoea and/or bradycardia requiring stimulation.

Normal care practice for these infants was dependent on the consultant on service. Most commonly the infants would be weaned off CPAP once they reached 4cmH_2O, either to NHF 6L or to no respiratory support.

The study protocol was approved by the Institute Human Research Ethics Committee. Informed written consent was obtained from the parents.

CPAP system

CPAP was delivered using a BCPAP system consisting of a BC161 delivery system (Fisher and Paykel Healthcare, Auckland, New Zealand) with BC190 nasal tubing and appropriately sized nasal prongs (Fisher & Paykel) with pressures set at 5-8 cmH_2O.

NHF system

The Fisher & Paykel humidified high flow system, consisting of a breathing circuit and the MR850 humidifier, was used with a low resistance neonatal nasal cannula (Fisher & Paykel Healthcare, New Zealand). The infants were studied using either the RT239 circuit with appropriately sized nasal cannula (BC2425) or the updated RT330 circuit with OPT312 nasal cannula.

The infants were measured on flow rates of 2, 4 and 6 L/min through the NHF system with the order of the applied flow rate randomised. Oxygen saturations were targeted within the range of 91-95%.[21] At the conclusion of the study, infants were placed back on their pre-study BCPAP. Infants were nursed in the supine position throughout the study.

If the following 'failure criteria' occurred during the study, the baby was placed back on BCPAP.

- Oxygen requirement > 40%
- > 2 apnoea or bradycardias requiring stimulation to resolve
- Respiratory rate >75 breaths per minute
- Significant increase in the work of breathing as per their observation chart.

Measurements

A Gottingen GoeMF II tomograph (VIASYS Healthcare, Netherlands) was used to measure EEL, amplitudes and regional ventilation distribution. Sixteen conventional electrocardiography (ECG) electrodes (Kendall, Kittycat 1050NPSM, Tyco Healthcare Group, Mansfield, Massachusetts) were placed circumferentially around the infants' chest at nipple level. Whilst on BCPAP, a three-minute Electrical

Impedance Tomography (EIT) measurement was performed with a frame rate of 44 Hz. This period was used for referencing of all following measurements.

Three-minute measurements were then taken 30 minutes after being placed on each of the flow rates of 2, 4 and 6L/min. When assessing ventilation distribution with EIT, a 15-minute stabilisation period should be allowed following any position change.[22] Software provided with the equipment was used for data acquisition and reconstruction of functional relative EIT images.[23] Data were further analysed off-line using Matlab 7.7 (R2008b, The MathWorks Inc, Natick, MA, USA).

EEL is the relative impedance measured at end expiration and is analogous with functional residual capacity. Changes in EEL at the three different flow rates were compared to the pre-study CPAP level for the global, the dependent, and nondependent lung. Regional impedance amplitudes describe the magnitude of regional tidal volume change within an individual over time. Impedance amplitudes were calculated by averaging the impedance differences in each pixel of the measurement period between the end expiratory and end inspiratory periods. To account for the unequal number of pixels analysed in each region of interest (ROI), the average amplitude for each ROI was reported.

A Global Inhomogeneity (GI) index was also calculated for the entire lung region using a tidal EIT image of the end-expiration to end-inspiration differences. The GI index is used as an indicator of inhomogeneous ventilation by describing variations in the pixel values of the tidal EIT image.[24] The higher the GI value the more ventilation inhomogeneity exists.

Data processing and analysis

As preterm infants commonly show irregular breathing patterns, regular sections of breathing were selected for analysis based on previously described criteria.[25]

EIT data were band pass filtered to include the first and second harmonic of the respiratory rate.[26] A cut-off mask of 20% of the peak impedance signal was applied to reduce cardiac interference. [27,28]

A respiratory inductance plethysmograph (Respitrace Q.D.C., CareFusion Corporation, San Diego, USA) with self-calibration functionality was used to determine the volume state of the lung. Two separate stretch bands (XactTrace Disposable Belts (Embla, Denver, USA) were placed with one around the chest circumference at the nipple level and one around the abdomen at navel level. Physiological data generated by the RIP represent the Ribcage (RC), Abdomen (ABD) and overall respiratory (Sum) movement. These RIP signals were fed directly from the Respitrace Q.D.C. to a PowerLab polygraph (ADInstruments Ltd, Dunedin, New Zealand).

Parameters calculated for the overall respiratory RIP signal were the end-expiratory level (RIP_{EEL}) and the amplitude of tidal breathing (RIP_{AMPL}).[29]

To enable analysis of the pharynx and intrathoracic pressure delivered by the NHF system, pressures were recorded from the pharynx ($P_{pharynx}$) and from the oesophagus (P_{oe}). $P_{pharynx}$ was measured using a 6F silastic feeding tube positioned in the pharynx. Oesophageal pressure (P_{oe}) measurements were taken as an indication of end expiratory pressure. The in situ NG tube was connected to a pressure transducer and pulled back to the distal third of the oesophagus to achieve a wave form that was free from cardiac artefact with a negative deflection during inspiration.[30]

To keep the catheter free of gas bubbles which could dampen the pressure trace, saline was infused at a rate of 1 mL/hr. The liquid-filled catheter method has previously been validated using the dynamic occlusion test in preterm infants.[31] Feeds were discontinued for the length of the study. The PowerLab polygraph was used to record the pressure trace.

Data processing and analysis

All PowerLab pressure signals were recorded using the data acquisition and analysis software, LabChart v6.1 (ADInstruments Ltd, Dunedin, New Zealand). All signals were sampled at 1 kHz. $P_{pharynx}$ and P_{oe} were taken at end-expiration and end-inspiration determined by the RIP SUM signal. The pressure rate product (PRP) was calculated using the pressure amplitude multiplied by the measured respiratory rate to give an indication of inspiratory load and effort of breathing.

Respiratory rate (RR), heart rate (HR), and oxygen saturations (SpO_2) were monitored throughout the study using the Dräger Infinity Delta XL monitoring system (Dräger Medical AG & Co. KG, Lübeck, Germany) incorporating Masimo pulse oximeter technology (Masimo Corporation, Irvine, CA, USA). FiO_2 was recorded from the settings of a calibrated air/oxygen blender (Bird 10040A, SensorMedics, San Diego, CA, USA). These variables were manually recorded at the time of each EIT recording. From the collected data the SpO_2/FiO_2 ratio was calculated.[32]

Statistics

Results are described using mean and confidence intervals (CI), or standard deviations (SD) for the biometric data. To account for missing data, mixed linear models (MLM) were used to analyse the impact of NHF flow rate on EEL, regional

ventilation distribution, pressure, RIP signal and physiological variables compared with BCPAP. Post hoc analysis used ANOVA with Bonferroni correction. A p-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS (v15.0, Lead Technologies, Inc., Chicago, IL, USA).

A sample size of 24 infants was enrolled to allow every randomised flow rate combination to be used four times. In previous studies, EIT measurements in infants have an intra-individual coefficient of variance <6%. There is no existing information on the size of the treatment effect.

RESULTS

Twenty-four infants requiring BCPAP respiratory support were included in the study. At the time of the study, the infants had a mean ± SD corrected gestational age of GA of 31.2 ± 1.2 weeks, a study weight of 1260.0 ± 305.3 grams, and a postnatal age of 21.9 ± 12.9 days. All babies were on caffeine citrate. There were equal numbers of males and females. All other demographic details are in Table 1.

There were no significant differences in global or regional EEL ($p>0.09$) between BCPAP and delivered NHF rates (Figure 1a). Similarly, the measurements using RIP showed no overall significant difference between BCPAP and NHF ($p=0.06$). (Figure 1b)

No differences in global or regional impedance amplitudes measured by EIT were detected ($p>0.55$) (Figure 2a) and ventilation distribution measured by GI also remained unchanged ($p=0.27$). The RIP measurements for tidal volume amplitudes were significantly different and showed that BCPAP had similar amplitudes to 2L NHF ($p=0.23$) and significantly higher amplitudes than 4L and 6L ($p<0.01$) (Figure 2b).

The average BCPAP pressure level delivered at entry into the study was 5.8 cmH_2O (± 1.3) with the $P_{pharynx}$ pressures measured at 2.3 (± 1.2) cm H_2O.

There was a clear trend of increasing pharynx pressures with increasing NHF flow rates, but the changes did not reach statistical significance ($P = 0.06$) (Figure 3). The mean pharyngeal pressure at 6L NHF was similar to that delivered by 5.8cm BCPAP.

There was no significant difference between flow rates in terms of inspiratory or expiratory P_{oe}, ($P = 0.13$) (Figure 4a), or in the pressure rate product (PRP) ($p=0.56$) (Figure 4b).

There was a significant increase in FiO_2 ($p<0.01$) on NHF and a drop in SpO_2/FiO_2 ($p<0.01$) between BCPAP and NHF. There were no significant differences for heart rate, RR or SpO_2 (Table 2).

Adverse events

Four infants 'failed' according to the failure criteria of increasing apnoea, bradycardia and oxygen requirements. All babies had been on 5cm CPAP prior to NHF. Two failed when randomised on the 2L/min flow rate, one failed on 4L/min and one failed with handling at the commencement of the study.

- Baby 3 (ex 27+6 wk GA, CA 30+5 wk) 5cm CPAP at 21%, was initially randomised to 2L NHF and failed due to increasing oxygen requirements over the 30 minutes on 2L.
- Baby 10 (ex 25+6 wk GA, CA 30+4 wk) 5cm CPAP 21%, completed 6L NHF and failed whilst on 4L NHF due to gradually increasing oxygen requirements.
- Baby 12 (ex 30 wk GA, CA 31+4 wk) 8cm CPAP 30%, completed 6L NHF and then failed whilst on 2L NHF due to increasing oxygen requirements.
- Baby 24 (ex 27 wk GA, CA 30+3 wk) 5cm CPAP 21%, became bradycardic and apnoeic after the CPAP was removed.

DISCUSSION

In this interventional study, we investigated the physiological effect of randomly applied NHF flow rates of 2, 4 or 6 L/min compared with BCPAP in stable preterm infants. The changes observed in EEL, ventilation distribution and delivered airway pressures were small indicating that NHF was equally as effective as BCPAP. No consistent relationship between applied NHF rates and EEL or ventilation distribution could be shown.

Oxygenation was significantly better on BCPAP than on NHF, particularly at 2L/min, a significant finding considering that oxygen free radicals are implicated in chronic lung disease, retinopathy of prematurity, necrotizing enterocolitis and periventricular leukomalacia.[33]

NHF supports inspiratory effort if the inspiratory flow demand is matched, [34,35] whereas CPAP should maintain a constant positive airway pressure during the inspiratory and expiratory phase. Our measured inspiratory pressures were much less than the delivered pressures and we found large variations in oesophageal pressure measurements, and therefore limited capability to predict CDP.[14]

Despite minimal statistically significant findings for airway pressure, EEL and ventilation distribution, our data represents physiologic plausibility. Both NHF and BCPAP delivered some degree of positive airway pressure with similar pressures delivered, and hence little physiological difference between 5.8cm BCPAP and 6L NHF. Similar to other studies, we demonstrated a linear relationship between pharyngeal pressure and increasing flow, [36 9,13,14,16,37] however the pressures we recorded were less than have been reported previously.[9] These differences may be attributed to a few different factors. The techniques used to measure pharyngeal pressure differed. We recorded pressures with a water filled catheter whereas

Wilkinson et al[9] used a pressure-tip transducer. Additionally, in their study the infants were older and heavier than ours with a median age of 33.6 weeks (29-53) and weight 1.619 kg (0.816 – 4.400) compared to 27.5 weeks and 1.210 kg. This size difference which may impacted on the prong to nare diameter and hence the degree of flow delivery. Wilkinson et al[9] also used a step wise increase in NHF whereas the delivery of NHF in our study was randomised, potentially resulting in de-recruitment at lower flows.

In contrast to our pharyngeal pressure measurements, and to a previous study measuring oesophageal pressure in infants,[38] oesophageal pressures in this study were not proportional to the flow rate administered. Iyer et al [38] reported a significant association between flows of 2-8L delivered step-wise, and oesophageal pressure comprising 93 end-expiratory oesophageal pressures from 19 infants. We only took a single mean pressure measurement for each of our 24 included infants at each flow rate. Given the acknowledged variability in the generation of end expiratory oesophageal pressure,[38] it suggests a larger sample size was needed.

Similar to the findings by Rubin et al,[39] NHF rates of 4 L/min in preterm infants showed the lowest measured PRP. It is likely that at this flow the balance between inspiratory support and positive expiratory pressure was optimal in our cohort of stable preterm infants. Since we did not find great airway pressure changes using NHF rates between 2-6 L/min it was not surprising that no major changes in end expiratory lung volumes (measured by both EIT or RIP) or ventilation distribution were detected – either the measured airway pressure changes were too small to have a measureable impact on EEL or ventilation distribution, or some of these babies may not have required any pressure support at all.

Despite this, FiO_2 and SpO_2/FiO_2 were clearly better on CPAP, with increasing FiO_2 as the NHF rate reduced. Three infants (12.5%) were placed back on CPAP due to apnoea, bradycardia and increasing oxygen requirements, all infants failing on the lower NHF rates.

The improvement in SpO_2/FiO_2 with increasing flow is possibly a result of washout of nasopharyngeal dead space. Alternatively, with CPAP the improved oxygenation may be accompanied by carbon dioxide retention due to lung hyperinflation with increasing flows.[2] It would have been useful to measure carbon dioxide values to help ascertain the exact mechanism of the relationship with oxygenation in the 'nasal washout theory'. As there are studies showing that NHF is associated with a longer length of respiratory support and oxygen duration,[18 40,41] a greater likelihood of developing BPD or death, a delay in establishing oral feeds, increased use of postnatal steroids and prolonged hospitalization in preterm infants,[42] it is imperative that we investigate this further.

Limitations

This study represents a relatively small number of patients performed during a stable clinical phase and does not represent the demands during the acute period post extubation or when CPAP or NHF are used as a primary therapy for RDS. There may have been the potential for de-recruitment over the course of the study but this would have been limited by flow randomisation and the absence of a statistical interaction with the flow order.

Difficulties were encountered with data collection, with noisy signals obtained from the oesophageal monitoring and the EIT. A limitation of high flow use is that the variation of the applied positive airway pressure is affected by air leaks that occur around the nasal cannula and through the mouth.

Although our EIT and RIP results demonstrated similar patterns of change for amplitude and EEL, the results differed in their strength. Although they are both purporting to measure similar information, there are subtle differences between what they measure. RIP measures total thoracic volume but is not able to identify regional changes in ventilation whereas EIT is able to measure relative regional ventilation and not absolute lung volume changes. Due to these differences, there will be some discrepancies between the results they deliver.

What are the implications for NHF therapy?

Although NHF has greater ease of use and improved patient tolerance, it is apparent that too little flow can lead to failure of NHF. The mechanism underlying improved oxygenation with increasing flows remains unclear and little is known about the level of flow required to achieve a clinical and physiological benefit. Further investigations are required to determine what constitutes optimal flow.

Conclusion

In conclusion, NHF was equally as good as CPAP in maintaining EEL and ventilation distribution in stable preterm infants. Although no clear relationship could be determined between delivered flow rate and EEL or regional ventilation distribution, FiO_2 and SpO_2/FiO_2 were clearly better on CPAP, with an increasing FiO_2 requirement as the NHF rate reduced. Further research is required to determine the most appropriate flow rate delivery.

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Figure Legends

Figure 1: Change in EEL for BCPAP and delivered NHF rates measured with EIT (upper) and RIP (lower). No overall significant difference was found between BCPAP and NHF. Mean and CI.

Figure 2: Change in regional impedance amplitude for BCPAP and delivered NHF rates measured with EIT (upper) and RIP (lower). No overall significant difference was found between BCPAP and NHF. Mean and CI

Figure 3: Change in pharyngeal pressure between BCPAP and delivered NHF rates. No overall significant difference was found between BCPAP and NHF. Mean and CI

Figure 4: Change in inspiratory and expiratory oesophageal pressure (upper) and inspiratory load, measured by pressure rate product (lower), between BCPAP and delivered NHF rates. No overall significant difference was found between BCPAP and NHF. Mean and CI

Effect of Randomisation of Nasal High Flow Rate in Preterm Infants

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Key Words: Electrical impedance tomography; respiratory inductance plethysmography; ventilation distribution; CPAP; high flow nasal cannula

ABSTRACT

Objective: To assess the effect of nasal high flow cannula (NHF) on end expiratory lung volume (EEL), continuous distending pressure (CDP) and regional ventilation distribution in preterm infants.

Design: Prospective observational clinical study with randomly applied NHF rates.

Patients and Setting: Preterm infants requiring continuous positive airway pressure (CPAP) respiratory support in a Neonatal Intensive Care Unit.

Interventions: Infants were measured on randomly applied flow rates at 2, 4 and 6 L/min of NHF and compared with bubble CPAP (BCPAP).

Measurements and Results: Regional ventilation distribution and EEL were measured using electrical impedance tomography (EIT) and respiratory inductance plethysmography (RIP) in 24 preterm infants (31.19±1.17 weeks corrected age). Changes in CDP were measured from the oesophagus via the nasogastric (NG) tube. Physiological variables were also recorded. There were no differences in ventilation distribution, EEL or CDP between CPAP and NHF ($p>0.05$). However, the physiological variables of FiO_2 ($p=0.01$) and SpO_2/FiO_2 ($p<0.01$) were improved on CPAP compared with NHF.

Conclusion: NHF applied in random order with flow rates between 2-6 L/min was equally as good as CPAP in maintaining EEL and ventilation distribution in stable preterm infants. Overall oxygenation was better on CPAP compared to NHF.

Background

Respiratory support is fundamental to the care of the preterm infant, with continuous positive airways pressure (CPAP) the most commonly used respiratory support mode.[1] It is used to decrease the work of breathing, improve functional residual capacity, and reduce regional atelectasis associated with respiratory distress syndrome.[2]

Notwithstanding the acknowledged clinical usefulness of CPAP, respiratory therapy using nasal high flow (NHF) has gained acceptance in many neonatal units as an alternative mode of respiratory support.[3] Perceived benefits of NHF are; ease of application and maintenance,[4] apparent infant comfort,[3] and nurse and parent preference.[5] Heated and humidified gas delivered at high flows (>1L/min), may promote airway mucosa integrity and secretion quality,[6] prevent heat loss and drying of respiratory mucosa,[7,8] and create a flow dependant positive airway pressure.[4,9-14] Washout of nasopharyngeal dead-space has also been proposed as an important mechanism of action.[15,16]

Although randomised controlled trials have demonstrated equal clinical benefit using NHF post extubation compared to CPAP, [17-19] the evidence for the use of NHF as a weaning mode off CPAP is contradictory.[20] Also, significant concerns remain regarding starting flow rate choice; the absence of direct measurement and regulation of the pressure delivered by NHF, and the lack of evidence available on the effect of NHF on ventilation distribution.

Consequently, the purpose of this study was to determine the relationship of randomly applied rates of NHF, on airway pressures, end expiratory level (EEL), regional ventilation distribution and respiratory physiological variables in preterm infants compared with bubble CPAP (BCPAP).

Methods

Study design

In this prospective interventional study, stable preterm neonates requiring respiratory support were measured, initially on BCPAP and then on randomly applied NHF flow rates, to determine the effect of flow rate on lung function.

Subjects

Premature neonates were recruited from a tertiary Neonatal Critical Care Unit (NCCU). Inclusion criteria were; preterm infants aged 28–36 weeks corrected gestational ages, on BCPAP, $FiO_2 \leq 0.25$, nasogastric (NG) feeding tube, and deemed stable by treating medical staff. Exclusion criteria were; lung or cardiovascular anomalies that would substantially affect oxygenation, poor skin integrity, greater than 2 episodes within the last hour of apnoea and/or bradycardia requiring stimulation.

Normal care practice for these infants was dependent on the consultant on service. Most commonly the infants would be weaned off CPAP once they reached 4cmH_2O, either to NHF 6L or to no respiratory support.

The study protocol was approved by the Institute Human Research Ethics Committee. Informed written consent was obtained from the parents.

CPAP system

CPAP was delivered using a BCPAP system consisting of a BC161 delivery system (Fisher and Paykel Healthcare, Auckland, New Zealand) with BC190 nasal tubing and appropriately sized nasal prongs (Fisher & Paykel) with pressures set at 5-8 cmH_2O.

NHF system

The Fisher & Paykel humidified high flow system, consisting of a breathing circuit and the MR850 humidifier, was used with a low resistance neonatal nasal cannula (Fisher & Paykel Healthcare, New Zealand). The infants were studied using either the RT239 circuit with appropriately sized nasal cannula (BC2425) or the updated RT330 circuit with OPT312 nasal cannula.

The infants were measured on flow rates of 2, 4 and 6 L/min through the NHF system with the order of the applied flow rate randomised. Oxygen saturations were targeted within the range of 91-95%.[21] At the conclusion of the study, infants were placed back on their pre-study BCPAP. Infants were nursed in the supine position throughout the study.

If the following 'failure criteria' occurred during the study, the baby was placed back on BCPAP.

- Oxygen requirement > 40%
- > 2 apnoea or bradycardias requiring stimulation to resolve
- Respiratory rate >75 breaths per minute
- Significant increase in the work of breathing as per their observation chart.

Measurements

A Gottingen GoeMF II tomograph (VIASYS Healthcare, Netherlands) was used to measure EEL, amplitudes and regional ventilation distribution. Sixteen conventional electrocardiography (ECG) electrodes (Kendall, Kittycat 1050NPSM, Tyco Healthcare Group, Mansfield, Massachusetts) were placed circumferentially around the infants' chest at nipple level. Whilst on BCPAP, a three-minute Electrical

Impedance Tomography (EIT) measurement was performed with a frame rate of 44 Hz. This period was used for referencing of all following measurements.

Three-minute measurements were then taken 30 minutes after being placed on each of the flow rates of 2, 4 and 6L/min. When assessing ventilation distribution with EIT, a 15-minute stabilisation period should be allowed following any position change.[22] Software provided with the equipment was used for data acquisition and reconstruction of functional relative EIT images.[23] Data were further analysed off-line using Matlab 7.7 (R2008b, The MathWorks Inc, Natick, MA, USA).

EEL is the relative impedance measured at end expiration and is analogous with functional residual capacity. Changes in EEL at the three different flow rates were compared to the pre-study CPAP level for the global, the dependent, and nondependent lung. Regional impedance amplitudes describe the magnitude of regional tidal volume change within an individual over time. Impedance amplitudes were calculated by averaging the impedance differences in each pixel of the measurement period between the end expiratory and end inspiratory periods. To account for the unequal number of pixels analysed in each region of interest (ROI), the average amplitude for each ROI was reported.

A Global Inhomogeneity (GI) index was also calculated for the entire lung region using a tidal EIT image of the end-expiration to end-inspiration differences. The GI index is used as an indicator of inhomogeneous ventilation by describing variations in the pixel values of the tidal EIT image.[24] The higher the GI value the more ventilation inhomogeneity exists.

Data processing and analysis

As preterm infants commonly show irregular breathing patterns, regular sections of breathing were selected for analysis based on previously described criteria.[25]

EIT data were band pass filtered to include the first and second harmonic of the respiratory rate.[26] A cut-off mask of 20% of the peak impedance signal was applied to reduce cardiac interference. [27,28]

A respiratory inductance plethysmograph (Respitrace Q.D.C., CareFusion Corporation, San Diego, USA) with self-calibration functionality was used to determine the volume state of the lung. Two separate stretch bands (XactTrace Disposable Belts (Embla, Denver, USA) were placed with one around the chest circumference at the nipple level and one around the abdomen at navel level. Physiological data generated by the RIP represent the Ribcage (RC), Abdomen (ABD) and overall respiratory (Sum) movement. These RIP signals were fed directly from the Respitrace Q.D.C. to a PowerLab polygraph (ADInstruments Ltd, Dunedin, New Zealand).

Parameters calculated for the overall respiratory RIP signal were the end-expiratory level (RIP_{EEL}) and the amplitude of tidal breathing (RIP_{AMPL}).[29]

To enable analysis of the pharynx and intrathoracic pressure delivered by the NHF system, pressures were recorded from the pharynx ($P_{pharynx}$) and from the oesophagus (P_{oe}). $P_{pharynx}$ was measured using a 6F silastic feeding tube positioned in the pharynx. Oesophageal pressure (P_{oe}) measurements were taken as an indication of end expiratory pressure. The in situ NG tube was connected to a pressure transducer and pulled back to the distal third of the oesophagus to achieve a wave form that was free from cardiac artefact with a negative deflection during inspiration.[30]

To keep the catheter free of gas bubbles which could dampen the pressure trace, saline was infused at a rate of 1 mL/hr. The liquid-filled catheter method has previously been validated using the dynamic occlusion test in preterm infants.[31] Feeds were discontinued for the length of the study. The PowerLab polygraph was used to record the pressure trace.

Data processing and analysis

All PowerLab pressure signals were recorded using the data acquisition and analysis software, LabChart v6.1 (ADInstruments Ltd, Dunedin, New Zealand). All signals were sampled at 1 kHz. $P_{pharynx}$ and P_{oe} were taken at end-expiration and end-inspiration determined by the RIP SUM signal. The pressure rate product (PRP) was calculated using the pressure amplitude multiplied by the measured respiratory rate to give an indication of inspiratory load and effort of breathing.

Respiratory rate (RR), heart rate (HR), and oxygen saturations (SpO_2) were monitored throughout the study using the Dräger Infinity Delta XL monitoring system (Dräger Medical AG & Co. KG, Lübeck, Germany) incorporating Masimo pulse oximeter technology (Masimo Corporation, Irvine, CA, USA). FiO_2 was recorded from the settings of a calibrated air/oxygen blender (Bird 10040A, SensorMedics, San Diego, CA, USA). These variables were manually recorded at the time of each EIT recording. From the collected data the SpO_2/FiO_2 ratio was calculated.[32]

Statistics

Results are described using mean and confidence intervals (CI), or standard deviations (SD) for the biometric data. To account for missing data, mixed linear models (MLM) were used to analyse the impact of NHF flow rate on EEL, regional

ventilation distribution, pressure, RIP signal and physiological variables compared with BCPAP. Post hoc analysis used ANOVA with Bonferroni correction. A p-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS (v15.0, Lead Technologies, Inc., Chicago, IL, USA).

A sample size of 24 infants was enrolled to allow every randomised flow rate combination to be used four times. In previous studies, EIT measurements in infants have an intra-individual coefficient of variance <6%. There is no existing information on the size of the treatment effect.

RESULTS

Twenty-four infants requiring BCPAP respiratory support were included in the study. At the time of the study, the infants had a mean ± SD corrected gestational age of GA of 31.2 ± 1.2 weeks, a study weight of 1260.0 ± 305.3 grams, and a postnatal age of 21.9 ± 12.9 days. All babies were on caffeine citrate. There were equal numbers of males and females. All other demographic details are in Table 1.

There were no significant differences in global or regional EEL ($p>0.09$) between BCPAP and delivered NHF rates (Figure 1a). Similarly, the measurements using RIP showed no overall significant difference between BCPAP and NHF ($p=0.06$). (Figure 1b)

No differences in global or regional impedance amplitudes measured by EIT were detected ($p>0.55$) (Figure 2a) and ventilation distribution measured by GI also remained unchanged ($p=0.27$). The RIP measurements for tidal volume amplitudes were significantly different and showed that BCPAP had similar amplitudes to 2L NHF ($p=0.23$) and significantly higher amplitudes than 4L and 6L ($p<0.01$) (Figure 2b).

The average BCPAP pressure level delivered at entry into the study was 5.8 cmH_2O (± 1.3) with the $P_{pharynx}$ pressures measured at 2.3 (± 1.2) cm H_2O.

There was a clear trend of increasing pharynx pressures with increasing NHF flow rates, but the changes did not reach statistical significance ($P = 0.06$) (Figure 3). The mean pharyngeal pressure at 6L NHF was similar to that delivered by 5.8cm BCPAP.

There was no significant difference between flow rates in terms of inspiratory or expiratory P_{oe}, ($P = 0.13$) (Figure 4a), or in the pressure rate product (PRP) ($p=0.56$) (Figure 4b).

There was a significant increase in FiO_2 ($p<0.01$) on NHF and a drop in SpO_2/FiO_2 ($p<0.01$) between BCPAP and NHF. There were no significant differences for heart rate, RR or SpO_2 (Table 2).

Adverse events

Four infants 'failed' according to the failure criteria of increasing apnoea, bradycardia and oxygen requirements. All babies had been on 5cm CPAP prior to NHF. Two failed when randomised on the 2L/min flow rate, one failed on 4L/min and one failed with handling at the commencement of the study.

- Baby 3 (ex 27+6 wk GA, CA 30+5 wk) 5cm CPAP at 21%, was initially randomised to 2L NHF and failed due to increasing oxygen requirements over the 30 minutes on 2L.
- Baby 10 (ex 25+6 wk GA, CA 30+4 wk) 5cm CPAP 21%, completed 6L NHF and failed whilst on 4L NHF due to gradually increasing oxygen requirements.
- Baby 12 (ex 30 wk GA, CA 31+4 wk) 8cm CPAP 30%, completed 6L NHF and then failed whilst on 2L NHF due to increasing oxygen requirements.
- Baby 24 (ex 27 wk GA, CA 30+3 wk) 5cm CPAP 21%, became bradycardic and apnoeic after the CPAP was removed.

DISCUSSION

In this interventional study, we investigated the physiological effect of randomly applied NHF flow rates of 2, 4 or 6 L/min compared with BCPAP in stable preterm infants. The changes observed in EEL, ventilation distribution and delivered airway pressures were small indicating that NHF was equally as effective as BCPAP. No consistent relationship between applied NHF rates and EEL or ventilation distribution could be shown.

Oxygenation was significantly better on BCPAP than on NHF, particularly at 2L/min, a significant finding considering that oxygen free radicals are implicated in chronic lung disease, retinopathy of prematurity, necrotizing enterocolitis and periventricular leukomalacia.[33]

NHF supports inspiratory effort if the inspiratory flow demand is matched, [34,35] whereas CPAP should maintain a constant positive airway pressure during the inspiratory and expiratory phase. Our measured inspiratory pressures were much less than the delivered pressures and we found large variations in oesophageal pressure measurements, and therefore limited capability to predict CDP.[14]

Despite minimal statistically significant findings for airway pressure, EEL and ventilation distribution, our data represents physiologic plausibility. Both NHF and BCPAP delivered some degree of positive airway pressure with similar pressures delivered, and hence little physiological difference between 5.8cm BCPAP and 6L NHF. Similar to other studies, we demonstrated a linear relationship between pharyngeal pressure and increasing flow, [36 9,13,14,16,37] however the pressures we recorded were less than have been reported previously.[9] These differences may be attributed to a few different factors. The techniques used to measure pharyngeal pressure differed. We recorded pressures with a water filled catheter whereas

Wilkinson et al[9] used a pressure-tip transducer. Additionally, in their study the infants were older and heavier than ours with a median age of 33.6 weeks (29-53) and weight 1.619 kg (0.816 – 4.400) compared to 27.5 weeks and 1.210 kg. This size difference which may impacted on the prong to nare diameter and hence the degree of flow delivery. Wilkinson et al[9] also used a step wise increase in NHF whereas the delivery of NHF in our study was randomised, potentially resulting in de-recruitment at lower flows.

In contrast to our pharyngeal pressure measurements, and to a previous study measuring oesophageal pressure in infants,[38] oesophageal pressures in this study were not proportional to the flow rate administered. Iyer et al [38] reported a significant association between flows of 2-8L delivered step-wise, and oesophageal pressure comprising 93 end-expiratory oesophageal pressures from 19 infants. We only took a single mean pressure measurement for each of our 24 included infants at each flow rate. Given the acknowledged variability in the generation of end expiratory oesophageal pressure,[38] it suggests a larger sample size was needed.

Similar to the findings by Rubin et al,[39] NHF rates of 4 L/min in preterm infants showed the lowest measured PRP. It is likely that at this flow the balance between inspiratory support and positive expiratory pressure was optimal in our cohort of stable preterm infants. Since we did not find great airway pressure changes using NHF rates between 2-6 L/min it was not surprising that no major changes in end expiratory lung volumes (measured by both EIT or RIP) or ventilation distribution were detected – either the measured airway pressure changes were too small to have a measureable impact on EEL or ventilation distribution, or some of these babies may not have required any pressure support at all.

Despite this, FiO_2 and SpO_2/FiO_2 were clearly better on CPAP, with increasing FiO_2 as the NHF rate reduced. Three infants (12.5%) were placed back on CPAP due to apnoea, bradycardia and increasing oxygen requirements, all infants failing on the lower NHF rates.

The improvement in SpO_2/FiO_2 with increasing flow is possibly a result of washout of nasopharyngeal dead space. Alternatively, with CPAP the improved oxygenation may be accompanied by carbon dioxide retention due to lung hyperinflation with increasing flows.[2] It would have been useful to measure carbon dioxide values to help ascertain the exact mechanism of the relationship with oxygenation in the 'nasal washout theory'. As there are studies showing that NHF is associated with a longer length of respiratory support and oxygen duration,[18 40,41] a greater likelihood of developing BPD or death, a delay in establishing oral feeds, increased use of postnatal steroids and prolonged hospitalization in preterm infants,[42] it is imperative that we investigate this further.

Limitations

This study represents a relatively small number of patients performed during a stable clinical phase and does not represent the demands during the acute period post extubation or when CPAP or NHF are used as a primary therapy for RDS. There may have been the potential for de-recruitment over the course of the study but this would have been limited by flow randomisation and the absence of a statistical interaction with the flow order.

Difficulties were encountered with data collection, with noisy signals obtained from the oesophageal monitoring and the EIT. A limitation of high flow use is that the variation of the applied positive airway pressure is affected by air leaks that occur around the nasal cannula and through the mouth.

Although our EIT and RIP results demonstrated similar patterns of change for amplitude and EEL, the results differed in their strength. Although they are both purporting to measure similar information, there are subtle differences between what they measure. RIP measures total thoracic volume but is not able to identify regional changes in ventilation whereas EIT is able to measure relative regional ventilation and not absolute lung volume changes. Due to these differences, there will be some discrepancies between the results they deliver.

What are the implications for NHF therapy?

Although NHF has greater ease of use and improved patient tolerance, it is apparent that too little flow can lead to failure of NHF. The mechanism underlying improved oxygenation with increasing flows remains unclear and little is known about the level of flow required to achieve a clinical and physiological benefit. Further investigations are required to determine what constitutes optimal flow.

Conclusion

In conclusion, NHF was equally as good as CPAP in maintaining EEL and ventilation distribution in stable preterm infants. Although no clear relationship could be determined between delivered flow rate and EEL or regional ventilation distribution, FiO_2 and SpO_2/FiO_2 were clearly better on CPAP, with an increasing FiO_2 requirement as the NHF rate reduced. Further research is required to determine the most appropriate flow rate delivery.

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Figure Legends

Figure 1: Change in EEL for BCPAP and delivered NHF rates measured with EIT (upper) and RIP (lower). No overall significant difference was found between BCPAP and NHF. Mean and CI.

Figure 2: Change in regional impedance amplitude for BCPAP and delivered NHF rates measured with EIT (upper) and RIP (lower). No overall significant difference was found between BCPAP and NHF. Mean and CI

Figure 3: Change in pharyngeal pressure between BCPAP and delivered NHF rates. No overall significant difference was found between BCPAP and NHF. Mean and CI

Figure 4: Change in inspiratory and expiratory oesophageal pressure (upper) and inspiratory load, measured by pressure rate product (lower), between BCPAP and delivered NHF rates. No overall significant difference was found between BCPAP and NHF. Mean and CI

Table 1: Demographics of included infants

	Mean	SD	Med	Min	Max	Count (%)
GA (weeks)	27.63	1.79	27.5	25	31	
PNA (days)	21.88	12.97	24	3	51	
CGA (weeks)	31.19	1.17	30.8	28.86	33.71	
BWt (gms)	1076.38	367.78	1009	540	2040	
StWt (gms)	1260	305.34	1210	820	1940	
Gender (male)						12 (50%)
Inborn						22 (91.7%)
Singleton						15 (62.5%)
AN steroids						22 (91.7%)
Curosurf						18 (75%)

GA: Gestational Age; PNA: Postnatal Age; CGA: Corrected Gestational Age; BWt: Birth Weight; StWt: Study Weight; AN: Antenatal

Table 2: Physiological parameters (Mean ± SEM) MLM

	CPAP (5.8cm H_2O)	NHF 2L	NHF 4L	NHF 6L	P value
HR	165.65 ± 2.61	160.23 ± 2.51	159.61 ± 2.65	162.48 ± 1.82	0.24
RR	64.95 ± 2.97	64.31 ± 2.85	59.28 ± 65.56	58.82 ± 64.11	0.10
FiO_2	0.22 ± 0.004	0.25 ± 0.009	0.24 ± 0.009	0.23 ± 0.007	0.01*
SpO_2	95.43 ± 0.63	91.76 ± 0.92	93.85 ± 0.58	94.52 ± 0.78	0.19
SpO_2/FiO_2	445.32 ± 7.22	390.23 ± 14.61	398.06 ± 13.43	418.36 ± 11.01	<0.01*

*p<0.05

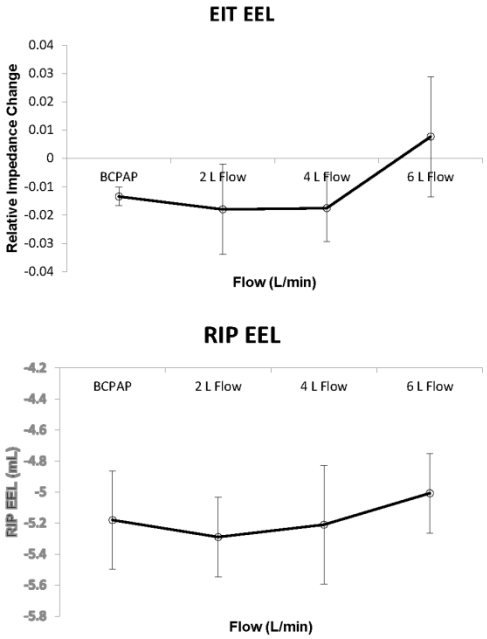

Figure 1: Change in EEL for BCPAP and delivered NHF rates measured with EIT (upper) and RIP (lower). No overall significant difference was found between BCPAP and NHF. Mean and CI.

210x297mm (200 x 200 DPI)

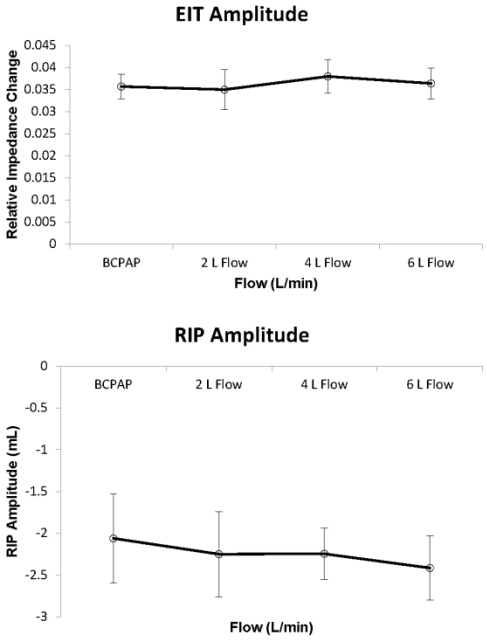

Figure 2: Change in regional impedance amplitude for BCPAP and delivered NHF rates measured with EIT (upper) and RIP (lower). No overall significant difference was found between BCPAP and NHF. Mean and CI

210x297mm (200 x 200 DPI)

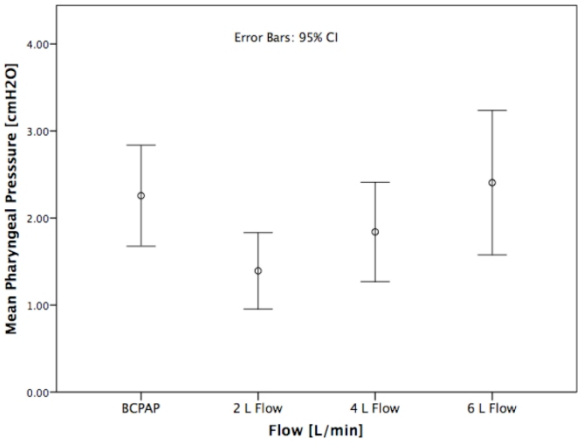

Figure 3: Change in pharyngeal pressure between BCPAP and delivered NHF rates. No overall significant difference was found between BCPAP and NHF. Mean and CI

210x297mm (200 x 200 DPI)

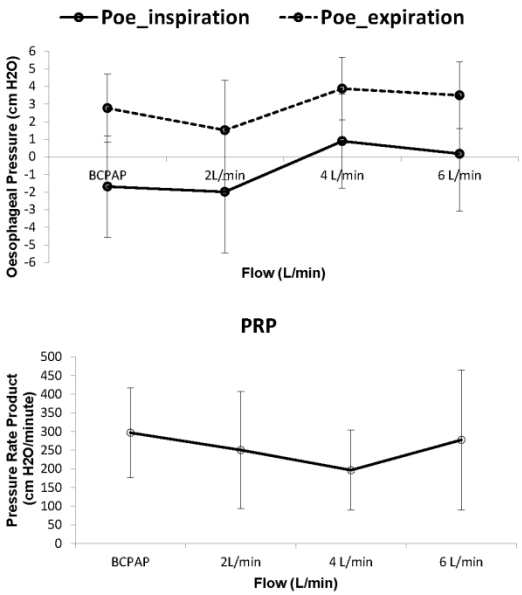

Figure 4: Change in inspiratory and expiratory oesophageal pressure (upper) and inspiratory load, measured by pressure rate product (lower), between BCPAP and delivered NHF rates. No overall significant difference was found between BCPAP and NHF. Mean and CI

210x297mm (200 x 200 DPI)