#### Research Proposal

**High Flow Nasal Cannula Dose Finding Study in Neonatal Intensive Care**

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**Lay Summary:** Delivery of air flow by high flow nasal cannula (HF) has become increasingly popular in neonatal and paediatric intensive care units throughout Australia and the world. Preliminary studies have been undertaken which have verified the safety and efficacy of HF use but what is not known is the level of high flow delivery which is adequate to sustain optimal ventilation. This study will determine the most appropriate flow rate for the infant by determining the optimal work of breathing. This will be achieved by measuring the electrical activity of the diaphragm. This study will also examine the physiological and ventilatory parameters which suggest optimal ventilatory delivery with HF.

1. **Background**

Respiratory distress syndrome in infants is treated with various forms of oxygen therapy. Delivery of oxygen can be via face mask, head box, nasal prongs, nasal cannula, non-invasive ventilation and invasive ventilation. Oxygen delivery using nasal cannula has become very popular, because the care of the patient is simplified when compared to other forms of oxygen delivery ([1-3](#_ENREF_1)). In the past, humidified or non-humidified pure oxygen was delivered nasally at a rate up to 2 L/min. The rate was then adjusted to obtain clinically satisfactory oxygen saturations (SpO2). Recently it has been described that the delivery of high nasal air flow (High Flow, HF) may cause inadvertent CPAP, changing the breathing pattern of infants and reducing the work of breathing ([4](#_ENREF_4)). There are a few studies that have dealt with the potential continuous distending pressure (CDP) these various non-invasive forms may deliver ([4-8](#_ENREF_4)). Unlike conventional nasal continuous positive airway pressure devices, high flow nasal cannulas deliver high flow rates without a mechanism to detect and prevent the generation of undesired or “desired” positive end-expiratory pressure.

Our group of researchers has the highest number of high flow publications nationally and recently published two physiological studies in which we described the physiological effect of high flow in infants with bronchiolitis and we have recently completed another study investigating high flow in neonates. We demonstrated that flow rates delivered at 8L/min increased lung volume, improved respiratory rate and oxygen saturation ([9](#_ENREF_9)). Moreover we were able to demonstrate using the electrical activity of the diaphragm (Edi) that flow rates delivered at 2L/kg/min significantly reduced the work of breathing ([10](#_ENREF_10)). However, both studies were limited by the fixed flow rates delivered. We concluded that the titration of the flow rates to the need of the patient would be more desirable. Additionally, we have also shown that the electrical signal obtained from the diaphragm is an ideal measure of the work of breathing. Therefore in this project we aim to perform a “dose finding” study to define the ideal flow rate for an individual patient.

The purpose of this study is 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. For this purpose of a dose finding study flow rates between 2 and 8 L /min in 2L steps will be randomly applied in premature infants with respiratory disease, and 0.5 L/kg/min up to 2 L/kg/min in 0.5 L/kg/min steps for infants with bronchiolitis. Optimal flow rate will be defined as the flow rate at which the electrical activity of the diaphragm is minimal. This study is similar to a previous study performed at the Mater Children’s Hospital but now with the follow up question of the dose finding for the correct use of High Flow.([10](#_ENREF_10))

## Aims and Hypotheses

***The primary hypothesis*** of the study is that there will be a non-linear relationship between HF flow rate and WOB.

The following ***specific aims of this study*** will address these hypotheses (in both preterm infants with respiratory disease and infants with bronchiolitis):

* To determine the relationship between applied flow rate of the Fisher & Paykel HF system and WOB.
* To identify an optimal flow rate 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.
1. **Study Design:** This study is a prospective interventional study. The study requires the use of diaphragmatic electrical activity (Edi) using an oesophagus probe and transthoracic diaphragmatic electrical activity signal to determine the effect of high flow nasal cannulae (HF) on work of breathing in infants with underlying lung pathology (either from prematurity or bronchiolitis).
2. **Methods**
	1. **Study Location:**
* Neonatal Critical Care Unit (NCCU), Mater Mothers Hospital, South Brisbane
* Paediatric Intensive Care Unit and Paediatric Respiratory Ward, Lady Cilento Children’s Hospital, South Brisbane
	1. Study Duration:

Recruitment, measurement and analysis of the data is anticipated to be completed in two years

* 1. **Subjects – Premature Infants**

Premature neonates (both male and female) admitted to the Neonatal Intensive Care Units (NICU 1 & 2) of the NCCU at the MMH, South Brisbane (Qld, Australia) during the period of data collection.

* + 1. ***Inclusion criteria:***
* Infants at 28 – 36 weeks corrected gestational age
* Are currently treated with nCPAP
* Are currently deemed stable enough by the treating medical and nursing staff to go onto HFNC
* Have an FiO2 requirement ≤ 0.40
* Nasogastric (ng) feeding tube in place
* Parent(s) or guardian able and willing to provide informed consent
	+ 1. ***Exclusion criteria***
* Lung or cardiovascular anomaly that would substantially affect oxygenation, lung recruitment or regional ventilation, e.g.;
	+ Cyanotic or other major congenital heart disease (not including Patent Ductus Arteriosus)
	+ Craniofacial malformations or congenital disease affecting the respiratory system
* > 2 episodes within the last hour of apnoea and/or bradycardia requiring moderate or vigorous stimulation and an increase in FiO2 or change in CPAP pressure
	+ 1. **Sample Size**

A convenience sample of 16 premature infants will be used. Based on our previous studies ([9](#_ENREF_9)), we can expect that 2 L/kg/min air flow causes an increase of CDP by 4.5 cmH2O (SD 2.7, n = 13). We expect a similar effect in the current study on Edi. Using a power of 90% and a P-value of < 0.05 we need to enrol approximately 12-15 patients.

* 1. **Subjects – Infants with bronchiolitis**
		1. ***Inclusion criteria***
* Clinical diagnosis of bronchiolitis with increased WOB (retraction, auxiliary respiratory muscle use) and respiratory distress due to viral infection
* An oxygen requirement treated with high flow in ICU
* Aged 0-12 months
* Nasogastric (ng) feeding tube in place
* Parent(s) or guardian able and willing to provide informed consent
	+ 1. ***Exclusion criteria***
* Oxygen requirement of more than 60%
* Upper airway obstruction
* Craniofacial malformations
	+ 1. **Sample Size**

A convenience sample of 30 infants will be used. In our previous study we investigated 15 infants with bronchiolitis on and off high flow and did find a significant difference in the electrical activity of the diaphragm. This proposal however will use a randomly applied flow rate, hence we need to account for a repeated measurement effect.

* 1. **Measurement techniques**

As previously published ([10](#_ENREF_10)), work of breathing will be measured with diaphragmatic electrical activity (Edi) and respiratory inductance plethysmography (RIP) as a standard measurement technique. Using the Edi signals we will measure the WOB during HF treatment and assess the impact of HF on patients with respiratory distress.

* + 1. ***Transoesophageal Diaphragmatic Electrical Activity (Edi):***

A specially designed Edi sensing nasogastric tube is inserted. This tube also serves as a normal nasogastric tube for feeding. The tube has sensors placed at the level of the diaphragm detecting the diaphragmatic electrical activity (Figure 1). The Edi signal is captured with an analysis and data processing module of the Ventilator. The measured signal is proportional to the patient’s respiratory effort (Figure 2). The signal is analysed using the peak value and the area under the curve. The maximum correlates with the effort of the diaphragmatic muscles as the signal is proportional to the number of muscles activated. 

**Figure 1:** Placement of Edi probe and measurement of Edi signal



**Figure 2:** The Edi signal is proportional to the effort of breathing

* + 1. ***Transdermal Diaphragmatic Electrical Activity (Tdi)***

A relatively newly developed generic electrical activity measurement device (Dipha-16) will be used, which detects electrical signals such signals generated by the heart (ECG), muscle electrical activity (EMG) or electrical signals generated by the brain (EEG). The device uses five regular skin electrodes that are normally used for ECG measurements. For the purpose of detecting electrical signal of the diaphragm an offline software package has been written to identify the correlation between work of breathing (EMG signal) and the flow rate delivered.

* + 1. ***Respiratory Inductance Plethysmography (RIP):***

RIP will be used in all subjects as a control measure to assess asynchrony of breathing as a surrogate for WOB measure. RIP is a non-invasive pulmonary function test that is widely used in sleep medicine, which does not interfere with the subjects breathing and does not cause any discomfort. It consists of two stretch bands placed around the chest and abdomen. Information on electrical impedance of the integrated copper wires is obtained while the stretch band is expanded during in- and expiration. Standard analysis of Lissajous Loop will be used with dedicated software.

Both Edi and RIP signal can be recorded continuously during the entire study period and recorded on a dedicated computer and further analysed.

* + 1. ***Physiological variables:***

Respiratory rate (RR), heart rate (HR), and oxygen saturations (SpO2) will also be monitored throughout the study. From the collected data the SpO2/FiO2 ratio will be calculated ([11](#_ENREF_11)).

* 1. **Study Procedure:**

Infants recruited into the trial will be on high flow nasal prong oxygen therapy using the Fisher & Paykel 850 humidifier according to unit standard protocol. Informed consent will be obtained by study personnel or doctor. The in situ nasogastric tube will be replaced by the Edi probe.

* + 1. **Study Procedure – Premature Infants**

The following sequence of measurements will be taken on HF.

* The first measurement will be done on 8 L/min HF treatment, when the infant is settled but within the first 24 hours of HF administration. A washout period of 10 minutes will be applied between each change in therapy and measurement period. Length of measurements will be 5 min or approximately 200-300 breaths.
* Flow rates between 2L/min and 8 L/min in 2L steps will be randomly applied. Randomisation will be undertaken by study personnel using a computer generated randomisation with allocation concealment by sequentially numbered sealed opaque envelopes. After each flow rate change an equilibration phase of 10 minutes will be allowed before undertaking a 5 minute measurement.
* Measurements of 5 minutes duration will be taken at baseline (8L/min), 2L/min, 4L/min, and 6L/min. The total study duration will be approximately 2 hours.
	+ 1. **Study Procedure – Infants with bronchiolitis**

The following sequence of measurements will be taken on HF.

* The first measurement will be done on 8 L/min HF treatment, when the infant is settled but within the first 24 hours of HF administration. A washout period of 10 minutes will be applied between each change in therapy and measurement period. Length of measurements will be 5 min or approximately 200-300 breaths.
* Flow rates will be randomly applied between 0.5 L/kg/min and 3 L/kg/min and inspired oxygen fraction adjusted to achieve transcutaneous oxygen saturation of >94%. At the completion of the study, the bands will be removed but the Edi probe is able to remain to deliver feeds.
	1. **Adverse Events**

If any of the premature infants meet any of the following ‘failure criteria’, the study will be 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)

In the instance that pulse oximetry (SpO2) saturations drop to <92 % off HF, then pre-study HF treatment will be reinstated in the infants with bronchiolitis and the study discontinued

1. Should any of these adverse events occur, these will be documented as study failures. A DSMB will review these events to enable an independent review of safety. **Data analysis**

As previously published ([10](#_ENREF_10)), Edi max, amplitude and area under the curve (AUC) will be measured for each breath and will be compared for the period on and off HF treatment. For the RIP data, the end expiratory level (RIPEEL), amplitude (RIPAMPL) and the ratio of the inspiratory phase to the entire respiratory cycle (RIPTi/Ttot). For the oesophageal pressure (Poe) signals, the minimum respiratory point (PoeMIN), the maximum respiratory point (PoeMAX) and the breath to breath change in pressure (PoeAMPL). The pressure rate product (PRP) will be calculated (PoeAMPL x RR) to examine work of breathing (WOB).

1. **Statistics procedure**

Data will be described using means and 95% confidence intervals. Standard deviation scores (SDS) will be used to describe changes from baseline, with a twofold sustained increase in SDS considered significant. ANOVA with Bonferoni correction for repeated measurements will also be used. A p-value of <0.05 will be considered statistically significant.

1. **Ethical Considerations**

All procedures in these studies will conform to the NH&MRC National Statement on Ethical Conduct in Human Research (2007) and will be conducted according to a protocol approved by the Human Research Ethics Committee, Mater Health Services Ltd, South Brisbane, Queensland.

* 1. **Vulnerable subject group**

In order to answer the questions posed regarding lung function in infants, it is necessary to perform this research on the vulnerable subject group of infants in neonatal and paediatric intensive care. Consequently, extreme care will be taken to ensure that the project is not contrary to the infant’s interest and there will be minimal intrusion. Prior to approaching the parents for consent the consultant on duty will be approached for approval to do so. Every effort will be made not to burden the parents and consent will be free and informed and refusal will not in any way compromise the care of the infant. Clinical care of the infant will always take priority over the study, and the clinical team caring for the infant can request cessation of the study procedures at any time if it is deemed to be in the baby’s best interests.

* 1. **Consent**

Written informed consent will be obtained from the parents of all infants prior to inclusion into the trial. Parents will be permitted to withdraw their infant at any time without need for explanation. Additionally it will be required that the parent providing informed consent is at least 18 years of age.

* 1. **Confidentiality**

Confidentiality usually applied to patient medical records and information will be adhered to. All data will be collected and stored as de-identified and no reference will be made in any publication or presentation that will allow identification of a child. Files will be stored in a locked cabinet in a locked room and under password protection in the data collection and analysis computers. Data will be stored after publication required by editorial policy, or as determined by Mater Health Services research governance, whichever is the greater. Clinical data collected for this study must be retained for 10 years from the participant attaining the age of 18 years.

* 1. **Risk**

The infants recruited in to the trial will be closely monitored as is standard practice for all infants requiring respiratory support within intensive care. As with any change in respiratory therapy, there is a risk that infants will ‘fail’ on HF and require return to CPAP prior to study completion. To minimise the risk of adverse events occurring, strict ‘failure criteria’ have been established (section 4.6) for this study.

The infants will need the nasogastric tube replaced with the Edi probe. This is an additional procedure for the study; however considering that nasogastric tubes may be changed multiple times over the course of an admission, this seems acceptable. The Edi probe itself is not different in size to a normal nasogastric tube and there is no additional risk in inserting it.

Measurements taken are considered to present a ‘low risk’, with the only foreseeable risk as being one of discomfort (as defined in the Chapter 2.1, National Statement 2007) to the infants participating.

1. **Potential benefits of study**

High flow nasal cannula (HFNC) has become a very popular mode of ventilation in the neonatal and paediatrics populations in the last 5 years. However research into its physiological effects is still limited. Currently, high flow is used with little knowledge as to the correct dosage guidelines. This study will inform clinicians as to the correct high flow dosage on which infants and children should be commenced. There is no direct benefit of the study to the enrolled infant, nor their parent or guardian. After finishing the study parents and patients may request study results from the investigators. Study results however will be not available at the time of the study so as not to interfere with the patient management.

1. **Indemnification**

No special arrangement for indemnification will be made as the patients are not exposed to additional risk.

1. **Budget**
	1. ***Equipment and Disposables Requested:***
* Equipment and software necessary to undertake this study is already available:
	+ PowerLab and RIP
	+ Edi probes and ventilator provided by Maquet
	+ Tdi equipment covered by Fisher and Paykel
	1. ***Salaries***
* Research Fellow (Dr. J. Hough) receiving Betty McGrath research fellowship at 0.2 FTE and therefore covered for for co-ordination, data collection, analysis and for paper write up
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