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Nasal High Flow in Preterm Infants: A Dose Finding Study

Running Title: High Flow Dose Finding

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ABSTRACT

Objective: To investigate the relationship between applied flows of nasal high flow (NHF) and physiological outcomes and work of breathing (WOB), to identify an optimal delivery flow which results in reduced WOB in preterm infants.

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

Patients and Setting: Preterm infants within 72 hours of commencement of NHF respiratory support.

Interventions: Infants were initially placed on 8L/min of NHF and flows of 2, 4 and 6 L/min were then applied in random order.

Measurements and Results: Work of breathing was measured using transcutaneous electromyography and respiratory inductance plethysmography (RIP). Physiological variables were also recorded. Measurements taken 10 minutes after each flow change were compared with 8L/min. Sixteen infants with a median gestational age of 28 (range 24-31)

weeks and postnatal age of 14 (2-55) days were included in the study. Median flow rate prior to the study was 6 (4-8) L/min and fraction of inspired oxygen (FiO2) was 0.21 (0.21-0.26). Changes in flow resulted in changes in activity in the front diaphragm (p=0.027) and intercostals (p=0.034). Electrical activity of the front diaphragm at 8L/min was significantly lower than at 2L/min (p=0.016). Respiratory rate was lowest at 6L/min (p=0.002) and SpO2/FiO2 was highest at 8L/min (p<0.04)

Conclusion: In preterm infants, changes in work of breathing resulting from randomly applied levels of NHF can be demonstrated by measuring electrical activity of the diaphragm and intercostal muscles with transcutaneous electromyography. In combination with physiological measurements, the similarities in electrical activity between 4, 6, and 8L/min suggest that these three flows may be equally as effective.

Background

In infants, assisted ventilation is delivered both invasively and non-invasively using various forms of oxygen therapy. Non-invasive oxygen delivery using nasal high flow (NHF) cannula is an alternative to continuous positive airway pressure (CPAP) in preterm infants because the care of the patient is simplified when compared to other forms of oxygen delivery. [1-3] Although large RCT's have shown the efficacy of NHF to be similar to CPAP when used as post-extubation respiratory support,[4] when used as primary support in newborn infants with respiratory distress, NHF has resulted in higher rates of treatment failure.[5,6]

Despite its increasing popularity, data on the physiological effects of NHF remains limited. A number of studies have investigated the potential continuous distending pressure (CDP) that NHF may deliver and its effect on work of breathing.[7-11 12-14]

Our group has described the physiological effect of high flow in infants with bronchiolitis, and in neonates.[15,16] We demonstrated in premature infants that flows delivered at ≥2L/min were equal to CPAP in maintaining end expiratory level and ventilation distribution,[16] and that flows of 8L/min resulted in increased lung volume, and improved respiratory rate and oxygen saturation.[15] Moreover, in infants with bronchiolitis, we were able to demonstrate using the electrical activity of the diaphragm, that flows delivered at 2L/kg/min significantly reduced the work of breathing.[17]

Electrical activity of the diaphragm measured by electromyography (dEMG) can be used in preterm infants and is able to detect changes in diaphragmatic activity and is reproducible during tidal breathing in different age groups.[18] It is considered to be a direct measure of neural respiratory drive and breathing effort and can be measured transcutaneously and non-invasively using adhesive surface electrodes.[19-21]

Current rates of NHF delivery in the neonatal population are variable throughout the world. In the UK, flows vary between 1 and 8 L/min,[22] in Canada starting flows ranged from 1 to 6 L/min with maximal flows ranging from 2 to 8 L/min,[23] whereas in Australia and New Zealand the most common flows used were 4 and 6 L/min, with flows up to 10 L/min reported.[24] The choice of flow is clinician driven, being adjusted to obtain clinically satisfactory

oxygen saturations (SpO_2). The titration of the flows to the need of the patient would be more desirable. Therefore, in this project we aimed to perform a "dose finding" study to define the ideal flow for an individual patient.

The purpose of this study was to demonstrate the physiological effect of the randomly applied levels of high flow on the work of breathing (WOB) indirectly measured with the electric diaphragmatic activity. We hypothesised that there would be a non-linear relationship between NHF flow and WOB. The specific aims of this study were:

- To determine the relationship between applied flows and WOB.
- To identify an optimal flow which results in reduced WOB
- To investigate the relationship between applied flow and physiological outcome parameters such as heart rate, respiratory rate and work of breathing.

Methods

Study design

In this prospective interventional study, stable preterm infants requiring NHF respiratory support were measured, initially on 8L/min and then at randomly applied flows of 2, 4, and 6L/min, to determine the effect of flow on work of breathing.

Subjects

Premature neonates (both male and female) requiring NHF respiratory support were recruited from the Neonatal Critical Care Unit (NCCU) at the

Mater Mothers Hospital, South Brisbane (QLD Australia). Inclusion criteria were preterm infants aged 28 – 36 weeks corrected gestational age, had an oxygen requirement of ≤ 0.40, who were within 72 hours of NHF commencement, were deemed stable by the treating medical and nursing staff, and who had a nasogastric (ng) feeding tube in place. Exclusion criteria were lung or cardiovascular anomalies that would substantially affect oxygenation, lung recruitment or regional ventilation; greater than 2 episodes within the last hour of apnoea and/or bradycardia requiring moderate or vigorous stimulation, an increasing inspired oxygen (FiO2), or recent change in flow. Procedures in the studies conformed to the NH&MRC National Statement on Ethical Conduct in Human Research (2007) and was conducted according to the study protocol approved by the Human Research Ethics Committee, Mater Health Services Ltd, South Brisbane, Queensland (HREC/15/MHS/68). Informed written consent was obtained from the parents.

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. The infants were studied using either the RT239 circuit with appropriately sized nasal cannula (BC2425) or the updated RT330 circuit with OPT312 nasal cannula. (Fisher & Paykel Healthcare, New Zealand). The nasal prong sizing was such that they occluded less than half the diameter of the nares. We did not ensure that the infant's mouth was closed during the study period to reflect routine clinical practice. Inspired oxygen concentration

was titrated to achieve pulse oximeter oxygen saturations (SpO2) between 91-95%.[25]

Regardless of their pre-study flow and to provide consistency, all infants were initially measured on a flow of 8 L/min (baseline) before flows of 2, 4 and 6 L/min were applied in a random order. Randomisation was undertaken by computer generated randomisation with allocation concealment using sequentially numbered sealed opaque envelopes. A washout period of 10 minutes was applied between each change in therapy to allow the infants to stabilise before taking measurements over a five-minute period. All infants were nursed in the supine position throughout the study.

If the following 'failure criteria' occurred during the study, the study was discontinued.

- Oxygen requirement > 50%
- More than 2 apnoea or bradycardias requiring stimulation to resolve
- Respiratory rate >75 breaths per minute
- Significant increase in the work of breathing (expiratory grunt, head bobbing, nasal flaring, intercostal recession, subcostal recession)

Measurement

Work of breathing was measured using transcutaneous diaphragmatic electrical activity (dEMG) and respiratory inductance plethysmography (RIP).

Diaphragmatic Electrical Activity

Electrical activity of the diaphragm was measured by placing seven ECG electrodes (Kendall, Kittycat 1050NPSM, Tyco Healthcare group, Mansfield, Massachusetts) on the chest of the infant. Two electrodes were placed bilaterally just under the clavicles in the nipple line (intercostal lead), two were placed bilaterally at the costoabdominal margin in line with the nipple (frontal diaphragm lead), two were placed posteriorly at the costoabdominal margin equidistant from the spine (posterior diaphragm lead) and the common electrode was placed on the sternum. The electrodes were connected to a portable 16-channel physiological amplifier (Dipha-16, Macawi Medical Systems, Eindhoven, The Netherlands) and the measured data were wirelessly transferred to a bedside personal computer where the raw signal was digitally pre-processed using the data acquisition and processing software Polybench (Applied Biosignals, Weener, Germany). Previous research has demonstrated that it is possible to differentiate EMG signals from different muscle groups and that the signals are not contaminated by the activity of other muscles.[26]

To analyse the electrical activity of the diaphragm for each flow, stable 30 second recordings were selected containing approximately 30 breaths, as recommended in infant lung function testing.[27] Stable recordings were defined as no movement or technical artefacts in the signal. After filtering the data to remove the cardiac signal and technical artefacts, the running average root-mean-square (RMS) of the EMG signal was then calculated to quantify the activities of the muscles involved in respiration, i.e. the front diaphragm (RMS

FDia), the intercostals (RMS Int), and the posterior diaphragm (RMS DDia).[28] Optimal flow was defined as the flow at which the electrical activity of the diaphragm is minimal according to the lowest RMS value.

Respiratory Inductance Plethysmography (RIP)

A respiratory inductance plethysmograph, Respitrace Q.D.C. (CareFusion Corporation, San Diego, USA), with self-calibration functionality was used to assess asynchrony of breathing as a surrogate measure for WOB. Two separate stretch bands, XactTrace Disposable Belts (Embla, Denver, USA), were placed; one around the chest circumference between the armpits at nipple level and one around the abdomen at navel level. The RIP wires of the DIPHA-16 were connected to the RIP modules (TSMi Respi V6) which were provided with the device and then connected to the RIP bands. Physiological data generated by the RIP are waveforms representative of the Ribcage (RC) and Abdomen (ABD).

For off-line processing and analysis of the RIP data, the raw data from the Polybench software (Applied Biosignals, Weener, Germany) was imported into LabChart (ADInstruments Pty Ltd, Bella Vista, Australia) for further analysis. The RIP Thorax and RIP Abdomen signals were added together to create a RIP SUM channel.[29] From the RIP SUM trace, an artefact free 30 second period of stable respiration was identified. The Peak Analysis program on LabChart (ADInstruments Pty Ltd, Bella Vista, Australia) was then used to measure the number of waveforms identified, amplitude (RIP_{AMPL}) and area under the curve (RIP_{Area}) for RIP SUM channels within the selected time period.[30]

Measurement of physiological variables

Respiratory rate (RR), heart rate (HR), and oxygen saturation (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). Ratio of inspired oxygen ($FiO_{2)}$ 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 dEMG and RIP recording. From the collected data the SpO_2/FiO_2 ratio was calculated.[31] As SpO_2/FiO_2 is a more accurate representation of the interrelationship between the delivered FiO_2 and the recorded SpO_2, only the SpO_2/FiO_2 results are reported.

Statistics

Descriptive data are presented as means and standard deviations (SD) or median (range) depending on their distribution. Generalized linear models (GLM) were used to analyse the impact of NHF on diaphragm activity, RIP signal and physiological variables. Post hoc pairwise analysis with Bonferroni correction was carried out if statistically significant differences were found across the flows. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (v25.0, Lead Technologies, Inc., Chicago, IL, USA).

Sample Size

A convenience sample of 16 premature infants was enrolled. There is no existing information on the size of the treatment effect.

RESULTS

Patient characteristics

Sixteen infants requiring NHF respiratory support were included in the study (Table 1). The infants had a median gestational age of 28 (range 24-31) weeks, a postnatal age of 14 (2-55) days, and a corrected age of 32 (28.1-34.1) weeks. Their birth weight was 1140 (625-2153) grams and weight at the time of study was 1445 (1026-2264) grams. The median flow rate prior to the study was 6 (4-8) L/min and the fraction of inspired oxygen (FiO2) was 0.21 (0.21-0.26). There were seven males and nine females.

Relationship between applied flow and diaphragm activity

Analysis of the electrical activity of the diaphragm showed that with changes in flow, the overall muscle activity changed significantly (p=0.006) with the muscle activity at 4L/min significantly less than at 8L/min (mean difference = -2.815, 95%CI -4.848, -0.783; p=0.007) with no difference noted between 8 and 6L/min (-0.805, 95%CI -2.939, 1.328; p=0.459) or between 8 and 2L/min (-0.707, 95%CI -1.826, 3.240; p=0.584). These changes occurred primarily in the front diaphragm (RMS FDia) (p=0.027) and intercostals (RMS Int) (p=0.034) but not in the posterior diaphragm (RMS DDia) (p=0.109). (Table 2)

Further exploration of where the differences lay showed that for the RMS FDia, the muscle activity at 2L/min was significantly greater than at 8L/min (1.286, 95%CI 0.238, 2.334; p=0.016) with no difference noted between 8 and 4L/min (0.249, 95%CI = -0.470, 0.968; p=0.498) or between 8 and 6L/min (0.430, 95% CI = -0.470, 0.968; p=0.312). (Figure 1)

Although the overall effect of flow was significant for the RMS Int (p=0.034), compared to the 8L/min baseline there was no significant difference for 6L/min (-0.861, 95%CI = -2.423, 0.701; p=0.280), 4L/min (-1.38, 95%CI = -2.854, 0.096; p=0.067), or 2L/min (-0.486, 95%CI = -1.965, 0.993; p=0.519) (Figure 2).

Although we did not find an overall statistical significance for the RMS DDia, the muscle activity 4L/min was significantly lower than 8L/min (-1.589, 95%CI = -2.929, -0.249; p=0.020) (Figure 3). ***Relationship between applied flow and RIP***

There were no significant associations between flows and RIP_{AMPL} (p=0.492) or the RIP_{Area} (p=0.135).

Relationship between applied flow and physiological outcome parameters

Analysis of the physiological data showed that with change in flows, there was a significant difference in RR (p<0.001) and SpO_2/FiO_2 (p=0.001), but not HR (p=0.999). When body weight was included as a covariate, no change to the outcome was noted.

RR was significantly lower at 6 than at 8L/min (-8.753, 95% CI = -14.164, -3.342; p=0.002), with no differences between 8 and 2L/min (3.514, 95% CI = -3.214, 10.243, p=0.306) or between 8 and 4L/min (-3.753, 95%CI = -8.910, 1.404; p=0.154) (Figure 4).

SpO_2/FiO_2 at 8L/min was significantly higher than at 6L/min (-11.542; 95% CI = -22.160, -0.924; p<0.035), 4L/min (-13.984; 95% CI = -25.704, -2.263; p=0.001), and 2L/min (-55.043; 95% CI = -82.204, -27.883; p<0.001). (Figure 5)

Adverse events

One infant 'failed' according to the failure criteria of increasing apnoea, bradycardia and oxygen requirements and was withdrawn from the study. Any already collected data was included in the analysis. This baby was an ex 28+3-week male infant and was 30 days old at the time of the study (corrected age 32+5 weeks). He had been on 6L/min NHF at 21% prior to the study and was initially randomised to 2L/min NHF when he failed due to decreasing oxygen saturations and was noted to have increased work of breathing.

No other adverse events such as pneumothorax or nasal trauma were reported during the study period.

DISCUSSION

In this study on preterm infants we have been able to demonstrate a relationship between applied NHF rate and WOB, and between applied flow

and the physiological measures of respiratory rate and SpO2/FiO2. NHF of 4L/min resulted in reduced WOB, while the lowest respiratory rate was at 6L/min.

Impact of NHF on diaphragmatic electrical activity

The pattern of respiratory muscle activation differed depending on which muscle was measured. The overall lowest electrical activity, indicative of a reduced work of breathing, was at a flow of 4L/min, suggesting that a NHF rate of 4L/min may be just as effective as providing respiratory support as 6 and 8L/min.

However, we found no difference in electrical activity of the frontal diaphragm between 8, 6 and 4L/min, with 2L/min significantly greater than 8L/min. This is consistent with previous findings by Jeffreys et al,[32] who found no difference in transcutaneous electrical activity of the frontal diaphragm between flows of 4, 6 and 8L/min. Similarly Waal et al[19] described that neural respiratory drive measured by electrical activity of the diaphragm is not influenced by changes in NHF flow rates.

Both studies only assessed the electrical activity of the frontal diaphragm, and not the posterior diaphragm and intercostal muscles, which is where we found differences in diaphragm activation at the different flows. Their reasoning for not measuring the intercostal muscles was based on timeworn evidence suggesting that the intercostal muscle do not contribute substantially to breathing effort during tidal breathing in preterm infants,[33] and that the frontal

diaphragm would provide sufficient information to describe changes in breathing effort over time.[19]

Our finding, that intercostal muscle activity changes with flow, is in alignment with the understanding that the intercostal muscles help stabilize the compliant infant rib cage to reduce inward displacement of the rib cage by contraction of the diaphragm,[34] and the diaphragm and intercostal muscles work synergistically to maximise respiratory performance.[35] The intercostal muscles are recruited first to increase the volume of the ribcage by lifting up the thorax, and thereafter the volume is increased further by activation of the diaphragm.[36] Infants able to recruit their intercostal muscles at the commencement of inspiration have been shown to be better able to prevent clinical deterioration, diaphragm fatigue and resultant apnoea.[35] Those infants with a low functional residual capacity need to activate inspiratory muscle activity earlier and longer in order to generate more pressure to reach a critical intrathoracic pressure to generate a flow.[35,36]

Impact of NHF on respiratory inductance plethysmography

The RIP measurements did not detect any change of WOB between the applied flows. Either RIP is not sensitive enough to detect these small differences or these findings can be explained by the fact, that the infants are partitioning the use of respiratory muscle groups by switching between thoracic and abdominal breathing patterns to balance energy expenditure and gas exchange.[37]

Impact of NHF on physiological parameters

We demonstrated that there was a relationship between applied NHF and RR and SpO_2/FiO_2. Similar to a previous study, which showed a significant difference in RR between NHF of 6L/min and 1L/min,[38] we found that RR decreased from 2L/min to 6L/min before increasing again at 8L/min. This increase of the RR with 8L/min may be best explained by a potentially reduced tidal volume and increase of RR to maintain minute volume. We showed that SpO_2/FiO_2 increased as flows increased from 2L/min to 8L/min indicating improved oxygenation. The study by Lampland[38] did not report on SpO2/FiO2, but they demonstrated a non-significant decrease in SaO2 and increase in FiO_2 as flows decreased.

Limitations

Despite the limitation of the small sample size, we were able to demonstrate clinically significant and important findings. Although the primary pulmonary diagnosis for each patient was RDS of prematurity, most of the infants were in room air with minimal lung disease and hence may have only required minimal respiratory support, therefore making exploration of NHF more difficult.

The most significant limitation was the presence of strong 50 Hz noise in the EMG signal, making data analysis difficult. This may have been influenced by the known influence on the amplitude of the EMG signals by electrode position. Transcutaneous EMG remains a relatively new method of breathing effort in preterm infants, and its results should be interpreted with caution.

Additionally, the infants in this study were receiving relatively low levels of respiratory support, and therefore findings may not be generalisable to those with more severe lung disease.

Conclusions

In this study on preterm infants, we were able to demonstrate the physiological effect of randomly applied levels of NHF on neural respiratory drive and breathing effort by measuring electrical activity of the diaphragm and intercostal muscles with transcutaneous EMG and RIP. In combination with physiological measurements, the similarities in electrical activity between 4, 6, and 8L/min suggest that these three flows may be equally as effective.

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Authors' Contributions:

JH: co-designed the study and was involved in data collection, data analysis, and the production of the manuscript.

ASh: was involved in data collection, data analysis, and production of the manuscript.

LJ: was involved in the analysis of the data and production of the manuscript.

ASc: co-designed the study, was involved in the analysis of the data and the production of the manuscript.

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Compliance with ethical standards:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest:

ASc and JH have received support for travel and accommodation from Fisher&Paykel to attend conference presentations

Informed consent:

Parents gave informed written consent

Figures:

Figure 1: Relationship between the electrical activity of the Front Diaphragm and flow rate. Electrical activity at 8L/min was significantly lower than at 2L/min (p=0.016) but not different from 6 (p=0.312) or 4L/min (p=0.498). Mean and 95% CI.

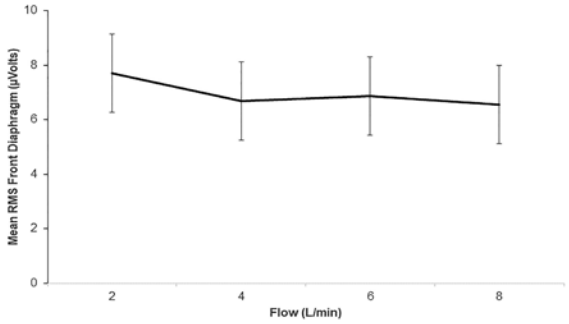


Figure 2: Relationship between the electrical activity of the Intercostal muscles and flow rate. Although there was an overall significant difference between flows (p=0.034), post hoc analysis showed no differences in electrical activity between 8 and 6L/min (p=0.280), between 8 and 4L/min (p=0.067), or between 8L and 2L/min (p=0.519). Mean and 95% CI.

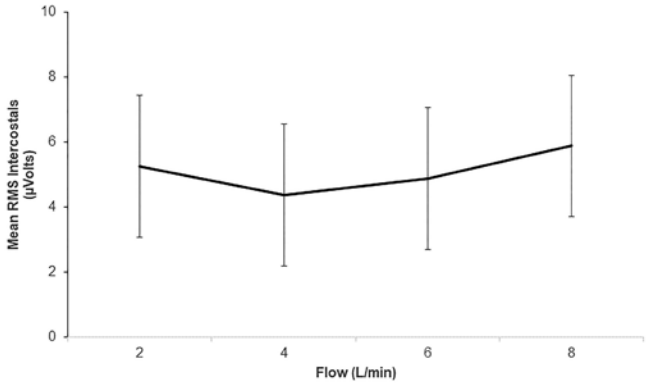


Figure 3: Relationship between the electrical activity of the Posterior Diaphragm and flow rate. There was no overall significant difference between flows however, post hoc analysis showed that electrical activity at 4L/min was significantly lower than 8L/min (p=0.020). Mean and 95% CI.

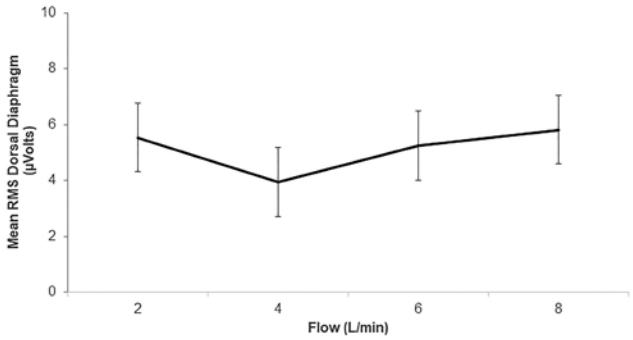


Figure 4: Relationship between respiratory rate and flow rate. RR was significantly lower at 6 than at 8L/min (p=0.002) with no differences between 8 and 2L/min (p=0.306) or between 8 and 4L/min (p=0.154): Mean and 95% CI.

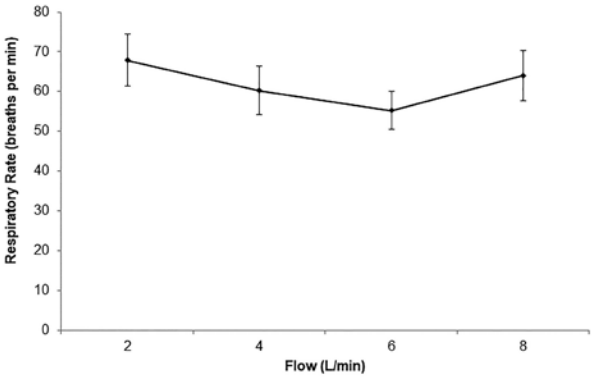
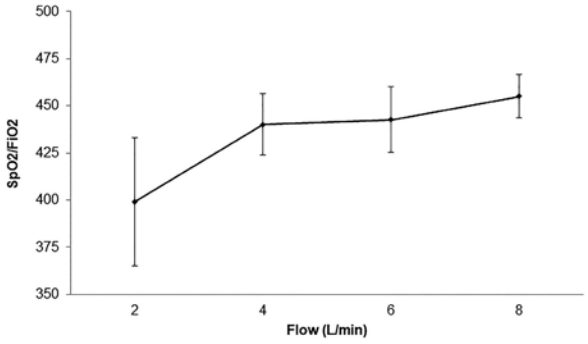


Figure 5: Relationship between SpO_2/FiO_2 and flow rate. At 8L/min, SpO_2/FiO_2 was significantly higher than at 6 (p=0.035), 4 (p=0.001), and 2L/min (p<0.001): Mean and 95% CI.



References

1. Kelly GS, Simon HK, Sturm JJ. High-flow nasal cannula use in children with respiratory distress in the emergency department: predicting the need for subsequent intubation. *Pediatr Emerg Care.* 2013;29(8):888-892.

2. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. *J Pediatr.* 2009;156(4):634-638.

3. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, Hough JL. Reduced intubation rates for infants after introduction of

high-flow nasal prong oxygen delivery. *Intensive Care Med. 2011;*37(5):847-852.

4. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, Donath SM, Davis PG. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med.* 2013;369(15):1425-1433.

5. Roberts CT, Owen LS, Manley BJ, Fr'island DH, Donath SM, Dalziel KM, Pritchard MA, Cartwright DW, Collins CL, Malhotra A, Davis PG. Nasal high-flow therapy for primary respiratory support in preterm infants. *New England Journal of Medicine.* 2016;375(12):1142-1151.

6. Manley BJ, Arnolda GRB, Wright IMR, Owen LS, Foster JP, Huang L, Roberts CT, Clark TL, Fan WQ, Fang AYW, Marshall IR, Pszczola RJ, Davis PG, Buckmaster AG, Hunter Trial Investigators. Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries. *N Engl J Med.* 2019;380(21):2031-2040.

7. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respir Med.* 2009;103(10):1400-1405.

8. Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. *J Perinatol.* 2007;27(12):772-775.

9. Wilkinson DJ, Andersen CC, Smith K, Holberton J. Pharyngeal pressure with high-flow nasal cannulae in premature infants. *J Perinatol.* 2008;28(1):42-47.

10. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. *J Intensive Care Med.* 2009;24(5):323-328.

11. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics.* 2008;121(1):82-88.

12. Saslow JG, Aghai ZH, Nakhla TA, Hart JJ, Lawrysh R, Stahl GE, Pyon KH. Work of breathing using high-flow nasal cannula in preterm infants. *Journal of Perinatology.* 2006;26(8):476-480.

13. Lavizzari A, Veneroni C, Colnaghi M, Ciuffini F, Zannin E, Fumagalli M, Mosca F, Dellacs RL. Respiratory mechanics during NCPAP and HHHFNC at equal distending pressures. *Archives of Disease in Childhood: Fetal and Neonatal Edition.* 2014;99(4):F315-F320.

14. Shetty S, Hickey A, Rafferty GF, Peacock JL, Greenough A. Work of breathing during CPAP and heated humidified high-flow nasal cannula. *Archives of Disease in Childhood: Fetal and Neonatal Edition.* 2016;101(5):F404-F407.

15. Hough JL, Pham TM, Schibler A. Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. *Pediatr Crit Care Med.* 2014;15(5):e214-219.

16. Hough JL, Shearman AD, Jardine L, Caldararo D, Schibler A. Effect of randomization of nasal high flow rate in preterm infants. *Pediatr Pulmonol.* 2019;54(9):1410-1416

17. Pham TM, O'Malley L, Mayfield S, Martin S, Schibler A. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. *Pediatr Pulmonol.* 2014;50(7):713-720

18. Maarsingh EJ, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WM. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol (1985).* 2000;88(6):1955-1961.

19. de Waal CG, Hutten GJ, Kraaijenga JV, de Jongh FH, van Kaam AH. Electrical activity of the diaphragm during nCPAP and high flow nasal cannula. *Archives of Disease in Childhood.* 2017;102(5):F434-F438.

20. Kraaijenga JV, De Waal CG, Hutten GJ, De Jongh FH, Van Kaam AH. Diaphragmatic activity during weaning from respiratory support in preterm infants. *Archives of Disease in Childhood: Fetal and Neonatal Edition.* 2017;102(4):F307-F311.

21. Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH. Transcutaneous electromyography of the diaphragm: A cardio-

respiratory monitor for preterm infants. *Pediatr Pulmonol.* 2015;50(9):889-895.

22. Ojha S, Gridley E, Dorling J. Use of heated humidified high-flow nasal cannula oxygen in neonates: a UK wide survey. *Acta Paediatr.* 2013;102(3):249-253.

23. Mukerji A, Shah PS, Shivananda S, Yee W, Read B, Minski J, Alvaro R, Fusch C, Canadian neonatal network investigators. Survey of noninvasive respiratory support practices in Canadian neonatal intensive care units. *Acta Paediatr.* 2017;106(3):387-393.

24. Hough JL, Shearman AD, Jardine LA, Davies MW. Humidified high flow nasal cannulae: Current practice in Australasian nurseries, a survey. *J Paediatr Child Health.* 2012;48(2):106-113.

25. The BOOST-II Australia and United Kingdom Collaborative Groups, Tarnow-Mordi W, Stenson B, et al. Outcomes of Two Trials of Oxygen-Saturation Targets in Preterm Infants. *N Engl J Med.* 2016;374(8):749-760.

26. Hutten J, van Eykern LA, Cobben JM, van Aalderen WM. Cross talk of respiratory muscles It is possible to distinguish different muscle activity? *Respir Physiol Neurobiol.* 2007;158(1):1-2;author reply 3-4.

27. Bates JH, Schmalisch G, Filbrun D, Stocks J. Tidal breath analysis for infant pulmonary function testing. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory

Society/American Thoracic Society. *Eur Respir J.* 2000;16(6):1180-1192.

28. O'Brien MJ, Van Eykern LA, Oetomo SB, Van Vught HA. Transcutaneous respiratory electromyographic monitoring. *Crit Care Med.* 1987;15(4):294-299.

29. Poole KA, Thompson JR, Hallinan HM, Beardsmore CS. Respiratory inductance plethysmography in healthy infants: a comparison of three calibration methods. *Eur Respir J.* 2000;16(6):1084-1090.

30. Collett PW, Perry C, Engel LA. Pressure-time product, flow, and oxygen cost of resistive breathing in humans. *J Appl Physiol (1985).* 1985;58(4):1263-1272.

31. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. *Chest.* 2007;132(2):410-417.

32. Jeffreys E, Hunt KA, Dassios T, Greenough A. Diaphragm electromyography results at different high flow nasal cannula flow rates. *Eur J Pediatr.* 2019;178(8):1237-1242

33. Taylor A. The contribution of the intercostal muscles to the effort of respiration in man. *J Physiol.* 1960;151:390-402.

34. Gaultier C. Respiratory muscle function in infants. *Eur Respir J.* 1995;8(1):150-153.

35. Lopes J, Muller NL, Bryan MH, Bryan AC. Importance of inspiratory muscle tone in maintenance of FRC in the newborn. *J Appl Physiol Respir Environ Exerc Physiol.* 1981;51(4):830-834.

36. Hutten GJ, van Eykern LA, Latzin P, Kyburz M, van Aalderen WM, Frey U. Relative impact of respiratory muscle activity on tidal flow and end expiratory volume in healthy neonates. *Pediatr Pulmonol.* 2008;43(9):882-891.

37. De Jongh BE, Locke R, Mackley A, Emberger J, Bostick D, Stefano J, Rodriguez E, Shaffer TH. Work of breathing indices in infants with respiratory insufficiency receiving high-flow nasal cannula and nasal continuous positive airway pressure. *Journal of Perinatology.* 2014;34(1):27-32.

38. Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *J Pediatr.* 2009;154(2):177-182.

Table 1: Demographics of included infants

	Mean	SD	Med	Min	Max	Count (%)
GA (weeks)	28.1	1.67	28	24	31	
PNA (days)	21.25	15.46	14	2	55	
CGA (weeks)	31.53	1.79	32	28.1 4	34.1 4	
BWt (gms)	1250.3 8	430.4 2	114 0	625	2153	
StWt (gms)	1465.3 1	363.6 5	144 5	1026	2264	
Pre-Study flow (L/min)	6.12	1.15	6	4	8	
Pre-Study FiO_2	21.44	1.31	21	21	26	
AN steroids						15 (93.8)
Surfactant						12 (75.0)

Male Gender	7 (43.7)

Table 2: Details of the different outcomes at each of the different Nasal High Flows (Mean ± SEM), p value of overall difference between groups.

	Baseline NHF 8L/min	NHF 6L/min	NHF 4L/min	NHF 2L/min	P value
RMS FDia	6.54 ± 0.71	6.97 ± 0.42	6.79 ± 0.37	*7.83 ± 0.53	0.027
RMS DDia	5.64 ± 0.61	5.36 ± 0.50	*4.05 ± 0.68	5.64 ± 0.51	0.109
RMS Int	5.88 ± 1.08	5.02 ± 0.80	4.50 ± 0.75	5.40 ± 0.75	0.034
RMS Entire	18.21 ± 2.00	17.40 ± 1.09	*15.40 ± 1.04	18.92 ± 1.29	0.006
RIP_{AMPL} - Change from baseline	0	6.25 ± 9.68	6.90 ± 8.02	21.39 ± 14.20	0.492
RIP_{Area} – Change from baseline	0	31.65 ± 20.09	8.85 ± 16.15	38.08 ± 24.88	0.135
HR	159.00 ± 3.49	159.08 ± 2.22	159.02 ± 2.66	159.38 ± 2.59	0.999
RR	64.06 ± 3.10	55.31* ± 2.76	60.31 ± 2.63	67.58 ± 3.43	<0.001

FiO_2	0.21 ± 0.21	*0.22 ± 0.26	0.22 ± 0.31	*0.24 ± 1.01	0.020
SpO_2	96.81 ± 0.54	96.55 ± 0.33	*95.49 ± 0.46	*93.38 ± 0.96	0.001
SpO_2/FiO_2	455.08 ± 5.70	*443.54 ± 5.42	*441.098 ± 5.98	*400.039 ± 13.86	0.001

*$p<0.05$ – compared to baseline (8L/min)