A Proof of Concept Study of Respiratory Physiology in Preterm Neonates during High Flow Nasal Cannula Therapy

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Abstract

Introduction and rationale: High flow nasal cannula therapy is being increasingly used as a form of respiratory support across the world. Its adoption and popularity have been rapid but little is known regarding its key mechanism of action even after more than a decade of its use. I conducted a proof of concept study of respiratory physiology during high flow therapy in preterm neonates.

Methods: The study protocol involved measurement of nasopharyngeal airway pressures and gas concentrations as well as measurement of tidal breathing indices. A detailed descriptive review of clinical efficacy of high flow nasal cannula in preterm infants was performed. In order to identify the optimum measuring techniques, in this proof of concept study, three types of pressure measuring techniques, a gas analyser device and a non-invasive tidal breathing indices device were studied and the results are presented in this thesis. In addition, a detailed protocol for a larger randomised crossover study of respiratory physiology during continuous positive airway pressure of 6 cm H$_2$O and high flow nasal cannula therapy ranging from 2-8 litres per minute flow was designed.

Results: In this thesis, the results of a proof of concept physiological study have been presented. The results of the measurements performed in six babies of varying gestational age (less than 37 weeks of gestation) and birth weight are presented. Valid tidal volumes were measured in all babies, nasopharyngeal gas concentrations and pressure measurements in five and two babies respectively. There were no adverse events.

Conclusions: It is feasible to measure nasopharyngeal air way pressures and gas concentrations as well as non-invasive tidal breathing indices in babies on high flow nasal cannula therapy safely. This study was successfully followed up by a larger randomised cross over study involving 45 infants with the same protocol.
Dedication

For Madhura, Sameeksha and Samarth.
Acknowledgements

First and foremost, I am extremely grateful to my primary supervisor, Dr Chris O’Brien, who provided me the window of a great opportunity to learn research and guided me during this work. I had many long hours of physiology teaching from him, which was invaluable in my understanding of some of the difficult concepts involved in this study. He has not only taught me his knowledge and expertise but also supported and encouraged me to take decisions which helped me progress in my career. I will always remember that I owe it to him in becoming a Respiratory Paediatrician.

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I am indebted to Dr Alan Fenton and Dr Sundeep Harigopal for their whole-hearted support and encouragement throughout the study period. I was adequately supervised on site by them for all situations that I came across during the conduct of the study. They provided significant amount of their time in developing the protocol, providing input from their experience and knowledge as senior neonatologists.

I would also like to thank all the hard working and dedicated medical and nursing staff on the neonatal unit at the Royal Victoria Infirmary who supported me like their own family member. I offer my sincere gratitude to all the infants and their parents on the Neonatal intensive care unit at the Royal Victoria Infirmary, Newcastle upon Tyne, UK for their participation in this study.

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<td>Krypton</td>
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<td>Arterial Blood Gas</td>
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<td>ABW</td>
<td>Anterior Bony Window</td>
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<td>AOP</td>
<td>Apnoea of Prematurity</td>
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<td>BCAW</td>
<td>Bony Choanal Aperture Width</td>
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<td>BCPAP</td>
<td>Bubble Continuous Positive Airway Pressure</td>
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<td>BiPAP</td>
<td>Bilevel Positive Airway Pressure</td>
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<td>BNC connector</td>
<td>Bayonet Neill–Concelman connector</td>
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<td>Bronchopulmonary dysplasia</td>
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<td>Confidence Interval</td>
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<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<td>COPD</td>
<td>Chronic Pulmonary Obstructive Disease</td>
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<td>COSHH</td>
<td>Control of Substance Hazardous to Health</td>
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<td>DC</td>
<td>Direct Current</td>
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<td>EMBASE</td>
<td>Excerpta Medica dataBASE</td>
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<td>FiO$_2$</td>
<td>Fraction of inspired Oxygen</td>
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<td>Fr</td>
<td>French (refers to size)</td>
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<td>FRC</td>
<td>Functional Residual Capacity</td>
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<td>Expiratory Flow Volume loop centre of gravity</td>
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<td>Heart Rate</td>
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<td>Inaccuracy$^2$</td>
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<td>INSURE</td>
<td>Intubation, Surfactant administration, Extubation</td>
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<td>IRAS</td>
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<td>KiloPascals</td>
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<td>Low Flow Oxygen</td>
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<td>Limit of Agreement</td>
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<td>Litres Per Minute</td>
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<td>Micro Electro Mechanical Systems</td>
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<td>Minute Volume</td>
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<td>NIV</td>
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<td>Nasopharyngeal Vertical Distance</td>
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<td>Outer Diameter</td>
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<td>PaCO$_2$</td>
<td>Arterial Carbon dioxide content</td>
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<td>PCA</td>
<td>Post Conceptional Age</td>
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<td>Partial pressure of Carbon dioxide</td>
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<td>PDA</td>
<td>Patent Ductus Arteriosus</td>
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<td>Positive End Expiratory Pressure</td>
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<td>Pes</td>
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<td>PETCO$_2$</td>
<td>Carbon dioxide with Pneumotach</td>
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<td>Post Menstrual Age</td>
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<td>Oesophageal Pressure</td>
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<td>Pressure Rate Product</td>
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<td>Prp</td>
<td>Retro Pharyngeal Pressure</td>
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<td>PSU</td>
<td>Power Source Unit</td>
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<tr>
<td>PTEF</td>
<td>Peak Tidal Expiratory Flow</td>
</tr>
<tr>
<td>Ptp</td>
<td>Trans pulmonary pressure</td>
</tr>
<tr>
<td>PTPdi</td>
<td>Pressure Time Product of diaphragm</td>
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<td>RABW</td>
<td>Right Anterior Bony Width</td>
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<td>%RC</td>
<td>Rib cage contribution</td>
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<td>RCT</td>
<td>Randomised Control Trial</td>
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<td>RD</td>
<td>Risk Difference</td>
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<td>RDS</td>
<td>Respiratory Distress Syndrome</td>
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<td>Rev Man</td>
<td>Review Manager</td>
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<td>Respiratory Inductance Plethysmography</td>
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<td>RR</td>
<td>Risk Ratio</td>
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<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
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<td>Synchronised Intermittent Positive Pressure Ventilation</td>
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<td>SpO₂</td>
<td>Oxygen saturation</td>
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<td>TAA</td>
<td>Thoraco Abdominal Asynchrony</td>
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<td>TAM</td>
<td>Thoracic Abdominal Motion</td>
</tr>
<tr>
<td>TcPCO₂</td>
<td>Transcutaneous Partial Pressure of Carbon dioxide</td>
</tr>
<tr>
<td>te</td>
<td>Expiratory time</td>
</tr>
<tr>
<td>TEF</td>
<td>Total Expiratory Flow</td>
</tr>
<tr>
<td>TGI</td>
<td>Tracheal Gas Insufflation</td>
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<td>Ti</td>
<td>Inspiratory times</td>
</tr>
<tr>
<td>TOSCA</td>
<td>Transcutaneous Oxygen and Carbon dioxide measurement</td>
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<td>tPTEF</td>
<td>Time to Peak Tidal Expiratory Flow</td>
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<td>TTC</td>
<td>Trans Tracheal Catheter</td>
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<td>Alveolar Ventilation</td>
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<td>Very Low Birth Weight</td>
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<tr>
<td>VT</td>
<td>Tidal Volume</td>
</tr>
<tr>
<td>WOB</td>
<td>Work of Breathing</td>
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Publication and Presentations


Chapter 1. Introduction
1.1 Prevalence of HFNC use

1.1.1 Definition

In the Cochrane review of HFNC in neonates the following definition was used to identify relevant studies – ‘High flow nasal cannulae (HFNC) are small, thin, tapered binasal tubes that deliver oxygen or blended oxygen/air at gas flows of more than 1 L/min’ (1).

The flow rate is considered high flow when it is above that used in conventional low flow system. In LFNC system, the oxygen is not humidified or heated and is delivered by standard nasal cannulae (1-3).

However, defining HFNC in absolute numbers without taking into account patient population that it is being used on is likely to be inaccurate. For example, a flow of 1-2 litres per minute in an older child or an adult may not be high flow. The flow has to be well above the inspiratory flow demands of a patient when in respiratory distress. The inspiratory flow demands rise significantly at times of respiratory distress.

In the context of this study, as this study is in neonates, a definition of more than 1 litre per minute flow is used.

1.1.2 History of HFNC usage

The current modern high flow nasal cannula therapy systems have evolved over time. This was possible due to inventions that led to the development of apparatus adapted to heat and humidify air and to deliver heated and humidified air to the respiratory tract of a human patient. The integration of blenders that deliver varying concentrations of oxygen to the patient has also been crucial. There were a series of inventions in the 1970s that led to humidification of gases and in 1980s heating and humidification technologies were further improved (4).

The delivery of oxygen and oxygen enriched air to the respiratory tract of a patient can cause discomfort. If this gas mixture also has low humidity it increases the respiratory irritation. The
respiratory irritation is worse when the oxygen and air mixture is administered over a long period of time (4).

Some of the early examples of inventions that tried to overcome this problem include a device developed by Richard H Blackmer in 1981 that allowed oxygen enriching apparatus to increase or regulate the humidity of the air. The air supplied to the patient may be heated by circulation of warm air over delivery tubing, use of electric resistance heaters or circulating warm liquid co-linearly with the delivery tubing (4, 5). Similarly Fisher and Paykel Ltd developed a heating and humidification device in 1985. In their design, the humidifier has the ability to create a vapour pressure sufficient to cause water vapour and deliver at a desired temperature (6).

Throughout the 1980s and 1990s, various companies and individual scientists developed heating and humidification devices for delivery of blended air/oxygen mixture to patients (4). Vapotherm produced the first Food and Drug Administration (FDA) approved device for delivering humidified high flow therapy in neonates in 2004. This device was called Vapotherm 2000i. This approval was for intended use to add moisture and to warm breathing gases for administration to patients, including neonates/infants and paediatric or adult patients (7).

These Vapotherm units were withdrawn from the market in January 2006 following concerns due to Ralstonia infection in some US neonatal units. This was followed by a period of individual units putting together their own systems for delivery of heated, humidified gas using basic components of a humidifier, respiratory circuit, adapter and nasal cannula (7).

This was followed by device produced by Fisher and Paykel Healthcare (Auckland, New Zealand). This device called RT329 Infant Oxygen Delivery System was able to deliver heated (37C) and humidified (44 mg/L) gas via nasal cannula at flow rates of up to 8 L/min (7).

Depending upon the manufacturer the methods of heating and humidification of gases in various high flow devices vary. For example, heating method in Vapotherm is by having a tube structure where warm water compartment encircles the respiratory gas delivery tube whereas in Fisher and Paykel system a heated wire coil is used which extends to the end of
the circuit (7). Currently there are many commercial systems available manufactured by different companies such as Vapotherm, Fisher and Paykel, ResMed. The relative merits of these devices need investigating.

1.1.3 Use of HFNC in neonatal units

The use of HFNC in neonatal units has been on the rise. The common reasons cited for the use of HFNC over CPAP has been increased patient comfort, easier to apply and reduction in nasal trauma and to provide positive airway pressure support. The increase in use predated completion of large clinical trials.

In an online survey of 157 neonatologists in Australia and New Zealand in the year 2012, 27 neonatal units were contacted (8). The response rate was 71% with 67% returning complete response to the questionnaire (8). 63% of the neonatal units at that time were using HFNC (8). 57% of the neonatologists replied that there was no published data on safety and clinical usefulness of HFNC in neonates, however 15 of the 27 neonatal units covered in this survey had some local policy in place for using HFNC (8). Rain out of the circuit with fluid instillation into the upper airway was the most common problem reported (8). Most reported (86%) that it was easier to apply and 84% reported HFNC was better tolerated by the babies (8) than CPAP. Only 21% of the units used HFNC as primary support for RDS whereas 62% were using as post extubation respiratory support (8). HFNC was used as a primary treatment for apnoea of prematurity in 58% of the units (8). Side effects including pneumothorax, hyperinflated lung fields, pulmonary haemorrhage, or feeding intolerance were not documented with HFNC use (8).

In the USA, Hochwald and Osiovich performed a questionnaire survey of 97 academic neonatal units, 69% of the responders were using HFNC (9).

In 2009, a telephone survey of senior nurses working in 214 UK neonatal units found 55% of the units using HFNC (10). The definition of HFNC was flow rate more than 1 litre per minute (10). However only 77% of these units were humidifying the gases before delivery as high flow (10). This reflects the evolution of high flow nasal cannula technology that earlier high flow gases were delivered without appropriate humidification or heating to appropriate temperature.
A telephone survey of 203 UK neonatal units was done in 2012 with 100% response rate (11): 113 (56%) of the neonatal units use some form of HFNC (11), 42% of the units used either HFNC initially or CPAP followed by HFNC following extubation (11). HFNC was used only as a step down from CPAP in 58% of the units (11). Flow rate at commencement varied between with 60% of the units starting at HFNC at 8 litres per minute and 30% of the units at 5-6 litres per minute (11). Most units weaned off the HFNC once the flow rate was 2-3 litres per minute (11).

A web based survey of 57 Level 2 and 3 neonatal units was done from November 2011 to May 2012 in the UK with 77% response rate (12). Among the responders 77% of the units used HFNC (12), 50% of the units did not have any guideline for use of HFNC (12). Vapotherm was the most commonly used device with 47% of the units using it whereas Fisher and Paykel bRT329 was used in 38% units (12). Indications included as an alternative to CPAP in 77%, for weaning CPAP in 71%, and for post extubation support in 53% (12). Gradual reduction in flow rate was the most common method of weaning where as one unit weaned by reducing the time spent on HFNC (12).

It is evident from the series of surveys that the prevalence of use of HFNC is increasing in neonatal units. This increase in use is not based on irrefutable evidence of its safety and efficacy. The ease of administration and no reports of significant serious short term adverse events might have allowed its acceptance.

Recent studies on HFNC use in neonates have not reported increased incidence of BPD but information about 'Severe BPD' is lacking. We examined the incidence of 'Severe BPD' by performing a retrospective audit of neonatal unit data from Royal Victoria Infirmary, Newcastle upon Tyne looking at the population of preterm babies less than 32 weeks’ gestation that required oxygen beyond the first 28 days of life (13). The aims of the audit were to examine trends in use of non-invasive respiratory support and respiratory outcomes in neonates <32 weeks’ gestation receiving non-invasive ventilation (NIV) and to identify association between type of non-invasive respiratory support and severe BPD.

A total of 776 babies with <32 weeks’ gestation were admitted during the five-year period between January 2008 and December 2012 (13). Among these, 282 preterm babies required oxygen >28days of life (13). Out of these, 128 babies received CPAP ± BiPAP alone and 154
received HFNC ± CPAP. The use of HFNC increased during this five-year period and that of CPAP as the sole non-invasive respiratory support decreased as illustrated in the Figure 1.

Figure 1. Five-year trend in NIV use

Figure 1 shows the increase in use of HFNC during the 5-year period associated with decline in use of CPAP alone as non-invasive therapy.
1.2 High Flow Nasal Cannula Device Set Up

HFNC system is composed of humidification unit and flow driver and different types of heating system to deliver warmed, humidified blended air/oxygen mixture at variable flow rate and adjustable FiO₂. These gases are heated to temperature close to 37°C, humidified to 100% relative humidity and delivered to the patient via nasal cannulae.

Several manufacturers currently produce different HFNC circuits and devices, which vary in heating and humidification methods.

The HFNC devices currently available in the market differ in their technology in different aspects of HFNC system but underlying principle is to administer the heated, humidified blended gas mixture at desired flow rate and FiO₂. A schematic diagram of a HFNC device is shown in figure 2.
Figure 2. Schematic diagram of a HFNC device

Figure 2 shows components of a typical HFNC device.
1.3 Mechanisms of Action

The following mechanisms of action of the heated, humidified high flow nasal cannula system have been suggested. It is important to note that the relative contribution of these mechanisms is not yet clearly elucidated. The possible role of these mechanisms has been either directly studied (14) or been extrapolated from similar studies done in animals and in vitro systems (14).

1. Heating and humidification of gas
2. Airway distending pressure
3. Airway dead space wash out
4. Effect on work of breathing
5. Reducing metabolic demand

1.3.1 Heating and humidification of gas

It is a function of the upper airway particularly the nasal space to warm and humidify the inspired gas before delivery to lower airways. However, the inspiratory gas flows delivered by high flow systems are far higher than the inspiratory flows normally taking place in an infant with tidal breathing or even during respiratory distress. The anatomical capacity of the natural humidification and heating system thus is limited to meet the humidification requirements for higher inspiratory flows. Consequently, the unhumidified and unheated gas flows can dry up the mucosa and result in mucosal injury and infection Kopelman (15).

The clinical effectiveness of systems with heated and humidification gas delivery is also likely to be better compared to unheated and unhumidified system. In a crossover study of 30 preterm infants, post extubation support with heated and humidified device (Vapotherm) fared better with no extubation failure compared to those receiving unheated and unhumidified high flow (16).

The possible reason for this improved clinical effectiveness with heated humidified high flow system is likely because of its effects on pulmonary compliance and conductance. Saslow and colleagues compared 6 cm of H₂O of conventional CPAP using standard humidification system with a high flow system delivering 5 L/min of heated humidified gas to infants. The
respiratory compliance profile was 1.03 ± 0.47 for HFNC whereas only 0.83 ± 0.49 ml/cm H2O / kg for CPAP (17).

This improved respiratory compliance seen with HFNC system when compared to CPAP was seen despite CPAP achieving better oesophageal pressure (a surrogate for airway end expiratory pressure) profile (1.76± 1.46 vs 1.32 ± 0.77 cm H2O)(14, 17). Thus HFNC system achieved better respiratory compliance despite achieving less distending pressure possibly due to better conditioning of delivered gas (14). This effect on compliance was observed in an earlier study in ventilated infants that even five minutes of ventilation with unheated and unhumidified gas resulted in significant reduction in pulmonary compliance and conductance (18).

1.3.2 Airway distending pressure

It is well established that the airway distending pressure is one of the main mechanisms of action of CPAP devices. That CPAP is effective in treating respiratory distress in infants was shown way back in 1971 (19). HFNC also delivers a certain amount of distending pressure to the airways as shown in several studies including in vitro studies (20-23) as well as a number of small clinical and interventional studies in humans (3, 17, 24-31).

The distending pressure increases the Functional Residual Capacity (FRC). FRC is the volume of gas remaining in the lungs at the end of a normal expiration. At this lung volume the outward recoil of the chest wall and inward lung recoil are equal. FRC is reduced when the lungs are stiff and chest wall has low elasticity such as seen with preterm infants. Thus reduction in FRC means the baby is breathing from a lung volume which is closer to the closing volume. Since CPAP increases transpulmonary pressure there is increase in lung volume at the end of a normal respiration i.e., FRC. The increase in FRC in turn results in improved ventilation (32).

The quantity of airway distending pressure achieved during HFNC is variable and unpredictable. This depends upon the quantity of leak at the nasal cannula –nares interface and at the mouth level. The flow rates used and size of the baby also influence the airway pressures measured during HFNC therapy.
1.3.3 Airway dead space wash out

The Carbon dioxide (CO\(_2\)) removal is enhanced by enhancing the alveolar ventilation. The alveolar ventilation is determined by the minute volume which is calculated from the equation,

Respiratory Minute Volume (MV) in litres (L) = Tidal Volume (TV) in litres X Respiratory Rate (f)

Alveolar Minute Ventilation = (Tidal Volume – Dead space) X Respiratory Rate (f)

Therefore, it is apparent that by reducing the dead space component, the alveolar ventilation can be improved.

Since HFNC delivers gas flow in excess of inspiratory gas flow demands there is wash out of exhaled CO\(_2\) and enrichment of delivered O\(_2\) concentration in the upper airways and possibly further along the conducting airways. This effectively reduces dead space volume as there is clearance of CO\(_2\) from conducting airways allowing the alveolar ventilation with new gas mixture achieved by HFNC. Therefore, the efficiency of gas exchange improves. This results in lesser need for the infant to increase MV by increasing the respiratory rate. Clinically this has been observed by reduction in respiratory rate in several retrospective (33, 34) and prospective studies (31, 35).

There is speculation that this improvement in ventilation is due to dead space wash out effect mainly and not due to distending pressure alone (22). In an animal study involving piglets with induced acute lung injury, HFNC administered within a range of 2-8 L/min, achieved improved ventilation and oxygenation. This effect was proportional to the flow levels used irrespective of pressures generated and higher leak resulted in better oxygenation (22).

1.3.4 Effect on work of breathing

Thoraco-abdominal asynchrony, Tidal volumes, pleural pressures (indirectly inferred by oesophageal pressures) measurements have been done to study the effects of HFNC and CPAP on respiratory mechanics and work of breathing (17, 30, 31, 36, 37).

Locke et al demonstrated that as the flow rate increases there is a reduction in thoraco-abdominal asynchrony (30). Since thoraco-abdominal asynchrony gives an estimate of work of breathing, increasing the HFNC flow rate resulted in reduction in work of breathing (38).
Boumeid demonstrated in 19 preterm infants that the thoraco-abdominal asynchrony seen in HFNC was comparable to that seen in constant-flow CPAP whereas variable – flow CPAP was better in improving thoraco-abdominal asynchrony (37).

The tidal volume measured by respiratory inductance plethysmography during HFNC when compared to CPAP was similar as found by two different investigators (17, 37). Similarly a respiratory mechanics study by Lavizzari involved 20 preterm infants who required non-invasive respiratory support within 96 hours after birth (36). They studied tidal volumes measured by respiratory inductance plethysmography, pleural pressures estimated from oesophageal pressures and also gas exchange during administration of a randomised sequence of CPAP at 2.4 and 6 cm H2O and HFNC at 2, 4 and 6 Litres per minute (36). Their study did not show any significant differences in breathing pattern, gas exchange or total work of breathing between HFNC and CPAP(36). Comparison of CPAP fixed at 6 cm of H2O was done with variable amounts of HFNC between 1-6 litres per minute flow rate was done by Lampland et al (31). They measured heart rate, respiratory rate, inspired oxygen concentration, and arterial oxygen saturation (31). They noticed increased oxygen requirements, increase in respiratory rate and also some apnoea events when HFNC flow rates were 1-2 litres per minute (31).

In a randomised crossover study in infants with evolving or established BPD, Shetty et al studied effects of HFNC and CPAP on work of breathing, thoracoabdominal asynchrony and oxygenation (39). They studied 20 infants (median gestational age of 27.6 weeks (range 24.6-31.9 weeks) at a median postnatal age of 30.9 weeks (range 28.1-39.1 weeks) (39). Infants were studied on 2 consecutive days (39). On the first study day, they were randomised to either CPAP or HHFNC each for 2 h, the order being reversed on the second day (39). The pressure time product of the diaphragm (PTPdi) was used to infer the work of breathing (39). There were no significant differences in the work of breathing on CPAP versus HFNC as the mean PTPdi 226 (range 126-294) was similar to HFNC mean PTPdi 224 cm H2O/s/min (95% CI for difference: -27 to 22; p=0.85) (range 170-318) (p=0.82) (39).

In a single centre, prospective study involving children less than 3 years of age, relationship between HFNC and effort of breathing was studied. The effort of breathing was estimated by measuring percent change in pressure rate product (PRP) (40). They used different levels of flow rates at 0.5, 1.0, 1.5, and 2.0 L/kg/minute based on body weight (40). In 21 patients with
49 episodes they reported that increasing flow rates resulted in a significant difference in the percent change in PRP from baseline (of 0.5 L/kg/minute). The highest change was seen at flow rate of 2.0 L/kg/min (-21%) (40). Further, this effect was particularly significant in children less than 8 kg in weight.

1.3.5 Reducing metabolic demand

The inspired air is warmed to 37°C and humidified to 100% relative humidity by the nasal passages (14). There is energy cost to this process of conditioning the gas before delivery to lower airways (14). The nasal passages do capture moisture and heat from expired gas for recycling with subsequent inspirations (14). However as this is not 100% efficient system, there is metabolic energy expenditure by nasal mucosa to warm and humidify the inspired gas to ideal conditions (14). In an adult breathing at 12 breaths per minute with 500ml tidal volume in an environment of 21°C temperature and 50% relative humidity will spend an additional 156 calories per minute to warm and humidify the inspired air to ideal condition (14). HFNC by delivering gases warmed to 37°C and humidified to 100% relative humidity reduce the metabolic cost to the baby (14).

1.4 Effects of HFNC on Airway Distending Pressures

1.4.1 Airway pressure - Principle factors

Airway pressure due to HFNC is determined by three principle factors (41):

- Flow
- Anatomical dimensions
- The leak –Around nasal prongs & mouth

A schematic representation of the resistors in series and pressure compartments that can be identified is shown in figure 3.
Figure 3 illustrates the two resistors and two pressure compartments in the circuit - patient HFNC system applied to patient. Resistor ($R_1$) is the nasal cannula and therefore pressure compartment ($P_1$) is the patient circuit (41). Resistor ($R_2$) represents the components resistive to gas release from the patient’s nose (around the cannula) and mouth and therefore pressure compartment ($P_2$) is the pressure in the nasopharynx (41).

Unlike CPAP, High flow nasal cannula is an open system. Gas flow delivered to a patient via nasal cannula and the cannula prongs should not occlude the nares and where the patient’s mouth should not be actively closed (41). The reason for this is explained by the understanding of resistance locations and pressure segments in the whole HFNC and patient airway continuum. The pressure in each compartment is a function of the resistor(s) that lie in series downstream from that compartment (41). Therefore, circuit pressures will always be substantially greater than pressure in the nasopharynx (41).

1.4.2 Pressure in the Device Circuit

Nasal cannula outer diameter is very small in the range of 2-3.7 mm (2). Therefore, this offers very high resistance to airflow. Therefore to achieve high flows into the patients airway the circuit pressure needs to achieve high levels up to 3 to 4 PSI range (41). It has been shown that limiting the pressure by pressure limiting valve (PLV) limits the ability to deliver higher flows (31). It is not possible to transfer the same amount of high pressure into the patient’s airway because of the nasal cannula resistor which is upstream to airway. The key findings of role of pressure limiting valve in HFNC device is shown in figure 4.
Figure 4 shows the data from Lampland et al (31) using a Fisher and Paykel HFNC system with and without a pressure limiting valve (PLV) set to 45 cmH₂O noted that with the pressure limiting valve in place, the system does not permit more than 2 L/min to pass through the cannula regardless of the flow entering the humidifier (31, 41).

### 1.4.3 Anatomy of upper airway

The nostrils and nasal cavities are the first anatomical points through which HFNC is delivered. It is therefore important to study the distribution and velocity of the airflow in the nasal cavity. In order to understand this phenomenon, knowledge of nasal anatomy and its geometrical influence has to be understood.

The nasal cavity has tortuous passages that form a large surface area and are lined with mucosa (42). The nasal cavity extends from nasal vestibule till the beginning of nasopharynx. This is actually two separate airways partitioned by the nasal septum within the nasal cavity (42). The nasal vestibule is the area enclosed by the external cartilages of the nose and is lined with small, filtering hairs (42). The turbinates (or concha) are long, narrow and curled bone shelves that protrude into the nasal cavity, creating a large surface area and forming the inferior, middle and superior airways and meatus passageways (42). The nasal valve occurs just posterior of the nasal vestibule and is the region of smallest cross-sectional area (See figure number 5) (42).
These cross-sectional areas at the nasal valve has been found to be 0.54–1.21 cm² measured by Ozcan Cakmak et al (43). They determined this from their study on 25 healthy adults using CT scan data. However the nasal valve size is not constant but constantly changing with the nasal cycle with changes in the surrounding erectile tissues (44). The nasal valve leads into the nasal cavity expanding both in height and in cross sectional area. The relative anatomy of both half of nasal cavity is similar although they are not symmetric in dimensions (42). The right side tends to be larger in cross sectional area (42). The cross sectional area of the right nasal cavity 7.2 cm posterior of the external naris is 30% larger than on the left (42).

In a study examining the dimensions of human nasal cavity using CT scan data of 30 healthy adults reported that the internal volume of middle region of the left and right nasal cavities vary by up to 65% (45). The cross-sectional area narrows down to 1.1 cm² in the oropharynx. The oropharynx size depends upon the position of soft palate (42).

Since the nasal passages have complex geometry and inaccessible passageways, it is difficult to study flow pattern within nasal cavities. However the flow patterns can be studied using in vitro artificial nasal models (42). Using computational models, Wolf et al (46) found that on inspiration, maximum velocities of 6–18 ms⁻¹ were measured at the nasal valve, 2 ms⁻¹ in the main passage and 3 ms⁻¹ in the nasopharynx (46). Largest flow was through the middle airway. During expiration, maximum velocities of 3–6 ms⁻¹ were measured in the nasal valve and velocity of 1–2 ms⁻¹ throughout the nasal cavity (46).
Figure 5. Coronal cross sections of nasal cavity with respective locations illustrated on the sagittal view(42)

Figure 5 shows a series of anatomical areas of the nose starting from nares anteriorly and proceeding posteriorly. The corresponding anatomical areas are depicted in sagittal view.
In infants and children nasal cavity measurements have been made using CT scan. Likus et al examined the CT scans of 180 Polish Caucasian children (83 girls and 97 boys) with age range of birth to 3 years, with normal development and with no evidence of craniofacial abnormalities in the age range of birth to 3 years (47). The children were divided into following groups:

A: 0–3 months (23 children: 13 females and 10 males)
B: 4–6 months (35 children: 20 females and 15 males)
C: 7–12 months (53 children: 27 females and 26 males)
D: under 2 years of age (13–24 months) (42 children: 14 females and 28 males)
E: under 3 years of age (25–36 months) (27 children: 9 females and 18 males).

They measured several nasal dimensions, of particular importance to this study were, firstly, anterior bony width between the two maxillary ridge called as piriform aperture (ABW) and this refers to site of nasal valve, secondly, nasopharynx vertical distance between posterior vomer and cranial base (NVD) which relates to nasopharyngeal size and finally, bony choanal aperture width between both pterygoid processes in posterior nasal cavity called choanal aperture (BCAW) which relates to any possibility of resistance in series further down in the nasal cavity. These nasal dimensions are illustrated in figure 6.

The results for above three parameters are shown in table 1 (47).

<table>
<thead>
<tr>
<th>Group</th>
<th>ABW [mm]</th>
<th>BCAW [mm]</th>
<th>Nasopharynx NVD [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14.87 ± 1.62</td>
<td>16.86 ± 2.16</td>
<td>21.06 ± 3.48</td>
</tr>
<tr>
<td>B</td>
<td>15.60 ± 1.15</td>
<td>16.70 ± 1.26</td>
<td>24.86 ± 2.66</td>
</tr>
<tr>
<td>C</td>
<td>17.11 ± 1.27</td>
<td>17.77 ± 1.45</td>
<td>25.60 ± 2.67</td>
</tr>
<tr>
<td>D</td>
<td>18.46 ± 1.35</td>
<td>19.26 ± 1.47</td>
<td>25.62 ± 2.40</td>
</tr>
<tr>
<td>E</td>
<td>18.87 ± 1.28</td>
<td>20.65 ± 1.53</td>
<td>26.18 ± 3.27</td>
</tr>
</tbody>
</table>

Table 1 shows the typical nasal cavity dimensions seen in various age groups of children from 0-36 months of age.
There is progressive growth in the nasal cavity dimensions with age but it is not uniform or linear (47). In a study on 39 infants, using continuous wide-band noise acoustic rhinometry, using a specific probe optimized for infants examined at infancy and 1 year of age, the nasal dimensional growth and maturation was reported by Djupesland et al (48). During the first year of life, the acoustically determined dimensions of the nasal airways increased significantly (48). The total minimal cross-sectional area increased by 67% (0.21 cm$^2$--$>$0.35 cm$^2$)(48), the volume of the anterior 4 cm of the nasal airway by 36% (1.80 cm$^3$--$>$2.44 cm$^3$) and the distance to the minimum cross-sectional area by 19% (0.78 cm--$>$0.93 cm) (48).

During inspiration, the air flow velocity is higher initially and its path of flow is mainly through the lower half of the nasal cavity. Therefore, the olfactory grove which is located in
the upper portion of the nasal cavity receives air flows with lower velocity (49). The sniffing manoeuvre alters this flow and directs increased air flow towards the upper portion of the nasal cavity.

The narrowest part of the nasal passage relevant to air flow resistance is at the functional nasal valve in the anterior nasal cavity and therefore it is a major determinant of flow (49). The posterior cavity, however is wider and circular. The expiratory flow in the nasal cavity is along the turbinates (49).

The relationship of nasal air flow is linear to the nasal cavity volume and area (49). The nasal tissues, however, cause dynamic changes to the nasal resistance which affects flow. This is due to a number of factors including collapse of soft tissues and downstream resistance of the lower airways (49).

The neonates are obligate nasal breathers supplemented by oral breathing during sleep (49). Primary oronasal breathing occurs normally with crying and returns to uninterrupted nasal or some combination of oronasal (49).

A premature infant’s skin is especially susceptible to injury from nasal interface devices (49). Researchers have used different scoring systems based on site of nasal trauma. The damage may occur at any of these sites including the nares, intranasal septum, the septum’s anterior tip (columella), or philtrum (49).

In summary, the nasal and nasopharyngeal airway anatomy of preterm, infants and adults poses a physiologically complex pattern of airway resistance.

### 1.4.3 Effects of mouth position on nasopharyngeal pressure

When the HFNC circuit is connected to the patient with the nasal interface there are mainly 2 sites which allow leak. First is at the nasal cannula and nare interface and second is at the mouth. It has been shown in studies on CPAP that pharyngeal pressures drop when the mouth is open (50).
Kubicka et al. studied delivered oral cavity pressures during HFNC flow rate range of 1-5 litres per minute in 27 infants (3). Small (outer diameter: 0.2 cm) cannulae were used for all infants and prescribed flow rate was opportunistically studied with no changes made for the study (3). In their study infants (postmenstrual age: 29.1–44.7 weeks; weight: 835–3735 g; flow rate: 1–5 L/minute), no pressure was generated with the mouth open at any flow rate (3). With the mouth closed, the oral cavity pressure was related to both flow rate and weight. For infants of <1500 g, there was a linear relationship between flow rate and oral cavity pressure (3). They concluded that firstly, their technique of measuring oral cavity pressure can estimate the level of continuous positive airway pressure and secondly, continuous positive airway pressure generated with heated, humidified, high-flow nasal cannula treatment depends on the flow rate and weight (3). According to their data, the more smaller infants when their mouths were closed had clinically significant and unpredictable levels of continuous positive airway pressure during high flow therapy (3).

In the study by Arora et al. involving 25 (mean 78.1 [SD 30.9] days; weight 5.3 [SD 1.1] kg) patients with bronchiolitis, nasopharyngeal pressures were measured at varying flow rates of HFNC (28). They found that nasopharyngeal pressures increased linearly with flow rates up to 6 L/min (28). Nasopharyngeal pressure increased by 0.45 cm H2O for each 1 L/min increase in flow rate (28). There were significant differences between pressures in open and closed mouth states for flow rates up to 6 L/min (28). At 6 L/min, the pressure in open mouth state was 2.47 cm H2O and that in closed mouth state was 2.74 cm H2O (P<0.001) (28).

In a lung model study, two HFNC devices Vapotherm 2000i and Fisher-Paykel were studied to understand the relationship between the device, intraprong, and proximal airway pressures and the flow values. Fisher-Paykel system had a pressure release valve (23). A paediatric size cannula of 2-mm inner diameter was used in a lung model and the device, intraprong, and proximal airway pressures at random flow values between 0 L/min and 12 L/min with an FIO2 of 0.21 were measured under simulated minimal and moderate nares-prong leak as well as varying mouth leak (23).

Irrespective of leak, all the three pressures increased with increasing flows with both devices (23). Under conditions of minimal leak and flow rates <8 L/min, the Fisher-Paykel device generated larger pressures than the Vapotherm device although this was not seen at higher flows because of pressure release valve (23). The intra prong pressures were about 1/5th to
1/3rd (between 22% and 27% and 20% and 32%) of the corresponding device pressure value for Fisher-Paykel and Vapotherm (23). There was further reduction in proximal airway pressure downstream by about 20% to 30% relative to the intraprong pressure values with the two devices (23). Interestingly, the device pressure was not affected by nares-prong leaks or mouth leak (23). However, the increase in leak at nares or mouth caused reduction in intraprong and proximal airway pressures (23). The authors concluded that HFNC may deliver uncontrolled continuous positive airway pressure to infants (23).

However, the results of some studies evaluating mouth position and effects on airway pressure are in conflict with the results of above studies. Wilkinson et al. studied pharyngeal pressure in 18 preterm neonates (median gestational age 34 weeks, weight 1.619 kg) during high flow therapy (27). A catheter-tip pressure transducer was introduced into the nasopharynx (27). Flow was sequentially increased to a maximum of 8 litres per minute and decreased to a minimum of 2 litres per minute (27). There was a strong association between pharyngeal pressure and both flow rate and infant weight (P<0.001, $r^2=0.61$), but not mouth closure (27). They concluded that high flow nasal cannulae at flow rates of 2 to 8 litres per minute can lead to clinically significant elevations in pharyngeal pressure in preterm infants (27). Flow rate and weight but not mouth closure are important determinants of the pressure transmitted (27). They felt that the amount of nasal gas leakage with HFNC was more important than the degree of mouth leak, particularly in comparison to the tightly fitting nasal prongs used with CPAP, which allow very little gas to escape from the nostrils (2, 27).

1.4.4 **Effects of flow rate on nasopharyngeal pressure**

CPAP machines are capable of varying the flow delivered to achieve set amount of pressure when the circuit has varying amounts of leak. Generally, the flow to the magnitude of around 8 litres per minute is used to achieve a CPAP of about 5-6 cm H2O. Thus, this implies that varying amounts of flow can have varying amount of pressure generation downstream in the airways. This aspect has been looked in more detail with respect to HFNC by various investigators.

In an animal study, Frizzola et al studied effects of flow rate on the tracheal pressures (22). Neonatal piglets (n=13; 2-6kg) were injured with IV oleic acid and supported with HFNC at 2-8 L/minute (22). Tracheal pressures were recorded by transmural catheters (22). Oxygenation
and tracheal pressures increased in a flow dependent manner and at 8L/minute, tracheal pressures did not exceed 6±1 cmH2O (22).

Kubicka et al studied oral cavity pressures during HFNC flow rate range of 1-5 litres per minute in 27 infants (3). Small (outer diameter: 0.2 cm) cannulae were used for all infants and prescribed flow rate was opportunistically studied with no changes made for the study (3). In their study infants (postmenstrual age: 29.1–44.7 weeks; weight: 835–3735 g; flow rate: 1–5 L/minute), under the conditions of mouth open no pressure was generated irrespective of the flow rate (3). The oral cavity pressure was related to flow rate and weight of the infant when the mouth was closed. The relationship was linear between flow rate and oral cavity pressures for infants <1500 grams (3).

Lampland et al conducted both in vitro and in vivo study of effects of HFNC flow rate on the airway pressures (31). In the in vitro part, the HFNC pressure and flow was measured with varying degrees of leak and with and without the use of a pressure-limiting valve (31). In the in vivo part, they measured end expiratory oesophageal pressures in 15 newborns on NCPAP 6 cm H2O and then on HFNC at 6 L/minute, with flow decreased by 1 L/minute every 30 minutes (31). In the in vitro study, in the absence of leaks, the pressures were limited by the pressure-limiting valve only at flows > 2 L/minute (31). With leaks of 30% and 50%, delivered pressures were always < 3 cmH2O(31). They found wide variation in intrapatient and interpatient results (31). The end expiratory oesophageal pressures were similar with CPAP and HFNC (31).

Spence et al studied intra pharyngeal pressures (IPP) in 14 infants in an observational study on a sample of stable term and preterm infants who were being treated either with NCPAP or with HFNC (26) with 6 babies were studied on both (26). Two infants only had IPP measured on CPAP, and six infants had IPP measured on HFNC (26). IPPs were recorded for 2 to 3 min or until airway pressure and infant were stabilized at each level NCPAP of 2, 4 and 6 cm H2O and HFNC of 1, 2, 3, 4 and 5 l/min average pressures were documented over the 2 to 3 min observation period at each NCPAP and HFNC level and a single value was recorded (26). Infants’ mouths were kept closed by gentle chin support and/or pacifier placement (26). A Viasys 5 French Tracheal Catheter (PN 10635, Viasys Healthcare, Yorba Linda, CA, USA) was introduced to the posterior pharynx through the infant’s nares or mouth for measuring pressure (26). Depth of insertion was estimated by measuring the distance between the corner of the nare and the ear lobe (26). The catheter was connected to a pressure-measuring device.
(Viasys avea ventilator) and IPP was recorded continuously (26). The Viasys Infant Flow CPAP System was the primary device used for this study (26). HFNC was delivered via Fischer & Paykel (Fisher & Paykel Healthcare Inc. Irvine, CA, USA) humidification system and Salter brand infant nasal cannula (26). All the infants had the ‘infant size’ prongs from Salter (26). Except for one patient, HFNC consistently generated a significant amount of CPAP: the average IPP (cm of H$_2$O) for flow rates of 1, 2, 3, 4 and 5 litres per minute was 1.7±0.3, 1.7±0.2, 2.6±0.3, 3.8±0.4 and 4.8±0.5 respectively (26). In one patient, flows at 1 to 5 LPM generated an IPP of <2 cmH$_2$O (26). This study did not find a correlation between the size of the baby and the IPP generated at each flow rate, as it was not powered to detect this correlation if any (P = 0.707) (26).

In another study involving 16 VLBW infants over 3 days of age, range of airway pressures with Optiflow HFNC device was studied (51). Both pharyngeal and oesophageal pressures were measured using a 6Fr solid state manometric catheter (Unisensor, NH) with dummy in and out for mouth leak evaluation (51). The infants characteristics at study entry were age of mean (SD)) 36(22) days, gestation age 27(2) wks, Birth weight 850 (220) g and FiO2 26(6)% (51). At the 7L/min flow rate, the end inspiratory and end expiratory pressures (cm H$_2$O) for pharyngeal and oesophageal measuremen were 5.5 (4.6, 6.7), 6.5 (5.4, 7.6), 2.2 (1.0, 3.3) and 13.3 (10.6, 14.2) respectively (51). There was a significant relation between flow and pharyngeal pressure although flow rates greater than 4 L/min had little additional effect on pharyngeal pressure (51). Their conclusion was that alteration of flow has a significant effect on pharyngeal but not oesophageal pressure (51). This is difficult to explain apart from any possibility of methodology of pressure measurement being the cause of their finding.

1.4.5 Effects of nasal cannula size on nasopharyngeal pressure

The nasal cannula and nares interface is a site for leak in the HFNC circuit when applied to the patient. Therefore, relative size of nasal cannula to the nare diameter is of practical relevance. Some of the earliest studies of oesophageal pressures during high flow therapy have shown that larger nasal cannula tends to produce higher pressures (2, 30).
Nasal cannula outer diameter (OD) is specified by manufactures(2). In general, the OD is around 2.4 mm in premature and new born neonates, and 2.4 to 3.7 mm in infant and paediatric patients (2, 49). Locke et al. measured oesophageal pressure produced with varying
OD of nasal cannulae (2, 30). The 3 mm OD nasal cannula delivered higher pressures with a mean of 9.8 cm H2O at a flow of 2L/min in infants who were 30 weeks’ gestation at 28 days of age(2, 30). In contrast, the 2 mm OD cannula, did not deliver any pressure (30). One possible explanation for this is there may be increase in leakage of flow around the smaller cannulae (2). It is important to note that this study dates back to 1993 and the high flow device was not a standardised equipment capable of heating and humidifying to optimum conditions (30).

The ratio of nasal cannula to the nasal opening is more important than the absolute size of the cannula (30). The entire nasal passage is important in the development of positive end-distending pressure (30). Both anatomic and physiologic factors can affect the nasal gas flow pattern and turbulence will cause resistance to gas flow similar to a mechanical occlusion of the nasal passage (30).

Since size of nares is proportional to the size of the baby, baby’s weight influences the likely pressures delivered to the airways (2).

Volsko et al in an in vitro study described the relationship between the pressure generated at the airway opening and flow through a nasal cannula using a simulated infant model (21). A range of nare sizes including small, medium and large were drilled into a plastic fixture (21). A lung simulator was used to simulate spontaneous breathing (21). A range of tidal volumes from 3 mL to 12 mL were delivered by adjusting the amplitude in a simulated respiratory wave form (21). The simulated lung model had a lung compliance and resistance set at 0.5 mL/cm H2O and 125 cm H2O/L/s, respectively (21). They optimally sized cannulae for premature, infant and paediatric nares to ensure that they were not occluded (2, 21). The prong occlusion of the nares did not exceed 50% (21). A flow rate range of 2–6 L/min in 1-L/min increments was used (21). They recorded Mean airway pressure and percent change in tidal volume (VT) (21). The greatest effect on tidal volume was seen with the premature cannula (21). The least effect on pressure and VT change occurred with the infant cannula (21). The differences in spontaneous tidal volume across all flows were negligible (21). The maximum pressure generated was 2 cm H2O, which was not clinically significant (2, 21). These findings were similar to Locke’s study on infants using 2 mm OD nasal cannula (2, 30).
Using a simulated in vitro system Sivieri et al. measured proximal airway pressures delivered by a HFNC system while varying flow and ratio of cannula to nares size. Airway pressure increased progressively with increased flow and with nasal prong to nares ratio (20). They concluded that safe and effective use of HFNC requires careful selection of appropriate nasal prongs for the individual infant even with an integrated pressure limiting valve (20).

1.4.6 Summary of effects of HFNC on airway pressures

The physiology studies looking at airway pressures have been summarised in the table number 2. The relationship of airway pressures to other parameters can be summarised as follows,

1. When compared to CPAP the airway pressures (oesophageal, nasopharyngeal, oral) are similar to, or less than, those usually set with CPAP (3, 21, 26, 27, 38). However the pressures measured with older HFNC devices recorded higher airway pressures beyond the pressures usually used in CPAP therapy (30).
2. The flow rate positively correlates with pressure; airway pressures increasing with increasing flow (3, 22, 26, 31, 38, 52).
3. The airway pressures increase with decreasing infant weight (3, 27, 38).
4. There is significant inter-patient variability in airway pressures mainly due to varying leak at the mouth and nose (3, 20, 23, 31, 38).
### Table 2. Summary of studies examining airway pressures during HFNC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Weight (grams)</th>
<th>Flow (L/min)</th>
<th>Conclusions of Airway Pressure</th>
<th>Relevant Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke(30) Pediatrics</td>
<td>13</td>
<td>Mean 1,377</td>
<td>0.5-2</td>
<td>No pressure generation with smaller prongs at any flow rate</td>
<td>Unheated and unhumidified Mean oesophageal pressure of 9.8 cm H2O at 2 L/minute</td>
</tr>
<tr>
<td>Sreenan(24) Pediatrics</td>
<td>40</td>
<td>1,260</td>
<td>1–2.5</td>
<td>Flow rate required to generate similar oesophageal pressure as generated by NCPAP of 6 cm H2O increases with increasing flow</td>
<td>Unheated, humidified Oesophageal pressure</td>
</tr>
<tr>
<td>Volsko(21) Respir Care</td>
<td></td>
<td>Lung model</td>
<td>&gt;2</td>
<td>Highest &amp; lowest airway pressure</td>
<td>Positive expiratory pressure with all cannula sizes</td>
</tr>
<tr>
<td>Saslow(17) J Perinatol</td>
<td>18</td>
<td>580 – 1990</td>
<td>3 - 5</td>
<td>Not more than CPAP of 6 cm H2O</td>
<td>Oesophageal pressure</td>
</tr>
<tr>
<td>Pyon(53) PAS (abstract)</td>
<td>8</td>
<td>&lt; 2000</td>
<td>6 - 8</td>
<td>Not more than CPAP of 6 cm H2O</td>
<td>Oesophageal pressure</td>
</tr>
<tr>
<td>Lampland J(31) Pediatr</td>
<td>15</td>
<td>1324 ± 424</td>
<td>1 - 6</td>
<td>Similar to CPAP of 6 cm H2O</td>
<td>Oesophageal pressure</td>
</tr>
<tr>
<td>Spence(26) J Perinatol</td>
<td>14</td>
<td>1589 +/- 170</td>
<td>Up to 5</td>
<td>Intrapharyngeal pressure 4.8 ± 0.5 cm H2O at 5 LPM</td>
<td>Study weight 1589±170</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mouth closed 800 g (high pressures) 2100 g (low pressures)</td>
<td></td>
</tr>
<tr>
<td>Study (cont)</td>
<td>n</td>
<td>Weight (grams)</td>
<td>Flow (L/min)</td>
<td>Conclusions of Airway Pressure</td>
<td>Relevant Circumstances</td>
</tr>
<tr>
<td>-------------</td>
<td>---</td>
<td>----------------</td>
<td>--------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Wilkinson(27) J Perinatol 2008</td>
<td>18</td>
<td>534 - 1868</td>
<td>2 - 8</td>
<td>Mean pharyngeal pressure of 5.3 cm H$_2$O at 5 L/m</td>
<td>No effect of mouth position on pressures. Study weight 1.619 kg (0.816 to 4.400).</td>
</tr>
<tr>
<td>Kubicka(3) Pediatrics 2008</td>
<td>27</td>
<td>835 – 3735</td>
<td>1 - 5</td>
<td>Highest oral cavity pressure recorded was 4.8 cm H$_2$O</td>
<td>Mouth closed Snug nasal prongs 2 babies &lt;1000 g; (900g &amp; 835g)</td>
</tr>
<tr>
<td>Collins(29) Journal of Paediatrics and Child Health 2013</td>
<td>9</td>
<td>-</td>
<td>2-8</td>
<td>Nasopharyngeal pressures measured</td>
<td>7 l/min - VAPO- 4.7 (2.2) F&amp;P- 4.23 (2.2)</td>
</tr>
<tr>
<td>Arora et al(28) 2012</td>
<td>25</td>
<td>weight, 5300 [SD 1100]</td>
<td>Up to 6L/kg/min</td>
<td>Acute bronchiolitis - Prospective, observational study Heated humidified HFNC system. Linear increase in NP pressures with flow rates up to 6 L/minute but with significant differences between pressures in open and closed mouth states. Bronchiolitis severity scores improved significantly</td>
<td>Nasopharyngeal (NP) pressures Vital signs Bronchiolitis severity scores Oxygen saturation</td>
</tr>
<tr>
<td>Mile´si et al(54). 2013</td>
<td>21</td>
<td>-</td>
<td>1, 4, 6 and 7L/kg/min</td>
<td>Pharyngeal pressure (PP) and oesophageal pressure (Pes) measured simultaneously. Flow &gt;2 L/kg/minute generated a mean PP &gt;4 cm H$_2$O. Significant reduction in respiratory rate noted with increase in flow from baseline to maximal flow rate.</td>
<td>Prospective observational study Heated and humidified HFNC (RT329 system with MR850 humidifier, Fisher and Paykell)</td>
</tr>
</tbody>
</table>
1.5 Measuring Airway Pressure

The most popular devices currently used for medical pressure measurement are based on catheters and guidewires (55).

1.5.1 Types of pressure measuring technology

- Air filled balloons
- Fluid (Saline/Water) filled Catheter
- Air charged catheter
- Solid state Catheter with inbuilt transducer
- Optical fibre pressure sensor

The air-filled balloon pressure sensor is less expensive compared to other sensors (56). However, they do not last long and performance may alter with repeated use and cleaning (56). The performance is also affected by the dimensions of the balloon which determines the efficiency with which pressure signal is transmitted to the external pressure transducer (56). The balloon volume needs to be monitored to maintain optimum performance (56). Since the transducer is externally located it is difficult to use this device for ambulatory pressure monitoring (56).

Although air-charged catheters are less expensive, fluid-filled catheters have relatively more stable response (55). Cooper et al compared the efficiency in pressure transduction of air charged and water filled catheters for urodynamic pressure measurement (57). The catheters were exposed to sudden change in pressure. During this time, they assessed frequency response of the two systems. In addition, they also measured the response of the catheters to movement artefacts and different gravity effects by changing the height of the catheter tips to different levels (57).

Water-filled catheters do not attenuate the pressure signal as much as the air-charged catheters because water is not compressible (57). However, the column of water in the tube can vibrate and cause peak pressure amplification (57). Since air is compressible, it results in attenuation of the pressure signals (57). Thus while the water filled catheter may affect mainly higher frequencies, the air-charged systems attenuate lower frequencies as well (57). Unlike the
water filled catheters, air-charged catheters are less affected by movement and gravity effects (57).

The length of the water filled catheter is inversely related to frequency response of the whole system. The wider the diameter, more will be the attenuation of the natural frequency of the water column itself (55).

Solid state catheter with inbuilt transducer at the tip is next in the development of the pressure transducers. A schematic diagram is shown in the figure 7. Although these pressure guidewires are a further improvement and alternative to catheters they are more expensive (55). Guidewires and catheter pressure transducers are known as electro-mechanical pressure transducers (55). The pressure-sensing device can be a part of a catheter containing multiple channels to perform other functions (55).

**Figure 7. Sensor attached to the side of a catheter (from Gaeltec Ltd) at its distal end**

![Schematic diagram](image)

Figure 7 showing the side wall mounted pressure transducers at the distal end of the catheter.

An example of solid state guide wire with pressure sensors was used by Pavel Mazmanyan et al whilst measuring airway pressures during HFNC and CPAP in infants (58). This Mikro-Cath pressure catheter is said to deliver accurate data for analysis of airway pressures. The advantage is these provide continuous, real-time data. The catheter is used for monitoring pressures as a minimally invasive device but it can be used only for less than 24 hours with body contact.
These catheters have several advantages. Pressure is measured at the site of interest, can be measured in ambulatory patient, it is not influenced by gravity and the movement of the subject does not give rise to significant motion artefacts unlike a fluid filled catheter.

The main disadvantages are that they need re-calibration, are fragile and expensive. The salient features of the measurements from the solid-state catheters and fluid filled catheters are shown in table 3.

Table 3. Solid-state pressure sensor compared to traditional Fluid-filled pressure measurements (55)

<table>
<thead>
<tr>
<th>Solid state guide wire technology</th>
<th>Fluid filled catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate dP/dt</td>
<td>Unreliable dP/dt</td>
</tr>
<tr>
<td>True pressure signal</td>
<td>Pressure signal needs augmentation-overshoot and resonance possibilities</td>
</tr>
<tr>
<td>No time delay in signal conduction</td>
<td>Time taken for signal transmission</td>
</tr>
<tr>
<td>Not affected by movements</td>
<td>Motion artefacts are frequent</td>
</tr>
<tr>
<td>True pressure readings in any height in fluid</td>
<td>Gravitational effects can cause change in baseline with change in height of catheter after calibration</td>
</tr>
<tr>
<td>No effect of gravity before or after calibration</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 shows the differences between solid-state and fluid-filled pressure measurements.

Optical fibre sensors are more recent improvement over catheter based sensors. Since they are very small they are useful for medical applications. The optical fibres made up of silica glass have about 125-micron diameter. Optical fibres of even 80 microns diameter are now available (55).

They can be used even when tight bending is needed. The bend – insensitive fibres are capable of transmitting signals through tight bends. A single catheter can hold multiple numbers of optical fibre pressure sensors enabling multiple type of applications or measurements (55).
Another distinct advantage is that optical fibre sensors can be built in a way that they are able to detect different signal types such as strain or pressure, temperature at multiple points along the length of the optical fibre. These multiple points can detect either single type or different types of physical parameters (55).

Finally, these fibres are extremely stable over long periods of recording. The sensor prototypes are quoted as having a stability of 1 mm Hg/hour and the commercially available sensors come with a stability of 3 mmHg/28 days (55).

1.5.2 Technical requirements for airway pressure sensors

Range of a pressure sensor can be defined as the difference between the maximum and minimum value that can be measured by that sensor in the site of interest (55).

Since the pressure range is different in different body systems the appropriate site-specific pressure sensor with the capability to measure pressure should be used. For example, the left ventricular pressure range is 0 - 150 mm Hg (0 - 203.9 cm H₂O) whilst that in intra cranial site is only 0 - 7.5 mm Hg (0 – 10.1 cm H₂O) (55).

Similarly, the pressure range varies at different sites in the respiratory system. The intra alveolar and intra tracheal pressures change dynamically as well and can reach to levels of – 75 mmHg (101.9 cm H₂O) (55). Pressure ranges vary based on the application needs and condition of the infant’s breathing, for example, in a spontaneously breathing infant to that in a ventilated infant (59). A European Task Force set up to provide guidance on standards for Infant Lung Function Testing recommended following pressure ranges shown in table 4 (59).

Accuracy of the sensor requirements depends on the area of interest to be measured. The clinical relevance of magnitude of changes in pressure readings on organ function or disease state assessment (55). For example, a small pressure error in reported pressures in left ventricular pressure may not affect clinical judgement whereas similar range of error in intracranial pressure would affect clinical decision making.
The sampling rate is defined as the number of measurements obtained per second. The sampling rate of a pressure signal is determined its waveform and periodicity (55). A system should be able to record at least double the highest frequency present in the signal so that all the data in the signal can be reproduced accurately (55). In the case of the medical sensors, the general recommendation is that they should acquire 5–10-times more samples than the highest frequency of the pressure wave that is being measured (55).

The linearity of a pressure sensor should be within 1% of the reading or 1.01 cm H2O whichever is greater (59). It is important to note that the linearity is a different concept from accuracy. A pressure sensor can have acceptable linearity being consistently inaccurate. It is possible to apply correction if there is linearity.

Table 4. Pressure ranges normally encountered during pulmonary function tests in infants and young children (59)

<table>
<thead>
<tr>
<th>Pressure Transducer</th>
<th>Pressure range kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal pressure</td>
<td>-5 to 5</td>
</tr>
<tr>
<td>Airway opening pressure</td>
<td>-10 to 10</td>
</tr>
<tr>
<td>Plethysmographic box pressure (100 L)</td>
<td>-0.1 to 0.1</td>
</tr>
<tr>
<td>Jacket Pressure (forced flows)</td>
<td>0 to 15</td>
</tr>
</tbody>
</table>

The Table 4 shows pressure range in various pulmonary function tests in infants and young children.

1.5.3 Other factors affecting sensor performance

The physical characters of the catheter that cause damping effect on the pressure signal include its own elasticity, mass and friction. The catheter has a natural frequency that will affect the sensor performance in the sensors located within the catheters (55). The main effect will be on the frequency response of the sensor equipment (55).

The sampling site should not be affected by eddies or current effects. These currents will particularly affect the lateral pressure measurements (59). Another significant factor is the
Bernoulli effect which is greater when the diameter of the tube is small such as seen in infants (59).

The common reasons for baseline instability of the equipment include drift of transducers (intrinsic property of the material of the transducer) and sensitivity to temperature, position (gravity, e.g. water filled catheter systems) and other changes in environmental conditions (59). Baseline instability is crucial for calibration and measurement procedures (e.g. when using catheter tip transducers for oesophageal manometry) and must be specified by the manufacturer (59).

1.5.4 Principles of Pressure Sensors

There are two main types of pressure measurement sensors namely strain gauge transducer and diaphragm displacement sensors.

The strain gauge transducers change their output in response to the strain (pressure changes) (55). Their working principle is governed by the following relation between sensitivity (Gauge factor GF) and relative change in resistance (∆R/R) and relative change in length (∆L/L), also called as strain ε (55). A schematic representation of this principle is shown in the figure number 8.

\[
GF = \frac{\Delta R}{R} / \frac{\Delta L}{L} = \frac{\Delta R}{R} / \varepsilon \quad (55)
\]

The technology in diaphragm displacement sensors is known as micro electro mechanical systems (MEMS) technology (55). These sensors have a very thin structure which deforms and has a flat surface called as diaphragm. The diaphragm is located in a sealed cavity (55). The diaphragm deforms when the pressure impacting on its surface changes. The principle mechanism of this type of diaphragm sensors can be capacitance based or based on a piezoelectric transducer (55). At baseline, the cavity has an initial volume \( V_0 \) and pressure \( P_0 \). Then a change in pressure \( \Delta P \) causes the medium inside the cavity to compress or expand \( \Delta V \) depending on the direction of pressure change. This is possible because medium is enclosed in the cavity (55). A schematic representation of this principle is shown in the figure number 9.
Figure 8. Schematic representation of a piezo resistive sensor (55)

Figure 8 shows a schematic diagram of a piezo resistive type of sensor with change in dimension under the influence of a strain (or pressure)

L refers to the length of the sensor element

ΔL refers to the change in length of the sensor element on application of strain (or pressure)
Figure 9. Schematic representation of a diaphragm displacement sensor (55)

Figure 9 shows a schematic diagram of a diaphragm displacement sensor depicting the volume change in sensor cavity when diaphragm is displaced due to the pressure differential applied on its surface.

V0 - Initial volume of the sensor cavity
P0 - Initial pressure in the sensor cavity
ΔP - Change in pressure on the diaphragm of the sensor
ΔV – Change in the volume of the cavity
D- Diaphragm of the sensor
1.5.5 *Types of airway pressure measurements*

The airway pressures can be reported at different points in the waveform. Some authors have reported the end expiratory pressure whereas some other studies have reported mean airway pressures.

1.5.6 *Practical challenges in pressure measurement in neonates*

1. Size of nasopharyngeal airway smaller and therefore need smaller calibre diagnostic instruments.

2. The neonates typically have less reserve in terms of maintaining adequate gas exchange and decompensate quickly, therefore interventional studies are riskier and difficult to perform.

3. Since neonates feed relatively frequently time window for performing measurements is small and for the same reason prolonged airway pressure measurement is difficult.

4. The fidelity of data acquired and that used for reporting needs to be defined strictly with clear criteria.

5. The motion artefacts are a significant practical problem due to neonates crying, moving and secretions if any.

6. Calibration requirements: Any interruptions in measurements due to neonate requiring care, desaturations would mean that recalibration of the measuring equipment may be required.
1.6 Effects of HFNC on Washout of Airway Dead Space

1.6.1 Airway dead space wash out effect and its impact on CO\textsubscript{2} removal

The minute ventilation consists of alveolar ventilation and dead space ventilation. By flushing the dead space/ expired CO\textsubscript{2} off and enriching it with set FiO\textsubscript{2} the dead space can be reduced and alveolar ventilation can form a greater proportion of the minute ventilation. This results in improved efficiency of respiratory efforts to achieve adequate gas exchange.

Tracheal gas insufflation (TGI) method can be used to promote CO\textsubscript{2} elimination (60-64). In experimental animal models TGI reduces dead space and promotes pulmonary gas exchange and reduces ventilator pressure and volume requirements (65, 66). Studies evaluating acute lung injury using modified endotracheal tubes designed to reduce physiological dead space during mechanical ventilation in animal models, noted that compared to conventional mechanical ventilation the requirement for pressure and volume were less with reduction in dead space strategy (67, 68). The markers of lung and systemic inflammation were also reduced.

Nakos et al studied effects of TGI in spontaneously breathing patients with COPD (69). These patients had been weaned from mechanical ventilation (69). The study had two groups, one with oral tracheal tube and a second with tracheostomy (69). They found that the tidal volume (VT), minute volume (MV), PaCO\textsubscript{2}, and dead space volume VD/VT were dependent on the flow rates used via oral-tracheal tube (69). The distal catheter position was better in terms of efficacy than the proximal position. The TGI gas delivery through tracheostomy tube was less effective compared to oral tracheal tube (69). They concluded that reduction in CO\textsubscript{2} levels reduced the VT needed and this in turn reduced the work of breathing required to achieve the VT and MV (69).

The physiologic effects of TGI was further studied by Miller et al in an acute lung injury model involving neonatal piglets. The piglets (n=19, Weight 2.4±0.4 kg) were spontaneously breathing and were supported with CPAP of 5 cm H\textsubscript{2}O. The aim of the study was to understand TGI effects on gas exchange and pulmonary mechanics (70). The acute lung injury was induced by intravenous oleic acid administration. They were given either CPAP and TGI (n=9) or CPAP alone (n=10) (70). The target SaO\textsubscript{2} of >93% was maintained by
increments in FiO₂ by 0.05 every 15 min during the study. Apart from vital signs, they recorded the following parameters namely, arterial blood gases, pulmonary mechanics, and Thoraco abdominal motion (TAM) (70). The group receiving TGI achieved better oxygenation and CO₂ removal compared to the control (70). Consequently, the pH was also higher and closer to the baseline value in TGI group. The oxygen requirement noted by the FiO₂ titration data showed that TGI group required lesser oxygen supplementation by 4 hours into the study. They also required lower minute ventilation (MV) and showed greater compliance compared to the control group (70). The resistance and TAM were similar between the two groups (70). They concluded that the use of TGI with CPAP in the treatment of acute lung injury results in better gas exchange and improved pulmonary mechanics (70). In this study, the piglets were intubated and therefore application of TGI was done through endotracheal tube. Therefore if one were to achieve TGI by some other means than by endotracheal intubation then that would result in improved ventilation and CO₂ clearance and reduced need for mechanical ventilation (14).

Dewan and Bell studied the effects of airway dead space wash out in 10 patients of COPD on respiratory support with trans tracheal catheters (TTC) by administering low flow and high flow oxygen and assessing effects on dyspnoea and exercise tolerance (71). The study protocol involved four sessions of modified progressive treadmill tests on two separate days (71). Two tests were performed when the patients receiving Low Flow Trans Tracheal Oxygen (LFTTO) and High Flow Trans Tracheal Oxygen (HFTTO) and other two tests were done when the patients were receiving low flow nasal prong (LFNP) and high flow nasal prong (HFNP) oxygen (71). Equivalent oxygen saturation was achieved by adjusting the flow rate (71). The exercise distance with HFTTO was 2.5 times greater than with LFTTO and HFNP was 2.38 times greater than with LFNP (p<0.005) (71). Interestingly, there was no significant difference in exercise distance and dyspnoea scores with HFTTO as compared with HFNP and LFTTO compared with LFNP (71). They concluded that the exercise tolerance was greater with the use of high flow oxygen irrespective of the route when compared to low flow oxygen (71). The maximum exercise tolerance was not improved by Trans Tracheal oxygen as compared to nasal prong oxygen when the oxygen saturations were maintained similar (71).

Holleman-Duray et al showed in their neonatal study which incorporated an early extubation protocol that infants extubated to high flow therapy from a significantly greater ventilator rate
compared to other non-invasive support modes (33± 8 vs 28 ±8 breaths per minute; p<0.05) (72). This indicates that the babies requiring higher respiratory rate to achieve adequate MV for satisfactory gas exchange were able achieve satisfactory ventilation by increasing alveolar ventilation fraction with high flow therapy because of airway dead space wash out effect (72).

1.6.2 Airway dead space wash out effect and its impact on oxygenation

Chatila et al conducted a prospective but non randomised and non-blinded study in 10 patients with COPD and compared the effects of high flows of humidified oxygen (HFO) to conventional low flow oxygen (LFO) delivery at rest and during exercise (73). All the patients had advanced airflow obstruction but were clinically stable with no evidence of exacerbation (73). Baseline recording was done on rest and then patients exercised on a cycle ergometer for up to 12 min starting on LFO first (73). They had a period of rest followed by exercise when using the high-flow oxygen (HFO) system. The HFO was delivering 20 L/min and was adjusted to deliver similar FiO\textsubscript{2} as that of LFO system (73). They measured the work of breathing, tidal volume, respiratory rate, inspiratory time fraction, rapid shallow breathing index and pressure-time product from a pulmonary mechanics monitor (73). The patients whilst receiving HFO exercised longer and reported less dyspnoea with better breathing pattern compared to when on LFO (73). Although the FiO\textsubscript{2} was maintained equivalent when on HFO and LFO, the exercise period with HFO achieved higher oxygenation (73). They concluded that high flows of humidified oxygen by enhancing oxygenation improved exercise performance in patients with COPD and severe oxygen dependency (73).

In studies with in vitro models, airway oxygen fractions were higher with the HFNC versus non-rebreathing masks (14, 74). This is likely due to the effect of a high flow on the upper airway dead space, with the high flow of oxygen 'washes out' the end-expiratory gas containing reduced O\textsubscript{2} and higher CO\textsubscript{2} content(54). In the next breath, the lower airways receive gas with higher oxygen concentration because of this washout effect (54).
1.6.3 Methods of measuring airway gas concentrations

Airway gas concentration can be measured by sampling the air by a catheter and analysing it with a gas analyser. The sampling can be continuous or intermittent. Commercial gas analysers with high degree of accuracy are available. These are generally electronic analysers that can perform rapid and continuous gas analysis.

Broadly gas analysers can be classified into O₂ analysers, CO₂ analysers and multiple gas analysers. These devices can be incorporated in a single unit which can be used for gas analysis in clinical and research setting.

Oxygen analyser types include those using paramagnetic technique, galvanic technique and polarographic technique.

Paramagnetic technique is based on the principle that oxygen has a free electron which makes it to be attracted towards a magnetic field (75). These analysers are made up of two compartments, one for sampling and other acts a reference compartment (75). They are separated by a pressure transducer (75). When the expired gas is channelled through the sampling compartment it is subjected to an electromagnetic field which agitates the oxygen molecules (75). At the same time the reference compartment receives room air with 21% oxygen (75). Thus a differing concentration of oxygen creates a differing partial pressure and this is picked up by the pressure transducer and is converted to a DC voltage (75). This is proportional to the concentration of oxygen (75).

Galvanic technique is based on chemical properties of the oxygen molecules. Oxygen is made to diffuse across the membrane and an electrolyte solution (Potassium hydroxide) to a cathode made up of gold or silver and the anode is usually lead (75, 76). Depending on the partial pressure of oxygen an electrical current is generated which gives quantitative estimation of oxygen concentration (75). They have a response time of approximately 20 seconds with an accuracy of 3% (75). These devices do not need water vapour trap as they are not affected by water vapour. However, the limitation is limited life of electrolyte solution which is affected by the oxygen over time.
In the polarographic technique current flows between a silver cathode and a platinum anode (75). The oxygen molecules move across a Teflon membrane (75). An external current is required to drive the cathode reaction, hence the name polarographic (76).

CO₂ analyser types include Infrared absorption spectroscopy, refractometry, piezoelectric absorption, Raman scattering and mass spectrometry.

Infrared absorption spectroscopy is based on the principle that molecules having dissimilar atoms absorb infrared radiation in a unique way specific to that molecule (75). In doing so, energy is generated which causes molecular vibration (75). This vibration has a specific frequency which is dependent upon the molecular mass and atomic bonding of the molecule of the gas (75). Thus the absorption of infrared by a specific molecule occurs at a specific wavelength and this obeys ‘Beer-Lambert law’ (75). According to Beer-Lambert law there is a logarithmic dependence between the transmission of light through a substance and the concentration of that substance (75). The infrared absorbance peaks for carbon dioxide with this technique is located at the 4-5 μm range (75). The device has a set of narrow band filters set in chopper wheel assembly through which infrared radiation is focused (75). The specific infrared rays filtered are captured or detected by photocells or thermopiles, amplified and signal is processed giving quantitative output of the levels of gas being analysed (75). The device can be set as a mainstream or as side stream to the ventilation channel (75). The mainstream attachment does not require gas sampling but the side stream requires gas sampling (75). Water trap is required in both set up as water vapour affects analysis (75). The sampling rate in side stream set up should be at around 50-250 ml/min (75).

Refractometry technique is based on the physical principle of refraction of a monochromatic light through the gas medium being analysed (75). There are calibrated refractometers (example, Rayleigh) which have a series of prisms which split the light source through sampling and control tubes (75). Different gases produce specific pattern of refraction and from this their type and concentration can be determined (75). This type of device is typically used for anaesthetic gases such as halothane but can be used for other gases including CO₂ (75). However, these do not give breath to breath analysis (75).

Piezoelectric absorption analysers are based on the resonance property of a piezoelectric compound such as quartz (75). Two quartz crystals (one coated with silicone based oil and
other remains uncoated) are mounted between electrodes (75). The oil-coated quartz crystal absorbs the gas being analysed and changes the resonant frequency in proportion to the concentration of gas present (75). Although these devices have a fast response time they are limited by inability to differentiate individual gases (75).

Raman scattering phenomenon is used in another type of CO₂ analysers. The scattering of light on contact with object is been theorised by two principles, first is called Rayleigh scattering and the second called Raman Scattering. This technique uses Raman scattering principle where an intense, coherent and monochromatic light interacts with the gas molecule being analysed, gets scattered (75). During this process, some of the light's energy is either absorbed or release of the energy as a photon with a different wavelength (75). This leads to change in the wavelength due to transformational shift in the gas molecule (75). The scattered light is passed through a series of narrowband filters onto a photo-detector followed by signal processing unit (75). Since the filters are specific for the gas to be analysed, the concentration of gas can be determined (75). This technique is fast and can analyse multiple gases with good accuracy (75).

Mass spectrometry is mainly a research tool but it is highly accurate. In this technique, a sample of the gas to be analysed is drawn into a low pressure chamber which is connected to another chamber subjected to vacuum pressure (75). The gas molecules get ionised due to this exposure to pressure change and they are accelerated by a cathode plate (75). These ionised molecules have different mass and charge based on the type of gas (75). They are separated by exposure to electromagnets or fixed magnets (75). They are filtered by narrow band filters and trapped by photovoltaic receptors, the electrical signal is amplified and processed into a quantitative estimate of the gas being analysed (75). The response time is long so it is not suitable for continuous inline monitoring but they are very accurate (75).
1.7 Effects of HFNC on Tidal Volume

1.7.1 Tidal volume and minute volume importance for ventilation

Minute volume is the amount of gas inhaled or exhaled from a person's lungs in one minute. If both tidal volume \((V_T)\) and respiratory rate \((f \text{ or } RR)\) are known, minute volume can be calculated by multiplying the two values.

\[ MV = TV \times f \]

Blood carbon dioxide \((\text{PaCO}_2)\) levels vary inversely with minute volume. Minute volume generally decreases when at rest, and increases with exercise. Minute volume comprises the sum of alveolar ventilation and dead space ventilation,

\[ V = V_A + V_D \]

Where \(V_A\) is alveolar ventilation and \(V_D\) represents dead space ventilation.

Tidal ventilation parameters have been used to assess the impact of HFNC on work of breathing (10). Non-invasive methods of lung function assessment in preterm and term infants can be done by tidal breathing measurements. This can help in management of respiratory support.

1.7.2 Tidal volume measurement studies during HFNC

Saslow et al studied eighteen preterm neonates <2.0 kg on HFNC and NCPAP support in a random order (17). A ventilator was used to deliver 6 cm H2O of NCPAP with nasal prongs (17). High-flow nasal cannula therapy was delivered with Vapotherm (VAPO) at 3, 4 and 5 l/min (17). Tidal ventilation was measured using respiratory inductance plethysmography which was calibrated with face-mask pneumotachography (17). The oesophageal pressure was measured to generate estimation of transpulmonary pressure (Ptp). The sampling frequency of data was at 100 Hz. The outcomes measured included tidal volume (ml/kg), respiratory rate, lung compliance, phase angle and end distending pressure (17). The tidal volume range they noted with high flow therapy (VAPOTHERM) and CPAP are shown in table 5 (17).
Table 5. The tidal volumes during CPAP and HFNC in the study by Saslow et al(17)

<table>
<thead>
<tr>
<th>Respiratory support levels</th>
<th>Tidal volumes (mean±s.d.)</th>
<th>n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCPAP 6</td>
<td>3.53±1.92</td>
<td></td>
</tr>
<tr>
<td>VAPOTHERM 3</td>
<td>3.15±1.36</td>
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<tr>
<td>VAPOTHERM 4</td>
<td>3.08±1.35</td>
<td></td>
</tr>
<tr>
<td>VAPOTHERM 5</td>
<td>3.21±1.31</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 shows the mean tidal volumes observed during HFNC and CPAP in 18 preterm neonates.

Boumecid et al studied thirteen infants (GA=29 ±1 Weeks; BW=1350±350 g) at a post-natal age of 3±1 days on three respiratory support devices each for 30 minutes in random order (37). The respiratory support modes were variable flow NCPAP generator (Infant-Flow, EME Tricomed, UK) at a pressure of 5 cm H2O, a conventional constant-flow NCPAP (Baby-Flow, Draeger, Germany) at a pressure of 5 cm H2O with gas flow rate 10 l/min and nasal cannulae (length=1 cm, internal diameter=1.5 mm; Kendal, Germany) connected to an air-O2 blender-flow meter (Sechrist, France) with flow rate of 2 l/min (37). They used respiratory inductive plethysmography (Respitrace Plus, Sensor Medics, USA) and obtained Tidal volume (VT), rib cage contribution to the VT (%RC), phase angle between abdominal and thoracic motions (h), respiratory rate (RR), and inspiratory times (Ti) (37). Mean tidal volume, VT, measured from the flow-volume loops was higher during variable-flow than during either constant-Flow NCPAP or during nasal cannulae (p<0.05) (37).

Lavizzari et al conducted a randomised crossover trial in 20 preterm infants (gestational age: 31±1 weeks) with mild-moderate RDS requiring non-invasive respiratory support within 96 h after birth (36). Infants were exposed to a randomised sequence of CPAP and HFNC at different settings (2, 4 and 6 cmH2O for NCPAP and 2, 4, 6 L/min for HFNC) to enable comparison at the same level of retropharyngeal pressure (Prp) (36). A 6 Fr feeding catheter with four side holes at the distal extremity was inserted in the pharynx and connected to a pressure transducer to measure retropharyngeal pressure (Prp) (36). To avoid occlusions of
the catheter by secretions, a 40 mL/h airflow produced by a micro infuser was applied at the inlet of the catheter (36).

Tidal volume was measured from respiratory inductance plethysmography and they found that the VT was similar in the two modalities as shown in table 6 (36).

Table 6. The tidal volumes in mL at equal distending pressures - Lavizzari et al(36)

<table>
<thead>
<tr>
<th>Respiratory support</th>
<th>Prp=2 cm H2O</th>
<th>Prp=4 cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP</td>
<td>5.77 (4.76; 6.75)</td>
<td>6.89 (4.33; 8.41)</td>
</tr>
<tr>
<td>HFNC</td>
<td>5.29 (3.46; 7.95)</td>
<td>7.54 (3.97; 10.17)</td>
</tr>
</tbody>
</table>

Table 6 shows the tidal volumes at equal distending pressures during HFNC and CPAP in 20 preterm infants.

1.7.3 Methods of measuring tidal volume

The pneumotachometer is currently the most accepted device to measure tidal breathing (77). However, this requires application of a face mask over the face which has been shown to alter the respiratory parameters. In a physiology study on 10 normal, sleeping term infants aged 1-4 days, investigators studied the effects of application of pneumotachograph in addition to full face mask compared to facemask rim alone on the tidal volume and respiratory rate. The tidal volume and respiratory rate were determined by a transthoracic impedance pneumograph (78). There was a significant reduction in respiratory rate both in quiet sleep (12%) and during rapid eye movement sleep (17%) with face mask rim alone. When the complete face mask plus pneumotachograph was applied, the respiratory rate reductions were 10% in quiet sleep and 14% in rapid eye movement sleep (78). Tidal volumes on the other hand showed increase in both types of instrumentation and quantitatively the increase in tidal volumes were of similar magnitude to respiratory rate reduction (78). They concluded that the change in respiratory pattern was due to trigeminal stimulation from the face mask used (78).

Respiratory inductance plethysmography (RIP) provides a non-invasive measurement of lung volume using recording bands around the thorax and abdomen. In its simplest form it involves inductance coils placed around the child’s chest and abdomen and changes in the impedance
of the coils are proportional to changes in the volume of the chest and abdomen and the sum of the two impedances is proportional to lung volume (79).

RIP is based upon the two-compartment model of thoraco abdominal movement during respiration (80). The valid measurements are obtained when initial calibration is done accurately, the body movements are stable and changes in respiratory movements are recorded accurately (80). Measurement errors occur when there is displacement of transducer bands and when body position changes (80). RIP detects changes in the volume of the chest and abdomen during inspiration and expiration, which can be used to measure tidal volume (80).

Saslow et al used RIP in 18 preterm neonates <2.0 kg, when they studied in a random order on HFNC or CPAP support (17). CPAP at 6 cm H2O with nasal prongs was delivered by a ventilator while HFNC was by Vapotherm (VAPO) at 3, 4 and 5 l/min flow rates (17). Tidal ventilation was obtained using respiratory inductance plethysmography by recording chest wall and abdominal movements (17). They used respiratory inductance plethysmography (RIP) bands (Respibands Plus, Sensormedics Corp., Yorba Linda, CA) placed around the infant’s rib cage and abdomen(17). Calibration was done by direct comparison of volume changes measured by face-mask pneumotachography (Hans Rudolph Inc., Kansas City, MO) (17). No differences were found in the work of breathing for all settings (17).

In study of 13 premature infants (GA=29 ±1) weeks; BW=1350±350 g) at a post-natal age of 3±1 days Boumecid et al used Respiratory Inductance Plethysmography (RIP) when they compared variable flow CPAP to constant flow CPAP and nasal cannula (at a flow rate of 2 l/min) (37). They used Respitrace Plus for RIP and calibrated it using face mask pneumotachography (37). The RIP was useful in obtaining the respiratory parameters and allowed the authors to make comparison between variable flow CPAP and constant flow CPAP as well as nasal cannula therapy (37). They found that mean tidal volume was higher during variable-flow compared to other modes in their study (37).

Lavizzari et al studied 20 preterm infants between 28+0 and 32+6 weeks gestational age (GA) and postnatal age <96 h receiving either NCPAP or HFNC for mild to moderate RDS(36). They used RIP to calculate tidal volumes (36). Tidal changes were computed from the abdominal (AB) and thoracic (RC) displacements measured by respiratory inductance plethysmography (RIP) (36). The calibration was done comparing with a face-mask
pneumotachography over several spontaneous breaths (36). Using this RIP method, they did not find any statistically significant differences in breathing pattern, gas exchange, lung mechanics and total WOB in either mode of respiratory support (36).

Volusense is a recently developed system using electromagnetic inductive plethysmography technique for evaluating tidal breathing indices in infants. Respiratory measurements are derived from changes in electromagnetic inductance in a wrap-around vest worn by the baby. The vest is disposable and used for one patient only to avoid cross-infection. The vest is made from soft elastic. The vests contain thin conductive coils that are isolated. Thorax and abdominal volumes and volume changes are measured and stored digitally. This allows measurement of tidal volume, respiratory rate and tidal flow volume loops non-invasively and without application of masks or instrumentation of the infant’s airway. The calibration is done with a pretested and validated cylinder provided with the device (24-26). This has been recently validated as reliable as pneumotachography and safe in babies of gestation 28 weeks and above (24, 26). The technique is therefore ideal for measuring the effects of HFNC and CPAP on tidal breathing indices non-invasively and may improve our understanding of its mechanism of action. It may also allow us to detect the effects of varying pressure on Functional Residual Capacity (FRC) baseline and improve understanding of the role of pressure on recruitment of lung volume.

Using a device employing this new technique of electromagnetic inductance plethysmography (EIP), Pickerd et al measured tidal breathing in 49 healthy spontaneously breathing infants between 32 and 42 weeks postconceptional age (PCA) (81). They noted that the tidal volume/kg and minute volume decreased with advancing PCA (81). In another study using similar electromagnetic inductive plethysmography technique, tidal ventilation and breathing pattern were measured and compared simultaneously with pneumotachography in 43 infants either receiving no respiratory support or continuous positive airway pressure (CPAP) (82). Twenty-three infants were receiving CPAP (gestational age 28 ± 2 weeks, mean ± SD) and 20 were breathing spontaneously (gestational age 34 ± 4 weeks) (82). The two methods were in reasonable agreement, with VT ($r^2 = 0.69$) ranging from 5 to 23 ml (4–11 ml kg$^{-1}$) with a mean difference of 0.4 ml and limit of agreement of $-4.7$ to $+5.5$ ml (82).
1.8  HFNC – Summary of Literature Review

1.8.1  Summary of physiology studies

In summary, the use of HFNC is an increasing trend across the world. The device setup has basic components of humidification, air and oxygen blender and a flow driver delivering conditioned gases via nasal cannulae. There are some evidences in support of various proposed mechanisms of action in the form of in vitro and in vivo physiology studies in animals and humans. The measurement techniques differ greatly in their working mechanism, accuracy and applicability to the intended study question. Various investigators have conducted focused research on respiratory physiology parameters. The conditions of study, equipment used and methods employed differ and making inference is difficult. The physiology studies are listed in table 7.
Table 7. List of physiology studies evaluating respiratory parameters and HFNC mechanisms

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Setting Type of subjects</th>
<th>Study type and design</th>
<th>Respiratory support devices used</th>
<th>Outcomes measured</th>
<th>Findings</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locke et al (30) 1993</td>
<td>NICU Preterm infants Mean GA 30 weeks, mean birth weight 1,377 g</td>
<td>Observational study</td>
<td>Unheated and unhumidified HFNC (Salter Labs)</td>
<td>Oesophageal pressure</td>
<td>No pressure generation with smaller prongs at any flow rate</td>
<td>Mean pressure of 9.8 cm H2O at 2 L/minute Flow rates 0.5–2 L/Minute 0.2 and 0.3 cm prongs</td>
</tr>
<tr>
<td>Sreenan et al (24) 2001</td>
<td>NICU Preterm infants Mean GA 28.7 weeks, mean study weight 1,260 g</td>
<td>Observational study</td>
<td>Unheated, humidified HFNC (Salter Labs) vs. NCPAP (Infant Star)</td>
<td>Treatment of Apnoea of Prematurity (AOP) Oesophageal pressure</td>
<td>No difference in efficacy of treatment for AOP</td>
<td>Salter Labs ‘infant’ size prongs used Low flow rates used at 1–2.5 L/minute</td>
</tr>
<tr>
<td>Saslow et al (17) 2006</td>
<td>NICU Preterm infants Mean GA 28.2 weeks, mean study weight 1,542 g</td>
<td>Observational crossover study</td>
<td>Heated and humidified HFNC (Vapotherm 2000i) vs. NCPAP (Infant Bird Ventilator)</td>
<td>Work of breathing Respiratory inductance plethysmography Respiratory rate Oesophageal pressure</td>
<td>No difference noted between two modalities. Oesophageal pressure was significant only at 5 L/minute of HFNC</td>
<td>Used flow rates ranging from 3–5 L/minute</td>
</tr>
<tr>
<td>Spence et al (26) 2007</td>
<td>NICU Preterm infants Median study GA 30 weeks, median study weight 1,589 g</td>
<td>Observational study</td>
<td>Heated and humidified HFNC (Fisher and Paykell) and NCPAP (Infant Flow)</td>
<td>Pharyngeal pressure</td>
<td>Pharyngeal pressure increases with increasing flow</td>
<td>‘Infant’ size Salter prongs were used</td>
</tr>
<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
<td>Study type and design Respiratory support devices used</td>
<td>Outcomes measured</td>
<td>Findings</td>
<td>Additional information</td>
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<tr>
<td>Kubicka et al(3) 2008</td>
<td>NICU Preterm infants GA range 25–40 weeks, birth weight 605–3,657 g</td>
<td>Observational study Heated and humidified HFNC (Vapotherm 2000i or Fisher and Paykell RT329)</td>
<td>Oral pressure</td>
<td>No pressure generated with mouth open When mouth in closed position pressure increases with flow in infants &lt; 1,500 g</td>
<td>Flow rates 1–5 L/minute, 0.2 cm prongs More mature and larger infants included in study</td>
<td></td>
</tr>
<tr>
<td>Wilkinson et al(27) 2008</td>
<td>NICU Preterm infants Median GA 27.1 weeks, median birth weight 944 g</td>
<td>Observational study Heated and humidified HFNC (Fisher and Paykell RT329)</td>
<td>Pharyngeal pressure</td>
<td>Pharyngeal pressure increases with increasing flow but decreases with increasing weight</td>
<td>Included extremely premature infants Higher flows up to 8 L/minute Mouth position is irrelevant</td>
<td></td>
</tr>
<tr>
<td>Lampland et al(31) 2009</td>
<td>NICU Preterm infants Mean GA 29.5 weeks, mean birth weight 1,324 g</td>
<td>Observational study Heated and humidified HFNC (Fisher and Paykell RT329) vs. NCPAP (Draeger Babylog 8000)</td>
<td>Physiological parameters including heart rate, respiratory rate, FiO2, PaO2 RDS scoring system Oesophageal pressure</td>
<td>As flow rate decreases respiratory rate increases As flow rate increases oesophageal pressure increases</td>
<td>Fisher and Paykell neonatal size prongs of 0.24 cm used Slightly higher flow rates studied 1–6 L/minute</td>
<td></td>
</tr>
<tr>
<td>Corley et al(35) 2011</td>
<td>ICU Mean age 65.3 years, weight 93.3 kg</td>
<td>Post cardiac surgery adult patients Prospective interventional study LFNC vs. HFNC</td>
<td>Electrical impedance tomography Respiratory rate Borg scores</td>
<td>Significant correlation between airway pressures and end expiratory lung impedance</td>
<td>A trend towards HFNC improving subjective dyspnoea scoring</td>
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<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
<td>Study type and design Respiratory support devices used</td>
<td>Outcomes measured</td>
<td>Findings</td>
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<tr>
<td>Volsko et al(21) 2011 Simulation model</td>
<td>Laboratory based study Active simulator lung model</td>
<td>Observational study Lung model simulated a sick neonate of approximatel y 1 kg with lung compliance 0.5 mL/cm H2O and resistance 125 cm 2O/L/s</td>
<td>Highest and lowest airway pressure Mean airway pressure VT drop</td>
<td>Flows of &gt;2 L/minute generated positive expiratory pressure with all cannula sizes</td>
<td>Cannulae used were (Comfort Flow models) Premature Infant Infant</td>
<td></td>
</tr>
<tr>
<td>Arora et al(28) 2012 n = 25</td>
<td>PICU Mean age 78.1 [SD 30.9] days; weight, 5.3 [SD 1.1] kg</td>
<td>Acute bronchiolitis Prospective, observational study Heated humidified HFNC system</td>
<td>Nasopharyngeal (NP) pressures Vital Signs Bronchiolitis severity scores Oxygen saturation</td>
<td>Linear increase in NP pressures with flow rates up to 6 L/minute but with significant differences between pressures in open and closed mouth states Bronchiolitis severity scores improved significantly</td>
<td>No effect of gender or weight noted on generated pressure</td>
<td></td>
</tr>
<tr>
<td>Mile´si et al(54) 2013 n = 21</td>
<td>PICU Infants &lt; 6 months old Acute RSV bronchiolitis</td>
<td>Prospective observational study Heated and humidified HFNC RT329 system Fisher and Paykell</td>
<td>Pharyngeal pressure (PP) and oesophageal pressure (Pes) measured simultaneously</td>
<td>Flow &gt;2 L/kg/minute generated a mean PP &gt;4 cm H2O Significant reduction in respiratory rate noted with increase in flow</td>
<td>Measured at flows of 1, 4, 6 and 7 L/minute</td>
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<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
<td>Study type and design</td>
<td>Respiratory support devices used</td>
<td>Outcomes measured</td>
<td>Findings</td>
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<tr>
<td>Sivieri et al(20)</td>
<td>Laboratory based study</td>
<td>Observational study</td>
<td>HFNC (Fisher &amp; Paykel system with integrated pressure relief valve)</td>
<td>Cannula and airway pressures</td>
<td>For all ratios mouth open 6 L/minute flow pressures were &lt; 1.7 cm H2O</td>
<td>Neonatal and infant sized nasal prongs (3.0 and 3.7 mm outer diameter)</td>
</tr>
<tr>
<td></td>
<td>Simulaton model</td>
<td></td>
<td>In vitro evaluation of effect of nasal prong-to-nares ratio and mouth leak on airway pressures generated by HFNC device</td>
<td>Cannula and mouth leak flows</td>
<td>Ratios &lt;0.9 mouth closed airway pressure was &lt;10 cm H2O</td>
<td>Seven sizes of simulated nares (range: 3-7 mm internal diameter)</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td></td>
<td></td>
<td></td>
<td>Ratios &gt;0.9 50% mouth leak airway pressure rises to 18 cm H2O at 2 L/minute flow</td>
<td>Nasal prong-to-nares ratio range (0.43 to 1.06)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>24 cm H2O at 6 L/minute flow (pressure relief valve limited)</td>
<td></td>
</tr>
<tr>
<td>Collins et al(29)</td>
<td>NICU mean gestational age at birth of 27.4 completed weeks (SD 1.5) and birthweight 1139 g (SD 253).</td>
<td>Observational study</td>
<td>HFNC Devices Fisher &amp; Paykel Vapotherm</td>
<td>Pharyngeal pressure measurements recorded with both HFNC devices at flow rates of 2–8 L/min.</td>
<td>There was no difference in pharyngeal pressures recorded between devices at flow rates of 2–6 L/min; measured pressure was linearly associated with flow ($R^2 = 0.9$).</td>
<td>The pressure limiter valve of the Fisher &amp; Paykel device attenuated the pharyngeal pressures at flows of 7 and 8 L/min.</td>
</tr>
<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
<td>Study type and design Respiratory support devices used</td>
<td>Outcomes measured</td>
<td>Findings</td>
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<tr>
<td>Parke et al (83) 2013 n=15</td>
<td>Adults Age 59.5 ±10.6 years Weight 85.1 ±17 kg Cardiac post-operative patients</td>
<td>RT033/034 Optiflow nasal cannula, MR880 heated humidifier, and RT241 heated delivery tube, Fisher &amp; Paykel</td>
<td>Nasopharyngeal pressure measurements at gas flows of 30, 40, and 50 L/min</td>
<td>mean ± SD nasopharyngeal airway pressures were 1.5 ± 0.6, 2.2 ± 0.8, and 3.1 ± 1.2 at 30, 40, and 50 L/min</td>
<td>The expiratory pressure during HFNC was higher than the mean pressure previously reported for nasal high flow.</td>
<td></td>
</tr>
<tr>
<td>Shetty et al (39) 2016 n=20</td>
<td>Median gestational age of 27.6 weeks (range 24.6–31.9 weeks)) Studied at a median postnatal age of 30.9 weeks (range 28.1–39.1 weeks).</td>
<td>Randomised crossover trial HFNC - Fisher and Paykel using optiflow neonatal and infant nasal prongs</td>
<td>WOB assessed by measuring the pressure time product of the diaphragm (PTPdi). Thoracoabdominal asynchrony (TAA) SaO2</td>
<td>no significant differences in the results on CPAP versus HHFNC mean PTPdi mean TAA mean SaO2</td>
<td>Oesophageal (Poes) and gastric (Pgas) pressures were measured using a dual pressure transducer tipped catheter (Gaeltec).</td>
<td></td>
</tr>
<tr>
<td>Frizzola et al 2012 Animal Study n=13</td>
<td>Neonatal piglets (n=13; 2-6kg) were injured with IV oleic acid and supported with HFNC at 2 through 8 L/min.</td>
<td>Treatment order randomised Vapotherm 2000i CPAP VIP Bird infant ventilator</td>
<td>Tracheal pressures Respiratory parameters – respiratory rate and relative tidal volume CO2 levels PaO2 levels were measured</td>
<td>CO2 trended downward in a flow dependent manner independent of leak. Double prong (low leak) had greater impact on O2</td>
<td>At 8L/min, tracheal pressures did not exceed 6±1 cm H2O. Single prong(high leak) greater CO2 removal</td>
<td></td>
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<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
<td>Study type and design Respiratory support devices used</td>
<td>Outcomes measured</td>
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<tr>
<td><strong>Moller et al(84)</strong> 2015</td>
<td>Models 1st - simple tube model consisting of a nozzle to simulate the nasal valve area, connected to a cylindrical tube to simulate the nasal cavity. The second anatomically representative upper airway model (from CT-scan images)</td>
<td>HFNC at rates of 15, 30, and 45 l/min. Tracer gas clearance investigated</td>
<td>The tracer gas clearance was determined using dynamic infrared CO2 spectroscopy and 81mKr-gas radioactive gamma camera imaging.</td>
<td>There was complete tracer-gas removal from the nasal cavities within 1.0 s. The level of clearance in the nasal cavities increased by 1.8 ml/s for every 1.0 l/min increase in the rate of NHF.</td>
<td>For both models, the anterior compartments demonstrate faster clearance levels (half-times &lt; 0.5 s) and the posterior sections showed slower clearance (half-times &lt; 1.0 s).</td>
<td></td>
</tr>
<tr>
<td><strong>Moller et al(85) 2016</strong> n=10 +3</td>
<td>Observational study 10 healthy adult volunteers And 3 tracheotomised patients</td>
<td>Scintigraphy with 81mKrypton (81mKr) gas during a breath-holding manoeuvre with closed mouth and in 3 nasally breathing tracheotomised patients by HFNC rates of 15, 30, and 45 l/min.</td>
<td>Volumetric capnography and oximetry through sampling CO2 and O2 in the trachea and measuring the inspired volume with inductance plethysmography.</td>
<td>decrease in 81mKr gas clearance half-time with an increase of HFNC flow rate in the nasal cavities. Tracheal gas showed an HFNC dependent decrease of inspired CO2 that correlated with an increase of inspired O2.</td>
<td>NHF clears upper airways of expired air. The dead space clearance is flow and time dependent, and it may extend below the soft palate.</td>
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<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
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<tr>
<td>Miller et al(70) 2004</td>
<td>Spontaneously breathing neonatal pigs (2.4_0.4 kg)</td>
<td>Randomised controlled randomized to receive CPAP with TGI (TGI; n=9) or CPAP alone (control; n=10)</td>
<td>arterial blood gases, pulmonary mechanics, and thoracoabdominal motion (TAM) were evaluated 30 min after injury and at 1-hr intervals for 4 hr</td>
<td>TGI group PaCO2 was lower while the oxygenation indices were greater pH was greater ventilation was accomplished with a lower minute ventilation (MV)</td>
<td>Examined role of TGI (wash out effect)</td>
<td>HFNC was not studied</td>
</tr>
<tr>
<td>Chang et al(52) 2011</td>
<td>In-Vitro study To study the effect of flow on temperature, humidity, device pressure, and resistance</td>
<td>Nasal cannula (NC), continuous positive airway pressure (CPAP), and high-flow nasal cannula (HFNC) Flow ranges (0-3 L/min and 0-8 L/min)</td>
<td>Effect of flow on temperature, in humidity, pressure and resistance</td>
<td>For all devices at 0-3 L/min, there was a difference (p&lt;0.01) in temperature, humidity pressure and resistance as a function of flow. For HFNC and CPAP at 0-8 L/min, there was a difference (p&lt;0.01) in temperature, in humidity, pressure and resistance as a function of flow.</td>
<td>Gas delivered by HFNC was more humid than NC and CPAP. Higher pressure and resistance was delivered by the HFNC system</td>
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<tr>
<td>Study Year number (cont)</td>
<td>Setting Type of subjects Age/gestational age (GA) and weight</td>
<td>Study type and design Respiratory support devices used</td>
<td>Outcomes measured</td>
<td>Findings</td>
<td>Additional information</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
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<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Sivieri et al(86)</td>
<td>Premature infant lung model</td>
<td>Fisher &amp; Paykel cannulas (2.8 and 3.2mm O.D.)</td>
<td>The lung was primed with 5% CO₂. Washout times were determined at HFNC settings of 3, 4, 5, 6, and 8 L/min and NCPAP at 3, 4, 5, 6, and 8 cm H₂O with simulated open and closed mouth conditions and full and half inserted HFNC prongs.</td>
<td>Overall combined mean washout times for NCPAP with mouth closed were significantly longer than HFNC over all five pressure and flow device settings. CO₂ washout times decreased as flow or pressure device settings were increased.</td>
<td>Simulated mouth opening was a 5mm I.D. side tap below the nasal interface. There were negligible differences in washout times between NCPAP and HFNC with mouth open.</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>Piston cylinder lung simulator, having a fixed volume of 30 ml and a 4.8 ml dead space, simulated spontaneous breathing (6.5 ml tidal volume, Rate 50/min, Ti 0.5 sec)</td>
<td>Infant-Flow NCPAP cannulas (3.4 and 4.1mm O.D.) Simulated airways with either 3.5 or 4.5mm I.D. nares.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.9 Concerns with HFNC Therapy

1.9.1 Delivery of airway pressure – unmonitored and unpredictable

Some of the earlier studies on high flow therapy documented delivery of inadvertently high mean airway pressures when nasal cannula diameter 0.3 cm was used in neonates (30). Studies of airway pressures since have not consistently identified dangerously high pressures (3, 17, 27, 31). However there is wide variation in the techniques and protocol used to measure pressures (2).

1.9.2 Microbial colonisation of delivery systems

In 2005 there were reports of Ralstonia species infection in the neonatal units using Vapotherm 2000i (87, 88). This was noted to be due to the humidification system used in the HFNC units. Since then strict infection prevention measures such as disposal of humidifier fluid routinely and standardised cleaning of equipment has made these systems safer. However, as HFNC circuit contains moist, humidified system, continued vigilance and strict adherence to cleaning must be followed to avoid infections. Shoemaker et al noted increased gram-negative infections in their observational study (89).

1.9.3 Effects on lung volumes

Long term effects of inadequate lung expansion or over distension due to effects on end expiratory lung volume (EELV) – does it increase incidence of CNLD? Inadequate end expiratory pressure may lead to reduction in end expiratory lung volume or Functional Residual Capacity. This can lead to atelectasis and can give rise to atelectotrauma. It is possible that in the presence of atelectasis lung units that are still recruited may in advertently receive a greater proportion of tidal volume and become over distended.

On the contrary, over distension can lead to volutrauma. Dreyfuss et al studied this phenomenon of volutrauma in rats with or without strapped chests (90). This allowed limiting the thoracoabdominal movements (90). They compared the consequences of normal tidal volume ventilation in mechanically ventilated rats at a high airway pressure (HiP-LoV) with those of high tidal volume ventilation at a high (HiP-HiV) or low (LoP-HiV) airway pressure
An application of PEEP (10 cm H2O) and its effects on both oedema and lung ultrastructure was also studied (90). In rats with low tidal volumes (VT) there was no cases of pulmonary oedema, even when high airway pressures were used (90). The lungs from the rats submitted to high volume ventilation had significant permeability type pulmonary oedema (90). This oedema was more pronounced in LoP-HiV rats and it was markedly reduced by application of PEEP (90).

Both these phenomena are harmful to developing lung tissue. It is not known; however exact dose-response value for these adverse effects to occur during HFNC. Whether transient elevations or drop in airway pressures have any clinic-pathological effects is unknown.

**1.9.4 Effects of noise**

The noise levels produced vary with the type of machine used. It also depends upon the flow driver and the way the system is built. It also depends upon the flow rate used during therapy.

Roberts CT et al performed a study in 21 infants to determine whether HFNC (n=21) was noisier than bubble CPAP n=13) (BCPAP) for preterm infants (91). They measured noise levels within the external auditory meatus (EAM) with a microphone probe tube connected to a calibrated digital dosimeter (91). HFNC flow rate range was 2–5 L/min, and BCPAP pressures were 5–7 cm of water using 6–10 L/min of gas flow (91). There was no evidence of a difference in average noise levels measured at the EAM for HFNC compared to BCPAP(91). HFNC was quieter than BCPAP only at low frequency (500 Hz), mean (95% CI) 3.0 (0.3 to 5.7) dBA (91). Noise increased with increasing BCPAP gas flow (p=0.007), but not with increasing set pressure (91). There was a trend to noise increasing with increasing HFNC gas flows (91). They concluded that HFNC are not noisier than BCPAP for preterm infants at the gas flow range that they studied.

An In-Vitro study was done to record the noise levels produced by Fisher & Paykel NHF™ and Vapotherm Precision Flow®) and one CPAP device (Dräger Babylog® 8000 plus in the oral cavity of newborn manikin model in an incubator in a quiet environment (92). HFNC flows of 4-8 l/min and CPAP pressures of 4-8 cm H2O with CPAP flow at 8 l/min was used (92). Vapotherm HFNC generated the highest noise levels, measuring 81.2-91.4 dB(A) with increasing flow (92). Fisher & Paykel HFNC noise levels were between 78.8 and 81.2 dB(A)
The CPAP device generated the lowest noise levels between 73.9 and 77.4 dB(A)(92). Thus in this study both HFNC devices generated higher noise levels than the CPAP device (92).

1.9.5 **Possibilities of air leak syndromes**

A case series with HFNC including one involving pneumocephalus, pneumo orbitis and scalp emphysema raised concerns with air leak syndromes (93). Since there have been few more case reports of air leak (94, 95). However, this has not been supported by further larger clinical trials involving HFNC (96-98).

1.9.6 **Monitoring while on HFNC**

Delayed recognition of a deteriorating patient with progressive respiratory failure may occur due to the ability of the HFNC system to give up to 100% oxygen without necessarily improving ventilation and CO$_2$ removal. However, not much has been published in neonatal or paediatric literature regarding the likely short term adverse events due to HFNC apart from few case reports. This may be because there is no clear evidence as to how to wean, escalate or stop high flow therapy (99). A Cochrane systematic review in 2015 failed to identify any relevant studies evaluating discontinuation of HFNC in preterm infants (99). Therefore, any adverse event may not be appreciated as due to the way HFNC as administered or prescribed to the neonate. In the adult ICU however, there have been some observational and retrospective data regarding possible delays in intubation due to reliance on HFNC contributing to mortality (100, 101).

1.10 **HFNC - Gaps in knowledge**

Although various mechanisms of action for HFNC in neonates have been proposed the relative contributions of these mechanisms is not well understood. In addition there are a number of factors influencing the measurements of physiology parameters depending on the technique used making comparisons and inferences of earlier studies particularly difficult.
1.10.1 *Airway pressure measurement during HFNC therapy*

The magnitude of pressure generated in the airway varies depending upon the site of measurement, measurement technique used and the fidelity of the data acquired and used to report the pressures. Thus clinicians and researchers are still not clear as to the pressure effects of HFNC on the airway. Therefore it is important to identify appropriate and fit for purpose techniques and record accurate pressure measurements in the airway.

1.10.2 *Nasopharyngeal gas concentrations during HFNC therapy*

Dead space washout effects of HFNC in human patients has not been unequivocally answered. The proposed evidences have largely been drawn from tracheal insufflation studies and animal models. Thus recording airway gas concentrations at various stages of respiratory cycle gives clarity regarding any role for dead space washout mechanism for HFNC.

1.10.3 *Tidal volume changes during HFNC therapy*

The tidal volume measurement is challenging as application of pneumotach devices on the face to capture tidal breathing results in alternation in respiratory rate and depth. Thus non-invasive techniques are needed which can continuously measure changes in tidal volumes with changes in HFNC therapy. However, measuring techniques involving conventional plethysmography equipment are cumbersome. Therefore a simple, minimally invasive device is needed. Although it has been shown that following initiation of HFNC there is improvement in respiratory rate and heart rate parameters in children with respiratory distress it is not clear whether this effect is due to effects on the tidal volumes.

1.10.4 *Gaps in knowledge regarding HFNC clinical application*

There is currently no consensus and evidence basis for the treatment initiation parameters such as HFNC flow levels and whether to wean oxygen or flow as well as the rate of weaning to be employed. The influence of different pathologies and population for which it is being used also needs to be studied.
Chapter 2. Aims
The work presented in this thesis was a proof of concept study for a larger randomised crossover study to investigate respiratory physiology during high flow nasal cannula therapy in preterm neonates.

In order to evaluate the respiratory physiology, various parameters had to be measured. This included nasopharyngeal pressures, nasopharyngeal space oxygen and carbon dioxide concentration, tidal volumes and measures of gas exchange such as transcutaneous carbon dioxide levels and transcutaneous oxygen saturation. I investigated the feasibility and accuracy of methods to measure these parameters in preterm neonates during high flow therapy. In parallel I designed and developed the protocol for the randomised crossover study and successfully applied for ethical approval.

Therefore, the specific aims of my project were to,

1. Perform a descriptive review of available evidence for clinical efficacy and safety of high flow nasal cannula therapy in preterm neonates

2. Assess the range, accuracy and feasibility of three different types of nasopharyngeal airway pressure measuring techniques in preterm neonates during high flow therapy

3. Assess the feasibility and accuracy of airway gas concentration assessment in preterm neonates during high flow therapy

4. Assess the feasibility and accuracy of measuring tidal volumes in preterm neonates during high flow therapy using Volusense equipment
Chapter 3. Descriptive Review of Key Outcomes with High Flow Nasal Cannula Therapy in Preterm Infants
3.1 Introduction

In preterm infants, Respiratory Distress Syndrome (RDS) is an important clinical entity requiring intensive care support. The disease has a wide spectrum in severity and therefore different levels of respiratory support may be required. It is important to identify optimum respiratory support which is safe in the short term as well as long term and efficacious in terms of clinical outcomes. This is particularly important at present because it is evident from surveys that a significant number of neonatal units and clinicians have reported existence of equipoise when deciding between CPAP and HFNC.

HFNC was initially used as a post extubation respiratory support or while weaning from CPAP. However, as experience with its use increased with time, neonatal units started using it as primary respiratory support following birth or when RDS set in. This clinical application was not preceded by well conducted clinical trials. Since the first paper on its use as primary respiratory support was presented by Nair et al in an academic meeting in 2005 there have been several studies examining the clinical efficacy and safety of HFNC in neonatal population.

In this chapter, a descriptive review of these studies followed by a table listing the key features of each study is presented. A discussion on the current evidence for and against its use as respiratory support in various clinical situations has been presented.
3.2 Background

3.2.1 Definitions

In this review following definitions were used,
Preterm infants – Infants born at gestation less than 37 weeks completed.

HFNC therapy – Treatment with heated, humidified air/oxygen mixture with flow rates more than 1 litre per minute.

CPAP therapy – Treatment with a device delivering air/oxygen mixture via a nasal interface which maintains a continuous positive airway pressure.

BPD – NIH definition – Infants requiring oxygen at 28 days of life and further classified according to gestation at birth and oxygen/positive pressure requirement as shown in table 8.
**Table 8. Bronchopulmonary Dysplasia Definition(102)**

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>&lt;32 wk</th>
<th>≥32 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point of assessment</td>
<td>36 wk PMA or discharge to home, whichever comes first</td>
<td>&gt;28 d but &lt;56 d postnatal age or discharge to home, whichever comes first</td>
</tr>
<tr>
<td>Mild BPD</td>
<td>Breathing room air at 36 wk PMA or discharge, whichever comes first</td>
<td>Breathing room air by 56 d postnatal age or discharge, whichever comes first</td>
</tr>
<tr>
<td>Moderate BPD</td>
<td>Need * for &lt;30% oxygen at 36 wk PMA or discharge, whichever comes first</td>
<td>Need * for &lt;30% oxygen at 56 d postnatal age or discharge, whichever comes first</td>
</tr>
<tr>
<td>Severe BPD</td>
<td>Need * for ≥30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first</td>
<td>Need * for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first</td>
</tr>
</tbody>
</table>

Table 8 shows the current consensus definition of BPD(102)
3.2.2 Rationale

This review is relevant because of the widespread use of HFNC despite it being just over a decade old therapy. This has the implications for lung health of the individual patient as well as implications for health care burden for family and health care providers because of unclear risks for efficacy in the short term and bronchopulmonary dysplasia in the long term. This is particularly relevant for extremely low birth weight infants.

Pathophysiology in BPD can be considered in three areas as lung parenchymal disease, pulmonary vascular disease and airways disease.

In BPD, pulmonary gas exchange is abnormal due to changes in lung parenchyma. The changes include alveolar simplification and abnormal development of the pulmonary vascular bed (103). The lung parenchyma shows different areas of hyperinflation, atelectasis and fibrosis. This results in increased dead space, abnormal lung resistance and compliance in a patchy distribution, V/Q mismatch and intrapulmonary shunting (104-106). The differences in pulmonary resistance and compliance in different lung units results in differences in ventilation causing ventilation inhomogeneity.

The main features of pulmonary vascular abnormality seen in BPD are poor growth of pulmonary vascular bed and inflammation due to endothelial cell dysfunction (103). This results in poor gas exchange. Pulmonary hypertension develops over time when this process is severe (103).

Increased airway obstruction is seen in BPD due to airway remodelling, decreased airway and alveolar growth, and mechanical ventilation associated complications such as tracheomalacia, bronchomalacia, and stenosis of glottis, sub glottis and trachea. Airway obstruction leads to air trapping (107). Pulmonary mechanics are also altered because of reduction in the lung parenchymal elastic framework. This results in reduced airway support and allows airway closure and collapse of alveoli. These changes result in overall reduced lung compliance and reactance whilst increasing pulmonary resistance (108, 109).
3.3 Aims and Outcomes

3.3.1 Aims

The aim of this review is to present an up to date evidence regarding the efficacy and safety of HFNC as respiratory support for preterm infants (<37 weeks’ gestational age at birth), when compared with other modes of non-invasive respiratory support.

3.3.2 Outcomes

Main outcomes of interest are treatment failure as defined by study criteria (failure of extubation), mortality, nasal trauma, BPD, air leak syndromes, length of respiratory support, duration of oxygen therapy and duration of hospitalisation.

3.4 Methods

3.4.1 Search strategy

I searched the following electronic databases Ovid Medline, EMBASE, HMIC and CINAHL as well as The Cochrane Library. In addition, the references from the extracted articles were cross checked for further articles. All languages were included during the search for articles. The study types searched included Cochrane Reviews, Systematic Reviews, Meta-Analyses, Controlled Clinical Trials, and Randomized Controlled Trials. The key words used in earlier Cochrane Review and another earlier meta-analysis done by Kotecha et al were used for the search and are listed below (1, 110).

Key words used as in the study by Kotecha et al - Non-invasive ventilation, CPAP, continuous positive airway pressure, nasal cannula, nasal prong, oxygen inhalation therapy, high-flow, high-flow therapy, Infant, Low Birth Wt., Infant, Extremely Low Birth Wt., Infant, Premature, Premature Birth, Fetal Growth Retardation, Birth Wt., Low Birth Wt., IUGR, Randomized Controlled Trials, Random Allocation, Double-blind Method, Single Blind Method, clinical trial, controlled clinical trial, multicentre study (110).

Key words used as in the Cochrane review- infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW (1).
In this review, I included prospective, randomized controlled trials involving preterm infants born at <37 weeks’ gestational age. Studies involving both term and preterm babies were included but only preterm data was taken into consideration. Trials were included if participating infants received non-invasive respiratory support, and randomly assigned to HFNC or any other form of non-invasive respiratory support as primary respiratory support after birth, after extubation from mechanical ventilation or while weaning from non-invasive respiratory support.

3.4.2 Selection of studies

A total of 35 studies published as full text articles (24, 29, 91, 96-98, 111-139) and 2 studies as abstracts (140, 141) were extracted from the literature search. Among these, five articles were used for qualitative analysis only such as for review of other clinical outcomes (118, 133, 137-139). A total of 20 studies published as full-text articles (96-98, 113, 114, 116-118, 122-132, 134) and 2 studies published as abstracts (140, 141) with treatment failure data were included in the final review. Of the studies published as abstracts, one study evaluated HFNC as primary support but was terminated early and the data was extracted from previous reviews (1, 110, 140, 142) and in another study only abstract data was used to review HFNC as weaning mode (141). Both these abstracts were included because data needed for the review question was available.

All included studies compared HFNC with CPAP, except 2 studies of which one compared HFNC with Nasal Intermittent Positive Pressure Ventilation (NIPPV) (126) and Nasal Intermittent Mandatory Ventilation (NIMV) in the other (123). All the studies involved preterm infants who were <37 weeks’ gestation except in 2 studies which included both term and preterm infants but stratified data of only preterm babies were included in the analysis (97, 111).

One study compared HFNC with CPAP both as a primary mode of respiratory support and as post extubation respiratory support and stratified data for primary outcomes were available for both uses and therefore this study was included review questions (97). Thus, 6 studies were included for examining HFNC as primary respiratory support (97, 122, 127, 130, 131, 140) and 11 studies were included for examining HFNC as post extubation respiratory support (96-
98, 111, 112, 116, 117, 124, 125, 128, 132). Google Translate was used for an automated translation from Chinese to English (Google Inc, Mountain View, CA). Characteristics and clinical details of all the included studies are presented in table 9.

3.4.3 Statistical analysis

Although this was a descriptive review, I calculated risk ratio for various outcomes using the data from included studies. I used Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark) for statistical analysis. The data was extracted for each intervention group and Risk Ratios (RR) was calculated, along with 95% confidence intervals (CIs). Significance was set at P<0.05.
Table 9. List of studies included in HFNC clinical efficacy review

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study Type</th>
<th>Study population</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoder 2013</td>
<td>RCT</td>
<td>Primary n=141</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>Nair 2005</td>
<td>RCT</td>
<td>n=67</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure requiring intubation</td>
</tr>
<tr>
<td>Iranpour 2011</td>
<td>RCT</td>
<td>n=70</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure requiring intubation</td>
</tr>
<tr>
<td>Lavizzari 2016</td>
<td>RCT</td>
<td>n=316</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure requiring intubation</td>
</tr>
<tr>
<td>Shin 2017</td>
<td>RCT</td>
<td>n=87</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure requiring intubation</td>
</tr>
<tr>
<td>Roberts 2016</td>
<td>RCT</td>
<td>n=564</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure requiring intubation</td>
</tr>
<tr>
<td>Kugelman 2011</td>
<td>RCT</td>
<td>n=76</td>
<td>HFNC vs NIPPV</td>
<td>Treatment failure requiring intubation</td>
</tr>
<tr>
<td>Iranpour 2016</td>
<td>RCT</td>
<td>n=60</td>
<td>HFNC vs NIMV</td>
<td>Total respiratory support</td>
</tr>
<tr>
<td>Collins 2013</td>
<td>RCT</td>
<td>n=132</td>
<td>HFNC vs CPAP</td>
<td>Respiratory support after 1st day</td>
</tr>
<tr>
<td>Manley 2013</td>
<td>RCT</td>
<td>n=303</td>
<td>HFNC vs CPAP</td>
<td>Extubation failure in the first 7 days after extubation</td>
</tr>
<tr>
<td>Liu 2014</td>
<td>RCT</td>
<td>n=255</td>
<td>HFNC vs CPAP</td>
<td>Treatment failure within 7 days of randomisation</td>
</tr>
<tr>
<td>Mostafa-Gharehbaghi 2014</td>
<td>RCT</td>
<td>n=85</td>
<td>HFNC vs CPAP</td>
<td>Extubation failure in the first 7 days after study entry</td>
</tr>
<tr>
<td>Chen 2015</td>
<td>RCT</td>
<td>n=66</td>
<td>HFNC vs CPAP</td>
<td>Re-intubation within 3 days of study entry</td>
</tr>
<tr>
<td>Chen 2016</td>
<td>RCT</td>
<td>n=129</td>
<td>HFNC vs CPAP</td>
<td>Extubation failure within 7 days</td>
</tr>
<tr>
<td>Kang 2016</td>
<td>RCT</td>
<td>n=161</td>
<td>HFNC vs CPAP</td>
<td>Extubation failure within 7 d after extubation</td>
</tr>
<tr>
<td>Kadivar 2016</td>
<td>RCT</td>
<td>n=54</td>
<td>HFNC vs CPAP</td>
<td>Remaining extubated for at least 3 days after INSURE method.</td>
</tr>
<tr>
<td>Soonsawad 2017</td>
<td>RCT</td>
<td>n=49</td>
<td>HFNC vs CPAP</td>
<td>Extubation failure within 3 days after endotracheal tube removal</td>
</tr>
<tr>
<td>Elkhwad 2017</td>
<td>RCT</td>
<td>n=60</td>
<td>HFNC vs CPAP</td>
<td>Failure of extubation within 5 days of initial extubation</td>
</tr>
<tr>
<td>Abdel Hady 2011</td>
<td>RCT</td>
<td>n=60</td>
<td>HFNC vs no HFNC</td>
<td>Duration of extubation</td>
</tr>
<tr>
<td>Badiee 2015</td>
<td>RCT</td>
<td>n=88</td>
<td>HFNC vs CPAP only</td>
<td>Duration of oxygen Requirement</td>
</tr>
<tr>
<td>Soonsawad 2016</td>
<td>RCT</td>
<td>n=101</td>
<td>HFNC vs CPAP only</td>
<td>Time, it took to wean off the use of the CPAP or HFNC devices</td>
</tr>
<tr>
<td>Bao 2017</td>
<td>RCT</td>
<td>n=82</td>
<td>HFNC vs LFNC</td>
<td>Rate of one time successful weaning of CPAP</td>
</tr>
</tbody>
</table>

TOTAL 3297

Table 9 shows the list of studies included in this review and key characteristics.
3.5 Primary respiratory support for RDS - HFNC versus CPAP

3.5.1 Descriptive review of studies evaluating HFNC for primary respiratory support compared to CPAP

I identified 6 RCTs addressing this question in this review. 3 studies were small trials and 3 studies had large number of infants. Overall 1245 babies have been studied. A brief description of these studies is followed by a meta-analysis of the primary outcome of treatment failure. The treatment failures in the studies were defined by need for intubation and mechanical ventilation.

A study by Yoder et al consisted of essentially two subgroups- one subgroup where HFNC was used as primary support for respiratory distress and compared with CPAP, and other subgroup where HFNC was used as post extubation support and compared with CPAP in its efficacy against treatment failure (97). Over all 432 term and preterm infants of more than 28 weeks' GA who were planned to receive non-invasive respiratory support either as primary support after birth or as post extubation support were enrolled onto the study (97). Among the study patients, 351 infants were preterm and rest were term babies (97). The primary support subgroup had 125 preterm infants and post-extubation subgroup had 226 preterm babies(97).

The respiratory support provided by HFNC was in the range of 3 to 5 L/min or nasal CPAP was 5 to 6 cmH₂O and this was administered after randomisation (97). The primary outcome was defined as the need for intubation based on pre-determined criteria, within 72 hours of commencing the treatment allotted by randomisation with either HFNC or CPAP (97). There was no significant difference in the primary outcome between CPAP and HFNC. More infants in the HFNC group crossed over to the alternative treatment after 72 hours. Any type of positive pressure requirement was shorter for CPAP group as compared to HFNC group but there was no difference in time to wean to room air or BPD rate.

They concluded that in infants >28 weeks’ gestational age, HFNC appears to have similar clinical efficacy and safety to CPAP as a mode of non-invasive respiratory support.

The study had prespecified criteria for intubation and used random number generation and opaque sealed envelopes for randomisation but the study was non-blinded. The risks for bias include, non-blinded study, selective reporting of outcomes, and loss of power when making subgroup analysis of preterm babies from the whole study group which had both term and preterm babies.
Nair et al conducted a single-centre study looking at HFNC efficacy as a primary support for respiratory distress in preterm infants (140). They enrolled 67 preterm infants of mean (range) 32 (27-34) weeks gestational age and mean birth weight of 1700 grams with respiratory distress in the first six hours after birth (140). They were randomised to HFNC (mean flow rate was 5 to 6 L/min) or CPAP (pressures of 5 to 6 cmH2O) (140). The primary outcome was pre-determined with set criteria and was met if the infant required intubation due to respiratory failure (140). They found that 4/33 (12.1%) in HFNC group and 4/34 (11.7%) in NCPAP group ended up with treatment failure as per their pre-determined criteria in the trial (p= 0.96).

This was one of the first studies which looked at HFNC as primary support for RDS in neonates. The study was well structured with pre specified criteria (140). In addition unlike some other studies during the same time, the Vapotherm units used in the study were modern and delivered both heated as well as humidified gas (140). However, the study had to be stopped early due to reports of infection with Ralstonia species in other neonatal units using Vapotherm device for delivery of HFNC (1). The study was unpublished but was presented in Paediatric Academic Society meeting (1, 140). The recruited infant numbers did not reach the power to discriminate superiority of HFNC over CPAP (1). The study did not examine the extremely premature babies or VLBW babies (140).

The risks of bias include non-blinded study, the Vapotherm device was provided by the company.

In a single centre study by Iranpour et al conducted in a University Hospital in Iran, 70 preterm infants of 30 to 35 weeks' gestation were enrolled at 24 hours of age. The inclusion criteria was presence of ongoing features of respiratory distress and oxygen requirement (122). Infants were then randomised to either HFNC (gas flow 1 to 4 L/min) or to continuing nasal CPAP (6 cmH2O)(122). In this study they also used INSURE (Intubation, Surfactant administration, Extubation) technique if the infants met prespecified criteria and this was done either before or after randomisation as per infants clinical requirement (122). They found that there was no difference in failure of treatment. In addition, there were no differences in death, duration of hospitalization, duration of improvement of respiratory distress, chronic lung disease (CLD) and pneumothorax. There was less nasal trauma in
HFNC group (P<0.0001). They concluded that HFNC was as effective as CPAP in the management of RDS in premature neonates more than 30 gestational weeks. This study was a prospective randomised trial with clear segregation of two treatment arms and included complications data such as nasal trauma and air leak episodes. The randomisation process was unclear and criteria for treatment failure/intubation was not stated. This was a non-blinded study. The HFNC flow rates were much lower than conventionally used at present. Despite this, the HFNC arm did not show poorer primary outcome compared to CPAP. The use of INSURE treatment might have altered the course of RDS and might have changed the respiratory support requirement significantly. In addition, the pre-treatment of 24 hours duration with nasal CPAP might influence the subsequent lung compliance due to CPAP effects on end expiratory lung volume.

The risks of bias in this study includes unclear randomisation process where information about sequence generation being not available. This results in selection bias. The criteria for treatment failure or re-intubation was not specified resulting in performance bias.

Ciuffini et al in 2013 at halfway stage and Lavizzari et al on completion in 2016 published their single centre study of 316 preterm infants, mean (range) gestational age of 33 (29-36) weeks and mean birth weight of 1900 grams with mild to moderate respiratory distress after birth (119). Infants were randomised to receive HFNC (flow rates of 4 to 6 L/min) or nasal CPAP (pressures of 4 to 6 cmH2O). The primary outcome was the need for intubation within 72 hours of life, based on a prespecified criteria (119). At halfway stage of the recruitment, they found that 11/85 (12.9%) in HFNC group and 5/92 (5.43%) in NCPAP group ended up with intubation within 72 hours of enrolment into the trial (p= 0.11) (119). The study used block randomisation method with sealed envelopes. They had pre-specified criteria for intubation. The study included infants who had INSURE technique who may have a different course of RDS compared to other infants without surfactant. The study was published prior to completion full trial of planned study population of 316 infants and this was a non-blinded study.

The completed trial was then published by the same group Lavizzari et al in 2016 as a randomized, clinical, non-inferiority trial (127). The treatment arms were HFNC on one arm and CPAP/biphasic positive airway pressure (BiPAP) in the other arm (127). The primary outcome was treatment failure within 72 hours, defined by the need for mechanical ventilation.
The non-inferiority margin was set at 10% (127). The study was done between 2012 and 2014 (127).

Their study objective was to determine whether HFNC provides respiratory support as a primary approach with efficacy levels of being non-inferior to nasal continuous positive airway pressure (CPAP) or bi-level CPAP (BiPAP) in preterm neonates (127).

The inclusion criteria were preterm in the gestational age 29+0 to 36 +6 presenting with mild to moderate RDS requiring non-invasive respiratory support (127). Pre specified criteria for starting non-invasive respiratory support were in place in the protocol (127). The study arms were HFNC at flow rates of 4 to 6 L/min or CPAP/BiPAP at pressures of 4 to 6 cm H2O (127).

They recruited a total of 316 infants with 158 in the HFNC group (mean [SD] GA, 33.1 [1.9] weeks; 52.5% female) and 158 in the CPAP/BiPAP group (mean [SD] GA, 33.0 [2.1] weeks; 47.5% female) (127). The primary outcome failure of treatment was seen in 17 out of 158 infants in HFNC group (10.8%) and 15 out of 158 infants in CPAP/BiPAP group (9.5%). The 95% CI of risk difference was −6.0% to 8.6%; P = .71 (127). In this study, the use of HFNC was noninferior to CPAP with regard to the primary outcome because the upper 95% confidence limit (8.6%) was below the non-inferiority margin of 10%, and the lower 95% confidence limit (−6.0%) was below 0% (127). The result was similar when applying a per-protocol analysis (127).

Since their findings were in agreement within the limits of non-inferiority margins set initially, they concluded that HFNC showed efficacy and safety similar to those of CPAP/BiPAP when applied as a primary respiratory support to mild to moderate RDS in preterm infants older than 28 weeks’ gestational age (127).

This study achieved total study numbers as per their sample estimates and used pre-specified and standardised criteria for study entry. The non-inferiority margin of 10 percentage points allows reasonable degree of certainty to claim non-inferiority of one treatment compared to the other.

This study also used INSURE (intubation, surfactant treatment, and extubation) treatment and this did not amount to treatment failure. Moreover, the surfactant administration was
common, occurring in >40% of infants in both treatment groups. They did not report the age at randomisation and the respiratory support data before entry to the study was not explicitly stated. The risks of bias in this study include non-blinded study affecting performance bias.

Shin et al conducted a randomised controlled trial involving 87 preterm infants with gestational age range of 30 - 35 weeks with respiratory distress within 24 hours after birth (131). The primary outcome was defined as the need for intubation or mechanical ventilation due to treatment failure (131). The treatment failure included any of the following: respiratory acidosis at maximum setting of the allocated device [flow 7 L/min or PEEP 7 cmH2O]), degree of hypoxia (defined by FiO2>0.4 to maintain SpO2 88 to 94%) or frequency and severity of apnoea (>2–3 episodes of apnoea/hour requiring repeated stimulation or bag-and-mask ventilation) despite optimising therapy delivery either during HFNC or during CPAP (131). The primary outcome events in HFNC was 16 out of 42 neonates and in CPAP was 9 out of 43 neonates reached treatment failure criteria (Risk difference 17.17 [−1.90–36.23]; P = 0.099) (131). The most frequent reason for treatment failure was hypoxia (p=0.020) seen predominantly in HFNC group (131). The authors concluded that their study did not support the noninferiority of HFNC compared to CPAP as an initial management of respiratory distress in premature infants at between 30 and 35 weeks gestational age (131).

The randomization was performed by using computer-generated random-number followed by sequentially numbered sealed opaque envelopes. Babies who received intubation and surfactant were excluded and criteria for treatment failure was explicitly stated. This was a non-blinded study with small study numbers, therefore it is possible that it did not have the power to identify effectiveness between two modalities of respiratory support.

Roberts et al conducted a multicentre, randomized, noninferiority trial, where 564 preterm infants (gestational age, ≥28+0 weeks) with early respiratory distress were studied with one arm being nasal high-flow therapy and the other arm being nasal CPAP (130). The primary outcome was treatment failure within 72 hours after study entry (130). In this non inferiority trial the margin was 10 percentage points and it was determined by the absolute difference in the risk of the primary outcome (130). CPAP rescue provided to HFNC arm in case of failure and if CPAP also failed, they were mechanically ventilated (130).
Treatment failure was observed in 71 of 278 infants (25.5%) in the HFNC group and in 38 of 286 infants (13.3%) in the control group (risk difference, 12.3 percentage points; 95% confidence interval [CI], 5.8 to 18.7; P<0.001) (130). The rate of intubation within 72 hours and rate of adverse events was similar between two groups (130). Since the treatment failure rate was 25.5% in HFNC group they concluded that when used as primary support for preterm infants with respiratory distress, HFNC results in higher treatment failure compared to CPAP (130).

This study also did not adopt INSURE treatment and the randomisation process was robust. Trial recruitment was stopped early after review by safety monitoring committee. In order to achieve 90% power, the study needed 750 infants to identify non-inferiority of HFNC over CPAP. The risks of bias are non-blinded study, allowed CPAP cross over from HFNC and therefore could have affected secondary outcomes.

These 6 studies have been summarised in table 10.
<table>
<thead>
<tr>
<th>Author, date, Country Publication journal</th>
<th>Study population</th>
<th>Type of study</th>
<th>Primary outcome</th>
<th>Results Events/Tota l</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoder et al(97) 2013 USA Pediatrics</td>
<td>141 neonates in primary support arm – 28–42/40 gestational weeks, birth weight ≥1000 g 125 babies were preterm</td>
<td>Multi-centre RCT Unblinded</td>
<td>Extubation failure any time after initiation of study support</td>
<td>HFNC – 6/58 CPAP- 9/67</td>
<td>Pre-intervention respiratory support also included neonates who were initially on non-invasive support Pre-extubation caffeine use was not standardised</td>
</tr>
<tr>
<td>Nair et al(140) 2005 USA PAS meeting unpublished</td>
<td>67 preterm infants 27 to 34 weeks' gestational age (GA) mean GA of 32 weeks and birth weight of 1700 grams</td>
<td>Single centre RCT Unblinded</td>
<td>Respiratory failure requiring intubation, based on prespecified criteria (pH ≤ 7.25 and PaCO₂ ≥ 60 mmHg , or FiO₂ &gt; 0.70, or severe or frequent apnoea)</td>
<td>HFNC 4/33 CPAP 4/34</td>
<td>Vapotherm units were recalled following reports of Ralstonia infection – therefore study ended prior to full recruitment Randomisation was standardised with Sealed envelopes and Stratified into 27 to 30 weeks' and 31 to 34 weeks' gestation. Permuted block randomisation</td>
</tr>
<tr>
<td>Author, date, Country Publication journal (Cont)</td>
<td>Study population</td>
<td>Type of study</td>
<td>Primary outcome</td>
<td>Results Events/Tota l</td>
<td>Additional information</td>
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</tr>
<tr>
<td>Iranpour et al (122) 2011 Iran Archives of Disease in Childhood.</td>
<td>70 preterm infants 30–35 weeks gestation</td>
<td>RCT Group 1 (CPAP) received NCPAP from birth and Group 2 (HFNC) received CPAP for the first 24 hours after birth, then standard HFNC</td>
<td>Rates of treatment failure (and need for intubation) within seven days of trial entry</td>
<td>HFNC 0/35 CPAP 0/35</td>
<td></td>
</tr>
<tr>
<td>Lavizzari et al (127) 2016 Italy JAMA Pediatrics</td>
<td>316 infants with 158 in the HFNC group (mean [SD] GA, 33.1 [1.9] weeks; and 158 in the CPAP/BiPAP group (mean [SD] GA, 33.0 [2.1] weeks; randomized clinical non-inferiority trial The babies were randomised to either HFNC at 4 to 6 L/min or CPAP/BiPAP at 4 to 6 cm H2O</td>
<td>Treatment failure within 72 h, defined as the need for mechanical ventilation</td>
<td>HFNC 17/158 CPAP 15/158</td>
<td>In the CPAP group, infants were shifted to BiPAP in the case of more than 4 episodes of apnoea per hour or more than 2 episodes per hour requiring positive pressure ventilation or if deemed by clinicians because of increased work of breathing.</td>
<td></td>
</tr>
<tr>
<td>Author, date, Country Publication journal (Cont)</td>
<td>Study population</td>
<td>Type of study</td>
<td>Primary outcome</td>
<td>Results Events/Total</td>
<td>Additional information</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Shin et al (131) 2017 South Korea J Korean Med Sci</td>
<td>87 preterm infants 30 weeks and less than 35 weeks of gestational age</td>
<td>Single centre RCT HFNC Flow of 5 L/min initially and adjusted between 3–7 L/min CPAP-PEEP of 5 cmH2O initially and adjusted between 4–7 cmH2O</td>
<td>Pre-specified treatment failure criteria</td>
<td>HFNC 16/42 CPAP 9/43</td>
<td>HFNC Optiflow System Fisher &amp; Paykel Optiflow CPAP Infant Flow CPAP system or Millennium ventilator Short binasal prongs with different sizes according to weight</td>
</tr>
<tr>
<td>Roberts et al (130) 2016 International trial The New England Journal of Medicine</td>
<td>564 infants included in the analysis HFNC 278 CPAP 286</td>
<td>RCT HFNC Optiflow Junior Fisher and Paykel or Precision Flow Vapotherm device. Initial gas flow of 6 to 8 LPM CPAP ventilator, an underwater “bubble” system, or a variable-flow device.</td>
<td>Pre-specified treatment failure criteria</td>
<td>HFNC 71/278 CPAP 38/286</td>
<td>HFNC The size of the nasal cannulae was determined according to the manufacturers instructions CPAP short binasal prongs or a nasal mask</td>
</tr>
</tbody>
</table>
3.5.2 Results and discussion:

I performed a meta-analysis of the primary outcomes of all the available studies to date up to January 2018. This is summarised in a Forest plot in figure 10. When the later studies are taken into account, the updated pooled analysis shows that CPAP is better than HFNC in primary respiratory support in terms of the primary outcome of treatment failure (defined by individual studies at different timescales). This is consistent with the meta-analysis presented by Roberts et al excluding the relatively smaller Shin et al study (131, 142).
**Figure 10.** Forest plot of comparison: HFNC versus CPAP soon after birth for primary respiratory support in RDS, Outcome: Treatment failure as defined by the studies.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFNC Events</th>
<th>CPAP Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin 2017</td>
<td>16</td>
<td>42</td>
<td>1.82 [0.91, 3.66] 2017</td>
<td></td>
</tr>
<tr>
<td>Roberts 2016</td>
<td>71</td>
<td>278</td>
<td>1.92 [1.34, 2.75] 2016</td>
<td></td>
</tr>
<tr>
<td>Lavizzari 2016</td>
<td>17</td>
<td>158</td>
<td>1.13 [0.59, 2.19] 2016</td>
<td></td>
</tr>
<tr>
<td>Yoder 2013</td>
<td>6</td>
<td>58</td>
<td>0.77 [0.29, 2.03] 2013</td>
<td></td>
</tr>
<tr>
<td>Irampour 2011</td>
<td>0</td>
<td>35</td>
<td>Not estimable 2011</td>
<td></td>
</tr>
<tr>
<td>Nair 2005</td>
<td>4</td>
<td>33</td>
<td>1.03 [0.28, 3.78] 2005</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>604</td>
<td>623</td>
<td>1.57 [1.20, 2.05]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>114</td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.81, df = 4 (P = 0.31); I² = 17%

Test for overall effect: Z = 3.33 (P = 0.0009)

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Figure 10 shows risk ratio with 95% confidence intervals in brackets when comparing HFNC versus CPAP as the primary respiratory support mode for RDS in preterm neonates.
When HFNC was compared with CPAP as a primary respiratory support mode in preterm neonatal respiratory distress there was increased risk of treatment failure as shown in the Forest plot figure 10 with RR 1.57 95% CI (1.20, 2.05).

The studies by Yoder et al (97), Nair et al (140), Iranpour et al (122) and initial publication of the part of the study by Lavizzari group (119) were systematically reviewed and meta-analyses was published by different investigators in 2015 (110) and 2016 (1). They found no differences in treatment failure, intubation, or other clinical outcomes. Subsequently there have been further larger studies published by Lavizzari et al (127), Shin et al (131) and Roberts et al (130). These later studies are larger, more rigorous in terms of statement of criteria for treatment interventions and were pre-registered as clinical trials reducing the reporting bias.

The Cochrane review in 2016 presented their meta-analysis from studies up to 2016 (1). They found a cumulative risk ratio of 1.30 (0.73, 2.34) based on 439 patients from 3 trials with 211 patients in HFNC arm and 228 patients in CPAP arm (1). They concluded that for preterm infants needing primary respiratory support after birth, there were no differences in the rates of primary or secondary outcomes between HFNC and CPAP (1).
3.6 Primary Respiratory Support for RDS in Neonates – HFNC versus NIPPV

HFNC has been compared with bi-level type of pressure support devices. There have been 2 RCTs comparing HFNC to other bi-level type of non-invasive respiratory support as primary respiratory support after birth in preterm infants.

3.6.1 Descriptive review of studies evaluating HFNC for primary respiratory support compared to NIPPV

In this single-centre, prospective, randomized, controlled, pilot study, Kugelman studied 76 preterm infants (gestational age <35 weeks, weight >1000 g) with RDS comparing HFNC with NIPPV for primary respiratory support after birth (126). Infants were treated with either HFNC (starting gas flow 1 L/min, increased up to 5 L/min as required) or synchronised NIPPV (positive inflation pressure 14 to 22 cmH2O, positive end-expiratory pressure 6 cmH2O, rate 12 to 30 inflations per minute) (126). The primary outcome was the proportion of infants who failed non-invasive respiratory support and needed endotracheal intubation or were switched to another form of non-invasive respiratory support (126).

A total of 76 infants participated in the trial (38 in each treatment group) (126). The type of respiratory support mode was associated with duration of the non-invasive support. The BPD rates were similar between the two groups (126). Nasal trauma was not recorded and air leak was reported in 2 patients receiving HFNC (126). The study did not include ELBW babies. The risks of bias include being a non-blinded study the equipment was supplied by Vapotherm company. The randomisation sequence generation method was not described.

The study by Iranpour et al compared Nasal Intermittent Mandatory Ventilation (NIMV) to HFNC in preterm infants with RDS after the first 24 hours of life (123). Those requiring NIMV respiratory support more than one day and showed the signs of respiratory distress were randomized into two groups of NIMV and HFNC (123). There were 30 infants in each group (123). All patients with RDS were treated with NIMV for the first day (123). They evaluated the rates of chronic lung disease, mechanical ventilation, failure to treatment, the time to establish full enteral feeding and the mortality rate (123). No incidence of treatment failure, chronic lung disease, mechanical ventilation or endotracheal intubation was observed in either group (123). Nasal mucosal damage was mainly seen in NIMV group (123). In view of the favourable complications profile, they concluded that HFNC was more tolerable than
NIMV in the treatment of RDS in premature neonates ≥30 weeks when initiated after the first 24 hours of life (123).

The study employed simple randomisation to allocate the study groups. The administration of surfactant with INSURE method might affect the results although there was no statistical significant difference in its use between the two groups. The minimum respiratory flow rate of oxygen was 2 L/min and the optimum was calculated based on the patient’s weight [0.68W (kg) + 0.92] formula from Sreenan et al study (24). The NIMV device characteristics were not specified.

3.6.2 Results and discussion

The above two studies have been summarised in table 11. The primary outcome and events per study arm has been extracted from the studies. I performed a risk ratio analysis using the data from above two studies shown in figure 11.

When HFNC was compared with NIPPV as a primary respiratory support mode, there was no significant increased risk of treatment failure, RR 0.85 95% CI (0.44, 1.65).

Cochrane review took into account data from one study and reported that there was no difference between HFNC and NIPPV in rates of treatment failure, death or CLD (1, 126). Also, from the same study it was noted that infants randomised to HFNC spent a longer period of time receiving non-invasive respiratory support (median 4 days vs median 2 days, P < 0.01) (1, 126).

Since then there has been one more study from 2016 which did not find any further differentiating data with regards to primary outcome of treatment failure as defined by the study (123).

Since there were no events relating to death, CLD or treatment failure in either arm of treatment in the study by Iranpour et al, there was no difference between HFNC and NIPPV in rates of treatment failure, death or CLD.
Table 11. Summary of clinical studies comparing HFNC versus NIPPV as primary respiratory support for RDS in preterm neonates

<table>
<thead>
<tr>
<th>Author, date, Country Publication journal</th>
<th>Study population</th>
<th>Type of study</th>
<th>Level of evidence Equipment</th>
<th>Primary outcome</th>
<th>Results Events/Total</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kugelman et al (126) 2015 Israel Pediatric Pulmonology</td>
<td>76 neonates Gestational age &lt;35 weeks, mean 33 weeks and weight &gt;1000 g, mean 1800 grams</td>
<td>Single-centre RCT Unblinded Vapotherm device, Precision Flow or 2000i NIPPV SLE 2000 or 5000</td>
<td>Treatment failure defined by requiring mechanical ventilation</td>
<td>HFNC 11/38</td>
<td>NIPPV 13/38</td>
<td>HFNC Vapotherm nasal prongs NIPPV nasal prongs</td>
</tr>
<tr>
<td>Iranpour et al (123) 2016 Iran British Journal of Medicine &amp; Medical Research</td>
<td>60 infants Gestational age of 30 to 35 weeks (mean 31.8 in NIMV and 31.83 weeks in HFNC)</td>
<td>HFNC-RT329 (Fisher and Paykel Healthcare, Salter Lab, Arvin, California). The external diameter of the nasal cannula was 2 mm.</td>
<td>NICU duration Post-NICU hospitalisation period Age when oral feeding began Age when full oral feeding established</td>
<td>HFNC 0/30</td>
<td>NIMV 0/29</td>
<td>Treatment failure criteria not specified Sreenan et al study used to calculate HFNC flow rates NIMV – Device not specified</td>
</tr>
</tbody>
</table>

Table 11 is a summary of two studies comparing HFNC versus NIPPV as a primary respiratory support mode for treatment of RDS in preterm infants.
Figure 11. Forest plot of comparison: HFNC versus NIPPV for primary respiratory support in RDS, Outcome: Treatment failure as defined by the studies.

Figure 11 shows risk ratio with 95% confidence intervals in brackets when comparing HFNC versus NIPPV as the primary respiratory support mode for RDS in preterm neonates.
3.7 Post Extubation Respiratory Support – HFNC versus CPAP

There are now more than 1000 preterm babies who have been studied regarding the efficacy of HFNC over CPAP in providing adequate post extubation respiratory support. A detailed description of each study and a table summarising key features has been presented. I performed meta-analysis of key outcomes and discuss the findings in relation to existing knowledge from previous systematic reviews.

3.7.1 Descriptive review of studies evaluating HFNC for post extubation respiratory support compared to CPAP

In a prospective, single-centre study involving 132 very preterm infants below 32 weeks’ gestation at birth Collins et al evaluated clinical efficacy of HFNC as post extubation respiratory support (96). The mean gestational age was 28 weeks and birth weight was 1100 grams (96). The study groups were HFNC (Vapotherm 8 L/min) as treatment arm and nasal CPAP (Hudson Respiratory Care, 8 cmH₂O) as control arm as per randomisation (96). They used nasal cannula with 1.5 mm outer diameter for HFNC and bi-nasal prongs with outer diameter of 3.7-4.6 for nasal CPAP. The primary outcome was extubation failure in the first seven days after extubation (96). Their pre-defined extubation failure criteria included episodes of apnoea occurring at a frequency of >6 episodes in 6 hours or severe enough to require intermittent positive pressure ventilation, acidosis (pH <7.25 and PCO₂ >66 mmHg) and sustained increase in FiO₂ of >15% from extubation (96). The study population included 132 infants with 67 in HFNC arm and 65 in CPAP arm. The primary outcome rate was similar in both groups (96). The study conclusion was that the extubation failure rates are similar between HFNC and CPAP therapy at 7 days in premature infants (96).

The study had several strengths with adequate randomisation process and clearly defined failure criteria. However, the study was non-blinded and extremely premature and extremely low birth weight babies were not included. The risks of bias in this study includes being an unregistered trial there may have been selective reporting.

Manley et al conducted a multi-centre, non-inferiority study of 303 preterm infants (< 32 weeks’ gestation at birth) and studied efficacy of HFNC versus CPAP post extubation in providing respiratory support (98). The mean gestational age was 27 weeks and mean birth
weight was 1000 grams (98). Infants were randomised to receive either HFNC (5 to 6 L/min) or CPAP (7 cmH2O) after extubation (98). The primary outcome was treatment failure within seven days of randomisation, based on prespecified criteria (98). Infants who failed HFNC were treated with CPAP (98).

HFNC was noninferior to CPAP in terms of primary outcome (risk difference 8.4 percentage points; 95% confidence interval [CI] -1.9, 18.7 (98). There were no significant differences between HFNC and CPAP groups for treatment failure reasons although 48% of HFNC failure infants were rescued with CPAP without reintubation (98). There was no significant difference between the HFNC and CPAP groups for reintubation within 7 days of extubation (risk difference -7.4 percentage points; 95% CI -16.6, 1.8; p=0.12) (98). The nasal trauma rate was significantly less with HFNC (98). The study concluded that the efficacy and safety of respiratory support with HFNC and CPAP are similar in very preterm infants following extubation (98).

This was a multi-centre trial with large numbers and therefore with adequate power to address their primary outcome measure. A pragmatic, real life approach to study protocol with HFNC failure babies being able to be offered period of CPAP was incorporated. However, the non-inferiority margin was generous. Stricter interpretation i.e., 10% rather than 20% percentage points for non-inferiority would have shown that HFNC was not non-inferior to CPAP as a post extubation respiratory support strategy. The risks of bias in this study include non-blinded study, selective reporting as not all the outcomes listed have been reported.

Yoder et al conducted a multicentre study where HFNC was compared with CPAP as a respiratory support for neonatal respiratory distress. A subgroup analysis of babies in whom HFNC was used as primary support for respiratory distress and compared with CPAP was done (97). Over all 432 term and preterm infants of more than 28 weeks' GA who were planned to receive non-invasive respiratory support either as primary support after birth or post-extubation were enrolled onto the study (97). Of these, 351 infants were preterm and rest were term babies (97). The primary support subgroup had 125 preterm infants and post-extubation subgroup had 226 preterm babies (97). The respiratory support provided by HFNC was in the range of 3 to 5 L/min and nasal CPAP was 5 to 6 cmH2O and this was
administered after randomisation (97). The primary outcome was defined as the need for intubation within 72 hours of randomisation (97).

There was no significant difference in the primary outcome between CPAP and HFNC in the subgroup analysis (97). More infants in the HFNC group crossed over to the alternative treatment after 72 hours (97). They concluded that in infants >28 weeks’ gestational age, HFNC appears to have similar clinical efficacy and safety to CPAP as a mode of non-invasive respiratory support (97).

The study protocol had prespecified criteria for intubation and they used random number generation with opaque sealed envelopes for randomisation and like other studies included this review, it was non-blinded. The risks of bias include selective reporting and non-blinded study.

In a prospective, multi-centre randomised control study, conducted in China, 255 infants (< 7 days old) were studied (111). In this study 150 were preterm and the mean gestational age was 35.5 weeks and mean birth weight was 2,472 ± 788 grams (111). A total of 128 infants were in the HFNC group, and 127 infants were in the CPAP group (111). Post extubation respiratory support was allotted following randomisation to either HFNC or CPAP (111). BPD or death in hospital, extubation failure defined by requiring reintubation within 7 days of study entry were the primary outcomes (111). During the first 72 hours of the study, crossover was not allowed between the two groups (111).

The difference in the extubation failure for HFNC (12/128, 9.4%) versus nasal CPAP (12/127, 9.4%) (P > 0.05), or in mortality for HFNC (12/128, 9.4%) versus nasal CPAP (15/127, 11.8%) (P > 0.05) were not statistically significant (111). They concluded that among infants in the first week of postnatal age, HFNC appears to have efficacy and safety similar to those of CPAP group when used as post extubation respiratory support (111).

Although this was a multicentre, prospective randomised controlled study, it included diverse mixture of infants where pathology is widely different ranging from RDS to meconium aspiration syndrome. Subgroup data was not given in detail to understand the distribution of outcome data among more vulnerable group i.e., preterm infants. The risks of bias include
non-blinded study, trial was not registered raising the possibility of reporting bias and also the random sequence generation method was not explicitly stated.

Mostafa-Gharehbaghi et al conducted a single-centre randomised controlled study with 123 preterm infants where 85 neonates who met inclusion criteria were enrolled (128). The mean gestational age was 32.15 ± 1.59 weeks and the birth weight was 1895 ± 438 grams (128). All the babies were given CPAP as well as surfactant with INSURE technique (128). After extubation they were then randomised to either HFNC (flow rate of 6 L/min) or nasal CPAP (pressures of 5 to 6 cmH2O) (128). The primary outcome was re-intubation according to prespecified criteria within three days of study entry (128).

The primary outcome was noted in 8 patients (18.6%) in CPAP group and 5 (11.9%) in HFNC group (128). HFNC device manufacturer was not mentioned in the article and the CPAP device was Bubble CPAP System Fisher and Paykel Health Care, Inc (128). Their conclusion was that HFNC was as effective as nasal CPAP for respiratory support in preterm infants after INSURE treatment (128).

This was a randomised controlled study with prespecified criteria for primary outcome. Since Vapotherm was not accessible in Iran, the country in which this study was done, they used bi-nasal prongs for HFNC. However, it is not mentioned in the study whether they used a local custom-made assembly of heated humidified device or any other pre-tested commercial device. The risks of bias in this study includes non-blinded study and unclear methodology regarding primary outcome. The intubation criteria not specified.

In a randomised, controlled study in preterm infants aged 26 to 31(+6 days) weeks with respiratory distress syndrome after extubation Kang et al studied 161 infants (125). The HFNC (n=79) was compared with CPAP (n=82) (125). They also made subgroup analysis of babies according to the gestational age (125). HFNC device was Fisher & Paykel Healthcare and CPAP device was Infant Flow, VIASYS Healthcare (125). The treatment failure rate, reintubation rate within 7 days after extubation, incidence of complications, and mortality during hospitalization were the outcomes studied (125). The treatment failure rate and reintubation rate showed no significant differences between the HFNC and CPAP groups (125). They concluded that in preterm infants aged 29-31(+6) weeks, HFNC has a similar
efficacy as CPAP after extubation, while in those aged less than 29 weeks, HFNC should be used with caution (125).

The main strength of this study is that it also included preterm infants of under 29 weeks’ gestation. However, the study was inadequately powered to provide definitive conclusion about the role of HFNC in comparison to CPAP control therapy. The risks of bias in this study includes non-blinded study.

Kadivar et al in their randomised, controlled study compared the effect of HFNC with nasal CPAP in post-extubation of 54 preterm infants with RDS. They used INSURE method for all babies in their study (124). The primary outcome was remaining extubated for at least 3 days after INSURE method (124). The patient was reintubated if there was hypercapnia (pCO2≥60) with pH<7.25 and/or paO2<50 with FiO2>0.6(124). HFNC device used was Fisher & Paykel, Healthcare, Auckland, New Zealand and the CPAP device used was Dragger, Lubeck, Germany (124). Nasal prong details were not mentioned.

The rate of reintubation was higher in the HFNC compared with the nasal CPAP group (124). The rate of either IVH or ROP, duration of oxygen requirement and hospitalization were not statistically different (124). There were no cases of BPD or mortality seen (124).

Although the authors concluded that that preterm infants with RDS could be managed post-extubation after INSURE method with either CPAP or HFNC, their primary outcome showed that the rate of reintubation was higher in the HFNC group (124). The study was randomised, controlled study with prespecified failure criteria in the protocol however, the flow rates used were below the conventional flow rates used in preterm infants.

Soonsawad et al conducted a randomised, controlled, single centre study involving 49 preterm infants with gestational age <32 week or birth weight of <1500 g post extubation onto HFNC (n=24) or CPAP (n=25) (132). A block-of-four randomization stratified by gestational age (<28 week, 28 to 30 week and >30 week) and implemented with concealed, opaque envelopes with the computer generated sequence numbers (132). The primary outcome was extubation failure within 72 h after endotracheal tube removal (132). HFNC set up included binasal cannula (BC2425 model, Fisher and Paykel Healthcare, Auckland, New Zealand), 2.4 mm in outer diameter, occupying approximately half of the nares diameter. Fisher and Paykel
Healthcare humidifier was used. The CPAP support was by variable flow CPAP generator (Fabian, Acutronic, Hirzel, Switzerland) via nasal mask.

There was no difference in the primary outcome between the two groups with 8 infants in HFNC vs. 6 in CPAP group (p = 0.47). However, 6 infants (75%) in HFNC and 4 infants (66%) in CPAP group who met failed extubation criteria were rescued by bi-level CPAP. Therefore, the reintubation rate was similar [2 infants (8.3%) in HFNC vs. 2 infants (8%) in CPAP group]. Study concluded that the extubation failure rate was not statistically different between infants who were on HFNC or CPAP support.

The strength of the study includes adequate randomisation process although the overall numbers were small to make definitive conclusions about efficacy.

Elkhwad et al conducted a single centre randomised controlled trial in Iran. The study included 60 preterm infants between 24 and 28 weeks’ gestation (mean 26.7 weeks) with respiratory distress syndrome. The mean birth weight was similar in two groups. They were randomized to either HFNC or CPAP. The primary outcome was failure of extubation defined by the need for re-intubation and mechanical ventilation within 5 days of initial extubation. HFNC machine used was Tri-Anim Vapotherm the Precision Flow and CPAP machine was Fisher and Paykel Healthcare, Bubble CPAP System. No information about nasal prongs used was given.

Preterm infants who remained intubated for more than 24 hours were excluded from the study. They analysed 53 infants’ data with 24 in HFNC arm and 29 in CPAP arm. Their results showed that 17.2% of neonates placed on HFNC failed extubation and required re-intubation within 5 days of initial extubation compared with 20.8% of neonates placed on CPAP (p value 1.000). Similarly mean duration of respiratory support using HFNC was 37.45 days compared to 40.04 days using CPAP (p value 0.66) and duration of oxygen requirement for infants placed on HFNC was 49.41 days compared to 43.75 days for infants placed on NCPAP (p value 0.58). The study concluded that HFNC use was comparable to the use of CPAP in the immediate post-extubation period for preterm infants between 24 and 28 weeks gestations with Respiratory Distress Syndrome and does not increase risk for co-morbid conditions.
This study included extremely preterm babies and study groups were randomised before allotment. However, there was no information about nasal prongs used and whether this allowed adequate leak at nasal interface. This is an important data as the study included babies with mean birth weight of under 1000 grams. The risks of bias include non-blinded study and unclear risk in terms of reporting bias.

Chen et al evaluated 66 VLBW babies of less than 37 weeks gestational age in a single centre randomised controlled study to compare the clinical efficacy of HFNC versus nasal CPAP in treatment of respiratory distress syndrome. Babies received surfactant and conventional treatment initially after birth. The primary outcome was rate of re-intubation within 7 days of extubation was significantly lower in HFNC group. In addition, HFNC babies had significantly shorter oxygen exposure time and invasive ventilation time, and suffered lower incidences of nasal injury, air leak, and abdominal distention, as compared with the CPAP group. They recommended HFNC as the first choice of non-invasive ventilation in the treatment of RDS in VLBW infants.

The article was in Chinese and Google Translate was used to understand the methods and results. The randomisation method was not clear.

Chen et al conducted the only study which studied exclusively ELBW babies. In this single centre randomised, controlled study 129 ELBW infants born <34 weeks of gestation were allocated to HFNC or CPAP group. The primary outcome included the incidence of extubation failure, nasal injury, air leak, abdominal distension and bronchopulmonary dysplasia. The extubation failure rate was lower in HFNC group (25.8%) compared to the nasal CPAP group (47.6%) which was statistically significant. The BPD rates similar in two groups. They concluded that HFNC was an effective and safe method for prevention of extubation failure in ELBW infants.

The article was in Chinese and Google Translate was used to understand the methods and results. The randomisation method was not clear.
3.7.2 Results and discussion

A summary of the studies evaluating HFNC compared to CPAP as post extubation respiratory support is shown in table 12.

I generated a pooled meta-analysis from the studies available up to date and compared with Cochrane review (1) from 2016 and another review published in 2017 (142). This is shown in figure 12.
Table 12. Summary of clinical studies comparing HFNC versus CPAP as post extubation respiratory support for RDS in preterm neonates

<table>
<thead>
<tr>
<th>Author, date, Country, Publication journal</th>
<th>Study population</th>
<th>Type of study population</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoder et al (97) 2013 USA Pediatrics</td>
<td>291 ventilated neonates 28–42/40 gestational weeks</td>
<td>Multi-centre RCT Nonblinded</td>
<td>Extubation failure any time after initiation of study support</td>
<td>HFNC 11/107 CPAP 9/119</td>
<td>Pre-intervention respiratory support also included neonates who were initially on non-invasive support Pre-extubation caffeine use was not standardised</td>
</tr>
<tr>
<td>Collins et al (96) 2013 Australia The Journal of Pediatrics</td>
<td>132 very preterm infants (&lt; 32 weeks Mean gestational age &amp; birth weight were 28 weeks &amp; 1100 grams)</td>
<td>Single centre RCT nonblinded HFNC Vapotherm CPAP Hudson Respiratory Care</td>
<td>Extubation failure in the first seven days after extubation</td>
<td>HFNC 15/67 CPAP 22/65</td>
<td>Extubation failure Apnoea Acidosis pH &lt;7.25 &amp; PCO2&gt;66mmHg Sustained increase in FiO2 of &gt;15% from extubation</td>
</tr>
<tr>
<td>Manley et al (98) 2013 Australia NEJM</td>
<td>303 preterm infants &lt;32 weeks</td>
<td>Multi centre RCT nonblinded HFNC Optiflow CPAP mechanical ventilator or an underwater “bubble” system</td>
<td>Treatment failure within seven days of randomisation, based on prespecified criteria</td>
<td>HFNC 52/152 CPAP 39/151</td>
<td>HFNC- binasal infant cannulae Fisher &amp; Paykel Healthcare</td>
</tr>
<tr>
<td>Author, date, Country Publication journal (cont)</td>
<td>Study population</td>
<td>Type of study Equipment</td>
<td>Primary outcome</td>
<td>Results</td>
<td>Additional information</td>
</tr>
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</tr>
<tr>
<td>Liu et al (111) 2014 China Zhonghua Er Ke Za Zhi journal</td>
<td>255 cases included, 128 were in the HFNC group 127 were in the NCPAP group</td>
<td>Multi centre RCT nonblinded HFNC Fisher Paykel Optiflow CPAP Infant Flow Stepheni</td>
<td>Extubation failure within 7 days after study entry</td>
<td>HFNC 12/128 CPAP 12/127</td>
<td>The study included late preterm and term infants</td>
</tr>
<tr>
<td>Mostafa-Gharehbaghi et al (128) 2014 Iran Zahedan Journal of Research in Medical Sciences</td>
<td>85 neonates enrolled in the study The mean gestational age 32.15 ± 1.59 weeks and mean birth weight was 1895 ± 438 grams</td>
<td>Single centre RCT nonblinded HFNC Manufacturer was not mentioned Bubble CPAP System Fisher and Paykel</td>
<td>Re-intubation according to prespecified criteria within three days of study entry</td>
<td>HFNC 5/42 CPAP 8/43</td>
<td>The failure criteria: PaO₂ &lt;85% or PaO₂ ≤ 50 mm Hg while receiving FiO₂ ≥ 0.4; PCO₂ &gt; 65 mm Hg with a pH &lt; 7.2; &gt;4 apnoeic episodes in the first hour or need for &gt;2 episodes of bagging per hour</td>
</tr>
<tr>
<td>Chen et al (116) 2015 China Chin J Contemp Pediatr</td>
<td>66 VLBW infants Gestational age &lt;37 weeks Weight &lt;1500 grams</td>
<td>HFNC Fisher &amp; Paykel Optiflow CPAP Infant Flow System</td>
<td>Re intubation within 3 days</td>
<td>HFNC 8/34 CPAP 7/32</td>
<td>7-day re-intubation rate was significantly higher in the CPAP group</td>
</tr>
<tr>
<td>Chen et al (117) 2016 China Chinese Journal of Neonatology</td>
<td>129 ELBW infants Gestational age &lt; 34 weeks Birth weight &lt;1000 g</td>
<td>HFNC Fisher &amp; Paykel Optiflow CPAP Infant Flow System Bubble CPAP</td>
<td>Re intubation within 7 days</td>
<td>HFNC 17/66 CPAP 30/63</td>
<td></td>
</tr>
<tr>
<td>Author, date, Country Publication journal (cont)</td>
<td>Study population</td>
<td>Type of study Equipment</td>
<td>Primary outcome</td>
<td>Results</td>
<td>Additional information</td>
</tr>
<tr>
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</tr>
<tr>
<td>Kang WQ (125) 2016 China Chinese journal of contemporary pediatrics</td>
<td>161 preterm infants HFNC (n=79) CPAP (n=82).</td>
<td>Single centre RCT nonblinded HFNC- Fisher &amp; Paykel CPAP - Infant Flow</td>
<td>Treatment failure within 7 days after extubation.</td>
<td>HFNC 29/79 CPAP 19/82</td>
<td>The failure rate (45%) in preterm infants treated with 26-28 +6 weeks was higher than that in controls (21%) ($\chi^2 = 4.70, P = 0.03$)</td>
</tr>
<tr>
<td>Kadivar (124) 2016 Iran Iranian Journal of Medical Sciences</td>
<td>54 preterm infants 27 in each group HFNC and CPAP</td>
<td>Single centre RCT nonblinded</td>
<td>Remaining extubated for at least 3 days after INSURE method.</td>
<td>HFNC 14/27 CPAP 4/27</td>
<td>Nasal prong details were not mentioned. HFNC - Fisher &amp; Paykel CPAP - Dragger, Germany</td>
</tr>
<tr>
<td>Elkhwad et al (112) 2017 Qatar Neonat Pediatr Med</td>
<td>60 preterm infants enrolled (54 analysed) (mean 26.7 weeks)</td>
<td>Single centre RCT nonblinded</td>
<td>Failure of extubation (need for reintubation) within 5 days of initial extubation</td>
<td>HFNC 5/29 CPAP 5/24</td>
<td>The mean birth weight CPAP - 995.33 (SD 201.66) HFNC - 994.54 (SD 202.82)</td>
</tr>
</tbody>
</table>

Table 12 shows a summary of 11 studies comparing HFNC versus CPAP as a post extubation respiratory support mode in preterm infants.
Figure 12. Forest plot of comparison: HFNC versus CPAP for post extubation respiratory support in RDS, Outcome: Treatment failure as defined by the studies.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFNC Events</th>
<th>Total</th>
<th>CPAP Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shantale 2013</td>
<td>52</td>
<td>152</td>
<td>39</td>
<td>151</td>
<td></td>
<td>1.32 [0.83, 2.10]</td>
<td>2013</td>
</tr>
<tr>
<td>Yoder 2013</td>
<td>11</td>
<td>107</td>
<td>9</td>
<td>119</td>
<td></td>
<td>1.30 [0.89, 1.90]</td>
<td>2013</td>
</tr>
<tr>
<td>Collins 2013</td>
<td>15</td>
<td>107</td>
<td>22</td>
<td>129</td>
<td></td>
<td>1.30 [0.89, 1.90]</td>
<td>2013</td>
</tr>
<tr>
<td>Liu 2014</td>
<td>12</td>
<td>128</td>
<td>12</td>
<td>127</td>
<td></td>
<td>0.39 [0.26, 0.59]</td>
<td>2014</td>
</tr>
<tr>
<td>Montefeto-Sharenbargh 2014</td>
<td>6</td>
<td>42</td>
<td>6</td>
<td>48</td>
<td></td>
<td>0.84 [0.23, 3.19]</td>
<td>2014</td>
</tr>
<tr>
<td>Chen 2015</td>
<td>8</td>
<td>34</td>
<td>7</td>
<td>41</td>
<td></td>
<td>1.09 [0.47, 2.52]</td>
<td>2015</td>
</tr>
<tr>
<td>Sorg 2016</td>
<td>14</td>
<td>27</td>
<td>4</td>
<td>31</td>
<td></td>
<td>3.83 [1.32, 10.23]</td>
<td>2016</td>
</tr>
<tr>
<td>Kang 2016</td>
<td>29</td>
<td>79</td>
<td>19</td>
<td>98</td>
<td></td>
<td>1.58 [0.97, 2.58]</td>
<td>2016</td>
</tr>
<tr>
<td>Chen 2016</td>
<td>17</td>
<td>85</td>
<td>30</td>
<td>115</td>
<td></td>
<td>0.54 [0.33, 0.86]</td>
<td>2016</td>
</tr>
<tr>
<td>Elliston 2017</td>
<td>6</td>
<td>29</td>
<td>6</td>
<td>35</td>
<td></td>
<td>0.83 [0.27, 2.52]</td>
<td>2017</td>
</tr>
<tr>
<td>Soonsame 2017</td>
<td>6</td>
<td>24</td>
<td>6</td>
<td>30</td>
<td></td>
<td>1.39 [0.57, 3.41]</td>
<td>2017</td>
</tr>
</tbody>
</table>

Total events: 755, 758

Risk Ratio M-H, Fixed, 95% CI: 1.09 [0.96, 1.31]

Total events: 176, 161

Heterogeneity: Chi² = 21.88, df = 10 (P = 0.02); I² = 54%

Test for overall effect: Z = 0.88 (P = 0.38)

Figure 12 shows a Forest Plot analysis of risk ratio when comparing HFNC versus CPAP as a post extubation respiratory support mode.
HFNC resulted in a RR (95% CI) of 1.09 (0.90, 1.31) for treatment failure. This is similar to Cochrane review where treatment failure with HFNC as defined by the studies was similar to CPAP (1).

A Cochrane review performed meta-analysis of the studies available until 2016 (1). However since then there have been number of RCT adding to the total number of babies where HFNC as post extubation respiratory support was studied (142). However the previous drawbacks of the studies remain that studies are varied in methodology, performed in different clinical settings, different levels of flow have been utilized (126). For example, Yoder et al used initial flows based on infants’ weight (3 L/min for 1,000–1,999 g, increased by a maximum of 3 L/min) whereas Collins et al used an initial flow of 8 L/min and Manley et al used an initial flow of 5–6 L/min (126).

The Cochrane Review authors noted that RCTs thus far have included relatively few extremely preterm infants (<28 weeks’ GA) (1). However in infants >28 weeks’ gestation they found that HFNC resulted in a RR (95% CI) of 0.80 (0.44, 1.44) for treatment failure, and 0.51 (0.27, 0.97) for intubation in comparison to CPAP (1). Therefore the review concluded that post-extubation HFNC may be an appropriate therapy in this group of infants with rescue CPAP being available (1).

The studies by Soonsawad et al (132) and Kang et al (125) reached similar conclusions as Cochrane review. Study by Kadivar et al found a higher rate of intubation in HFNC infants (124).
3.8 HFNC for Weaning from CPAP/NIV

3.8.1 Descriptive review of studies evaluating HFNC as a weaning mode

Abdel Hady et al conducted a randomised, controlled, single-centre study involving 60 preterm infants of gestational age 28 weeks and above (mean gestational age of 31 weeks and mean birth weight of 1600 grams) (113). The infants were eligible when they were stable on low levels of non-invasive respiratory support (CPAP 5 cmH2O and supplemental oxygen ≤ 30%) (113). The two arms of the study were HFNC of 2 LPM and remaining on CPAP until they came off supplemental oxygen (113). The primary outcome in this study was the duration of supplemental oxygen and respiratory support (113).

The two groups had 30 infants each and were similar in study entry characteristics (113). The CPAP group had fewer days on oxygen [median (interquartile range): 5 (1–8) vs 14 (7.5–19.25) days, pb0.001] and shorter duration of respiratory support [10.5 (4–21) vs 18 (11.5–29) days, p=0.03] (113). There were no differences between groups regarding success of weaning from nasal CPAP (113). The study concluded that weaning preterm infants from nasal CPAP to HFNC will cause increase in exposure to oxygen and longer duration of respiratory support (113).

Badiee et al also conducted a single centre randomised controlled study involving 88 preterm infants of gestational age 28 to 36 weeks (mean gestational age at birth of 31 weeks) who were stable on CPAP 5 cmH2O and less than 30% supplemental oxygen (114). They were randomised to HFNC (2 L/min) or to remain on CPAP (114). The primary outcome in this study was the duration of supplemental oxygen (114).

The mean duration of oxygen therapy (20.6 ± 16.8 h vs. 49.6 ± 25.3 h, P < 0.001) and mean length of hospital stay (11.3 ± 7.8 days vs. 14.8 ± 8.6 days, P = 0.04) was significantly lower in HFNC group compared to non-HFNC group (114). However, the successful weaning rate was similar between two groups (114). The study concluded that by using HFNC as step down from CPAP, the duration of oxygen therapy and length of hospitalization in preterm infants can be reduced (114).
Soonsawad et al conducted a single centre, randomised, controlled study involving 101 preterm infants with a gestational age of <32 weeks who met the predefined criteria of stability for weaning off CPAP. The study groups included one group weaning by using HFNC and the other group weaning directly from CPAP (141). The stable infants were defined by those requiring CPAP pressures of ≤6 cm H2O and a FiO2 of ≤0.3 for at least 24 h (141). The rate of weaning in HFNC was 1 litre/min every 24 h to 2-3 litters/min depending on body weight where <1000 grams babies 2 litres per minute and >1000 grams 3 litres per minute and in the CPAP group rate of weaning was by reducing pressure by 1 cm H2O every 24 h until stable on CPAP 4 cm H2O (141). The HFNC or CPAP was weaned off after this stage was reached. The primary outcome was the time it took to wean off either CPAP or HFNC.

There were 51 infants in the HFNC and 50 infants in the CPAP group (141). There was no difference in time to successfully wean between the 2 groups (141). Infants in the HFNC group had significantly less nasal trauma (20% vs. 42%; p = 0.01) (141). The study concluded that the time to wean off CPAP using HFNC was not different from when weaning directly from CPAP (141).

Baozhi et al conducted a single centre randomised controlled study involving 82 preterm infants of gestational age ≤34wk and birth weight ≤2000g who were ready to wean CPAP (129). One group was HFNC and the control group received nasal cannula oxygen therapy (129). Primary outcomes were rate of one-time successful weaning CPAP, duration of respiratory support, weight gain rate, incidence of BPD and retinopathy of prematurity(ROP), nosocomial infection rate and air leak after weaning CPAP (129).

They reported that one-time successful weaning CPAP and oxygen duration and respiratory support duration were lower and weight gain rate was higher (P<0.05) in HFNC group (129). Their conclusion was compared to nasal cannula oxygen therapy HFNC achieves higher rate of one-time successful weaning from CPAP (129).
3.8.2 Results and discussion

A summary of the studies evaluating efficacy of HFNC as a weaning mode is presented in table 13.

The earlier study by Abdel Hady used very low flow rates and unsurprisingly found babies weaned by HFNC did worse than those by CPAP. However surprisingly subsequent study in 2015 by Badiee found favourable results for weaning by HFNC despite using similar flow rate. The mean duration of oxygen therapy in CPAP group in the Badiee study was about 2 days compared to 5 days in the Abdel Hady study. This difference could partially be due to shorter maintenance on CPAP after initial stabilization in the Badiee study (6 h instead of 24 h). The reduction in HFNC flow rate was faster in Badiee study (0.5 L/min every hour as compared to 0.5L/min every 6h by Abdel Hady.

Finally, in 2016, Soonsawad study showed no difference when HFNC was used as a step down from CPAP as opposed to weaning directly from CPAP.

Therefore, at present there is no evidence to suggest that HFNC helps in improving outcomes when used as a weaning method from respiratory support.
Table 13. Summary of clinical studies comparing HFNC versus CPAP alone as weaning from CPAP in preterm neonates

<table>
<thead>
<tr>
<th>Author, date, Country</th>
<th>Study population</th>
<th>Type of study</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel Hady et al (113) 2011 Egypt</td>
<td>60 preterm infants Gestational age &gt;28 wk (mean 31), mean birth weight 1600 grams</td>
<td>Randomized Open label Controlled trial</td>
<td>Duration of oxygen requirement</td>
<td>Non HFNC group had fewer days on oxygen and shorter duration of respiratory support</td>
<td>HFNC flow rate was 2 L/min with FIO2 = 0.30</td>
</tr>
<tr>
<td>Badiee et al (114) 2015 Iran</td>
<td>88 preterm infants of gestational age 28 to 36 weeks (mean 31 weeks)</td>
<td>Randomized controlled trial</td>
<td>The main outcome was the duration of oxygen requirement</td>
<td>The duration of oxygen therapy and length of hospitalization in preterm infants can be reduced with weaning by HFNC</td>
<td>HFNC – 44 babies CPAP – 44 babies</td>
</tr>
<tr>
<td>Soonsawad (141) 2016 Thailand</td>
<td>101 preterm infants with a gestational age of &lt;32 weeks</td>
<td>Randomized controlled trial</td>
<td>Time taken to wean off the use of the CPAP or HFNC devices</td>
<td>Time to wean off CPAP using HFNC was not different from when weaning directly from CPAP</td>
<td>Infants in the HFNC group had less nasal trauma</td>
</tr>
<tr>
<td>Baozhi (129) 2017 China</td>
<td>82 preterm infants of gestational age ≤34 wk and birth weight ≤2000 g</td>
<td>Randomized controlled trial</td>
<td>Rate of one-time successful weaning CPAP</td>
<td>One-time successful weaning CPAP was higher O2 duration, respiratory support duration was lower Weight gain rate was higher</td>
<td>(P&lt;0.05) in HFNC</td>
</tr>
</tbody>
</table>

Table 13 is a summary of clinical studies comparing HFNC versus CPAP alone as weaning from CPAP in preterm neonates.
3.9 Other Clinical Outcomes with HFNC

3.9.1 Bronchopulmonary Dysplasia (BPD)

I performed a pooled analysis of the BPD data from the review of studies undertaken on two specific indications of HFNC. The BPD rates with risk ratio when HFNC was compared to CPAP as primary respiratory support for preterm neonate respiratory distress and a Forest Plot analysis is shown in figure 13.

The BPD rates with risk ratio when HFNC was compared to CPAP as post extubation respiratory support for preterm neonate respiratory distress and a Forest Plot analysis is shown in figure 14.
Figure 13. Pooled estimate of BPD risk in preterm infants on HFNC compared with other modes of NIV as primary respiratory support

Figure 13 is Forest plot analysis of BPD risk in preterm infants on HFNC compared with other modes of NIV for primary respiratory support.

Figure 14. Pooled estimate of BPD risk in preterm infants supported post extubation on HFNC compared with other modes of NIV

Figure 14 is a Forest plot analysis of BPD risk when HFNC is compared with other modes of NIV in preterm infants for post extubation respiratory support.
When I performed a meta-analysis for the outcome BPD, comparing HFNC with CPAP, the risk ratio was suggestive of no increased risk either when HFNC was used as primary respiratory support [RR 1.17 95% CI (0.72, 1.90)] or as post extubation respiratory support [RR 0.88 95% CI (0.74, 1.05)].

The Cochrane Review reported a no increased risk when compared to CPAP in the clinical outcome of BPD (RD 0.96, 95% CI 0.78 to 1.18) from analysis of 893 infants pooled from post-extubation studies (1).

Taha and his group conducted a retrospective data analysis from the Neonatal Database for a 5-year period from January 2008. The inclusion criteria were that babies weighing ≤ 1000 g at birth, and having received HFNC or CPAP therapy (133). Their main objective was the rate of incidence of bronchopulmonary dysplasia (BPD) or death in extremely low birth weight infants who received HFNC versus CPAP (133).

In their study, 2487 infants were included with 941 in CPAP group, 333 in HFNC group, and 1546 in HFNC ± CPAP group (133). The BPD rate or mortality rate was significantly higher in the HFNC group (56.8%) compared with the CPAP group (50.4%, $P < .05$) (133). This was also seen in group receiving HFNC ± CPAP group compared with the CPAP group (133).

Hoffman et al conducted a retrospective chart review with the objective to evaluate the effect of introducing HFNC on length of respiratory support and stay (139). They included 163 patients in 24–32 weeks’ gestation requiring mid-level support (HFNC/nasal CPAP) 1 year before and after HFNC implementation (139). Pre-HFNC group had eighty infants and the post-HFNC group had 83 infants (139). There was a trend towards higher BPD rates in post HFNC group whilst the rates of retinopathy of prematurity was significantly higher (139). The post-HFNC subjects had longer duration of non-invasive respiratory support (139). They concluded that HFNC introduction was significantly associated with a longer duration of non-invasive respiratory support in addition to being associated with increased retinopathy of prematurity rates (139).

There are methodological weaknesses in these studies. They have differing demographics in infants treated with HFNC, inconsistencies in the definition of BPD, and changes in practice during the study period and selection bias associated with any retrospective study (142).
Therefore, it is not possible to make firm conclusions regarding association or causation of HFNC therapy and BPD.

### 3.9.2 Mortality

In this review, the mortality outcome showed no significant increased risk when HFNC was compared to CPAP. This was seen when HFNC was used as post extubation respiratory support [RR 0.62 95% CI (0.28, 1.39)] as well as when used as a primary respiratory support [RR 0.61 95% CI 0.08, 4.57)]. (See Figures 15 and 16)

There was no statistically significant difference in the rate of deaths in the group of preterm infants randomly assigned to receive HFNC compared with other NIV in an earlier systematic review involving 922 infants (OR: 0.48 [0.18 to 1.24]) (110)
Figure 15. Pooled estimate of risk of death in preterm infants on HFNC compared with other modes of NIV as primary respiratory support

Figure 15 shows Forest plot analysis of risk of death in preterm infants on HFNC compared with other modes of NIV as primary respiratory support.

Figure 16. Pooled estimate of risks of death in preterm infants supported post extubation on HFNC compared with other modes of NIV

Figure 16 shows Forest plot analysis of mortality risk with HFNC versus other NIV modes for post extubation respiratory support in preterm infants.
3.9.3 Air leak complications

In this review, the risk of air leak syndrome was significantly less with HFNC compared to CPAP. This was seen in both as primary respiratory support [RR 0.42, 95% CI (0.17, 1.02)] shown in figure 17 and as post extubation respiratory support [RR 0.28, 95% CI (0.15, 0.55)] shown in figure 18.

There were some case reports and case series of air leak complications during HFNC (93-95). This has not been substantiated by prospective RCT involving more than 1000 babies collectively. The Cochrane Review reported a reduction in the rate of pneumothorax (RD −0.02, 95% CI −0.03 to −0.00) from analysis of infants from post-extubation studies (1, 142). The pooled analysis of air leak or pneumothorax data from primary respiratory support of neonatal respiratory distress have shown pneumothorax rates with (RD −0.02, 95% CI −0.02 to 0.02) with HFNC and CPAP (142).
Figure 17. Pooled estimate of risk of air leak complications in preterm infants on HFNC compared with other modes of NIV as primary respiratory support.

Figure 17 shows estimate of risk of air leak complications in preterm infants on HFNC compared with other modes of NIV as primary respiratory support.

Figure 18. Pooled estimate of risk of air leak complications in preterm infants supported post extubation on HFNC compared with other modes of NIV.

Figure 18 shows risk of air leak complications in preterm infants supported post extubation on HFNC compared with other modes of NIV.
3.9.4 Patient Comfort

In a randomised, crossover comparison of 24 h of treatment with CPAP or HFNC, followed by 24 h of the alternative therapy in infants with mild respiratory illness, patient comfort was the primary outcome. The study concluded that the parents preferred HFNC, but there were no significant differences in a patient comfort score (137).

Preterm infants are thought to be more comfortable on HFNC compared with CPAP by neonatal nurses (91).

In an observational cross-sectional study, 60 preterm infants, received CPAP (n=37) and HFNC (n=23)(138). Pain response was assessed using Premature Infant Pain Profile (PIPP), duration of first cry and salivary-cortisol concentrations (138). They reported PIPP scores were significantly higher in the CPAP compared with HFNC group and no infants in HFNC group had severe pain defined by PPP score >12 and salivary cortisol levels were higher in CPAP group (138). A lower incidence of cry was observed for infants in the HFNC group compared with the CPAP group (138). In addition, the respiratory rate was significantly lower with HFNC (138).

3.9.5 Nasal trauma

The risk of nasal trauma was significantly less when HFNC was compared with CPAP either as primary respiratory support [RR 0.50 95% CI (0.34, 0.72)] as shown in figure 19 or as post extubation respiratory support [RR 0.50 95% CI (0.40, 0.61)] as shown in figure 20.

This is consistent with other reviews performed with earlier studies up to and including from 2016 (1, 110). Nasal trauma was less common in HFNC group infants than infants treated with control (CPAP, SIPPV) means of respiratory support in majority of the studies including Nair (140), Iranpour (122), Collins (96), Manley (98), Yoder (97) and Mostafa-Gharehbaghi (128) and Soonsawad (132) but no difference was seen in two studies Liu (111) and Kugelman (126).

An earlier meta-analysis of HFNC versus CPAP to prevent extubation failure with secondary outcome as nasal trauma showed a RR 0.64 (95% CI of 0.51-0.79) (1).
Collins et al devised a nasal trauma score in a randomised controlled study comparing infants extubated to either HFNC or nasal CPAP (118). These infants were preterm <32 weeks’ gestation (118). The HFNC device used was Vapotherm and infants receiving this therapy used Sticky Whiskers type of nasal dressing and infants receiving nasal CPAP used either Sticky Whiskers or Cannualaide type of nasal dressings (118). The nasal trauma score consisted of six sites looking for erythema, bleeding or ulceration and were recorded three times daily during the first 7 days post extubation (118). The sum of these 21 scores was compared between the two groups. The scores in HFNC group (2.8 with SD 5.7) was much less compared to CPAP (11.7 with SD 10.4) group (118). They concluded that HFNC causes less nasal trauma compared to CPAP in the first 7 days post-extubation (118).
Figure 19. Pooled estimate of risk of nasal trauma in preterm infants on HFNC compared with other modes of NIV as primary respiratory support

Figure 19 shows risk of nasal trauma in preterm infants on HFNC compared with other modes of NIV as primary respiratory support.

Figure 20. Pooled estimate of risk of nasal trauma in preterm infants supported post extubation on HFNC compared with other modes of NIV

Figure 20 shows estimate of risk of nasal trauma in preterm infants supported post extubation on HFNC compared with other modes of NIV.
3.10 Discussion

3.10.1 Efficacy of HFNC

In their review on HFNC, Kotecha et al equated the efficacy of HFNC to failure of therapy as defined by the authors (110). They conducted their analysis with focus on HFNC as a primary mode of respiratory support as well as a post extubation respiratory support. They included four studies involving 321 preterm infants (97, 143-145) comparing HFNC with other NIV as a primary mode of respiratory support. The OR for failure of therapy was 1.02 (95% CI: 0.55 to 1.88). Since Kugelman et al study compared HFNC with NIPPV, excluding this yielded OR of 1.12 (0.51 to 2.50) (110).

In this review, I included a large multicentre RCT (130) and a smaller study (131) published later thereby increasing the number of preterm babies in the analysis. A total of 1227 preterm babies distributed evenly in two arms of HFNC and CPAP were analysed. When HFNC was compared with CPAP as a primary respiratory support mode in preterm neonatal respiratory distress there was increased risk of treatment failure as shown in the Forest plot figure 10 with RR 1.57 95% CI (1.20, 2.05)].

When larger number of babies including the later studies are included, the balance shifts towards CPAP favouring CPAP as a mode of respiratory support shows lesser risks of failure of therapy. This is consistent with the meta-analysis presented by Roberts et al excluding the relatively smaller Shin et al study (131, 142).

Thus for practical application, primary mode of respiratory support in RDS the findings of Kotecha et al study is being challenged by the higher risks of failure found in this review (110).

Similar to Kotecha et al study, the Cochrane review in 2016 presented their meta-analysis from studies up to 2016 (1, 110). They found a cumulative risk ratio of 1.30 (0.73, 2.34) based on 439 patients from 3 trials with 211 patients in HFNC arm and 228 patients in CPAP arm (1). They concluded that for preterm infants needing primary respiratory support after birth, there were no differences in the rates of primary or secondary outcomes between HFNC and CPAP (1).
The Cochrane review (1) had only half the numbers of Lavizzari et al (127) study published by Ciuffini et al prematurely whereas Kotecha et al (110) does not have the numbers from the later Shin et al (131) and Roberts et al (130) studies. These later studies are larger, more rigorous in terms of statement of criteria for treatment interventions and were pre-registered as clinical trials reducing the reporting bias.

In this review, when HFNC was compared with NIPPV as a primary respiratory support mode, there was no significant increased risk of treatment failure, RR 0.85 95% CI (0.44, 1.65).

Cochrane review took into account data from one study and reported that there was no difference between HFNC and NIPPV in rates of treatment failure, death or CLD (1, 126). Also, from the same study it was noted that infants randomised to HFNC spent a longer period of time receiving non-invasive respiratory support (median 4 days vs median 2 days, P < 0.01) (1, 126).

Since then there has been one more study from 2016 which did not find any further differentiating data with regards to primary outcome of treatment failure as defined by the study (123).

There was no separate analysis of HFNC versus NIPPV as a primary mode of support in Kotecha et al paper (110). However they did include Kugelman et al study (143) for pooled analysis of estimation of odds of failure of therapy as a primary mode of respiratory support.

As a post extubation respiratory support mode HFNC when compared to CPAP in a total of 661 babies in three studies (96, 97, 146), Kotecha et al (110) found odds of failure of treatment of 1.09 (0.58 to 2.02). This means HFNC and CPAP showed no difference in risk of failure. In this review, a total of eleven studies containing 1513 babies showed that HFNC resulted in a RR (95% CI) of 1.09 (0.90, 1.31) for treatment failure when compared to CPAP when used as a post extubation respiratory support mode. This is similar to Cochrane review where treatment failure with HFNC as defined by the studies was similar to CPAP (1).
The earlier studies included in Kotecha et al review are varied in methodology, performed in different clinical settings and different levels of flow have been utilized (110, 126). For example, Yoder et al (97) used initial flows based on infants’ weight (3 L/min for 1,000–1,999 g, increased by a maximum of 3 L/min) whereas Collins et al (96) used an initial flow of 8 L/min and Manley et al (146) used an initial flow of 5–6 L/min (126). These methodological inconsistencies continue in the later studies included in this review as well. Unlike the studies included in Kotecha et al review, a study by Kadivar et al, included in this review found a higher rate of intubation in HFNC infants (110, 124).

The Cochrane Review authors noted that RCTs thus far have included relatively few extremely preterm infants (<28 weeks’ GA) (1). This finding is echoed in the paper by Kotecha et al as well and they concluded that no recommendations can be made in extremely premature babies as there have been no significant studies including these babies (110). However in infants >28 weeks’ gestation they found that HFNC resulted in a RR (95% CI) of 0.80 (0.44, 1.44) for treatment failure, and 0.51 (0.27, 0.97) for intubation in comparison to CPAP (1). Therefore the review concluded that post-extubation HFNC may be an appropriate therapy in this group of infants with rescue CPAP being available (1).

In this review three studies arrive at different conclusions in terms of efficacy of HFNC as a weaning mode. The Abdel Hady study (147) found babies weaned by HFNC did worse than those weaned by CPAP whereas study by Badiee et al (148) found the opposite. More recently study by Soonsawad et al study (141) showed no difference when HFNC was used as a step down from CPAP as opposed to weaning directly from CPAP. The Kotecha et al paper did not analyse this aspect of HFNC use (110). Therefore, at present there is no evidence to suggest that HFNC helps in improving outcomes when used as a weaning method from respiratory support.

3.10.2 Other clinical outcomes

In this review looking at the BPD outcome, comparing HFNC with CPAP, the risk ratio was suggestive of no increased risk either when HFNC was used as primary respiratory support [RR 1.17 95% CI (0.72, 1.90)] or as post extubation respiratory support [RR 0.88 95% CI (0.74, 1.05)].
Kotecha et al review had a total of 932 infants in the studies having data on BPD outcome with OR of 0.93 (CI 0.67 to 1.28) showing they were comparable in two groups (110). The Cochrane Review reported a no increased risk when compared to CPAP in the clinical outcome of BPD (RD 0.96, 95% CI 0.78 to 1.18) from analysis of 893 infants pooled from post-extubation studies (1).

In this review, the mortality outcome showed no significant increased risk when HFNC was compared to CPAP. This was seen when HFNC was used as post extubation respiratory support [RR 0.62 95% CI (0.28, 1.39)] as well as when used as a primary respiratory support [RR 0.61 95% CI 0.08, 4.57)].

Similarly, there was no statistically significant difference in the rate of deaths in the group of preterm infants randomly assigned to receive HFNC compared with other NIV in an earlier systematic review by Kotecha et al involving 922 infants (OR: 0.48 [0.18 to 1.24]) (110).

In this review, the risk of air leak syndrome was significantly less with HFNC compared to CPAP. This was seen in both as primary respiratory support [RR 0.42, 95% CI (0.17, 1.02)] and as post extubation respiratory support [RR 0.28, 95% CI (0.15, 0.55)]. Similarly, Kotecha et al (110) reported no increased odds of air leak with HFNC in their pooled data with total of 992 infants with OR of 0.72 (CI 0.28 to 1.83).

There were some case reports and case series of air leak complications during HFNC (93-95). This has not been substantiated by prospective RCT involving more than 1000 babies collectively. The Cochrane Review reported a reduction in the rate of pneumothorax (RD −0.02, 95% CI −0.03 to −0.00) from analysis of infants from post-extubation studies (1, 142). The pooled analysis of air leak or pneumothorax data from primary respiratory support of neonatal respiratory distress have shown pneumothorax rates with (RD −0.02, 95% CI −0.02 to 0.02) with HFNC and CPAP (142).
3.10.3 Safety and comfort

The patient comfort scores have been reported variably in different studies (149, 150). However preterm infants are thought to be more comfortable on HFNC compared with CPAP by neonatal nurses (91) and parents (149).

The risk of nasal trauma was significantly less when HFNC was compared with CPAP either as primary respiratory support [RR 0.50 95% CI (0.34, 0.72)] or as post extubation respiratory support [RR 0.50 95% CI (0.40, 0.61)].

This is consistent with other reviews performed with earlier studies by Kotecha et al and Cochrane review (1, 110). Collins et al devised a nasal trauma score in a randomised controlled study comparing infants extubated to either HFNC or nasal CPAP (118). They concluded that HFNC causes less nasal trauma compared to CPAP in the first 7 days post-extubation (118).

3.11 Summary of descriptive review of studies evaluating clinical efficacy of HFNC

HFNC therapy results in less risk of nasal trauma and air leak complications irrespective of whether it is used as primary support or as post extubation support. However, when it is used as primary respiratory support in preterm babies with RDS, more babies will end up meeting failure criteria and need intubation or other forms of escalation of respiratory support compared to CPAP. The same outcome is equivocal when two small studies are reviewed together comparing HFNC with NIPPV. There is no difference between HFNC and CPAP when used as post extubation support and in BPD and mortality outcomes. There are equivocal results from the three studies that examined whether HFNC improves outcomes if used as a weaning mode instead of weaning on CPAP.
Chapter 4. Materials and Methods
4.1 Study Design Development

The study design was developed after undertaking a review of high flow therapy in infants (2) and conducting a retrospective neonatal data base study of use of HFNC in local neonatal unit (153).

The study protocol was internally peer reviewed followed by an external peer review process. My research team held consultations with neonatal nurses, parents and neonatal medical staff. The ideas and current knowledge about safe margins of therapy and applicability of study pathway in the protocol was discussed in formal meetings within the neonatal unit.

4.1.1 Study protocol

I developed the full study protocol for a comprehensive evaluation of respiratory physiology during high flow therapy. A copy of the full study protocol is in Appendix number 1. The study had two phases - initial proof of concept phase to identify reliable, feasible, safe and repeatable methods of measuring various respiratory parameters. The second phase involves larger number of babies. The study was registered in Clinical Trials Registry, Number: NCT02200900.

4.2 Ethics Approval

I submitted a detailed ethics application through the IRAS platform for submission of clinical trials in United Kingdom. The IRAS application document is attached in Appendix number 2. I presented the study to ethics committee along with the study Chief Investigator. I prepared the answers for the queries posed by all members of the Ethics committee including medical, research and lay representatives.

I made the required changes to the protocol and resubmitted to Ethics committee and received the approval with approval number 14/NE/0093. A copy of the ethics approval is attached in appendix number 3.
4.3 Informed Consent

I obtained informed written consent from parents after giving them a full verbal and written explanation of the study. In addition, the attending clinical team was also available to meet with the parents during the intervention period to ensure that they understood the study procedures and continue to consent to participate in the study.

Some preliminary written and verbal information was, whenever possible, offered to the parents when the baby was likely to be eligible. Additional information was also given once the baby was stable on non-invasive respiratory support.

A copy of the Participant Information Sheet has been presented in appendix number 4.

Further information about the study continued to be given to parents as and when they requested it after the baby was enrolled into the study. They were also offered an early appointment with the senior clinician responsible for the baby’s care so they could discuss participation in greater detail. It was made clear to the parents that they remained free to withdraw their baby from the study at any time but if they did withdraw their baby, we would ask them for consent to analyse the data that has been already collected.

Information about the study was continued to be offered to parents after their baby left the neonatal unit.

4.4 Selection and Withdrawal of Study Participants

In this proof of concept study, 6 infants were recruited and underwent measurements for the study. In the next stage, approximately 45 babies would be recruited for the study.

4.4.1 Inclusion criteria

Infants were eligible if:
1. They were less than 37 weeks’ gestation at birth
2. Were on non-invasive respiratory support and
3. The parent(s) were given written informed consent to their baby’s participation
4.4.2 Exclusion criteria

1. Infants who were clinically unstable and unsuitable for non-invasive respiratory support as judged by attending neonatology consultant clinician. The infant must be clinically stable for preceding 12 hours on non-invasive respiratory support. Indications of clinical stability were,
   - Stable $\text{FiO}_2$ requirement in the previous 12 hours – The $\text{FiO}_2$ has not increased more than 0.2 from baseline
   - Tolerating feeds
   - Stable observations including heart rate (100–180 per minute), respiratory rate (30–60 per minute), temperature (36.5–37.5°C)
   - No signs of infection – evidence of blood culture positive infection and or treatment for active infection

2. Participation in a concurrent study that prohibits inclusion in other trials
3. Known major upper airway, lower respiratory tract, cardiac or gastrointestinal tract anomaly
4. Co-existing complications such as pneumothorax.

4.4.3 Withdrawal of participants

Babies could be withdrawn for any of the reasons detailed in the discontinuation criteria. The reason for withdrawal was recorded on the data collection form.

4.5 Baseline Assessments

For eligible babies, clinical details were collected at study entry. This included details to confirm eligibility including gestational age, type of respiratory support, and clinical stability over the previous 12 hours and confirmation of a signed parental consent form. (See Appendix 5 for a copy of consent form)
4.6 Details of Study Design and Procedures

This was a randomised, crossover study. I performed the proof of concept phase with the following study design. A larger study followed the same protocol and methods after completion of first phase. The study procedures are summarised in figure number 21 and described in more detail in subsequent sections.
Figure 21. HFNC Study Flow Chart

Babies less than 37 weeks gestation

Inclusion criteria:
1. NIV support - on CPAP or HFNC
2. Age >5 days

Randomisation

Exclusion criteria:
1. Clinically unstable for NIV support
2. A concurrent study that prohibits participation.
3. Current complications like pneumothorax.
4. Known major upper airway, lower respiratory tract, gastrointestinal tract or cardiac anomalies.

Measurements
Nasopharyngeal pressures
O2 & CO2 concentrations
TOSCA CO2 reading
Tidal breathing indices

Exit criteria
Inadequate ventilation - (pH <7.20 and pCO2 >10 kPa)
Inadequate oxygenation – (FiO2 >0.6 and/or increase in FiO2 of 0.2 from baseline to maintain SpO2 >91%)
Recurrent unprovoked apnoea requiring intervention (not self-resolving) or one major apnoea requiring mask ventilation

Group 1
CPAP 6cm H2O
CPAP 6cm H2O

Group 2
HFNC 8 LPM
HFNC 7 LPM

0-30
30-60
60-70
70-80
80-90
90-100
100-110
110-120

Back on original support CPAP or HFNC
4.7 Description of Study Interventions

Non-invasive respiratory support was given to preterm babies where clinically indicated by the clinical team. The device used were the standard devices used in participating neonatal unit (Fabian therapy, ACUTRONIC Medical Systems AG). The baby was given non-invasive respiratory support either by HFNC or CPAP as deemed appropriate by the attending clinician. The standard neonatal policy (See Appendix 6) in maintaining baby’s oxygen saturations and clinical stability were followed.

The interventions were studied for total of about two hours as described below. After this time, the baby was returned to the non-invasive support that was originally administered by the clinical team.

The internal nare diameter was measured with a tape measure. The nasal cannula outer diameter was obtained from product information on the cover provided by the manufacturer. The ratio of nasal cannula to nare diameter was documented.

4.8 Airway pressure measurement – Gaeltec Catheter Tip Pressure Transducer

There are different types of catheter tip pressure transducers used in the medical field. Gaeltec, Brown Medical Systems and Millar Instruments are some of the leading manufacturers I tested a Gaeltec catheter (Gaeltec, Dunvegan, UK) with transducer mounted at the tip to assess whether it was suitable for measurement of airway pressures. The Gaeltec Catheter tested by us is shown in figure 22.
The Figure 22 shows the image of the Gaeltec catheter with catheter tip mounted transducer, catheter with cm markings and a connector assembly containing one tube with Luer lock end for gas analysis and the other containing electrical connection components to connect to the amplifier.
4.8.1 Gaeltec catheter tip pressure transducer

The Gaeltec catheter measures pressure at the site of catheter placement where the sensor is located at the distal tip of the catheter. The sensor is mounted on the side wall at the distal tip of the catheter.

The Gaeltec catheters have the following parts -

- Sensor assembly
- Connector assembly
- Silicone catheter with customised markings as needed
- Customised additional channel if needed – As I needed an additional channel for sampling nasopharyngeal air the company manufactured a custom made catheter with a small channel with additional port with leur lock connection at the other end.

The sensor was a resistive strain gauge type (55). This element was mounted in a catheter wall close to the tip as shown in figure 23.

The sensor has a metal diaphragm which is very thin and works as a resistive strain gauge membrane and is housed in the catheter in a unique arrangement. There is an atmospheric reference pressure channel that connects the back of the sensing area to the ambient air pressure via a hole in the connector. Therefore, all measurements are differential with respect to ambient air.

Apart from the sensor assembly, the catheter has a connector component. This has passive components to complete a full Wheatstone bridge circuit. This also has temperature compensation and a bridge balance network. Together, this connector assembly can be connected to most strain gauge amplifier systems. I used the Gaeltec S7d 4 channel amplifier.

It is important that these amplifiers provide electrical isolation. The amplifier must be patient isolated. These pressure sensors require an excitation voltage of 1V or less DC or 5V r.m.s or less AC to avoid electrical damage when in use.
Figure 23. Catheter tip pressure transducer with strain gauge sensor at the tip

The Figure 23 shows the sensor assembly (marked with arrow A) of the Gaeltec catheter. The sensor assembly as a silicon layered strain gauge component (marked with arrow C) an opening for the gas channel (marked with arrow B). The cm marking is shown with arrow D with first marking 3 cm from the tip of the catheter.
4.8.2 Dimensions

The Gaeltec catheter CTO-L1 and CTO-L2 are general purpose catheters. The total length of the catheter was 76 cm measuring from the tip to the connector assembly shoulder. The transducer assembly was located at the sidewall close to the tip of the catheter. There were markings at 1cm intervals from the tip of the catheter for measuring length of insertion.

I used the endoscope cleaning suite at the hospital for sterilisation of the catheter following use. The catheter is designed for multiple use and it was clearly critical to avoid any risk of cross infection. I extrapolated the cleaning process for bronchoscopes and liaised with the endoscopy cleaning service to set up a protocol to ensure there was no risk of cross infection. The catheter connector assembly part was protected by sealing with a silicone rubber cap provided by the company. This was done to prevent liquid from entering the small atmospheric reference pressure hole in the centre of the pins on the plug of the connector assembly. If liquid enters this channel then sensor may be permanently damaged and also will not be able to function as a differential transducer in relation to atmospheric pressure.

4.8.3 Storage, safety and standards certification

The catheter was stored in a plastic, crush proof transducer box and sent to cleaning and sterilisation in a transparent, plastic box labelled with date and time. The catheter like most medical equipment was subjected to The Health and Safety at Work Act (1974) and the Control of Substances Hazardous to Health (COSHH) regulations (1988). This means that equipment needs to be sterilised after use and used as per instructions for the safety of personnel handling it and patients in whom it is being used. CE 0120 EC Certificate was in place with full quality assurance system, Certificate GB 12/86323 and Gaeltec devices limited was assessed and certified as meeting the requirements of Directive 93/42/EEC on Medical Devices for medical pressure transducers.

4.8.4 Catheter assembly

This type of catheter needs an amplifier to process the transducer signals into readable analogue form as seen in figure 24.
Figure 24. Catheter tip pressure transducer assembly with amplifier in series

Figure 24 shows the amplifier (marked with arrow A) connected to the Gaeltec catheter. The sensor assembly (marked with arrow C) is located at the tip of the catheter and its signals are transferred as analogue output via the connector assembly (marked with arrow B).
4.8.5 Amplification

I used the Gaeltec S7d a general-purpose amplifier for interfacing Gaeltec Pressure Transducers to the AD instruments chart recorder (analogue device) for recording the pressure data.

This was a 4-channel device powered by a low voltage mains adaptor and it has a single output port for connection to the host device and a single input port for pressure transducer connection and also has a LCDE display for use during setup and configuration. It has electrical isolation with protection up to 5000 volts between the pressure transducer connected to a patient and the host analogue device. It was cleaned by alcohol wipes after each study. It was stored in normal environmental temperature, range between 5°C and 30°C.

4.8.6 Calibration

The transducer sensor is placed inside a calibration chamber provided by Gaeltec as shown in figure 25. This has a sealing compressible grommet that forms an airtight seal around the catheter.

The calibration involves 2 stages,
First, the Gaeltec S7d amplifier is calibrated followed by connecting to the host analogue device (Power lab, AD instruments, Oxford, UK) and calibrating to the likely range of pressures to be measured.

The following steps are followed for the Gaeltec S7d amplifier calibration, Firstly, the transducer is connected to amplifier and the transducer sensor was placed and sealed inside the calibration chamber and then the calibration chamber was connected to the manometer and left open to atmosphere. Then the host analogue device was connected to the amplifier (S7d). Finally, mains connection was done via adaptor. The second step was to switch the amplifier (S7d) on followed by zeroing all the inputs followed by zeroing the selected channel input. The last step was amplifier calibration to the desired range of pressures. I used 2-point calibration to calibrate to ‘0’ and ‘20’ cm H₂O pressures.
Figure 25. Schematic diagram and catheter mounted pressure transducer calibration

Figure 25 shows the schematic diagram of catheter mounted pressure transducer calibration.
4.8.7 Linearity

The linearity refers to the straightness of the output signal at various equally spaced pressure points applied in an increasing direction.

According to the manufacturers, Gaeltec catheters should have linearity when used within the pressure ranges of 0-300 mm Hg. The reported linearity and hysteresis error is ±1% FS BSL (Full Scale or Full Span stands for the difference between the lowest and highest measured point and BSL stands for Best Straight Line, a virtual line derived from a set of non-linear points).

I tested the linearity for the air-way pressure range that is likely to be seen in preterm infants against a known source of pressure delivered by a CPAP machine (B&D Electro medical, Stratford-upon-Avon, UK) as control. The CPAP machine pressures were cross checked against a water manometer to confirm accuracy and linearity. The trend was linear and CPAP and water manometer recorded pressures were the same. This is shown in figure 26.

Then I tested the linearity of the two Gaeltec catheters by comparing them with CPAP delivered pressures. Both catheters had pressure measurements difference of up to 1.3 cm H$_2$O pressure in either direction compared to the control. This is shown in the figures 27 and 28. The difference between two measures (Gaeltec catheter versus the control) on Y axis was plotted against the mean of the two measures.
Figure 26. Linearity of the CPAP pressure checked with water manometer

Figure 26 shows linearity and accuracy of CPAP machine when a series of pressures were plotted against the water manometer.
Figure 27. Linearity of the Gaeltec Catheter Tip Pressure transducer – CTO- L1 against the control (Bland Altman plot)

Figure 27 shows the difference between the two pressures on Y axis plotted against the mean of the two measures along the X axis with Gaeltec catheter CTO-L1.
Figure 28. Linearity of the Gaeltec Catheter Tip Pressure transducer – CTO- L2 against the control (Bland Altman plot)

Figure 28 shows the difference between the two pressures on Y axis plotted against the mean of the two measures along the X axis with Gaeltec catheter CTO-L2.
4.8.8 Frequency response

The manufactures report excellent frequency response since the sensor and catheter assembly is small in size. The frequency response of the pressure measurement instruments may degrade when additional equipment or catheters are connected in series. I tested the frequency response for the measuring unit with nasopharyngeal catheter attached to the amplifier.

The frequency range of airway pressure wave signal is influenced by the breathing frequency. Small mammals or preterm neonates, when in respiratory distress can have respiratory rate in the range of 60-120 breaths per minute. This gives a frequency range of 1-2 Hz (Frequency in Hz = number of cycles/60 seconds). In order for the measurement systems to have adequate frequency response, they should be able to measure up to four times the normal frequency of the study population. For example, in neonates with frequency of 1-2 Hertz, the measurement systems should have a frequency characteristic of at least 4-8 Hertz.

Frequency response of the pressure measuring systems was tested by ‘pop test’. In this test an inflated balloon is fitted over the pressure sensor and then burst, producing a sudden drop in input signals to the system(154). The time taken 10 to 90% of pressure change was noted from the laptop reading the electronic chart recorder data. Fourier transformation equation (fbw = (1/3Tr where Tr is in milliseconds) was used to calculate the frequency response of the system being checked, where fbw is the frequency response and Tr is the time taken for the pressure change from 10 to 90% of the final resting pressure.

The response to an instantaneous change in pressure was recorded on a laptop computer using electronic chart recorder software (Power lab 16/35, AD instruments, Oxford, UK). The frequency response for airway pressure measurement included the airway pressure transducer, the connecting tubing (in case of B&D differential transducer and Thermal sensor transducer) and the amplifier (in case of Gaeltec catheter tip pressure transducer).

The frequency response of the Gaeltec catheter tip pressure transducer (CTO-L1) and the amplifier was measured with the above technique and showed a 10-90% response time of 75 milliseconds giving frequency response of 4.4 Hertz. A second catheter set was also tested (CTO-L2) which had response time of 63 milliseconds which equates to frequency response of 5.2 Hertz.
This was less than that reported by manufacturers as well as in other studies that used similar catheter systems (39, 155).

4.8.9 Stability

According to manufacturers, the Zero drift factor is typically less than 1mmHg over 24 hours. This amounts to about 1.35 cm H$_2$O pressure. This can be considered as a significant pressure difference particularly in a very small premature baby. I performed stability of pressure readings over a period of time with 2 sets of Gaeltec catheters. The catheter tip with transducer was kept in the Gaeltec calibration tube. After calibration of the pressure transducer, different pressures were delivered to the calibration tube from the CPAP machine (B&D Electro medical, Stratford-upon-Avon, UK). The resulting analogue output from the transducer was recorded continuously on an electronic chart recorder (Power lab, AD instruments, Oxford, UK). The drift from baseline was noted over a period of 2 hours. The stability was $\pm$1.3 cm H$_2$O off baseline at lower pressures (3-6 cm H$_2$O) and about $\pm$0.3 cm off baseline at 20 cm H$_2$O pressures.

4.8.10 Factors influencing catheter performance

According to manufacturers the catheter has a life of at least 10 years. However, this is affected by the care taken during its use. The catheter tip transducer system is affected by extreme pressures, thermal stress and if any liquid enters the channel communication between atmosphere and sensor chamber.

4.8.11 Description of airway pressure measurement with Gaeltec Catheter

A catheter (Gaeltec Devices Ltd, Dunvegan, UK) with pressure transducer and port for gas sampling at the tip was placed at the nasopharynx or oropharynx by using standard measurement for placing nasopharyngeal airways(27, 29). Distance between nare of the nose to tragus of ear was measured with a measuring tape. The nasopharyngeal catheter was introduced to about 1 cm less than this measurement to ensure adequate placement in nasopharynx and to avoid gagging or undue stimulation of cough reflex (27, 29). This was connected to an O$_2$ and CO$_2$ analyser (AD instruments Gas analyser) and electrically isolated excitation amplifier to measure pressure. Where possible this was timed to coincide with
routine replacement of the feeding tube which was facilitated at the conclusion of the study. The pressure recording was done when mouth was passive and also with mouth closed gently with a finger pressing on the chin.

4.8.12 Results of Gaeltec catheter pressure measurement

Nasopharyngeal pressure measurement was tried in two babies (Study ID 01 and 02) with Gaeltec catheter tip transducer. No accurate, acceptable airway pressure profile was obtained in both these measurements. The catheter however allowed sampling for airway gas concentration measurement.

4.8.13 Summary of catheter mounted pressure transducer

The catheter tip pressure transducer is an attractive option to measure airway pressures and has been cited as practical in a number of published series. The manufacturer also felt it was suitable for use in infants and that it would be capable of measuring pressures typical for a child on respiratory support. The ability to measure pressure at the desired location in the airway without being affected by gravity and also any movement of the patient is attractive. However, the device is manufactured for a wide range of pressure measurement and its applicability to measure a small range of pressure at the lower end of its range is suspect. The stability of the measurements is another factor which needs to be more stable. Despite previous published work my investigations have shown this technology lacks the necessary accuracy and stability for use in small infants. Results from previous published series using this technique need to be interpreted with caution.
4.9 Airway Pressure Measurement - Thermal Sensor Pressure Transducer

4.9.1 Introduction

Thermal sensor pressure transducers work on a different principle to differential pressure sensors and find application in medical, automobile and other precision industries. They are small in size and have signal-conditioning circuit on a single microchip. There are different manufacturers (examples: Sensirion AG, Switzerland and First Sensor AG, Berlin, Germany). There are a range of products and a transducer suitable for the pressure range likely to be seen in this study is shown in figure 29. This device comes with a sensor component which is combined with the analogue and digital signal processing circuit on a small silicon chip.
Figure 29 shows the thermal micro sensor pressure transducer and its constituent parts. The micro sensor is housed in a case (marked with arrow B) and is powered by an AC adopter (marked with arrow D). The gas flow ports Hi and Lo are indicated (arrow marked C) and the output is via BNC connector (marked with arrow A).
4.9.2 *Measuring principle of a thermal flow sensor*

The microchip has a heating element. This releases heat into the medium through which the gas flows. Two temperature sensors are placed on either side of the heating element. When the gas flows across the sensors it detects a difference in temperature with high sensitivity. This change in temperature is read as pre-calibrated flow signal by the micro sensor chip. This is shown in figure 30. Since all the elements of this system are assembled on a single silicon chip the analogue sensor signals are amplified and processed without interference.

4.9.3 *Equipment details*

The thermal sensor is a small compact unit measuring 2cmX2cm in size. It has high and low flow ports and an analogue output cable with BNC connectors for connection to the electronic chart recorder.

The sensor assembly was packaged in a heat resistant plastic container by the biomedical engineering department at our institute. This enabled cleaning with surface active cleaning agents used in the neonatal unit for equipment cleaning. The device was cleared for electrical safety as per the standards for medical equipment.

4.9.4 *Sensor assembly*

The nasopharyngeal catheter is connected to the ‘high’ flow port of the sensor assembly and the ‘low’ flow assembly is open to the atmosphere. The output from the sensor assembly is connected to the electronic chart recorder (Power lab, AD instruments, Oxford, UK) via BNC connector.

4.9.5 *Calibration*

I calibrated the transducer with a 2-point calibration against known pressure source delivered by a calibrated CPAP device. The calibration points were recorded by the electronic chart recorder (Power lab, AD instruments, Oxford, UK) and the calibrated voltage values were entered in the chart recorder to generate the pressure values.
The Figure 30 shows micro sensor chip with a heating element in the centre and two temperature sensors on either side allowing the gas to flow in a straight channel.
4.9.6 Linearity

The linearity of the pressure transducer was checked against a known source of pressure. The control was various levels of CPAP pressures delivered by a calibrated CPAP machine (B&D Electro medical, Stratford-upon-Avon, UK).

In the linearity testing the pressure signals correlated well with control pressure as seen by the Bland Altman plot in the figure number 31 with pressures range from 3 cm H$_2$O to 20 cm H$_2$O closely following the bias line.

4.9.7 Frequency response

The frequency response of the thermal sensor type of transducer was tested with the ‘pop’ test method (154). This test was done when the transducer was connected in series with the nasopharyngeal catheter (Argyle Gentle Flow Suction Catheter, Size 8FR, Covidien Ltd, Ireland) used to measure pressure in the nasopharyngeal airway. The response time was 33 milliseconds giving a frequency response of 9.9 Hertz.

4.9.8 Factors influencing sensor performance

The thermal sensor requires an uninterrupted flow of gas down the nasopharyngeal catheter enabling temperature changes at the sensor. Therefore, it is different from differential pressure transducer. The main limitation in using this in very small preterm babies is that flow can easily be interrupted by secretions and may not be uniform. There is no effect of gravity unlike the water filled catheter systems. However, the effect of local changes in temperature may be substantial as in-vitro calibration may not be applicable to in-vivo use.
Figure 31. Linearity of the thermal sensor pressure transducer against the control
(Bland Altman plot)

Figure 31 shows the two measures with thermal transducer and control along Y axis plotted against the mean of the two measures along the X axis showing good linearity.
4.9.9 Description of thermal sensor pressure measurement

A catheter (Suction catheter size Fr 8) was placed at the nasopharynx or oropharynx by using standard measurement for placing nasopharyngeal airways (27, 29). Distance between nare of the nose to tragus of ear was measured with a measuring tape. The nasopharyngeal catheter was introduced to about 1 cm less than this measurement to ensure adequate placement in nasopharynx and to avoid gagging or undue stimulation of cough reflex (27, 29). This was connected to the ‘high’ flow port of the sensor assembly and the ‘low’ flow assembly is open to the atmosphere. The output from the sensor assembly is connected to the electronic chart recorder (Power lab, AD instruments, Oxford, UK) via BNC connector.

Where possible this was timed to coincide with routine replacement of the feeding tube which was facilitated at the conclusion of the study. The pressure recording was done when mouth was passive and also with mouth closed gently with a finger pressing on the chin.

4.9.10 Results of thermal sensor pressure measurement

Nasopharyngeal pressure measurement was tried in two babies (Study ID 03 and 05) with thermal sensor transducer. No accurate, acceptable airway pressure profile was obtained in both these measurements. A pressure profile obtained with this method is shown in figure number 32.

4.9.11 Summary of thermal sensor pressure transducer

The thermal sensor is technically sound with good frequency response, linearity and response times. However, in the case of preterm neonates it was difficult to receive consistent, valid pressure signals because of the presence of secretions blocking the catheter and interrupting free flow of gas.
Figure 32. Airway pressure recording with thermal sensor – HFNC 5LPM – Dampening signal with movements

Figure 32 shows the pressure data obtained with thermal sensor transducer with varying amplitude and irregularity.
4.10 Airway Pressure Measurement - Differential Pressure Transducer

Differential pressure transducers are widely used in industries, gas and engineering equipment and in medical equipment. They can be used to either measure pressure or flow by differentiating the pressure signal

4.10.1 Principle of differential pressure transducer

The differential pressure transducers convert change in pressure into an electrical signal. This is achieved by the sensor contained in these transducers. The sensor can be of different types. In the B&D differential transducer that I used, the sensor is made up of a diaphragm with strain gauges attached. The strain gauges deform on application of a pressure difference and these are transmitted as electrical signals by the Wheatstone bridge transmitting system attached to the diaphragm. This deformation is proportional to the pressure changes. In B&D differential transducer, one of the pressures is always atmospheric pressure as one surface of the diaphragm is subjected to the atmospheric pressure.

4.10.2 Description of B&D differential transducer structure

The differential transducer sensor has a diaphragm type of sensor as its core element. The other essential part is the transmitting unit which conveys the electrical signal generated due to pressure changes as an analogue signal to the recording equipment. The transducer was cleaned after each use as per existing neonatal unit policy of cleaning medical equipment. The product had electrical safety and standards certification for use as medical equipment. The B&D differential transducer used in this study is shown in figure 33.

4.10.3 Transducer assembly

The transducer is connected to the nasopharyngeal catheter (Argyle Gentle Flow Suction Catheter, Size 8FR, Covidien Ltd, Ireland) through a leur lock connector. The nasopharyngeal catheter was kept patent with a constant flow of air through a syringe pump containing 50 ml syringe flushing air at a constant rate of at 20ml/hr. The output signal was recorded in electronic chart recorder (Power lab 16/35, AD instruments, Oxford, UK) via BNC connectors.
Figure 33. Differential pressure transducer and its assembly with nasopharyngeal catheter in series

Figure 33 shows the B&D differential transducer (arrow marked A) connected to the nasopharyngeal catheter (arrow marked D) through its port (arrow marked C). The output from B&D is shown digitally in this transducer but also collected as analogue output (arrow marked B).
4.10.4 Calibration

I calibrated the B&D transducer before each use with a known pressure source from a CPAP machine (B&D Electromedicals, Stratford-upon-Avon, UK). A 2-point calibration was done and voltages in the electronic chart recorders were appropriately adjusted.

4.10.5 Linearity

The linearity check gave satisfactory readings over the range 3-20 cm H$_2$O when compared with control pressures delivered by calibrated CPAP device as illustrated in figure 34.
The figure 34 shows the linearity profile for B&D differential pressure transducer plotted along the X axis against the control pressures along the Y axis for series of pressures ranging from 3 - 20 cm H\textsubscript{2}O.
4.10.6 Frequency response

The frequency response of B&D differential transducer was tested when connected in series with nasopharyngeal catheter (Argyle Gentle Flow Suction Catheter, Size 8FR, Covidien Ltd, Ireland) by the ‘pop’ test method(154). The response time was 20 milliseconds giving a frequency response of 16.2 Hertz.

4.10.7 Factors influencing differential transducer performance

The differential transducer works on the physical principle of deformation of strain gauge elements in its sensor. Therefore, it can be influenced by the ambient temperature. The accurate pressure measurement is dependent on a patent catheter leading up to the site of interest but not necessarily an active flow.

4.10.8 Description of Differential pressure transducer measurement

Differential transducer method (B&D Electromedical, Stratford-upon-Avon, UK): A suction catheter was placed at the nasopharynx or oropharynx by using standard measurement for placing nasopharyngeal airways. Distance between nare of the nose to tragus of ear was measured with a measuring tape(26). The nasopharyngeal catheter was introduced to about 1 cm less than this measurement to ensure adequate placement in nasopharynx and to avoid gagging or undue stimulation of cough reflex(26). This was connected to O2 and CO2 analyser and differential pressure transducer via a 3-way connection. The gas analysis sampling was done intermittently at flow rate changes as per the study pathway.

4.10.9 Summary of differential pressure transducer

The B&D differential transducer had very good accuracy, linearity and frequency response. It was also practicable to use in a small preterm baby due to the practical challenges of unpredictable flow into the measuring catheter. The results and discussion of airway pressure measurements done with this method are discussed in the results chapter –Chapter 5.
4.11 Gas Analysers for Respiratory Gases

There are different types of gas analysers available which are used predominantly in anaesthetic practice, intensive care and also by sports physiologists. I used a commercially available gas analyser (AD instruments, Oxford, UK), which provides analogue output for O$_2$ and CO$_2$ concentration from the gas sample being analysed.

4.11.1 Principle

The AD instruments gas analyser is an electronic gas analyser with transducers for infrared carbon dioxide and visible spectrum oxygen detection. A schematic diagram illustrating the gas analyser components is shown in figure 35.
Figure 35 shows a schematic diagram of a gas analyser with its constituent parts.
4.11.2 Materials and device assembly

The AD instruments gas analyser has a gas analyser unit, connecting tube called Nafion and output cable with BNC connectors for connection to electronic chart recorder. These are shown in figure 36.

Nafion is a copolymer of tetrafluoroethylene (Teflon) and perfluoro-3, 6-dioxa-4-methyl-7-octene-sulfonic acid i.e.a combination of Teflon with sulfonic acid group side chains interspersed in it. These side chains have a very high affinity to water, absorbing 13 molecules of water for every sulfonic acid group in the polymer and therefore Nafion tube absorbs 22% by weight of water. Unlike micro-porous membrane permeation, which transfers water through a relatively slow diffusion process, Nafion removes water by absorption. This absorption occurs as a first order kinetic reaction, so equilibrium is reached very quickly. Because this is a specific reaction with water, gases being dried or processed are not affected.

The Nafion tube is 30 cm in length and 0.13 mm in diameter. The material allows water vapour to pass through its walls so that the water vapour content of the gas sample inside the tube equilibrates with that of the room air. This happens very quickly within milliseconds.

The In-line Filter connects directly to the sampling port of the Gas Analyser to protect the transducers from moisture and damaging particulates. This has 0.45µm pore-size hydrophobic membrane and a disc size of 17mm.

The gas analyser (AD instruments, Oxford, UK) has an infrared carbon dioxide sensor and optical oxygen detector. The analyser samples expired gas from a mixing chamber with a damped, micro-vacuum sampling pump. A flow control knob on the front of the unit provides sampling rates of 35 to 200 ml/min. The maximum flow values may vary for different sizes and lengths of tubing. The gas analyser has the following operating requirements- power supply of 85–250 VAC 50/60 Hz, temperature range should be 5–35 °C and humidity between 0–90% (non-condensing). The salient features are shown in table 14.
Figure 36 shows a gas analyser with its different functionalities labelled, a nafion connecting tube and a bacterial filter.
### Table 14. Features of gas analyser (obtained from AD instruments, Oxford, UK)

<table>
<thead>
<tr>
<th>Features</th>
<th>CO₂ analyser</th>
<th>O₂ analyser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of analyser</td>
<td>Infrared, optical</td>
<td>Visible spectrum (760 nm) absorption</td>
</tr>
<tr>
<td>Range</td>
<td>0–10% CO₂</td>
<td>5–100% O₂</td>
</tr>
<tr>
<td>Output</td>
<td>Linear, 0–1 V (0–10% CO₂)</td>
<td>Linear, 0.05–1 V (5–100% O₂)</td>
</tr>
<tr>
<td>Resolution</td>
<td>0.1% CO₂</td>
<td>0.01% O₂</td>
</tr>
<tr>
<td>Linearity</td>
<td>±0.1% CO₂</td>
<td>±0.2% O₂</td>
</tr>
<tr>
<td>Drift</td>
<td>0.1% CO₂ over 8 hours</td>
<td>0.1% O₂ over 2 hours</td>
</tr>
<tr>
<td>Response time (10–90%)</td>
<td>90–130 ms @ 200–50 ml/min - transducer alone; 440 ms @ 200 ml/min sample flow with Nafion tubing and hydrophobic filter connected to sample inlet port</td>
<td>Transducer 130–300 ms between 200–50 ml/min</td>
</tr>
</tbody>
</table>

Table 14 shows performance features of gas analyser components.

The CO₂ transducer works on the principle of infrared absorptiometry. It is a Servomex model 1507 infrared transducer. It is calibrated so that output voltages in the range 0–1 V are proportional to CO₂ concentrations in the range 0–10%.

The O₂ transducer works on the principle of optical absorptiometry. It is an Oxigraf X2004 sensor which uses absorption spectroscopy in the visible spectrum (760 nm). The incoming gas sample is exposed to narrow-band light produced by a laser diode. The light is thermally tuned to a particular emission-line in the oxygen spectrum. A detector on the opposite side of the chamber detects changes or attenuation in the light intensity at the wavelength of the gas sample being studied. As the concentration of oxygen in the chamber increases, more energy is absorbed by the oxygen molecules in the gas and less light is received by the detector.

The exterior of the gas analyser was cleaned as per neonatal unit policy for medical equipment. The device had all the electrical and safety standards certificates for use as a medical device.
4.11.3 Calibration

The instrument was warmed up for at least 15 minutes prior to every test to minimize any possible electrical drift. Calibration of the O\textsubscript{2} and CO\textsubscript{2} analysers was performed immediately prior to every test using two-point calibration with two known gas mixtures. Oxygen analyser was calibrated with first calibration point being room air and the second was 12.5% O\textsubscript{2} cylinder with CO\textsubscript{2} 7.5% and balance N\textsubscript{2} gas mixture. For CO\textsubscript{2}, first calibration point was room air (0.004) and the second was 7.5% CO\textsubscript{2} from gas mixture cylinder (BOC Health care, UK).

4.11.4 Obtaining measurements

The machine was switched on for 15 minutes and then calibrated as per the protocol. Then the pump speed was set at 200ml/min. A nafion tube was connected to the gas inlet port. The nafion tube ensures optimising the water vapour content of the gas sample to the room air level. A bacterial filter was juxtaposed between nafion tube and patient catheter to prevent cross infection or contamination of the machine. The machine makes continuous measurements of the O\textsubscript{2} and CO\textsubscript{2} levels of the sampled gas sample which is recorded as an analogue signal on electronic chart recorder (Power lab, AD instruments, Oxford, UK).

4.11.5 Factors influencing gas analyser performance

The measured gases should be free of excessive water vapour. In addition, inadequate warming time might affect the results due to alteration in the electronic signals produced by the O\textsubscript{2} and CO\textsubscript{2} transducers.

4.11.6 Summary of gas analyser for air way gas concentrations

The features of the AD instruments gas analyser including the response time, range of measurement capability and ability to record continuous gas concentration in an analogue output were suitable for the purposes of this study.
4.12 Tidal volume measurement - Volusense Technology

4.12.1 Principle

Volusense uses electromagnetic inductive plethysmography technique for evaluating tidal breathing indices in infants (81, 156). A vest with conductive coils is wrapped around the baby’s chest and abdomen. The resultant change in magnetic field generated by the coils due to movements of the chest and abdomen is picked up by an antenna placed at a height over the baby. This allows measurement of tidal volume, respiratory rate and by differentiating volume signals over time tidal flow indices can be measured. A schematic diagram of Volusense principle is shown in figure 38.

The measurements are depicted continuously in the Volusense screen as flow volume signals. The measurement quality can be visually checked by the shape of the waves as shown in figure 39.

Thoraco abdominal asynchrony can be calculated from the Electromagnetic Inductance Plethysmography done via the Volusense software. The chest wall and abdominal movement signals have specific wave characteristics. The phase angle provides a quantitative estimation of Thoraco-abdominal asynchrony. In addition, the shape of the flow volume loop can give clues about airway obstruction to flow.

Volusense machine has been validated for tidal breathing indices measurement in both term and preterm infants in the earlier studies (157, 158).
Figure 37. Schematic representation of Volusense Electromagnetic Inductance Plethysmography (157)

Figure 37 shows a schematic representation of Volusense machine. The key components are labelled (157).
Figure 38 shows the Volusense machine with its main components labelled.
4.12.2 Materials and device assembly

The Volusense machine comes with a standalone unit consisting of a base unit with device computer for onscreen instructions and conducting the calibration and test. The device extends onto an antenna. The device also comes with a calibration unit consisting of a metallic cylinder with known volume against which the calibration has to be performed in the area of interest. This test site specific calibration is crucial as the magnetic fields in an area that might interfere is specific to that area.

The vest containing conductive coils comes in 5 different sizes. These are colour coded and are ranging from vests suitable for a less than 1000 grams baby to a larger infant. Accurate size selection is done after measuring the distance between the armpit to hip in the baby and comparing it with the colour coded scale and colour coded vests provided by the company.

4.12.3 Factors influencing Volusense performance

The presence of a strong magnetic field or instruments that might generate electromagnetic field are likely to interfere with measurements. The baby needs to be quiet and not moving vigorously as movements will lead to artefacts. The size of the vest should be appropriate for the baby’s size as too loose or too tight vests will not accurately measure the actual tidal breathing indices. The calibration has to be done according to the guidelines and height of antenna needs to be as per guidance.

4.12.4 Measurement of tidal volumes

The Volusense vest was placed over the infant’s torso. Respiratory measurements are derived from changes in electromagnetic inductance in this wrap-around vest worn by the baby. The vest is disposable and used for one patient only to avoid cross-infection. Thorax and abdominal volumes and volume changes are measured and stored digitally by the Volusense device shown in figure 38. The device was used to record tidal volume, tidal flow volume loop, respiratory rate and to calculate tidal breathing indices. The device has the ability to export analogue signals of tidal volume and flow for simultaneous recording in the multichannel recorder for synchronous recording.
4.13 Transcutaneous CO₂ measurement

Transcutaneous (Radiometer UK Limited, Crawley, UK) sensor was applied to the baby’s skin to measure carbon dioxide (CO₂) levels.

4.14 Transcutaneous O₂ saturation measurement

Transcutaneous oxygen saturation percentage was measured by placing pulse oximetry probe on foot and connecting it to Masimo SET Pulse Oximetry machine (Masimo Europe Limited, Basingstoke, UK).

4.15 Data recording

All the above measurements were connected to a multi-channel recorder (Power lab chart recorder, AD Instruments, Oxford, UK) that allowed synchronised recording and graphical presentation of all the above parameters. These are saved as files allowing future analysis. The following measurements were attempted at a sampling frequency of 100Hz.

- Transcutaneous oxygen saturations.
- Transcutaneous CO₂ levels.
- Nasopharyngeal pressures.
- Concentration of CO₂ and O₂ in nasopharyngeal space during inspiration and expiration.
- Tidal volume, flow, respiratory rate and FRC baseline.

Clinical observations were done as per unit policy (Appendix Number 6).

A screenshot of simultaneous multichannel recording of respiratory physiology parameters is shown in the figure 39. The different channels are colour coded to identify different inputs from measuring equipment.
Figure 39. Example of simultaneous recording of physiology parameters in Lab Chart recorder – Study ID – 06

Figure 39 is a screenshot from the simultaneous multichannel recording of all the physiological parameters measured in this study. The individual parameters are represented in colour coded waveforms and the analogue measurements are displayed onscreen as well.

A study trolley was assembled containing the following devices as shown in figure 40 and a list of equipment used in the study is given in Table Number 15.
Figure 40. Study Trolley

Figure 40 shows the study trolley assembly with its components.

- Study laptop
- B&D differential transducer
- AD instruments chart recorder
- TOSCA Radiometer
- Gas analyser
- Pulse oximeter
- Storage areas
Table 15. Equipment used in the study

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Manufacturer</th>
<th>Standards</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>The HFNC and CPAP devices</td>
<td>Fabian therapy: ACUTRONIC Medical Systems AG</td>
<td>CE 0124. Fabian Therapy is an Equipment Class IIb ventilator per European directive.</td>
<td>It can provide both CPAP and HFNC therapy</td>
</tr>
<tr>
<td>Pressure monitoring</td>
<td>Differential pressure transducer B&amp;D Electromedical Ltd</td>
<td>CE 0120 Electrical safety certificate</td>
<td>Compact device easily portable for bedside measurements</td>
</tr>
<tr>
<td>Gas analyser</td>
<td>AD instruments, Oxford, UK</td>
<td>CE 0120 Electrical safety certificate</td>
<td>Needs calibration against known gas concentration before use</td>
</tr>
<tr>
<td>Tidal breathing indices</td>
<td>Volusense Pediatrics, Bergen, Norway</td>
<td>Class II A according to MDD. Electrical Classification: Class I, type B according to IEC 60601-1 Safety standards: EN/IEC 60601-1: 2005 and EN/IEC 60601-1-6</td>
<td>Bulky instrument, it’s a standalone device with its own software input from device laptop. However, data can be exported in analogue form to multichannel chart recorder</td>
</tr>
<tr>
<td>Transcutaneous carbon dioxide monitoring</td>
<td>Radiometer UK Limited, Crawley, UK</td>
<td>CE 0123 Instrument Class 1, type BF, defibrillator proof, fulfils the requirements of MDD 93/42</td>
<td>Compact device, amenable for bedside measurement</td>
</tr>
<tr>
<td>Transcutaneous O₂ saturation monitoring</td>
<td>Masimo Europe Limited, Basingstoke, UK</td>
<td>CE 0120 Electrical Safety certificates</td>
<td>Compact device for continuous measurements</td>
</tr>
</tbody>
</table>
4.16 Study Treatment

4.16.1 Adjustment of FiO2

FiO2 was continued at the same level as pre-study entry level. Any desaturations outside the standard target range (91-95%) were dealt with as per standard neonatal practice (FiO2 increased or decreased by 5% aliquots). A sustained increase (more than 15 minutes) in FiO2 by 0.2 above baseline or FiO2 > 0.6 was used as the cut-off to restore the infant to previous flow rate with no further reduction in flow. The study was continued but these infants were studied over a reduced range of flow rates.

4.16.2 Study Duration

Total study duration was around 120 minutes. I was directly observing the baby throughout the study.

4.16.3 Minimisation of Bias

The recordings were done simultaneously on an electronic chart recorder with no possibility of observer bias. The stability of pressure traces was based on the presence of a clean artefact free respiratory waveforms after recording. Only those segments with no noise and artefact were analysed and all artefact free data in its entirety was exported for analysis to avoid observer bias.

4.16.4 Discontinuation Criteria

The attending clinician had the powers to withdraw the baby at any time in the interests of the baby’s health and well-being. Babies would have been discontinued from study if (any of):

- Inadequate ventilation - pH <7.20 and pCO2 >10 kPa,
- Inadequate oxygenation - FiO2 >0.6 and/or increase in FiO2 of 0.2 from baseline to maintain SpO2 >91% (28),
- Recurrent unprovoked minor apnoea requiring intervention (not self-resolving; >2 per hour during study) or one major apnoea requiring positive pressure ventilation (28).
4.16.5 *Concomitant Treatments*

Throughout the study, the babies continued to receive prescribed concomitant treatments deemed necessary to provide adequate supportive care.

4.17 *Research Governance*

Babies recruited to the HFNC Study spent about two hours participating in the study. I monitored the babies closely throughout the study. In addition, babies continued to have routine neonatal observations as per the neonatal unit policy by the clinical team. There was no transfer of babies between neonatal units during this study as it was a short study of two hours duration. Timeline of proof of concept project development is given below in Table number 16.

**Table 16. Timeline of various physiology studies in the proof of concept study**

<table>
<thead>
<tr>
<th>Respiratory physiology study development</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFNC Review of evidence</td>
<td>July 2013-September 2013</td>
</tr>
<tr>
<td>Protocol development</td>
<td>October 2013-January 2014</td>
</tr>
<tr>
<td>Study Trolley assembly</td>
<td>July 2014</td>
</tr>
<tr>
<td>Gas analyser calibration set up</td>
<td>August 2014</td>
</tr>
<tr>
<td>Pressure monitoring calibration set up</td>
<td>August 2014</td>
</tr>
<tr>
<td>Volusense equipment training</td>
<td>December 2014</td>
</tr>
<tr>
<td>Airway pressure monitoring – Gaeltec catheter</td>
<td>February 2015</td>
</tr>
<tr>
<td>Airway pressure monitoring with thermal sensor</td>
<td>February 2015</td>
</tr>
<tr>
<td>Airway pressure monitoring with differential transducer</td>
<td>March 2015</td>
</tr>
<tr>
<td>Airway gas concentration</td>
<td>February-March 2015</td>
</tr>
<tr>
<td>Tidal breathing indices- Volusense</td>
<td>February-March 2015</td>
</tr>
</tbody>
</table>
4.18 Source data

Source data was obtained from:
- Hospital records for the baby’s clinical condition before study.
- Data downloaded from the electronic multi-channel recorder (Power lab, AD Instruments, Oxford, UK).

4.19 Assessment of efficacy

The primary outcome measures were recorded during the study on electronic chart recorder. The mechanism for recording any significant respiratory deterioration resulting in exit criteria being met was analysed on a case by case basis by the study team and the data monitoring committee. Each baby was monitored as per the current neonatal unit standards (Appendix 6).

4.20 Assessment of safety

Safety was assessed continuously during each baby’s study in the neonatal unit. Standard system was in place to address any adverse event.
4.21 Discussion and summary

I undertook investigation of the techniques available to measure respiratory physiology in preterm infants accurately, safely and also wanted to demonstrate that it was feasible in preterm infants.

Out of the three pressure measuring systems, though they all had specific advantages, the stability of the Gaeltec pressure catheter mounted pressure transducer was not optimal over a two-hour period at the pressure range we expected to see in preterm infants. I decided to test the quality of pressure tracings with these methods before choosing the most appropriate technique for larger randomised crossover study.

The gas analyser selection for measuring airway gas concentration was based on the features described namely response rate, accuracy and feasibility for ease of use at bed side in a neonatal unit.

I explored the features of a novel tidal volume measuring device called Volusense. This electromagnetic inductance plethysmographic device has been tested in neonates including preterm neonates but never during HFNC therapy situation (81, 160). The technical aspects of the machine when I examined in depth seemed to be suitable for the purposes of this study i.e., measuring tidal volumes continuously whilst measuring other physiological parameters in babies who were receiving varying flow rates of HFNC.

These devices in addition to the already standardised transcutaneous CO₂ and oximetry devices in use made up the core elements of the equipment used in this study.
Chapter 5. Results
5.1 Introduction

The body of literature on HFNC therapy in various clinical conditions is growing. Its use in the neonatal population has been increasing and it has been the subject of several studies as discussed in my literature review (96, 98, 130).

However, the key mechanism of action of HFNC is yet to be elucidated. Out of the several mechanisms of action proposed the predominant feature is not known (14). Without this knowledge, it is difficult and empirical to make guidelines and treatment protocols for its initiation, maintenance weaning and stopping the therapy (99).

In order to understand the role of airway distending pressure, dead space wash out effect and influence on tidal volume and hence minute ventilation, we planned a comprehensive physiological study. I undertook the initial study evaluating the equipment to be used in this study as above. I chose and built the cart that all the equipment was mounted on and wired all items up to the chart recorder. I established a protocol whereby the equipment could be calibrated then wheeled to the patient’s bedside in order to start the investigation.

I also performed proof of concept studies to assess feasibility and safety before undertaking a larger study involving a larger number of babies. A detailed study protocol (See Appendix Number 1) as described earlier was developed followed by approvals from North East Ethics Committee-2(See Appendix Number 3), Special Trustees at Newcastle Hospitals for funding (See Appendix Number 7) and finally Newcastle Hospitals NHS foundation Trust research governance for site specific research (See Appendix Number 8).

5.2 Baseline characteristics of study population

The median (IQR) gestational age at birth was 27 (25.71-29.28) weeks and the median (IQR) birth weight was 872.5 (705-1160) grams. The gender distribution was equal (3 male, 3 female). 5 babies were >1500 grams in weight at the time of the study. There was one baby <1000 grams in weight at the time of the study. The median (IQR) age at the time of study was 34.78 (32.86-36.14) weeks and the median (IQR) study weight was 1785 (1580-1980) grams. The participant summary and study entry characteristics are summarised in tables 17 and 18.
Table 17. Participant Summary

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Number of babies</th>
<th>Respiratory support starting mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consented</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Studies undertaken</td>
<td>6</td>
<td>1 CPAP 5 HFNC</td>
</tr>
<tr>
<td>Reasons for exclusion</td>
<td></td>
<td>2 babies came off high flow therapy soon after consent before study could commence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 baby - Volusense only started – Baby active and unsettled- data not obtained consistently.</td>
</tr>
</tbody>
</table>

Table 17 shows a summary of the participants in this pilot study.
Table 18. Description of baseline characteristics at study entry

<table>
<thead>
<tr>
<th>Participants</th>
<th>Gender</th>
<th>Gestational Age in weeks</th>
<th>Age at the time of study in weeks</th>
<th>Birth Weight in grams</th>
<th>Weight at the time of study in grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>27+6</td>
<td>36+1</td>
<td>675</td>
<td>1980</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>29+2</td>
<td>34+4</td>
<td>1160</td>
<td>1700</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>26+1</td>
<td>28</td>
<td>905</td>
<td>975</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>24+6</td>
<td>35</td>
<td>705</td>
<td>1870</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>25+5</td>
<td>37+1</td>
<td>840</td>
<td>2280</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>31+3</td>
<td>32+6</td>
<td>1400</td>
<td>1580</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>27</td>
<td>34.78</td>
<td>872.5</td>
<td>1785</td>
</tr>
<tr>
<td>IQR range</td>
<td></td>
<td>(25.71-29.28)</td>
<td>(32.86-36.14)</td>
<td>(705-1160)</td>
<td>(1580-1980)</td>
</tr>
</tbody>
</table>

Table 18 shows the baseline characteristics of the study population.
5.3 Airway Pressure Recordings

Two babies had a range of pressure measurement across different HFNC flows with the B&D differential transducer.

A pressure recording was taken as valid and real if it showed the typical wave pattern and without interference and was of uniform amplitude across several respiratory cycles. In this study, at least 10 breaths were needed to accept measurements from that epoch. Various pressure data were collected and the segment represented by each pressure parameter is shown in a valid pressure signal in figure 41.

![Figure 41. Valid Pressure tracing with respiratory waveform for at least 10 breaths](image)

Figure 41 shows a valid pressure waveform that would be accepted for analysis.
The range of pressures seen during HFNC in a preterm neonate is shown in table 19 and figure 42. In this example, maximum pressure in air ways was seen during HFNC of 8 LPM. In the HFNC flow range of 2-8 LPM, there was a flow dependent increase in mean air way pressures and maximum airway pressures.
Table 19. Airway pressure profile recorded with B&D differential transducer with HFNC varying flow rates (Study ID 04 and 06)

<table>
<thead>
<tr>
<th>Respiratory Support</th>
<th>Pressure Minimum cm H2O</th>
<th>Pressure Mean cm H2O</th>
<th>Pressure Maximum cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ID</td>
<td>04</td>
<td>06</td>
<td>04</td>
</tr>
<tr>
<td>CPAP 6 cm H2O</td>
<td>1.69</td>
<td>3.56</td>
<td>4.01</td>
</tr>
<tr>
<td>HFNC 8 LPM</td>
<td>2.39</td>
<td>5.62</td>
<td>4.15</td>
</tr>
<tr>
<td>HFNC 7 LPM</td>
<td>0.34</td>
<td>4.31</td>
<td>3.27</td>
</tr>
<tr>
<td>HFNC 6 LPM</td>
<td>0.09</td>
<td>3.36</td>
<td>3.51</td>
</tr>
<tr>
<td>HFNC 5 LPM</td>
<td>0.00</td>
<td>0.80</td>
<td>2.19</td>
</tr>
<tr>
<td>HFNC 4 LPM</td>
<td>0.07</td>
<td>0.97</td>
<td>0.7</td>
</tr>
<tr>
<td>HFNC 3 LPM</td>
<td>0.42</td>
<td>0.22</td>
<td>0.98</td>
</tr>
<tr>
<td>HFNC 2 LPM</td>
<td>0.20</td>
<td>0.52</td>
<td>1.44</td>
</tr>
</tbody>
</table>

Table 19 shows the complete range of various pressure parameters across all HFNC flow ranges and CPAP control mode.

Figure 42. Mean Airway pressure profile recorded with B&D differential transducer with HFNC varying flow rates (Study ID 04 and 06)

Figure 42 is a scatter plot of the mean airway pressures across HFNC flow ranges and CPAP.
5.4 Gas concentration measurement

5.4.1 In-vivo measurement of airway $O_2$ and $CO_2$ concentrations

The $O_2$ and $CO_2$ concentration in nasopharyngeal gas sample was sampled intermittently during each flow rate from 2-8 LPM and during CPAP of 6 cm H$_2$O pressures. The FiO$_2$ being administered was noted down at the same time. The transcutaneous CO$_2$ was continuously recorded throughout the study.

In the figure number 43, a snapshot of gas concentration analysis of nasopharyngeal space is illustrated with blue wave form from CO$_2$ transducer and red wave form from O$_2$ transducer of the gas analyser. The points in CO$_2$ curves which stands for End Inspiratory and End Expiratory CO$_2$ levels are indicated by black arrows.
Figure 43. Recording of nasopharyngeal airway O\textsubscript{2} and CO\textsubscript{2} concentrations during CPAP with FiO\textsubscript{2} 34%.

Figure 43 shows the recording of O\textsubscript{2} and CO\textsubscript{2} (marked with arrows) in nasopharynx during HFNC therapy.
5.4.2 Gas concentration measurements in this proof of concept study

Valid gas concentration measurement was available from Study ID 2, 3, 4 and 6 for different flow rates. The range of values seen is shown in table 20.
Table 2. Maximum, mean, minimum CO$_2$ and O$_2$ concentrations in nasopharyngeal airway at various HFNC flow rates

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Mode</th>
<th>O$_2$ Average Minimum %</th>
<th>O$_2$ Average Maximum %</th>
<th>O$_2$ Mean %</th>
<th>CO$_2$ Average Minimum %</th>
<th>CO$_2$ Average Maximum %</th>
<th>CO$_2$ Mean %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>CPAP 6</td>
<td>25.7</td>
<td>28.4</td>
<td>27.0</td>
<td>0.42</td>
<td>2.38</td>
<td>1.31</td>
</tr>
<tr>
<td>3</td>
<td>CPAP 6</td>
<td>33.2</td>
<td>36.0</td>
<td>34.5</td>
<td>1.90</td>
<td>4.40</td>
<td>3.05</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 8</td>
<td>18.6</td>
<td>21.8</td>
<td>20.3</td>
<td>0.28</td>
<td>3.12</td>
<td>1.50</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 8</td>
<td>16.8</td>
<td>20.8</td>
<td>19.4</td>
<td>0.33</td>
<td>4.05</td>
<td>1.50</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 7</td>
<td>33.3</td>
<td>36.4</td>
<td>34.8</td>
<td>1.01</td>
<td>3.64</td>
<td>2.22</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 7</td>
<td>17.2</td>
<td>20.7</td>
<td>19.0</td>
<td>0.25</td>
<td>3.11</td>
<td>1.49</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 6</td>
<td>31.0</td>
<td>35.1</td>
<td>32.7</td>
<td>0.81</td>
<td>3.46</td>
<td>1.46</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 6</td>
<td>21.0</td>
<td>26.0</td>
<td>23.2</td>
<td>1.18</td>
<td>3.80</td>
<td>2.52</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 4</td>
<td>20.0</td>
<td>23.1</td>
<td>21.5</td>
<td>0.79</td>
<td>3.12</td>
<td>1.95</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 4</td>
<td>17.1</td>
<td>20.9</td>
<td>19.7</td>
<td>0.06</td>
<td>3.85</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 3</td>
<td>32.3</td>
<td>36.8</td>
<td>34.4</td>
<td>0.98</td>
<td>4.35</td>
<td>2.51</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 3</td>
<td>15.8</td>
<td>20.8</td>
<td>19.0</td>
<td>0.22</td>
<td>4.91</td>
<td>1.64</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 2</td>
<td>34.6</td>
<td>37.5</td>
<td>35.8</td>
<td>1.36</td>
<td>3.52</td>
<td>2.53</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 2</td>
<td>22.3</td>
<td>25.0</td>
<td>23.6</td>
<td>0.44</td>
<td>2.68</td>
<td>1.48</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 2</td>
<td>15.9</td>
<td>20.7</td>
<td>18.5</td>
<td>0.46</td>
<td>5.38</td>
<td>2.54</td>
</tr>
</tbody>
</table>

P value calculated using the t-test (Difference -0.183; Standard error 0.294; 95% CI -0.8289 to 0.4636; t-statistic -0.622; DF 11; Significance level P = 0.5466)

Table 20 shows maximum, mean, minimum CO$_2$ and O$_2$ concentrations in nasopharyngeal airway at various HFNC flow rates. There was no difference between CO$_2$ levels between HFNC flow rates of 6-8 LPM compared to 2-4 LPM (P = 0.55 95% CI -0.83 to 0.46; t-statistic).
5.4.3 Relationship of administered O\textsubscript{2} to recorded O\textsubscript{2} concentration in nasopharyngeal airway

The administered FiO\textsubscript{2} by HFNC was slightly higher than the measured O\textsubscript{2} levels in the nasopharyngeal gas sample. Thus, the HFNC prescribed oxygen concentration is likely to deliver a slightly lesser FiO\textsubscript{2} concentration to the upper airways. The mean nasopharyngeal O\textsubscript{2} levels at different HFNC flow rates and CPAP 6 cm H\textsubscript{2}O respiratory support, recorded from nasopharyngeal gas samples is shown in table 21.
### Table 21. Relationship of administered O\(_2\) to recorded O\(_2\) concentration in nasopharyngeal airway during HFNC

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Respiratory support mode</th>
<th>Administered FiO(_2)</th>
<th>Mean Nasopharyngeal O(_2) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>CPAP 6</td>
<td>34.0%</td>
<td>27.0</td>
</tr>
<tr>
<td>3</td>
<td>CPAP 6</td>
<td>37.0%</td>
<td>34.5</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 8</td>
<td>24.0%</td>
<td>20.3</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 8</td>
<td>21.0%</td>
<td>19.4</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 7</td>
<td>37.0%</td>
<td>34.8</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 7</td>
<td>21.0%</td>
<td>19.0</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 6</td>
<td>37.0%</td>
<td>32.7</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 6</td>
<td>24.0%</td>
<td>23.2</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 4</td>
<td>26.0%</td>
<td>21.5</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 4</td>
<td>21.0%</td>
<td>19.7</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 3</td>
<td>45.0%</td>
<td>34.4</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 3</td>
<td>21.0%</td>
<td>19.0</td>
</tr>
<tr>
<td>3</td>
<td>HFNC 2</td>
<td>45.0%</td>
<td>35.8</td>
</tr>
<tr>
<td>4</td>
<td>HFNC 2</td>
<td>29.0%</td>
<td>23.6</td>
</tr>
<tr>
<td>6</td>
<td>HFNC 2</td>
<td>21.0%</td>
<td>18.5</td>
</tr>
</tbody>
</table>

| Mean (SD) | 29.53(8.87) | 25.56(6.88) |

Table 21 shows relationship of administered O\(_2\) to recorded O\(_2\) concentration in nasopharyngeal airway during HFNC.
5.5 Tidal breathing indices measurements by Volusense method

Tidal breathing indices were measured as per the study protocol during CPAP of 6 cm H2O and HFNC flow rate from 2-8 LPM. These were measured in all the 6 babies in the study.

5.5.1 Tidal volumes in HFNC

The mean tidal volumes at each flow rate was within the range of 3.1-3.9 ml/kg. However, the relationship of tidal volume and flow rate was not linear. There was no significant difference between the tidal volume seen at CPAP of 6 cm H2O and each of the flow rates 2-8 LPM. The mean tidal volume in ml/kg is shown in table 22.
Table 2 shows Tidal volumes in ml/kg determined by Volusense method at CPAP 6 cm H$_2$O and varying HFNC flow rates.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>CPAP 6 cm H$_2$O</th>
<th>HFNC 8 LPM</th>
<th>HFNC 7 LPM</th>
<th>HFNC 6 LPM</th>
<th>HFNC 5 LPM</th>
<th>HFNC 4 LPM</th>
<th>HFNC 3 LPM</th>
<th>HFNC 2 LPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>2.49</td>
<td>NA</td>
<td>NA</td>
<td>2.36</td>
<td>2.35</td>
<td>2.33</td>
<td>2.77</td>
<td>3.5</td>
</tr>
<tr>
<td>02</td>
<td>4.54</td>
<td>4.12</td>
<td>4.41</td>
<td>3.45</td>
<td>3.76</td>
<td>4.11</td>
<td>3.1</td>
<td>5.17</td>
</tr>
<tr>
<td>03</td>
<td>7.62</td>
<td>3.77</td>
<td>3.10</td>
<td>3.75</td>
<td>4.24</td>
<td>3.17</td>
<td>4.63</td>
<td>6.19</td>
</tr>
<tr>
<td>04</td>
<td>1.77</td>
<td>2.38</td>
<td>2.07</td>
<td>2.08</td>
<td>1.72</td>
<td>2.05</td>
<td>2.02</td>
<td>1.60</td>
</tr>
<tr>
<td>05</td>
<td>2.10</td>
<td>1.76</td>
<td>1.87</td>
<td>1.83</td>
<td>1.65</td>
<td>1.82</td>
<td>1.20</td>
<td>1.11</td>
</tr>
<tr>
<td>06</td>
<td>3.76</td>
<td>3.44</td>
<td>4.63</td>
<td>5.17</td>
<td>4.63</td>
<td>5.62</td>
<td>5.34</td>
<td>5.82</td>
</tr>
<tr>
<td>MEAN</td>
<td>3.71</td>
<td>3.10</td>
<td>3.22</td>
<td>3.11</td>
<td>3.06</td>
<td>3.18</td>
<td>3.18</td>
<td>3.90</td>
</tr>
<tr>
<td>STD DEV</td>
<td>2.18</td>
<td>0.99</td>
<td>1.28</td>
<td>1.26</td>
<td>1.31</td>
<td>1.45</td>
<td>1.56</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Table 22. Tidal volumes in ml/kg determined by Volusense method at CPAP 6 cm H$_2$O and varying HFNC flow rates.
5.5.2 *Tidal breathing indices including flow derivatives from Volusense*

The Volusense generated flow volume loops from the chest and abdominal wall movements. The various flow values are derived by differentiating the volume curves. This is shown in table 24. There were no statistically significant differences in either tidal volumes or flow indices derived from the flow volume loops when HFNC of 8 LPM was compared with CPAP of 6 cm of H$_2$O.

The mean peak tidal expiratory flow (PTEF) in mL/s during HFNC 8 LPM and CPAP 6 cm H$_2$O was similar with no statistically significant difference ($p=0.9150$). Similarly, time to peak tidal expiratory flow as a ratio of total expiratory time, referred as Tptef/Te, was also similar ($p=0.8111$) between the two respiratory support modalities of HFNC 8 LPM and CPAP 6 cm H$_2$O.

The phase angle obtained from the difference in thoracic and abdominal wall movements was similar ($p=0.7962$) indicating effect of HFNC and CPAP on thoracoabdominal asynchrony was the same in this instance.

The expiratory flow volume loop centre of gravity, referred as FVg, was also similar ($p=0.3706$) in the two modalities of respiratory support.
Table 23. Tidal breathing indices with tidal flow derivatives

<table>
<thead>
<tr>
<th>Indices</th>
<th>HFNC 8 LPM (n=5)</th>
<th>CPAP 6cm H2O (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at study in grams</td>
<td>1737 (975-2280)</td>
<td>1737 (975-2280)</td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vt (ml)/kg</td>
<td>2.82 (1.51)</td>
<td>3.14 (2.62)</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR(/min)</td>
<td>62.69 (21.45)</td>
<td>57.93 (18.90)</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V'E(mL)/kg</td>
<td>184.84 (127.53)</td>
<td>193.01 (207.80)</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEF (mL/s)</td>
<td>14.69 (2.94)</td>
<td>14.33 (6.69)</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tptef/Te (%)</td>
<td>62.61 (16.00)</td>
<td>65.11 (16.00)</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Te/Ti</td>
<td>203.20 (122.18)</td>
<td>188.62 (41.91)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase angle (Degree)</td>
<td>101.08 (62.46)</td>
<td>90.3 (65.19)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVg (dimensionless)</td>
<td>0.48 (0.07)</td>
<td>0.45 (0.01)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 23 shows tidal flow indices derived from the Volusense flow volume loops.

Vt (mL)/kg - Tidal volume per kilogram body weight
RR - Respiratory rate
V'E (mL)/kg - minute ventilation
PTEF - Peak tidal expiratory flow
Tptef/Te - Time to peak tidal expiratory flow as a ratio of total expiratory time
FVg - Expiratory flow volume loop centre of gravity (dimensionless)
5.6 Gas exchange profile of patients during the study

5.6.1 Heart rate, respiratory rate, transcutaneous O$_2$ and CO$_2$ levels

All the babies had continuous heart rate, respiratory rate, transcutaneous O$_2$ concentration and transcutaneous CO$_2$ levels measured as shown in Table 24, Table 25, Table 26 and Table 27 and figure 44, figure 45, figure 46, figure 47 respectively. The mean values of these basic respiratory parameters were recorded throughout the study across all HFNC flow ranges.

The mean heart rate and mean respiratory rates were stable across the flow ranges of HFNC as well as CPAP of 6 cm H$_2$O during the study period.

The oxygen saturation profile was stable within the limits agreed in the protocol (FiO$_2$ not exceeding more than 0.2 from baseline) throughout the study and 3 babies needed increase in FiO$_2$ in 5% aliquots.

The transcutaneous CO$_2$ mean values were within the acceptable range during the entire study period in all the babies. This shows that there were no transient elevations of TcPCO2 levels during the various HFNC flow levels during the study period.
Table 24. Heart Rate (mean) during the study

<table>
<thead>
<tr>
<th>Study ID</th>
<th>CPAP 6 cm H2O</th>
<th>HFNC 8 LPM</th>
<th>HFNC 7 LPM</th>
<th>HFNC 6 LPM</th>
<th>HFNC 5 LPM</th>
<th>HFNC 4 LPM</th>
<th>HFNC 3 LPM</th>
<th>HFNC 2 LPM</th>
<th>Total study Mean HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>154</td>
<td></td>
<td>142</td>
<td>148</td>
<td>146</td>
<td>151</td>
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<td>4</td>
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<td>175</td>
<td>162</td>
<td>165</td>
<td>167</td>
<td>159</td>
<td>156</td>
<td>152</td>
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<tr>
<td>5</td>
<td>159</td>
<td>155</td>
<td>144</td>
<td>154</td>
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<td>149</td>
<td>158</td>
<td>148</td>
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<td>149</td>
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<td>157</td>
<td>152</td>
<td>148</td>
<td>151</td>
<td>161</td>
</tr>
</tbody>
</table>

Table 24 shows the mean heart rate measured during the study.

**Figure 44. Heart Rate (mean) during the study**

![Heart Rate (mean) plot](image)

Figure 44 is a scatter plot of the mean heart rate measured during the study.
### Table 25. Respiratory rate (mean) during the study

<table>
<thead>
<tr>
<th>Study ID</th>
<th>CPAP 6 cm H₂O</th>
<th>HFNC 8 LPM</th>
<th>HFNC 7 LPM</th>
<th>HFNC 6 LPM</th>
<th>HFNC 5 LPM</th>
<th>HFNC 4 LPM</th>
<th>HFNC 3 LPM</th>
<th>HFNC 2 LPM</th>
<th>Total study Mean RR</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>78</td>
<td>81</td>
<td>72</td>
<td>46</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 25 shows the mean respiratory rate measured during the study.

### Figure 45. Respiratory rate (mean) during the study

Figure 45 is a scatter plot of the mean respiratory rate measured during the study.
Table 26. Transcutaneous O₂ saturation levels (mean %) during the study

<table>
<thead>
<tr>
<th>Study ID</th>
<th>CPAP 6 cm H₂O</th>
<th>HFNC 8 LPM</th>
<th>HFNC 7 LPM</th>
<th>HFNC 6 LPM</th>
<th>HFNC 5 LPM</th>
<th>HFNC 4 LPM</th>
<th>HFNC 3 LPM</th>
<th>HFNC 2 LPM</th>
<th>Total study Mean SPO₂</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>97.2</td>
<td></td>
<td>98.6</td>
<td>97.5</td>
<td>98.7</td>
<td>88.9</td>
<td>99.7</td>
<td>96.3</td>
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</tr>
<tr>
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<td>99.5</td>
<td>95.6</td>
<td>97.1</td>
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<td>95.6</td>
<td>89.4</td>
<td>94.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>89.8</td>
<td>93.6</td>
<td>93</td>
<td>89.5</td>
<td>89.7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>95.3</td>
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<td>90.4</td>
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<td>94</td>
<td>86</td>
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</tr>
<tr>
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<td>99.2</td>
<td>99.3</td>
<td>98.8</td>
<td>99.5</td>
<td>99.3</td>
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<td>99.4</td>
<td>99</td>
<td>98.5</td>
<td>98.5</td>
<td>98.7</td>
</tr>
</tbody>
</table>

Table 26 shows the mean O₂ saturation levels at different flow levels during the study.

Figure 46. Transcutaneous O₂ saturation levels (mean %) during the study

Figure 46 shows the mean O₂ saturation levels at different flow levels during the study.
Table 27. Transcutaneous CO$_2$ (mean) levels during the study

<table>
<thead>
<tr>
<th>Study ID</th>
<th>CPAP 6 cm H$_2$O</th>
<th>HFNC 8 LPM</th>
<th>HFNC 7 LPM</th>
<th>HFNC 6 LPM</th>
<th>HFNC 5 LPM</th>
<th>HFNC 4 LPM</th>
<th>HFNC 3 LPM</th>
<th>HFNC 2 LPM</th>
<th>Total study Mean TcPCO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>7.2</td>
<td>7.5</td>
<td>7.4</td>
<td>6.7</td>
<td>7.2</td>
<td>6.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9.7</td>
<td>9.1</td>
<td>9.0</td>
<td>8.9</td>
<td>9.6</td>
<td>8.8</td>
<td>9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.1</td>
<td>7.7</td>
<td>7.4</td>
<td>7.3</td>
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<td>7.3</td>
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<td></td>
</tr>
<tr>
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<td>6.9</td>
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<td>6.7</td>
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<td>6.8</td>
<td>6.4</td>
<td></td>
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<td>5.0</td>
<td></td>
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</tr>
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<td>6</td>
<td>5.8</td>
<td>6.8</td>
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<td>6.0</td>
<td>5.7</td>
<td>5.9</td>
<td>5.7</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 27 shows the mean transcutaneous CO$_2$ levels measured during the study.

Figure 47. Transcutaneous CO$_2$ (mean) levels during the study

![Graph showing transcutaneous CO$_2$ levels](image)

Figure 47 shows the mean transcutaneous CO$_2$ levels measured during the study.
5.6.2 Physiology parameters during respiratory support cross-over (CPAP to HFNC and vice versa)

The following FiO$_2$ increments had to be made during the study. These changes were within the limits of the protocol and did not warrant withdrawal from continuing the study.

Study ID 01, 05 and 06 – No FiO$_2$ changes were needed.

Study ID 02 - FiO$_2$ – Increased once by 5% as per protocol (one O$_2$ desaturation to low 80s).

Study ID 03 - FiO$_2$ increased on two occasions as per protocol – O$_2$ desaturations to mid-80s (FiO$_2$ returned to base line level at the end of the study)

Study ID 04 - FiO$_2$ increased twice as per protocol – back to the baseline post study.

A detailed analysis of physiology parameters profile 10 minute prior to and 10 minutes after cross over to other mode of respiratory support showed that the physiological status of the baby was back to baseline within 10 minutes of the change. This indicates that the wash out time of 30 minutes time adopted in the study protocol after cross over was probably sufficient. This is illustrated in figure 48.
Figure 48. The physiology parameters trend with change in respiratory support mode (CPAP to HFNC and HFNC to CPAP)

Figure 48 shows the basic respiratory physiology parameters status 10 minute before and after respiratory support mode crossover.
5.7 Safety and adverse events

None of the babies had apnoeic episodes requiring intervention. There were no episodes of major oxygen desaturations seen during any part of the study or handling.

One baby had one episode of oxygen desaturation with bradycardia which resolved without intervention within seconds. This episode was similar to the baby’s pre-study entry episodes but not frequent enough to meet exclusion criteria.

None of the babies had nasal trauma, air leak episode, escalation of respiratory support immediately after the study or deterioration of blood gases suggesting decompensation immediately following the study.

5.8 Conclusions

In this proof of concept physiology study, I was able to identify a suitable measuring technique and measure satisfactory nasopharyngeal pressure in preterm infants safely. The ability to measure nasopharyngeal gas concentrations for O$_2$ and CO$_2$ with the same catheter enabled assessment of this study outcome without additional instrumentation. I was able to use a novel tidal breathing measurement device in preterm infants during HFNC therapy and obtain consistent measurements across all flow levels for a period of about two hours. I was continuously monitoring the babies and was able to ensure safe conduct of the study and with minimal interference to neonatal care needs.
Chapter 6. General Discussion
6.1 Thesis Results and Current Literature

6.1.1 Retrospective study of HFNC use over a 5-year period in Royal Victoria Infirmary tertiary neonatal unit

This retrospective study involved a large number of babies (282 patients) treated with HFNC and CPAP over a 5-year period and the babies who received HFNC showed worse outcomes in terms of NIV days (22 days±15 SD in CPAP versus 49 days ±23 SD in HFNC group) and BPD rate (1.08% in CPAP versus 13.63% in HFNC group).

Though the study has inherent limitations due to being a retrospective study, any possible role of HFNC resulting in worse lung health outcomes needs to be considered and warrants further research.

More recently further studies have raised similar concerns. The study by Hoffman et al covered 2 different time epochs and was a retrospective chart review of HFNC use and outcomes(139). They reported a trend towards a higher rate of BPD in HFNC group compared to CPAP/BiPAP group (139). The study by Taha et al was a large retrospective review of a neonatal database and reported that babies who received HFNC either as lone NIV or in association with some CPAP use at some period had worse outcomes in terms of BPD (133).

The possible explanation for worse BPD outcomes noted in retrospective studies could be because of selection bias. The sicker babies might have required prolonged NIV and since HFNC has been increasingly used as a respiratory support often in place of CPAP there might have been higher representation of BPD in HFNC group.

Interestingly BPD outcomes in prospective randomised, controlled trials involving HFNC as either as primary respiratory support or as post extubation support or as a weaning mode of therapy instead of CPAP have not shown increased rates of BPD in HFNC group(1, 96-98, 114, 127, 130).

The mechanism of any lung damage due to HFNC is largely speculative. It is more likely to be due to under filled lung volumes rather than due to over distension since the air leak syndromes in HFNC are less frequent compared to CPAP as indicated in some RCTs (1). The
under ventilated lung may be prone to atelectotrauma. The possibility of episodic supra therapeutic levels of mean airway pressures is a theory that needs to be tested. The effects of transient rises in pressure are not known both in terms of duration or magnitude of higher pressures.

In light of the findings in this retrospective review it was decided to appraise available literature regarding safety and efficacy of HFNC in preterm neonates.

6.1.2 Evidence for efficacy and safety of HFNC in preterm neonates

In this review, I reviewed RCTs comparing efficacy and safety of HFNC to CPAP or other forms of NIV. The risk of treatment failure (needing escalation of respiratory support or intubation, as defined by study authors) with HFNC was similar to CPAP when used as post extubation support [RR (95% CI) of 1.09 (0.90, 1.31)].

A similar risk compared with CPAP was seen for clinical outcomes like BPD when HFNC was used as primary respiratory support, RR 1.17 95% CI (0.72, 1.90); as post extubation respiratory support, RR 0.88 95% CI (0.74, 1.05)] and mortality [as primary respiratory support, RR 0.61 95% CI (0.08, 4.57); as post extubation respiratory support, RR 0.62 95% CI (0.28, 1.39)].

Unlike CPAP, HFNC proved better when it came to complications of therapy. The complication risk of air leak syndromes as primary respiratory support, RR 0.42, 95% CI (0.17, 1.02); as post extubation respiratory support, RR 0.28, 95% CI (0.15, 0.55)] as well as nasal trauma [as primary respiratory support, RR 0.50 95% CI (0.34, 0.72); as post extubation respiratory support, RR 0.50 95% CI (0.40, 0.61)].

However, as a primary respiratory support, the risk of treatment failure was higher compared to CPAP [RR 1.57 95% CI (1.20, 2.05)]. The reason for this difference in outcome is unclear. The behaviour of lungs in the setting of initial RDS is likely to be different to that of the lungs in infants who are ready to be extubated. It may be because HFNC is inherently less efficacious in the setting of progressively worsening respiratory distress as compared to respiratory distress which is progressively improving. The degree of respiratory support or how much off-loading of work of breathing HFNC does has not been answered yet in the few
physiology studies done so far(73, 74).

In summary, on combining the studies performed to date, I conclude that HFNC is unlikely to be harmful in the short term because it’s not associated with increased mortality or BPD and has beneficial effect on nasal trauma and air leak syndromes rates. It does not appear to be as effective in primary respiratory support. The long-term consequences of this support remain uncertain and need further research.

6.1.3 Airway pressure measurement methods

In this study, I evaluated the accuracy, range and feasibility of three types of pressure transducers.

The Gaeltec catheter tip pressure transducer has been used in earlier studies investigating HFNC and various pressure ranges have been reported by different groups of researchers (27, 29). Earlier Lampland et al used saline filled catheters (24, 31) and Locke et al used an air filled balloon catheter(30) for measuring oesophageal pressure as an indicator of pleural pressure. These have the disadvantage of being influenced by gravity or height of the transducer in relation to the measuring site and in addition the transducer is outside the body, away from the measuring site. There is also the added effect of length of the catheter, catheter diameter, body movements leading to artefacts on the pressure wave form and they need considerable technical skill and expertise to reliably perform. Therefore, catheter mounted pressure transducers became an attractive option.

The Gaeltec catheter when tested in vitro showed drift in baseline occurring within minutes and attained levels of ± 1.3 cm H₂O pressure off baseline at the end of two hours. The drift in baseline was larger when pressures at the lower end were tested for stability. A second catheter that was available was also tested and produced similar results. This problem persisted despite it being sent back to the company and sensor components being re-laid and retested in factory conditions. The linearity although was reasonable, the performance of pressure recording was not stable at any given pressure point. Ultimately, attempts at recording pressure in two babies did not produce reliable pressure recording. The likely reasons for our experience with the Gaeltec catheter tip mounted pressure transducer include firstly, a faulty batch which is less likely as it was returned to the company
for repair. Secondly, these sensors have a very wide pressure range from 0-300 mm Hg (or 0-407.8 cm H₂O). This range is 40 times larger than our intended pressure range. Thus, at the very extreme ends of its range it may not be accurate enough. Thirdly, the influence of flow dynamics in a complex anatomical space like the nasopharynx on these sensors have not been well studied. A lateral wall mounted pressure sensor may not truly catch the pressure dynamics in the nasopharynx. Therefore, we concluded that Gaeltec catheter was not fit for purpose in this setting.

A thermal sensor was tested in vitro and found to be accurate with good linearity and frequency response. However, the main limiting factor in using these sensors is they are dependent on a flow of gas across their sensor surface in order to detect changes in temperature and then provide an analogue output of the likely pressure. Thus, it was tested in two babies’ in vivo and I could not get reliable pressure traces since in preterm babies the flow through the nasopharyngeal catheter tends to be intermittent and unreliable.

The B&D pressure transducer works with a simple technique of the transducer being exposed to two different pressure areas and the differential is picked up by a strain gage type of sensor and an electrical signal is generated based on pressure differential and provided as an analogue output. Thus, one pressure area is atmospheric and the other is the nasopharynx accessed through a nasopharyngeal catheter. It does not depend on flow and as long as the catheter is patent, the pressure differential is appreciated by the sensor. The transducer showed excellent linearity, stability over time and adequate frequency response for neonatal breathing frequency. I used this in two babies and obtained reliable pressure traces across all flow rates and CPAP in one baby and across some flow rates in the second baby.

To conclude, from these measurements, the B&D differential pressure transducer provided a consistently valid pressure signals with valid data across all flow ranges. This pressure transducer was found to be suitable to study the nasopharyngeal airway pressures in the context of preterm neonatal age group.

6.1.4 Airway gas concentration measurement methods during HFNC

The airway dead space wash out effect is one of the proposed mechanisms of action of HFNC. This has been noted by tracheal gas insufflation studies earlier and subsequently by observational clinical studies (71, 72). However, it’s not been confirmed or its relative
contribution to the efficacy of HFNC has not been studied. We hypothesised that simultaneous recording of transcutaneous CO\textsubscript{2} and airway CO\textsubscript{2} levels would help us understand whether HFNC has any significant role in washing out the airway dead space of expired air CO\textsubscript{2} content.

Firstly, in this study, I showed that it is possible to measure the nasopharyngeal airway gas concentration quickly with breath-to-breath almost instantaneous data allowing us to compare the other respiratory parameters at the same time. We used the same nasopharyngeal catheter used to record pressure thus eliminating the need for invasive instrumentation.

Secondly, the relationship of transcutaneous CO\textsubscript{2} to the nasopharyngeal CO\textsubscript{2} measured in this study was interesting. It has been shown in earlier studies that the End tidal CO\textsubscript{2} measurement trends correlate well with transcutaneous CO\textsubscript{2} (159). The measured value of average maximum CO\textsubscript{2} in the nasopharyngeal space in this pilot study was always much lower than that seen in transcutaneous CO\textsubscript{2} simultaneously. It could be because of the wash out effect. This effect is in the process of being tested in a larger study sample.

Finally, the shape of the CO\textsubscript{2} trace obtained needs to be explained. The CO\textsubscript{2} trace obtained during high flow has smooth edges unlike that seen during capnometry during tidal breathing obtained at pneumotach or during ventilation (160) (See Figure 4). The expired CO\textsubscript{2} waveform can provide important information concerning airway obstruction and endotracheal tube leak. Similarly, the shape seen in CO\textsubscript{2} analysis from the nasopharyngeal airway during high flow may be because of increased elimination of CO\textsubscript{2} due to high flow and leak. Indeed, it was seen in one study where they introduced varying amounts of leak during HFNC, the CO\textsubscript{2} clearance improved in the presence of leak at increasing flow levels (22). During high flow therapy, at any given litre of flow, the volume of dead space to be flushed is determined by the time allotted by end-expiration and the expiratory pause (22). Therefore, greater gas flows will flush more dead space until a flow rate is reached that can flush all of the available anatomical dead space in the available time (22).
Figure 49. CO₂ trace during high flow, during mechanical ventilation preterm neonate (160) and facemask ventilation via pneumotachograph (160, 161)

Figure 49 shows shape of the CO₂ trace during high flow, during mechanical ventilation preterm neonate and facemask ventilation via pneumotachograph.
The normal end tidal capnometry has a square shape and the plateau phase is truly alveolar CO\textsubscript{2} only when there is no obstruction in airways distal to site of CO\textsubscript{2} measurement or there is no washout from conducting airways allowing steady state (either of these scenarios, if present, there will be a reduction in end tidal CO\textsubscript{2}). Therefore, a possible reason for this shape during HFNC could be because of CO\textsubscript{2} wash out effect of HFNC.

HFNC therapy has been postulated to provide the prescribed FiO\textsubscript{2} concentration in view of the high inspiratory flows well above the inspiratory flow demands of the neonate\cite{162}. Thus there is less room for entrainment of room air during inspiration, diluting the FiO\textsubscript{2} in the inspiratory limb of HFNC circuit. However, from the available gas concentration test results in Table Number 21, there was slightly lower measured O\textsubscript{2} concentration compared to the administered FiO\textsubscript{2}.

6.1.5 Tidal breathing indices evaluation using Volusense in preterm neonates

There has been a renewed interest in measurement of tidal breathing indices in assessment of respiratory function. There is a pressing need for robust infant lung function testing in view of increasing interventions in infants for various respiratory conditions. However, the main limiting factor in infant lung function testing has been the need for sedation or need for instrumentation involving the face. The contact of measuring devices or a face mask on the facial skin elicits possible reflex neurologic responses altering the breathing characteristics and ventilation indices\cite{78}. In addition, pneumotach adds to the dead space and resistance component. Therefore, non-invasive measurement techniques like Respiratory Inductance Plethysmography have come into vogue. Electromagnetic Inductance Plethysmography by Volusense being a recent method of evaluating tidal breathing indices, I evaluated the feasibility of performing measurements using this technique in preterm neonates on HFNC support.

The tidal breathing indices were reliably obtained in all 6 infants. The measurement was easy to implement with minimal disruption to the neonates’ daily routine. The instrumentation did not interfere with respiratory care, feeding and other nursing care of a preterm neonate. There were no adverse events related to use of this device.
To my knowledge, there has been no similar study reported using Volusense electromagnetic inductance plethysmography (EIP) on preterm neonates during HFNC therapy.

In a study on preterm babies of gestation 28±2 weeks with respiratory support on CPAP and bi-level and when breathing was unsupported, Pickerd et al measured tidal breathing indices (154). They also measured weekly measurements using electromagnetic inductance plethysmography EIP. They could obtain consistent trends in respiratory rate and tidal volume per kg with varying respiratory support levels in preterm neonates (154). Earlier the same group measured tidal breathing indices using electromagnetic inductance plethysmography (EIP) in 49 healthy spontaneously breathing infants between 32 and 42 weeks gestational age(81).

Olden compared tidal breathing indices using electromagnetic inductance plethysmography (EIP) in normal infants with that seen in infants with BPD(163) and concluded that it is possible to measure tidal breathing parameters accurately, in healthy newborn infants, without prior calibration on the infant(163).

Bentsen and colleagues measured tidal breathing indices by electromagnetic inductance plethysmography (EIP) in 10 preterm infants weighing about 1500 grams and 10 term infants with trained nurse performing the measurements. They concluded that measurements were well tolerated by the infants and the repeatability was better for term infants and the repeatability was as reported in other infant lung function tests being relatively poor compared to older children and adults (164).

The same group compared tidal breathing indices obtained from Volusense to that obtained via a facemask using an ultrasonic flowmeter. They found agreement within ±5.5% except for peak tidal expiratory flow (PTEF)(157). They found that the application of the facemask significantly increased tidal volume, minute ventilation, PTEF, the ratio of inspiratory to expiratory time and the ratio of expiratory flow at 50% of expired volume to PTEF (157). They concluded that Volusense electromagnetic inductance plethysmography (EIP) was well suited for tidal breathing measurements in infants where facemask cannot be used (157).

In conclusion, I found that application of Volusense vests was easy, well tolerated by infants, the assembling of equipment was achieved with little hindrance to routine care and the
procedure was well tolerated by preterm neonates. Although I did not confirm the tidal volume accuracy with that obtained by face mask and pneumotach method, the range of tidal volumes I obtained was within the range expected in preterm neonates.

6.2 Safety Aspects of a Respiratory Physiology Study in Preterm Neonates

The basic respiratory physiology parameters namely, respiratory rate, gas exchange parameters including $S_P^O_2$ and $TcPCO_2$ levels were stable during the study in all cases. Only 3 babies out of 6 needed adjustment of $FiO_2$. This was well within the limits agreed in the protocol for safety reasons and did not require the study to be terminated. There were no nasal trauma or air leak complications. There were no immediate respiratory decompensation following the study.

There were no concerns raised by clinical team, nursing staff or parents during the conduct of the study.

6.3 Strengths and Limitations of the Study

This main strength of this study is an extensive exploration of evidences and methods of evaluation of respiratory physiology parameters including airway pressures and gas concentrations in nasopharyngeal airway as well as a novel method of determining tidal breathing indices. The study showed the likely valid tools for measuring airway pressures safely and accurately.

The airway pressures were measured with a catheter placed in nasopharyngeal airway connected to a differential pressure transducer. This method was shown to be feasible and the system had good agreement when checked in vitro against a control pressure source. The continuous measurement of pressures is an ideal goal but difficult to achieve. The main reason is because of the small size of preterm neonates; the instruments have to be of smaller calibre and hence are prone for blockage with secretions. Therefore, one has to rely on a consistent epoch of valid measurements at each level of respiratory support mode of interest. The segment that one chooses to report needs to be standardised, otherwise it is prone for reporting bias.
The measurement of gas concentration is an interesting aspect which has not been looked into much by other physiology studies on HFNC therapy. One of the strengths of this study is that I showed it is possible to rapidly obtain and record continuous gas concentration status in these preterm neonates. The simultaneous measurement of transcutaneous CO₂ gives added information about the gas exchange status or ventilation efficacy at that point in time. A larger study with adequate data points will help us quantify any CO₂ wash out from air way dead space during HFNC therapy.

A novel method determining tidal volumes non-invasively using Volusense was shown to be feasible and well tolerated by preterm infants. This machine though bulky, could fit within the space available in the neonatal unit. The study methods were demonstrated to be safe and tolerable by this vulnerable group of preterm neonates.

The study is limited by lack of some control measurements particularly with Volusense tidal breathing assessments. However, that would have added time and burden of instrumentation to the babies which was the reason for not including it in the protocol. Moreover, there has been published evidence that Volusense electromagnetic inductance plethysmography (EIP) is a valid tool to evaluate tidal breathing indices.

Since this is a proof of concept study the number of samples obtained with pressure and air way gas concentration techniques are not sufficient to make quantitative judgments.
6.4 Future Research

This study will be followed up with a larger randomised cross over study involving same protocol to obtain sufficient numbers of data points. Then it will be possible to make quantitative conclusions of the relative role of different mechanisms of HFNC in providing respiratory support in addition to humidification and oxygenation.

The non-invasive tidal volume measuring technique used in this study can be used for follow up measurements of tidal breathing indices serially for preterm infants with significant chronic neonatal lung disease. It can also be used to study changes in pulmonary function with different respiratory support modes and in different physiologic states such as sleep and awake. It can also be used to evaluate tidal breathing indices in various pulmonary disease states and response to therapy such as in bronchiolitis.

The areas where there are considerable lacunae in HFNC therapy are identifying best weaning strategy with HFNC, whether HFNC cause harm to ELBW babies and some other areas such as in improving quality of life to palliative patients by enabling home therapy and whether it is possible to deliver aerosol medications effectively during HFNC. There is also need for long term follow up of babies who received HFNC in the neonatal unit and post term babies with severe BPD who sometimes spend weeks on HFNC to assess effects on lung function and respiratory health.
6.5 My Personal Reflections about This Work

Personally, I have gained several important skills in conducting research from this project. The process of conceptualising the ideas into an ethically acceptable and practically implementable methodology in a protocol was an educational experience. I found that it is important to learn the skills of ‘thinking ahead’ to work out the likely issues, problems and seeking solutions to these issues. I had many long hours of physiology discussion with my supervisors, which helped improve my understanding of some of the difficult concepts involved.

The rigorous ethical approval process helped in improving my own understanding of what these investigations would mean to the ultimate stake holders in the study ‘the preterm neonates’. The research equipment and materials can be expensive and I learned that the process of convincing a funding source to provide financial support can be quite challenging. I needed to clearly know the likely benefits this research would give, to convince a committee to part with some of their money. The support structure and monitoring process of hospital trust showed me that at the core of this hospitals’ aim was patient safety and the research governance team was thorough in their evaluation before giving the permission to conduct this research.

The respiratory physiology investigations, especially in small preterm babies are challenging to conduct. I feel there is an immense need in developing miniature diagnostic tools particularly sensors and transducers which can be incorporated to the routine devices such as nasogastric tube for example, to measure oesophageal pressures. I read during my literature review the versatility of optical fibres and felt it was applicable for some of the equipment we needed. There is also need for developing the technology and improve the quality of data in non-invasive lung function measuring methods in infants.

By doing this project, I have improved my skills in research and I feel more confident with my research skills to pursue my interest, respiratory physiology and lung function in infants.
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**Study** of nasopharyngeal pressures, **tidal breathing** indices and inspired gas concentrations during **High Flow Nasal Cannula** (HFNC) and Continuous Positive Airway Pressure (CPAP) treatment in preterm neonates

**PROTOCOL**

What are the physiological effects of HFNC in neonates?

**VERSION 6**

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Study of nasopharyngeal pressures, tidal breathing indices and inspired gas concentrations during High Flow Nasal Cannula (HFNC) and CPAP treatment in neonates

1. INTRODUCTION, BACKGROUND AND RATIONALE

1.1 Introduction:
Raising airway pressure is one of the most important interventions at the disposal of clinicians treating patients with respiratory failure. In premature infants CPAP and HFNC are non-invasive techniques to raise mean airway pressure when intubation is not required. It is not clear how clinicians choose between these techniques and there is little data comparing the physiological effect of these popular treatments.

HFNC systems have achieved widespread acceptance in modern neonatal intensive care units (1-3). HFNC is effective in a variety of clinical applications (4-7) and is becoming popular with nurses, parents and clinicians. Despite HFNC’s popularity its mechanism of action is not well understood with a limited number of studies published in the literature (8). Neonates with ELBW are getting HFNC support with flow rates of up to 8 litres per minute with no robust data about airway pressures delivered in these smaller infants. Although there are some observational data, concerns remain of inadvertent high airway pressures particularly in smaller infants (9-11). There is no consistent data to guide what flow and inspired oxygen should be prescribed and how the relationship between these variables should be adjusted in individual infants.

1.2 Background:
We know that HFNC produces a degree of positive distending pressure (11). However, it is not continuously measured and is affected by flow rate, leakage via the mouth, patient weight and nasal cannula size (5, 12-14). The airway pressures have been studied by various investigators. Methods used to determine distending pressure, include measurement of intrapharyngeal, oesophageal, oral and tracheal pressures (15).
By measuring intraoropharyngeal pressures, Spence et al. found that increasing HFNC flows cause an increase in pressure. They noted that flows above 3L/minute produced significant pressures, and a flow of 5L/minute produced an average pressure equivalent to approximately 4.8 cm H2O of CPAP in 14 preterm neonates (11). Similar results were obtained by Wilkinson et al. in 18 preterm neonates on HFNC that pharyngeal pressure increased with flow rate and decreased with weight (15).

A few observational studies have looked at oesophageal pressures generated in HFNC. The earlier studies however used either unheated or unhumidified HFNC devices (5, 9). Sreeman et al. measured end-expiratory oesophageal pressure to compare the efficacy of HFNC and CPAP for apnoea of prematurity in 40 preterm neonates (5). HFNC flows of as little as 1 to 2.5L/min produced positive distending pressures up to 8cm H2O and the pressure generated depended on patient weight. According to their findings, a flow of 1.6L/min in a 1000g baby and 1.3L/min in a 500g baby would produce equivalent distending pressures to 6cm H2O of CPAP (5).

Subsequently, the end-expiratory oesophageal pressures reported by Lampland et al. in an observational study of 15 preterm infants with stable RDS were much lower than 6cm H2O of CPAP, even with flows up to 6L/minute with a closed mouth (16). Also they used different method of oesophageal pressure measurement and modern heated and humidified HFNC device compared to Sreeman et al. This may explain some of the differences in results (17). Whilst using modern heated and humidified HFNC device Saslow et al found no significant increases in oesophageal pressure in 18 preterm infants given HFNC at 3, 4 and 5L/min compared with 6cm H2O of CPAP (10).

There are conflicting reports about influence of mouth position on airway pressures in HFNC. Pharyngeal pressure is thought to reduce when the mouth is open, which has previously been demonstrated in patients receiving CPAP (18). Similarly, Kubicka et al. found that no distending pressure was produced in an observational study of 27 neonates with the mouth kept open with any flow rate delivered by HFNC (19). However, with the mouth closed, a relationship was found with weight, flow rate and oral cavity pressure. This relationship was linear in infants less than 1500g, with a maximum pressure of 4.8cm H2O produced by a flow of 4L/min (19). In contrast, Wilkinson et al. found in 18 preterm neonates that for HFNC mouth position had little effect on pharyngeal pressure (15). They felt that the amount of nasal gas leakage with HFNC...
was more important than the degree of mouth leak, particularly in comparison to the tightly fitting nasal prongs used with CPAP, which allow very little gas to escape from the nostrils (15).

Nasal cannula to nare ratio determines the leak at nasal interface. Thus distending pressure is also affected by nasal cannula size (9). Nasal cannula outer diameter (OD) is around 2.4mm in premature and newborn neonates, and 2.4 to 3.7mm in infant and paediatric patients (20). Locke et al. measured oesophageal pressure produced with nasal cannulae of two sizes of OD (9). The 3mm OD nasal cannula delivered positive pressures with a mean of 9.8cm H₂O at a flow of 2L/min in infants who were 30 weeks gestation at 28 days of age. The 2mm OD cannula, however, did not deliver any pressure (9). Volko et al. used a simulated model where they optimally sized cannulae for premature, infant and paediatric nares to ensure that they were not occluded (21). With HFNC flows of 2 to 6L/min, the maximum pressure generated was 2cm H₂O, which was not clinically significant. Using a simulated in vitro system Sivieri et al. measured proximal airway pressures delivered by a HFNC system while varying flow and ratio of cannula to nares size (22). Airway pressure increased progressively with increased flow and with nasal prong to nares ratio. They concluded that safe and effective use of HFNC requires careful selection of appropriate nasal prongs for the individual infant even with an integrated pressure relief valve. It is reasonable to assume that very small infants will be more susceptible to increased pressure because of their small nares size.

At the start of inspiration, the nasopharyngeal dead space contains end-expiratory gas, which heats and humidifies inspired air but reduces the efficiency of gas exchange. By washing out this dead space, HFNC improves alveolar ventilation and facilitates carbon dioxide removal (8). Tracheal gas insufflation (TGI) is a method comparable to HFNC that washes out nasopharyngeal dead space with gas inserted by a catheter or endotracheal tube. In ventilated animal models and preterm infants, TGI has been shown to reduce ventilation pressure and volume requirements (8, 14). A reduction in tidal volume, minute ventilation, dead space and PaCO₂ was found in a prospective study of spontaneously breathing hypercapnic adults with chronic obstructive pulmonary disease undergoing weaning of mechanical ventilation (23). In view of these similarities with TGI, HFNC is felt to have similar actions and benefits. There has
been very little work to look at the effects of HFNC and CPAP on washout in premature infants and how this contributes to its mechanism of action.

Tidal ventilation parameters have been used to assess the impact of HFNC on work of breathing (10). Tidal breathing measurements which provide a non-invasive measure of lung function in preterm and term infants are particularly useful to guide respiratory support. Using a new device which employs a new technique of electromagnetic inductance plethysmography (EIP), Pickard et al measured tidal breathing in 49 healthy spontaneously breathing infants between 32 and 42 weeks postconceptional age (PCA). They noted that the weight-corrected tidal volume (VT) and minute volume (MV) decreased with advancing PCA (24).

In another study using similar electromagnetic inductive plethysmography technique, tidal ventilation and breathing pattern were measured and compared simultaneously with pneumotachography in 43 infants either receiving no respiratory support or continuous positive airway pressure (CPAP). Twenty-three infants were receiving CPAP (gestational age 28 ± 2 weeks, mean ± SD) and 20 were breathing spontaneously (gestational age 34 ± 4 weeks). The two methods were in reasonable agreement, with VT (r² = 0.69) ranging from 5 to 23 ml (4–11 ml kg⁻¹) with a mean difference of 0.4 ml and limit of agreement of −4.7 to +5.5 ml (26).

Volusense is a recently developed system using electromagnetic inductive plethysmography technique for evaluating tidal breathing indices in infants. Respiratory measurements are derived from changes in electromagnetic inductance in a wrap-around vest worn by the baby. The vest is disposable and used for one patient only to avoid cross-infections. The vest is made from soft elastic. The vests contain thin conductive coils that are isolated. Thorax and abdominal volumes and volume changes are measured and stored digitally. This allows measurement of tidal volume, respiratory rate and tidal flow volume loops non-invasively and without application of masks or instrumentation of the infant’s airway. The calibration is done with a pretensed and validated cylinder provided with the device (24–26). This has been recently been validated as reliable as pneumotachography and safe in babies of gestation 28 weeks and above (24, 26). The technique is therefore ideal for measuring the effects of HFNC and CPAP on tidal breathing indices non-invasively and may improve our understanding of its mechanism of action. It may
also allow us to detect the effects of varying pressure on Functional residual Capacity (FRC) baseline and improve understanding of the role of pressure on recruitment of lung volume.

1.3 Rationale: Why this study is necessary?

The use of HFNC has spread before large randomised controlled studies have been published to support its use and there are few observational studies regarding its physiological effects, particularly in lower gestation and smaller babies (5, 9-11, 15, 16, 19). This study attempts to accurately measure pressures transmitted to airways in a wide range of premature neonates on HFNC therapy in the range of flow rates currently being used in neonates. In particular we will study infants less than 1000g which have not been extensively studied and are probably at greatest risk for inadvertent high pressure.

Along with airway pressures we will measure a composite physiological assessment of tidal breathing indices, gas exchange and washout effect. This would be the first physiologic study providing details of effects of HFNC on various parameters of neonatal physiology across all gestational age and weights. It may shed light how HFNC works and how to optimise delivery of this popular therapy.

The study will compare HFNC with CPAP and how the techniques differ in their physiological effects on airway pressure, tidal breathing indices, gas exchange and washout and may improve clinicians understanding of the risks and benefits of each therapy.

2. OBJECTIVES

2.1 Primary objective

To understand the effects of HFNC on following aspects of neonatal physiology

1. The nasopharyngeal pressures at range of flows on HFNC therapy.

2. To compare the nasopharyngeal pressures seen with HFNC to that employed with CPAP
devices.

3. To understand the effect of HFNC on wash out of airway dead space and to examine its role in explaining HFNC mechanism of action.

4. To understand the effects of different flows of HFNC on tidal breathing indices and gas exchange.

Research Questions (with Null hypothesis):

1. What are the actual nasopharyngeal pressures in neonates on HFNC therapy?

2. Does HFNC generate higher nasopharyngeal pressures than that employed with CPAP devices in neonates?

3. What effect does HFNC have on wash out of dead space and is this important in explaining HFNC mechanism of action?

4. What effects do different flows of HFNC have on tidal breathing indices and gas exchange?

Null hypothesis:

1. Differing flows of HFNC have little effect on nasopharyngeal pressure.

2. The HFNC does not deliver higher nasopharyngeal pressures than that used in CPAP in neonates with mild to moderate respiratory distress.

3. HFNC has no effect on washing out dead space.

4. HFNC has no effect on tidal breathing indices.
3. STUDY DESIGN

Randomised crossover study

3.1 Primary and secondary outcomes

Primary outcomes
1. Nasopharyngeal pressures generated at HFNC flow rate range of 2-8 L/min.

Secondary outcomes
1. Nasopharyngeal pressures generated at CPAP of 6 cm of water.
2. The effect of changing flow rate of HFNC on following physiological parameters
   a. Oxygen saturation and transcutaneous CO₂
   b. Respiratory rate
   c. Tidal volume and FRC baseline change.
3. The relationship of flow and inspired oxygen concentration on actual laryngeal inspired
   and expired O₂ and CO₂ concentration in HFNC and CPAP.

3.2 Details of study design and procedures
This is a randomised, crossover study. The study design and procedures are summarised in
Figure 1 and described in more detail in subsequent sections.
Figure 1: HFNC Study Flow Chart

Exclusion criteria:
1. Clinically unstable for NIV support
2. A concurrent study that prohibits participation.
3. Current complications like pneumothorax.
4. Known major upper airway, lower respiratory tract, gastrointestinal tract or cardiac anomalies.

Inclusion criteria:
1. NIV support - on CPAP or HFNC
2. Age >5 days

Randomisation

** Exit criteria
Inadequate ventilation - (pH < 7.2 and pCO2 > 10 kPa)

Inadequate oxygenation - (FiO2 < 0.6 and/or increase in FiO2 of 0.2 from baseline to maintain SpO2 > 95%)

Recurrent unprovoked episodes requiring intervention (not self resolving) or one major episode requiring mask ventilation

Nasopharyngeal pressures
O2 & CO2 concentrations
TOSCA CO2 reading
Tidal breathing indices

0-30
30-40
40-50
50-60
60-70
70-80
80-90
90-120

Group 1
CPAP 6cm H2O
HFNC 8 LPM
HFNC 7 LPM
HFNC 6 LPM
HFNC 5 LPM
HFNC 4 LPM
HFNC 3 LPM
HFNC 2 LPM
CPAP 6cm H2O

Group 2

0-30
30-40
40-50
50-60
60-70
70-80
80-90
90-120

Back on original support CPAP or HFNC

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Informed consent

Informed written consent will be sought from a parent after they have been given a full verbal and written explanation of the study. The attending clinical team will also be available to meet with the parents during the intervention period to ensure that they understand the study procedures and continue to consent to participate in the study.

Some preliminary written and verbal information will, whenever possible, be offered to the parents if the baby is likely to be eligible. Additional information will be given once the baby is stable on non-invasive respiratory support.

Further information about the study will continue to be given to parents as and when they request it after the baby has been enrolled into the study. They will also be offered an early appointment with the senior clinician responsible for the baby’s care so they can discuss participation in greater detail. At this stage it would always be made clear to the parents that they remain free to withdraw their baby from the study at any time but that, if they do withdraw their baby, we would ask them for consent to analyse the data that has been already collected.

A senior investigator will be available at all times to discuss concerns raised by parents or clinicians during the course of the study.

Information about the study will continue to be offered to parents after their baby leaves the neonatal unit or dies.

Randomisation

Babies will be randomised onto group 1 (CPAP first followed by HFNC) or group 2 (HFNC first followed by CPAP) by a computer software programme called ‘Quinim’ (27). This will take into account weight-based minimisation during the process of randomisation (27). The babies will be returned back to their original support system at the end of the study.

Baseline assessments

For eligible babies, clinical details will be collected at study entry. This will include details to confirm eligibility including gestational age, type of respiratory support, clinical stability (Appendix 1) over the previous 12 hours and confirmation of a signed parental consent form.
Research Governance

Level of responsibilities of health professionals caring for babies recruited to this study

Babies recruited to the HFNC Study will spend about two hours participating in the study. The baby will be monitored very closely by the research neonatal registrar throughout the study. In addition baby will continue to have routine neonatal observations as per the neonatal unit policy by the clinical team.

The transfer of babies between neonatal units is unlikely to affect this study as it is a short study of 2 hours duration.

3.3 Study Intervention

1. The internal nare diameter will be measured. The ratio of nasal cannula to nare diameter will be noted.

2. A catheter (Gaebic) with pressure transducer and port for gas sampling at the tip will be placed at the nasopharynx or oropharynx by using standard measurement for placing nasopharyngeal airways (Appendix 2). This will be connected to oxygen and CO₂ analyser and electrically isolated excitation amplifier to measure pressure. This method has been previously used in preterm neonates (11, 15). Where possible this will be timed to coincide with routine replacement of feeding tube which will be facilitated at the conclusion of the study. The pressure recording is done when mouth is passive and also with mouth closed gently with a finger pressing on the chin.

3. The Volusense vest will be placed over the infant’s torso. This will be timed to coincide with routine clothing change and will confer little extra handling burden. The device will record tidal volume, tidal flow volume loop, and respiratory rate as well as calculate tidal breathing indices. The device has also been modified to export as an analogue signal tidal volume and flow for simultaneous recording to the multichannel recorder for synchronous recording and to study effect of pressure on FRC baseline.

4. Transcutaneous (TOSCA) sensor will be applied to the baby’s skin to measure carbon dioxide (CO₂) levels.

5. Data recording - All the above measurement will be connected to a multi-channel recorder (Powerlab chart recorder – AD Instruments) that will allow synchronised recording and graphical
presentation of all the above parameters. The following measurements will be made at a sampling frequency of 100Hz.

1. Transcutaneous oxygen saturations.
2. Transcutaneous CO2 levels.
3. Nasopharyngeal pressures.
4. Concentration of CO2 and O2 in nasopharyngeal space during inspiration and expiration.
5. Tidal volume, flow, respiratory rate and FRC baseline.

3.4 Minimisation of bias
1. The recordings are done simultaneously on an electronic chart recorder with no possibility of observer bias.
2. The stability of pressure traces ascertained based on the actual waveforms which can be inspected after recording.

3.5 Duration of study
18 months

3.6 Discontinuation criteria
In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added 2002 and 2004, and updated 2008) and any other applicable regulations, a parent has the right to withdraw their baby from the study at any time and for any reason, without prejudice to the child’s future medical care by the clinician or at the institution, and is not obliged to give his or her reasons for doing so.

The attending clinician may withdraw the baby at any time in the interests of the baby’s health and well-being.

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Babies would be discontinued from study if any of the following occurs:

1. Inadequate ventilation - pH < 7.20 and pCO₂ > 10 kPa

2. Inadequate oxygenation - FiO₂ > 0.6 and/or increase in FiO₂ of 0.2 from baseline to maintain SpO₂ > 91%. (28)

3. Recurrent unprovoked minor apnoea requiring intervention (not self-resolving; > 2 per hour during the study) or one major apnoea requiring positive pressure ventilation (28).

3.7 Accountability of the study treatment

The following equipments will be used for interventions in this study:

1. The HFNC and CPAP devices - This will be the currently available device at neonatal unit.

   Product Name: Fabian therapy. ACUTRONIC Medical Systems AG
   Standards: CE 0124. Fabian Therapy is an equipment class IIB ventilator per European directive. It can provide both CPAP and HFNC therapy.

2. Device for pressure monitoring and gas sampling from nasopharyngeal airway.

   Product Name: Gaeltec catheter tip pressure transducer. Gaeltec Devices Ltd
   Standards: CE 0120
   Safety: EC Certificate full quality assurance system. Certificate GB-12/86323, Gaeltec Devices Limited has been assessed and certified as meeting the requirements of Directive 93/42/EEC on Medical Devices for medical pressure transducers.

3. Device for measuring the tidal breathing indices.

   Product Name: VoluSense Pediatrics

   As this device is going through improvements new certificates for VoluSense Pediatrics are being processed. Declaration and test report for the previous version of this product (known as FloRight) showed its suitability for clinical research.

   Regulatory classifications of the new product are being processed currently.

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MDD Classification: The system shall be classified as Class II A according to MDD.

Electrical Classification: The system shall be classified as Class I, type BF according to IEC 60601-1

System Labeling: Essential Requirements of MDD, Annex I

Safety and effectiveness standards: EN/IEC 60601-1: 2005 and EN/IEC 60601-1-6


Product Name: TOSCA 500 monitor by Radiometer Medical ApS

Standards: CE 0123

Safety: Classified as Instrument Class I, type BF, defibrillator proof, fulfills the requirements of MDD 93/42

3.8 Source data

Source data will comprise:

- Hospital records for the baby’s clinical condition before study.
- Data downloaded from the electronic multi-channel recorder (AD Instruments).

4. SELECTION AND WITHDRAWAL OF STUDY PARTICIPANTS

Approximately 45 babies will be recruited to this study.

4.1 Inclusion criteria

Infants are eligible if:

1. They are less than 37 weeks’ gestation at birth and more than 5 days of age

2. Are on non-invasive respiratory support and

3. The parent(s) have given written informed consent to their baby’s participation
4.2 Exclusion criteria
1. Infants who are clinically unstable and unsuitable for non-invasive respiratory support as judged by attending neonatology consultant clinician.
2. Participation in a concurrent study that prohibits inclusion in other trials
3. Known major upper airway, lower respiratory tract, cardiac or gastrointestinal tract anomaly
4. Current complications such as pneumothorax.

4.3 Withdrawal of participants

Babies may be withdrawn for any of the reasons given in Section 3.6, Discontinuation Criteria. The reason for withdrawal will be recorded on the data collection form. If the baby is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5. TREATMENT OF STUDY PARTICIPANTS

5.1 Description of interventions

Non-invasive respiratory support is given to preterm babies where clinically indicated. The device used will be the standard devices used in participating neonatal unit. The baby will be receiving non-invasive respiratory support either by HFNC or CPAP as deemed appropriate by the attending clinician. The level of support to be given will be individually tailored against the clinical condition of the baby. The standard neonatal policy (Appendix 3) in maintaining baby’s oxygen saturations and clinical stability will be followed.

The interventions will be studied for a total about two hours as described below. After this time the baby will receive the non-invasive support baby was originally administered by the clinical team.

1. The infant must be clinically stable for preceding 12 hours on non-invasive respiratory support
Indications of clinical stability –
i) Stable Oxygen requirement in the previous 12 hours – The FiO2 has not increased more than 0.2 from baseline.

ii) Tolerating feeds

iii) Stable observations including heart rate (100-180 per minute), respiratory rate (30-60 per minute), temperature (36.5-37.5°C)

iv) No signs of infection – evidence of blood culture positive infection and or treatment for active infection

2. Clinical observations as per unit policy (Appendix 3).

3. The baby will be placed into group 1 or group 2 following randomisation.

4. Babies in Group 1

   a) The initial respiratory support will be CPAP at 6 cm of water for 30 minutes. The physiologic measurements will be recorded in the final five minutes.

   b) The respiratory support will be changed to HFNC at 8 L/min for 30 minutes. The physiologic measurements will be recorded in the final five minutes.

   c) Then HFNC flow will be reduced by 1 L/min every 10 minutes within the range of 2-8 L/min. The physiologic measurements are repeated at each flow rate.

   d) After this baby will be returned to original form of respiratory support at the pre study level

5. Babies in Group 2

   a) The initial respiratory support will be HFNC at 8 L/min for 30 minutes. The physiologic measurements will be recorded in the final five minutes.

   b) Then HFNC flow will be reduced by 1 L/min every 10 minutes within the range of 2-8 L/min. The physiologic measurements are repeated at each flow rate.

   c) The respiratory support will be changed to CPAP at 6 cm of water for 30 minutes. The physiologic measurements will be recorded in the final five minutes.

   d) After this baby will be returned to original form of respiratory support at the pre study level.

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6. Adjustment of FiO2

FiO2 will be continued at the same level as pre study entry level. Any desaturations outside the standard target range (91-95%) will be dealt with as per standard neonatal practice (FiO2 increased or decreased by 5% aliquots).

A sustained increase (more than 15 minutes) in FiO2 by 0.2 above baseline or FiO2 > 0.6 will trigger restoration of infant to previous flow rate with no further reduction in flow. The study will continue but these infants will have a reduced range of low flow rates recorded.

6. Total study duration will be around 120 minutes. Respiratory support can be terminated at any point if clinically not indicated. The researcher is an experienced neonatal registrar who will be directly observing the baby throughout the study.

5.2 Concomitant treatments

Throughout the study, the babies may be prescribed concomitant treatments deemed necessary to provide adequate supportive care.

Compliance with protocol

The Chief Investigator will ensure that research registrar administering the intervention will understand how to adhere to the protocol. All stored data can be downloaded and these data will be reviewed to evaluate the process of intervention follows the study protocol.

6 ASSESSMENT OF EFFICACY

The primary outcome measures will be recorded during the study on electronic chart recorder. Any significant respiratory deterioration which results in exit criteria being met will be analysed on a case by case basis by the study team and the data monitoring committee. Each baby will undergo monitoring as per the current neonatal unit standards (Appendix 3).

7 ASSESSMENT OF SAFETY

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Safety will be assessed continuously during each baby’s study in the neonatal unit. Any adverse events which require expedited reporting will follow the standard system.

Other outcomes, which may also be considered safety outcomes, such as death or early neonatal morbidity, but which are anticipated outcomes for this group of very preterm babies, will be recorded on the data collection system and will be reviewed by the Data Monitoring Committee at regular intervals throughout the study.

8 STATISTICS

We aim to enrol 45 preterm (Less than 37 completed week’s gestation) babies who meet criteria for non-invasive respiratory support. The measurements will be done on HFNC and CPAP.

Babies will be stratified into three groups (15 babies in each group) based on weight at the time of study

- less than 1000 grams,
- 1000 to 1500 grams and
- above 1500 grams.

Initially 5 babies from the weight category of >1500 grams will be studied. The data will be compared to the pressures reported in earlier studies (7, 11) where the nasopharyngeal pressure monitoring has been done safely in this group.

Sample size calculation

We used the data from previous studies which measured nasopharyngeal pressures with HFNC (11). As a representative number from the range of flows we used nasopharyngeal pressures seen with 4 and 5 litres per minute flow of HFNC.
Power and Sample Size

This was calculated using data from previous studies using Minitab statistical software tool.

From a previous study (11) data was analysed for flow rate 4 & 5 litres per minute. Standard deviation of paired differences was calculated.

Descriptive Statistics: diff

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>N*</th>
<th>Mean</th>
<th>SE Mean</th>
<th>StdDev</th>
<th>Minimum</th>
<th>Q1</th>
<th>Median</th>
<th>Q3</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>diff</td>
<td>8</td>
<td>0</td>
<td>0.625</td>
<td>0.156</td>
<td>0.440</td>
<td>0.200</td>
<td>0.325</td>
<td>0.500</td>
<td>0.775</td>
<td>1.600</td>
</tr>
</tbody>
</table>

Paired t Test

Testing mean paired difference = 0 (versus ≠ 0)
Calculating power for mean paired difference = difference
α = 0.05 Assumed standard deviation of paired differences = 0.4

There is data from a previous study (15) of likely average increase in pressure between flows of 0.8 cm H2O for each 1 litre per minute increase in flow. Increasing this ability to detect pressure difference to 0.4 cm H2O, we get

<table>
<thead>
<tr>
<th>Difference</th>
<th>Sample Size</th>
<th>Target Power</th>
<th>Actual Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>12</td>
<td>0.8</td>
<td>0.817409</td>
</tr>
</tbody>
</table>

Therefore we estimated 15 babies in each group will ensure adequate sample size to detect pressure difference of 0.4 cm between flows with 80% power and type 1 error of 0.05. The addition of 3 babies will make up for any drop outs during the study.

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We plan to randomise using computer software called 'Q Minim' minimisation programme (27) and allocate babies randomly either to GROUP 1 (CPAP followed by HFNC) or to GROUP 2 (HFNC followed by CPAP).

The primary outcome and secondary outcomes will be analysed as follows.

A descriptive analysis will be performed to calculate the mean and standard deviations of the nasopharyngeal pressures and other physiological parameters generated on CPAP at the pressures 6 cm H2O and HFNC at the varying flow rates of 2, 3, 4, 5, 6, 7 and 8 litres per minute. A regression analysis will be performed to assess the correlation between the nasopharyngeal pressures generated on the HFNC and CPAP. Paired analyses (t-tests) will be used to compare nasopharyngeal pressures between the varying flow rates on HFNC to determine if there is a statistical significance between the different nasopharyngeal pressures measured between each incremental increase in flow rate. A value of P<0.05 will be considered statistically significant.

The data will be examined by chief investigator and study statistician regularly to assess for completeness. In case of any withdrawal during the study the data collected until the point of withdrawal will be used for analysis.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit study-related monitoring, audit, review by DMC/Independent Ethics Committee and regulatory inspection.

10 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Compliance with protocol will be ensured by a number of procedures:
10.1 Site set-up and training
The chief investigator (CI) will ensure that the research registrar is given training in using the study devices to the required standard. Regular CI visits will be made to ensure adherence to the protocol and to deal with any specific issues.

10.2 Data collection, processing and monitoring
All study data are:
- Collected using multichannel electronic chart recorder (Power lab – AD instruments)
- Processed and monitored at the Research Unit, Neonatal Medicine, Royal Victoria Infirmary, Newcastle, UK.
- Screened for out-of-range data

10.3 Statistical monitoring
All data are monitored for consistency and quality by the research team. The team reviews patterns of recruitment, disease severity among study populations, use of study devices, time of recruitment, etc. The team will intermittently examine some fields from the data which may include measures of eligibility criteria, interventions given after study entry and outcome.

The Chief Investigator with the research team will review the results generated for logic and for any patterns or problems. Outlier data will be investigated.

The Chief Investigator and study statistician will decide if any action needs to be taken.

10.4 On-site monitoring
- A random sample of cases is monitored at source as part of Source Document Verification.

10.5 Data Monitoring Committee (DMC)
The DMC will meet regularly throughout the study period to receive and review the progress and accruing data of this study and provide advice on the conduct of the trial to the research team involved in the study. The DMC will consist of an independent neonatologist and an independent respiratory paediatrician.
11 ETHICS

11.1 Declaration of Helsinki
The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004 and updated 2008).

11.2 MRC Guidelines for Good Clinical Practice (GCP)
The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the MRC GCP guidelines which are based on ICH Guidelines for GCP (CPMP/ICH/135/95) July 1996.

11.3 Informed consent
The study will be discussed and written information will be presented to the baby's parent detailing no less than: the exact nature of the study; the implications and constraints of the protocol. It will be clearly stated that the parents are free to withdraw their baby from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Babies are only eligible for the trial if they are less than 37 weeks gestation and are stable on non-invasive respiratory support. Therefore, the parent has plenty of time to consider the information, and the opportunity to question the Chief Investigator and other clinical staff to decide whether they will participate in the study. However, once the baby is enrolled, information about the study will continue to be given as and when parent's request, and they will be offered an appointment with the senior clinician responsible for the baby's care to discuss participation in detail.

Written informed consent will be obtained in accordance with the requirements of the local ethical committee. A copy of the signed informed consent will be given to the parents. A further copy will be retained in the baby’s medical notes, a copy will be retained by the Chief Investigator and a final copy will be sent to the Research Centre.

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11.4 Independent Ethics Committee
A copy of the protocol, proposed informed consent form, and written participant information will be submitted to an Independent Ethics Committee for written approval.
The Chief Investigator will submit and, where necessary, obtain approval from the Independent Ethics Committee for all subsequent protocol amendments and changes to the informed consent document.
The Chief Investigator will notify deviations from the protocol or SAEs occurring at the site to the sponsor and will notify the Independent Ethics Committee of these in accordance with local procedures.

11.5 Participant confidentiality
The Chief Investigator will ensure that the baby’s information is kept confidential. The baby will be identified by name (consent will have been given by the parent(s)) and study number on the data collection form. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998).

12 DATA HANDLING AND RECORD KEEPING
All study data will be entered into electronic database during collection and stored in the study laptop. The laptop will have password to restrict access to the raw data.
Data collected on the data collection forms will be stored in an electronic database in which the baby will be identified by a study specific number. The baby’s name and any other identifying details will be stored in a separate database linked only by the study number.
Data entered will undergo statistical analysis to produce the results of the study.
Standard operating procedures as directed by trust R&D will be followed for the collection and handling of data received.
Storage will be on a restricted area of the study computer. The study computer will be kept in a secure location and access will be restricted to a few named individuals. Data will be processed on a workstation by authorised staff.

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13 FINANCING AND INSURANCE

The following funding applications are in progress

1. Special Trustees, Newcastle Upon Tyne hospitals NHS Trust (application in process)

2. Puffin Appeal, Caring for children with breathing disorders, Newcastle, UK.

An application to The Newcastle Hospitals NHS Foundation NHS Trust has been made for sponsorship for research.

14 PUBLICATION POLICIES

The Chief Investigator will be co-ordinating dissemination of data from this study. All publications using data from this study to undertake original analyses will be submitted to the research team for review before release.

Acknowledgement will include members of the study team, and clinical staff. All contributors to the study will be listed at the end of the report, with their contribution to the study identified.

Parents will be sent a summary of the final results of the study, which will contain a reference to the full paper. A copy of the journal article will be available on request from the research team at Royal Victoria Infirmary, Newcastle.
15 REFERENCES


8.2 Appendix 2. IRAS integrated Research Application Form

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?
   - Yes
   - No

2b. Please answer the following question(s):
   a) Does the study involve the use of any ionising radiation?
      - Yes
      - No
   b) Will you be taking new human tissue samples (or other human biological samples)?
      - Yes
      - No
   c) Will you be using existing human tissue samples (or other human biological samples)?
      - Yes
      - No
   d) Will the study involve any other clinical procedures with participants (e.g. MRI, ultrasound, physical examination)?
      - Yes
      - No

3. In which countries of the UK will the research sites be located? (Tick all that apply)

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NHS SSI

☐ England
☐ Scotland
☐ Wales
☐ Northern Ireland

3a. In which country of the UK will the local NHS R&D office be located:

☒ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ This study does not involve the NHS

4. Which review bodies are you applying to?

☒ NHS/HSC Research and Development offices
☐ Social Care Research Ethics Committee
☒ Research Ethics Committee
☐ National Information Governance Board for Health and Social Care (NIGB)
☐ National Offender Management Service (NOMS) (Poo & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

☒ Yes ☐ No

6a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

☒ Yes ☐ No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP)

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

☒ Yes ☐ No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications

6. Do you plan to include any participants who are children?

☒ Yes ☐ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

☒ Yes ☐ No

Answer: Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of
8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

- [ ] Yes
- [ ] No

9. Is the study or any part of it being undertaken as an educational project?

- [ ] Yes
- [ ] No

Please describe briefly the involvement of the student(s):

Dr. Copakasho has registered this project with Newcastle University for an MPhil. He is involved in literature review, writing protocol, consenting and conducting the research. He will be involved in writing up the research outcomes and presenting the findings. He will be writing the thesis for the fulfillment of MPhil.

Dr. Alan Fenton will be the Academic Supervisor for this educational qualification.

9a. Is the project being undertaken in part fulfillment of a PhD or other doctorate?

- [ ] Yes
- [ ] No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

- [ ] Yes
- [ ] No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

- [ ] Yes
- [ ] No
**Site-Specific Information Form (NHS sites)**

Is the site hosting this research a NHS site or a non-NHS site? NHS sites include Health and Social Care organisations in Northern Ireland. The sites hosting the research are the sites at which or through which research procedures are conducted for NHS sites, this includes sites where NHS staff are participants.

- NHS site
- Non-NHS site

This question must be completed before proceeding. The form will customise the form, disabling questions which are not relevant to this application.

One Site-Specific Information Form should be completed for each research site and submitted to the relevant R&D office with the documents in the checklist. See guidance notes.

---

**The data in this box is populated from Part A:**

**Title of research:**
A study of nasopharyngeal pressures, tidal breathing indices and inspired gas concentrations during High Flow Nasal Cannula (HFNC) and Continuous Positive Airway Pressure (CPAP) treatment in preterm neonates.

**Short title:**
Study of respiratory physiology during HFNC in preterm neonates

**Chief Investigator:**
Dr. Christopher O'Brien

**Name of NHS Research Ethics Committee to which application for ethical review is being made:**
NNT1 REC-Newcastle and North Tyneside 1 REC Committee No-East (HEALTH RESEARCH AUTHORITY)

**Project reference number from above REC:**
54/NE/0093

---

1.1. Give the name of the NHS organisation responsible for this research site

Newcastle upon Tyne Hospitals NHS Foundation Trust

---

1.3. In which country is the research site located?

- England
- Wales
- Scotland
- Northern Ireland

---

1.4. Is the research site a GP practice or other Primary Care Organisation?

- Yes
- No

---

2. Who is the Principal Investigator or Local Collaborator for this research at this site?
3. Please give details of all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

Please list all locations/departments etc. where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Give details of any research procedures to be carried out off site, for example in participants' homes.

<table>
<thead>
<tr>
<th>Location</th>
<th>Activity/Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Neonatal Unit, Leazes wing, Royal Victoria Infirmary</td>
<td>1. Study participants are neonates already admitted in neonatal unit.</td>
</tr>
<tr>
<td>2 Neonatal Research Office, Old Ward 1, Royal Victoria Infirmary</td>
<td>1. Storage of data and study files in locked facility</td>
</tr>
</tbody>
</table>

6. Please give details of all other members of the research team at this site.

<table>
<thead>
<tr>
<th>Title Forename/Initials Surname</th>
<th>Work E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Belkiran Gopakale</td>
<td><a href="mailto:sakiran.gopakale@nuth.nhs.uk">sakiran.gopakale@nuth.nhs.uk</a></td>
</tr>
</tbody>
</table>

145881/637615/6/632/230524/30394G
NHS SSI

Employing organisation: Newcastle upon Tyne Hospitals NHS Foundation Trust
Post: Trust doctor in Neonates
Qualifications: MBBS, MD, MRCPCH
Role in research team: researcher

a) Approximately how much time (approximately) will this person allocate to conducting this research? Please provide your response in terms of Whole Time Equivalents (WTE). Ranging from 0.1 to 0.2 WTE (4-8 hours per week)

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

2

Title Forename/Initials Surname
Dr. Alan Fenton
Work Email: alan.fenton@nuth.nhs.uk
Employing organisation: Newcastle upon Tyne Hospitals NHS Foundation Trust
Post: Consultant Neonatologist
Qualifications: MBBS, MD, MRCP, FRCP
Role in research team: researcher

a) Approximately how much time (approximately) will this person allocate to conducting this research? Please provide your response in terms of Whole Time Equivalents (WTE). < 0.1 WTE (1-2 hours per week)

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

3

Title Forename/Initials Surname
Dr. Sundeep Harigopal
Work Email: sundeep.harigopal@nuth.nhs.uk
Employing organisation: Newcastle upon Tyne Hospitals NHS Foundation Trust
Post: Consultant Neonatologist
Qualifications: MBBS, MRCP
Role in research team: researcher

a) Approximately how much time (approximately) will this person allocate to conducting this research? Please provide your response in terms of Whole Time Equivalents (WTE). < 0.1 WTE (1-2 hours per week)
b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?  

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

4

Title Forename/Initials Surname  
Dr Malcolm Brodie

Employing organisation  
Newcastle upon Tyne Hospitals NHS Foundation Trust

Post  
Consultant Respiratory Paediatrician

Qualifications  
MBBS, MRCPCH, FHD

Role in research team:  
researcher

a) Approximately how much time (approximate) will this person allocate to conducting this research?  

<0.1 WTE (1-2 hours per week)

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation?  

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

6. Does the Principal Investigator or any other member of the site research team have any direct personal involvement (e.g. financial, share-holding, personal relationship etc) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?  

☐ Yes  ☐ No

7. What is the proposed local start and end date for the research at this site?  

Start date: 01/09/2014
End date: 31/10/2015
Duration (Months): 17

8.1. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. (These include seeking consent, interviews, non-clinical observations and use of questionnaires.)

Columns 1-4 have been completed with information from A19 as below:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention would have been routinely given to participants as part of their care, how many of the total would have been routine?
3. Average time taken per intervention (minutes, hours or days)
4. Details of who will conduct the procedure and where it will take place

Please complete Column 5 with details of the names of individuals or names of staff groups who will conduct the procedure at this site.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

145801/637615/6/023/2002/300346
2-2. Will any aspects of the research at this site be conducted in a different way to that described in Part A or the protocol?

☐ Yes  ☐ No

If Yes, please note any relevant changes to the information in the above table.

Are there any changes other than those noted in the table?

9-1. Give details of any clinical intervention(s) or procedures to be received by participants as part of the research protocol. (These include use of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.)

Columns 1-4 have been completed with information from A19 as below:
1. Total number of interventions to be received by each participant as part of the research protocol
2. If this intervention would have been routinely given to participants as part of their care, how many of the total would have been routine?
3. Average time taken per intervention (minutes, hours or days)
4. Details of who will conduct the procedure, and where it will take place

Please complete Column 5 with details of the names of individuals or names of staff groups who will conduct the procedure at this site.

<table>
<thead>
<tr>
<th>Intervention or procedure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring breathing rate</td>
<td>6</td>
<td>2</td>
<td>continuous recording</td>
<td>Dr. Gopalakajee - Neonatal Registrar At Neonatal Unit, Royal Victoria</td>
<td></td>
</tr>
<tr>
<td>Measuring transcutaneous oxygen saturation levels</td>
<td>8</td>
<td>2</td>
<td>continuous recording</td>
<td>Dr. Gopalakajee - Neonatal Registrar At Neonatal Unit, Royal Victoria</td>
<td></td>
</tr>
<tr>
<td>Measuring transcutaneous carbon dioxide levels</td>
<td>8</td>
<td>0</td>
<td>continuous recording</td>
<td>Dr. Gopalakajee - Neonatal Registrar At Neonatal Unit, Royal Victoria</td>
<td></td>
</tr>
<tr>
<td>Measuring nasopharyngeal pressures</td>
<td>8</td>
<td>0</td>
<td>5 minutes</td>
<td>Dr. Gopalakajee - Neonatal Registrar At Neonatal Unit, Royal Victoria</td>
<td></td>
</tr>
</tbody>
</table>

8
145881/8378158/632/230524/303948
<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Value</th>
<th>Time</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring Nasopharyngeal oxygen and carbon dioxide concentrations</td>
<td>5</td>
<td>0</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Measuring tidal volume</td>
<td>5</td>
<td>0</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Babies in group 1 - CPAP 6cm of water for 30 minutes Then HFNC 8 L/min for 30 minutes Then change HFNC flow from 8 litres per minute to 2 litres per minute</td>
<td>2</td>
<td>1</td>
<td>2 hours</td>
</tr>
<tr>
<td>Babies in group 2 - HFNC 8 L/min for 30 minutes Then change HFNC flow from 8 litres per minute to 2 litres per minute Then CPAP 6cm of water for 30 minutes</td>
<td>2</td>
<td>1</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

9.2. Will any aspects of the research at this site be conducted in a different way to that described in Part A or the protocol?  

☐ Yes ☐ No

If Yes, please note any relevant changes to the information in the above table.

Are there any changes other than those noted in the table?

10. How many research participants/samples is it expected will be recruited/obtained from this site?

45

11. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study.

Potential participants will be identified from admissions register.
The research registrar will approach the parents.

12. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?

<table>
<thead>
<tr>
<th>Name</th>
<th>Expertise/training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Gopalakaje</td>
<td>GCP training Currently obtaining informed consent for NHR portfolio studies.</td>
</tr>
<tr>
<td>Dr. Fennon</td>
<td>GCP training</td>
</tr>
</tbody>
</table>
16.1. Is there an independent contact point where potential participants can seek general advice about taking part in research?

No

18. Are there any changes that should be made to the generic content of the Information Sheet to reflect site-specific issues in the conduct of the study? A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.

No

Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. Unless indicated above, this must be the same generic version submitted (unapproved) by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).

17. What local arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters etc.)

Use of interpreters as per trust policy to be used in situations of parents unable to understand/speak English

19. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

The research protocol has a very safe exit criteria with very tight clinical criteria to stop the study if baby develops clinical distress during the study.

The research key investigator is present throughout the duration of study over 2 hours closely monitoring the baby.

The baby will continue to be monitored by the staff nurse allocated as per standard neonatal unit practice during the study.

The service of experienced neonatal consultant is available in the unlikely event of clinical deterioration and baby needs further support during the study.

This research is not expected to cause significant distress or discomfort to participants.

20. What are the arrangements for the supervision of the conduct of the research at this site? Please give the name and contact details of any supervisor not already listed in the application.
21. What external funding will be provided for the research at this site?

- Funded by commercial sponsor
- Other funding
- No external funding

Please give details of the funding:

Special Trustees Charity based in Newcastle Upon Tyne Hospitals NHS Foundation Trust

<table>
<thead>
<tr>
<th>Type of funding</th>
<th>Details (including breakdown over years if appropriate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Block grant</td>
<td>36000 pounds for the purchase of study equipments</td>
</tr>
<tr>
<td>(ii) Per participant</td>
<td></td>
</tr>
<tr>
<td>(iii) Other (give details)</td>
<td></td>
</tr>
</tbody>
</table>

Which organisation will receive and manage this funding?

Department of Respiratory Medicine, Newcastle Upon Tyne Hospitals NHS Foundation Trust.

23. Authorisations required prior to R&D approval

The local research team are responsible for contacting the local NHS R&D office about the research project. Where the research project is proposed to be coordinated centrally and therefore there is no local research team, it is the responsibility of the central research team to instigate this contact with local R&D.

NHS R&D offices can offer advice and support on the set-up of a research project at their organization, including information on local arrangements for support services relevant to the project. These support services may include clinical supervisors, line managers, service managers, support department managers, pharmacy, data protection officers or finance managers depending on the nature of the research.

Obtaining the necessary support service authorisations is not a pre-requisite to submission of an application for NHS research permission, but all appropriate authorisations must be in place before NHS research permission will be granted. Processes for obtaining authorisations will be subject to local arrangements, but the minimum expectation is that the local R&D office has been contacted to notify it of the proposed research project and to discuss the project's needs prior to submission of the application for NHS research permission via IRAS.

Failure to engage with local NHS R&D offices prior to submission may lead to unnecessary delays in the process of this application for NHS research permissions.

Declaration:

☑ I confirm that the relevant NHS organisation R&D office has been contacted to discuss the needs of the project and local arrangements for support services. I understand that failure to engage with the local NHS R&D office before submission of this application may result in unnecessary delays in obtaining NHS research permission for this project.

Please give the name and contact details for the NHS R&D office staff member you have discussed this application with:

Please note that for some sites the NHS R&D office contact may not be physically based at the site. For contact details refer to the guidance for this question.
The information in this form is accurate to the best of my knowledge and I take full responsibility for it.

I undertake to abide by the ethical principles underpinning the World Medical Association’s Declaration of Helsinki and relevant good practice guidelines in the context of research.

If the research is approved by the man REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application, of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.

If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.

I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guideline relating to the conduct of research.

I undertake to disclose any conflicts of interest that may arise during the course of this research and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.

I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.

I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation’s Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.

I undertake to complete any progress and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.

I undertake to maintain a project file for this research in accordance with the NHS organisation’s policy.

I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation’s policy for reporting and handling of adverse events.

I understand that information relating to this research, including the contact details on this application, will be held by the R&D office and may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

The section was signed electronically by Dr Chris O’Brien on 22/05/2014 15:59.

Job Title/Post: consultant paediatrician
Organisation: nuth
Email: christopher.obrien@nuth.nhs.uk
8.3 Appendix 3. Ethics Committee Approval Letter

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 1
TEDCO Business Centre
Room 002
Rolling Mill Road
Jarrow
NE32 3OT
Telephone: 0191 428 2665

6 June 2014

Dr Salkiran Gopalakaja
Neonatal Registrar
Newcastle upon Tyne Hospitals NHS Foundation Trust
Department of Neonatal Medicine
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Dear Dr Gopalakaja

Study title: A study of nasopharyngeal pressures, tidal breathing
indices and inspired gas concentrations during High
Flow Nasal Cannula (HFNC) and Continuous Positive
Airway Pressure (CPAP) treatment in preterm neonates

REC reference: 14/NE/0063
IRAS project ID: 145881

Thank you for your letter of 21 May 2014, responding to the Committee’s request for further
information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC.
A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA
website, together with your contact details. Publication will be no earlier than three months
from the date of this opinion letter. Should you wish to provide a substitute contact point,
require further information, or wish to make a request to postpone publication, please
contact the REC Manager Gillian Mayer (nrescommittee.northeast-
newcastleandnorthtyneside@dh.nn-net.net)

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a Favourable ethical opinion for the
above research on the basis described in the application form, protocol and supporting
documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of
the study,

A Research Ethics Committee established by the Health Research Authority
You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at [http://www.reform.nhs.uk](http://www.reform.nhs.uk).

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity, e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable permission applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHSASC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).
Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Governing letter on headed paper</td>
<td>Letter from Dr Gopalaaje</td>
<td>21 March 2014</td>
</tr>
<tr>
<td>Governing letter on headed paper [S Gopalaaje]</td>
<td></td>
<td>21 May 2014</td>
</tr>
<tr>
<td>GP/consultant information sheets or letters [GP letter]</td>
<td>1-29042014</td>
<td>29 April 2014</td>
</tr>
<tr>
<td>Investigator CV</td>
<td>C O’Brien (£)</td>
<td></td>
</tr>
<tr>
<td>IRAS Checklist XML [Checklist_20052014]</td>
<td></td>
<td>29 May 2014</td>
</tr>
<tr>
<td>Letter from funder</td>
<td></td>
<td>26 April 2014</td>
</tr>
<tr>
<td>Letter from statistician</td>
<td>Email from Kim Pearce</td>
<td></td>
</tr>
<tr>
<td>Other: CV for academic supervisor</td>
<td>A Fonton</td>
<td></td>
</tr>
<tr>
<td>Other: CV for key investigator</td>
<td>M Brodie</td>
<td></td>
</tr>
<tr>
<td>Other: CV for key investigator</td>
<td>S Harigopal</td>
<td></td>
</tr>
<tr>
<td>Other: CV for student investigator</td>
<td>S Gopalaaje</td>
<td></td>
</tr>
<tr>
<td>Participant consent form: Parent</td>
<td>3-29042014</td>
<td>29 April 2014</td>
</tr>
<tr>
<td>Participant information sheet: Parent</td>
<td>5-29042014</td>
<td>29 April 2014</td>
</tr>
<tr>
<td>REC Application Form [REC_Form_20052014]</td>
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<td>23 May 2014</td>
</tr>
<tr>
<td>Referee’s report or other scientific critique report [Internal review]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referee’s report or other scientific critique report [External review]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research protocol or project proposal [HFNC study Protocol]</td>
<td>8-29042014</td>
<td>29 April 2014</td>
</tr>
<tr>
<td>Response to Request for further information</td>
<td>S Gopalaaje</td>
<td>21 May 2014</td>
</tr>
</tbody>
</table>

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

A Research ethics Committee established by the Health Research Authority
Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hrq-trainin/

14/NE/0083 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Professor Philip Preshaw
Chair

Email:nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Dr Christopher O'Brien - Consultant in Paediatric Respiratory Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Mr Andrew Johnston – Joint Research Office, Newcastle upon Tyne Hospitals NHS Foundation Trust

A Research Ethics Committee established by the Health Research Authority

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8.4 Appendix 4. Patient Information Sheet

Information leaflet for Parents

A study of respiratory physiology during High Flow Nasal Cannula (HFNC) treatment in preterm neonates

Summary

We are studying the effects of High Flow Nasal Cannula (HFNC) therapy on babies’ breathing.

Your baby is currently on HFNC support or may need it soon. We would like to give you the opportunity to think about whether you would like your baby to take part in this study.

Premature babies often need help with their breathing and HFNC is often used to provide this help. We know it is effective but exactly how it works is not well understood. We would aim to make some breathing measurements when your baby is on HFNC. This could help us use HFNC more effectively in the future.

If, after reading this and discussing the study with the doctors and nurses in the neonatal unit, you decide to let your baby take part we will ask you to sign a consent form. Your baby will then be entered into the study. Your baby will require no extra blood tests because they are in the study.

Whether or not you decide to let your baby take part in the study is entirely up to you. You can withdraw your baby from the study at any time.

If you decide not to take part this will not in any way affect the care your baby receives.

The rest of this leaflet explains the study in more detail and describes what being in the study would mean for you and your baby.
What is the purpose of the study?

Babies with breathing difficulties are often helped to breathe by using either Continuous Positive Airway Pressure (CPAP) or High Flow Nasal Cannula (HFNC). These are breathing systems that blow gas through the baby's nose and the pressure this generates makes it easier for the baby to breathe. With the CPAP machine we can set this pressure, but with the HFNC machine we can only set how much gas (flow) goes in every minute. This means the pressure that the HFNC machine generates may be different in different babies. This flow generates some pressure when the baby breathes but may also help by "washing away" waste gas (carbon dioxide) from your baby's lungs.

HFNC is being used in many UK neonatal units. Studies have shown it is effective in helping breathing, but because of the different pressures generated we are uncertain regarding its effect on how fast or how hard your baby is breathing.

Therefore, this study aims to accurately measure the pressures generated by HFNC and CPAP as well as how this affects carbon dioxide and breath size.

Why am I being asked to participate in the study?

You are being asked to participate because your baby was born at earlier than 37 weeks. In babies who were born earlier than 37 weeks, we are approaching all parents if their baby needs breathing help with HFNC or CPAP to see if they would like their baby to take part in the study. Although the results may not directly benefit your baby, they may help us provide better care for babies who need breathing support in the future.

What will happen to my baby if I agree to take part in the study?

When a baby is admitted to the special care baby unit, nurses monitor breathing rate and oxygen levels, and babies are often fed by nasogastric or orogastric tube. This study is designed to collect the additional information we require by using similar procedures to what will happen to your baby during routine care. There are no blood tests. Your baby's involvement in the study will last about two hours. We will take measurements as part of your baby's routine care so that disturbance to your baby is minimised. Your baby will be monitored very closely by the medical and nursing staff in the neonatal intensive care unit throughout this time and in accordance with standard practices on the neonatal unit.

We will record three types of measurements:

1. Measuring your baby's airway pressure and breath carbon dioxide
   A small plastic tube (catheter) will be either inserted into your baby's nose or via mouth to sit just above the voice box. This will record the airway pressure and the concentration of carbon dioxide and oxygen in each breath. The procedure is painless and is the same as inserting a feeding tube (but is much shorter than a feeding tube). We will time the study to be at the same time as your baby is due a routine feeding tube change.
2. Measuring baby’s breath size
We will use a device called a Volusense Vest to measure your baby’s breath size. This looks like an item of clothing and will be put on when your baby is due their routine care. The vest will be removed as soon as the study is completed in about 2 hours.

Picture 1 - Volusense Vest

3. Measuring baby’s blood carbon dioxide
To measure blood carbon dioxide levels, we use a device called a TOSCA probe. This is placed on the skin surface like the oxygen saturation probe that is already being used routinely. This measures the levels of carbon dioxide in the blood. It works by gently warming the skin so you may see a red mark for about an hour afterwards but it will not burn or permanently mark your baby’s skin.

Picture 2 - TOSCA probe attached to skin

Once all the monitoring devices are attached and your baby is settled we can start the study. Your baby will be randomised to either receive CPAP first, and then HFNC, or will be randomised to receive HFNC first, and then CPAP. During the period of time that your baby is receiving breathing assistance from each machine, we will adjust the air flow rates in a range that is used in routine practice for 10 minute periods for each flow rate.

If your baby shows any signs of significant distress more than would be expected in routine practice or if your baby’s blood oxygen levels deviate from normal we will adjust the flow rates to bring things back to normal.

SG/MB/SH/AF/CIO
Version 5
29/04/2014
Does my baby have to take part?
You do not have to agree to your baby taking part in this study. If you decide not to take part, your baby will receive usual care. If you do decide that you would like your baby to take part and then change your mind later, your baby can be taken out of the study at any time, without having to give a reason. You can do this by speaking to the bedside nurses or any member of the research team. Your decision whether or not to take part will not affect the normal high level of care given in the neonatal unit.

What are the possible side effects or complications of the study?
There are no particular side effects or complications expected by participating in this study.
The insertion of the catheter via nose could cause some brief discomfort for your baby. This is similar to inserting a gastric feeding tube but the procedure should not be painful. Putting the Volusense vest on your baby is similar to applying a layer of clothing. We will aim to time this as closely with routine cares to prevent any disruption to your baby’s normal routine.
The lead researcher in this study is an experienced paediatrician and will be in attendance with your baby during the entire study period to make sure everything is alright.

What are the possible advantages and disadvantages of taking part in this study?
There are no particular advantages to your baby for taking part in this research, but the study will help us to provide better information for doctors who are using breathing machines to help baby’s breathe better in the future, including both HfNC and CPAP machines. This will help doctors choose the right amount of treatment required by the baby.

The disadvantages are that your baby will be connected to additional monitors and will need one additional tube in the nose for a period of two hours during the study. This may give rise to slight additional discomfort during this period. But these will be removed as soon as the study is completed, and your baby will be monitored for any signs of distress or discomfort throughout.

What if new information becomes available?
If any new information about these breathing machines becomes available during the course of the study, the clinicians caring for your baby would inform you of this.

What if something goes wrong?
As this study follows current standard practice to help very young babies breathe, your baby is unlikely to have any additional adverse effects while participating in this study. During the study, data about any adverse events will be collected and monitored. You will be covered by the NHS Trust indemnity scheme and participating in the study does not affect your legal rights.

Will taking part in this study be kept confidential?
Yes. We will follow all the usual hospital policies and procedures to maintain confidentiality. We think it is important that your GP know that your baby has participated in this study, so we will inform your GP, unless you request us not to. The data collected about your baby as part of the research will be kept securely, and
will be confidential to the study team and people from the regulatory authorities. Information about your baby will not be used for any purpose other than to answer the research question.

What will happen to the results of the research study?
At the end of the study, the results will be analysed and published in medical journals and will be presented in medical seminars and conferences. Your baby will not be identified in any reports or publications. If you would like us to, at the end of the study, we will send you a summary of the final results. Please let us know if you would like us to do this, and we will send you a summary of the outcomes once the study has been completed. The contact details for chief investigator are listed at the end of this leaflet.

Who is organising and funding this study?
The study is funded and sponsored by the Newcastle Hospitals NHS Foundation Trust. This study is also a topic for a research degree with the Newcastle University.

Who has reviewed the study?
The study has been assessed and approved by a group of people called an Ethics Committee. An ethics committee must review and approve all research before it is carried out on patients, to make sure that the study is safe and participants are protected. This research was reviewed and approved by the Newcastle and North Tyneside I NHS Research Ethics Committee. It has also been reviewed by parents of babies and by an external expert in the field of newborn ventilation.

What if I have concerns?
If you have any concerns or questions about this study, you can contact the Chief Investigator or any member of the research team. If you have any questions about this study you may also choose to get information from the Trust Research and Development department (Address: Level 6, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP. Telephone: 0191 282 5959, Fax: 0191 282 4524). You could also alternatively contact INVOLVE (http://www.involve.org.uk/resourcecentre/) or Tel 02380 651888 for more advice and support.

If you have any complaint about the conduct of the study, you could also contact PALS (Patient Advice and Liaison Service) Text: 01670 511090; Freephone 0800 0320202 or email at northtynesidepals@nhet.nhs.uk

Thank you for reading this information leaflet. Should you desire to discuss the study in more detail a member of the team would be happy to provide further information. Alternatively, the contact details of the study team are provided on this leaflet.

Local contact for your hospital:
Chief Investigator:
Dr. Chris O’Brien, Consultant Respiratory Paediatrician, Tel: 01912829567
Co-Investigators:
Dr. Alan Fenton, Consultant Neonatologist, Tel: 01912829082
Dr. Sundep Harigopal, Consultant Neonatologist, Tel: 01912829616
Dr. Malcolm Brodie, Consultant Respiratory paediatrician, Tel: 01912821752
Dr. S Gopalakaje, Trust Doctor, Neonatology, Tel: 01912821614

SG/MB/SY/AF/CJO Version 5 29/04/2014
8.5 Appendix 5. Consent Form

The study of respiratory physiology during high flow nasal cannula (HFNC) treatment in preterm neonates

Consent from Parents

Hospital Name: Royal Victoria Infirmary

Formal Title: Study of nasopharyngeal pressures, tidal breathing indices and inspired gas concentrations during High Flow Nasal Cannula (HFNC) and CPAP treatment in preterm neonates

Name of Researchers: Dr. S Gopala Krishna, Dr. M Brodie, Dr. S Harigopal, Dr. A Peston and Dr. C J O'Brien

I,…………………………………………..mother/father of ……………………………
Do hereby give my consent for my baby to be included in this study.

I confirm that I have been given the information leaflet (version (4) 10.02.2014) which I have read and understood. I have been given an opportunity to ask my questions which have been answered.

I can confirm that my baby’s participation in this study is entirely voluntary. I understand what will happen to my baby during this study. I am aware of my rights to withdraw my baby from the study at any time. In such an event if I choose to do so, his/her future care or legal rights will not be affected in any way.

I also give my consent to publish the study results in scientific journals and to present the data in national and international meetings and conferences provided no personal details will be made available at any stage.

I understand that relevant sections of any of my baby’s medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS trust, where it is relevant to my baby taking part in this research. I give permission for these individuals to have access to my baby’s records.

I agree for the Neonatal unit to inform my GP about my baby’s participation in this study.

Name of Parent
Signature
Date

Name of health professional taking consent
Signature
Date

Copy to — Parents
Case notes
Study file

Consent form - Version (2) 10.02.2014/HFNC study

SG/MB/SH/ACF/C/IO
# Appendix 6. Neonatal Unit Observation Charts

### APNOEA CHART

<table>
<thead>
<tr>
<th>Event</th>
<th>Action</th>
<th>C = Colour Change</th>
<th>D = Desaturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = Apnoea</td>
<td>1 = Self Resolving</td>
<td>2 = Stimulation</td>
<td></td>
</tr>
<tr>
<td>B = Bradyardio</td>
<td>3 = Oxygen</td>
<td>4 = Suction</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>5 - 10</th>
<th>10 - 15</th>
<th>15 - 20</th>
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<th>55 - 60</th>
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</table>

The Newcastle upon Tyne Hospital Foundation Trust

Appendix 6. Neonatal Unit Observation Charts -1
Appendix 6. Neonatal Unit Observation Charts -2

<table>
<thead>
<tr>
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<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>B = bradycardia</td>
<td>08</td>
<td>09</td>
<td>10</td>
<td>11</td>
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### Appendix 6. Neonatal Unit Observation Charts -3

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<tr>
<td>Jan 3</td>
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</table>

### Appendix 6. Neonatal Unit Observation Charts -4

282
| Parameter/Time | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---------------|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|---|---|---|---|
| Pressure      |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Flow          |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Imp T         |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Rate          |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| FiO2          |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Water Temp.   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Hm. Location  |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Heart rate    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Resp. rate    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| aPa          |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| SaO2%         |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Nasal/Oral    |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Suction      |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Ax Temp.      |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Incubator Temp|   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Humidity      |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Incubator H2O |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Infant Position |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Skin Assess.  |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| N. access     |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Check (Int lines) | |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
| Phototherapy  |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |   |   |   |   |
Dear Chris

Re: Observational study of nasopharyngeal pressures, tidal breathing indices and inspired gas concentrations during High Flow Nasal Cannula (HFNC) and Continuous Positive Airway Pressure (CPAP) treatment in preterm neonates

The Newcastle Healthcare Charity (the Trustees), on the recommendation of the Joint Research Executive Scientific Committee, are prepared to make a grant in respect of the above project, subject to the terms set out below.

TOTAL AMOUNT: £39,000

Comprising
Salary Costs: £
Equipment/Other: £39,000
Consumables: £

Total: £39,000

Nothing in this offer constitutes a contract of employment and there shall not be charged to the project any costs falling to the employer other than arises directly from the pursuit of the research (specifically, sick pay and maternity leave costs are excluded); nor do the Newcastle Healthcare Charity accept any responsibility for claims which might arise from the conduct of the project, directly or indirectly. It shall be the responsibility of the researcher and his/her employer to ensure that the project work is of an adequate quality, that the project is conducted in accordance with the protocol submitted to the JRE Scientific Committee (or as amended by it) and with all reasonable care.
Where appropriate, every endeavour will be made by the researcher and his/her employer to disseminate the results of the project. The grant holder shall be obliged to submit a report (circa 1,000 words), no later than six months after the cessation of funding. No further application from the grant holder will be considered if a final report is outstanding.

Any intellectual property arising from the Trustee-funded work should be commercially exploited when appropriate for the benefit of the Trustees and the institution. The Trustees waive any claim to ownership of intellectual property or data arising from the commercial exploitation of Trustee-funded research on the condition that grant holders and their administrative authorities agree to keep the Trustees fully informed of the development of any patentable property and to include the Newcastle upon Tyne Hospitals NHS Foundation Trust as an equitable partner (reasonably related to the Trustees' proportion of support) in any revenue-sharing agreements that may result from this.

It is essential that research is conducted to the highest ethical and scientific standards and all staff involved in the research should have read the Department of Health document 'Research Governance Framework for Health and Social Care' which defines the principles of good research. Researchers should fully understand the implications of research governance and make certain that their work meets its requirements.

Work cannot commence unless the completed Agreement has been returned to me. Please also enclose a copy of the approval letter from the relevant Human (or animal) Ethics Committee where appropriate.

I would be most grateful if you acknowledge support for the Newcastle Health Care Charity and the Newcastle upon Tyne Hospitals NHS Charity in all publications arising from this work.

Please indicate by signing and returning the attached copy of this letter whether you are willing to accept the grant offered on the terms stated above. It is also necessary to obtain the signed agreement of a finance officer who will be responsible for the administration of the grant.

Kind regards,

Yours sincerely

[Signature]

Professor J Goodship
Chair, Joint Research Executive Scientific Committee
On behalf of the Newcastle Healthcare Charity and
Newcastle upon Tyne Hospitals NHS Charity

The above offer of a grant is accepted upon the terms stated.

Principal Investigator

Date

Finance Officer for Trust/University

(Date)

Date
The Newcastle upon Tyne Hospitals NHS Foundation Trust

SS/SH/JH
11 July 2014

Dr Christopher O'Brien
Consultant Respiratory Paediatrician
Old Children's Outpatient Block
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Royal Victoria Infirmary

Dear Dr O'Brien

Trust R&D Project:
Title of Project: 7022
Observational study of nasopharyngeal pressures, tidal breathing indices and inspired gas concentrations during High Flow Nasal Cannula (HFNC) and Continuous Positive Airway Pressure (CPAP) treatment in preterm neonates

Principal Investigator:
Number of patients: 45
Funder (proposed): The Newcastle upon Tyne Hospitals NHS Charity
Sponsor (proposed): The Newcastle upon Tyne Hospitals NHS Foundation
REC number: 14/NE/0093
IRAS Project Code: 145881
First participant to be recruited by: 10 August 2014

After completing the necessary risk and site assessment for the above research project, The Newcastle upon Tyne Hospitals NHS Foundation Trust grants NHS Permission for this research to take place at this Trust dependent upon:

(i) you, as Principal Investigator, agreeing to comply with the Department of Health's Research Governance Framework for Health and Social Care, and confirming your understanding of the responsibilities and duties of Principal Investigators by signing the Investigator Responsibilities Document. A copy of this document will be kept on file within the Joint Research Office.

(ii) you, as Principal Investigator, ensuring compliance of the project with all other legislation and guidelines including Caldicott Guardian approvals and compliance with the Data Protection Act 1998, Health and Safety at Work Act 1974, any requirements of the MHRA (eg CTA, EudraCT registration), and any other relevant UK/European guidelines or legislation (eg reporting of suspected adverse incidents).

(iii) where applicable, you, as Principal Investigator, should also adhere to the GMC supplementary guidance Good practice in research and Consent to research which sets out the good practice principles that doctors are expected to understand and follow if they are involved in research – see http://www.gmc-uk.org/guidance/ethical_guidance/5991.asp

The NIHR requires NHS organisations to recruit patients to CLRN Portfolio studies within 30 days from the date of this letter. The 30 day deadline for recruiting the first patient is therefore 10 August 2014.

Please note: the Department of Health 70-day benchmark requires recruitment within 70 days of a valid SSI submission. Therefore, recruiting within the NIHR 30 day target will ensure compliance with both targets.
Sponsorship
The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as Sponsor for this project, under the Department of Health’s guidelines for research in health and social care.

In addition, the Trust has a Research Governance Implementation Plan, agreed with the Department of Health, in order to fully comply with Research Governance and fulfill the responsibility of a Sponsor.

As the Trust is acting as Sponsor for the research and were some of the research is taking place outside of Newcastle upon Tyne, then all costs must be met for research governance audit visits to those sites. It is the responsibility of the PI to provide confirmation to the Trust of who will pay these costs. Audit is required under the Research Governance Framework for Health and Social Care. (Please note that the Trust randomly audits 10% of approved research projects annually.)

NHS Permission applies to the research described in the protocol and related documentation as listed on the favourable ethical opinion(s) from NRES Committee North East – Newcastle & North Tyneside 1 Ethics Committee, dated 06 June 2014. Specifically, the following versions of the key documents are approved:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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<tbody>
<tr>
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<td>6-29042014</td>
<td>29 April 2014</td>
</tr>
<tr>
<td>Participant Information Sheet: Parent</td>
<td>3-29042014</td>
<td>29 April 2014</td>
</tr>
<tr>
<td>Participant Consent Form: Parent</td>
<td>5-29042014</td>
<td>29 April 2014</td>
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</table>

Any changes to these documents, or any other amendments to the study must be submitted to the Research Ethics Committee and MHRHA (if relevant) for review – see http://www.nres.nhs.uk/applications/after-ethical-review/amendments/ for guidance. All amendments must be submitted to the R&D office for review in parallel with ethical and regulatory review so that implications of the amendment can be assessed. You must send a copy of all amendment documents to the R&D office and if the changes or amendments to the study have implications for costs or use of resources, you must also submit details of these changes.

It is the Principal Investigator’s responsibility to ensure that all staff involved in the research have Honorary Research Contracts or the necessary Letters of Access. These must be issued prior to commencing the research.

In addition, unless otherwise agreed with the Trust, the research will be covered for negligence under the CNST (Clinical Negligence Scheme for Trusts), however cover for no-fault harm is the responsibility of the Principal Investigator to arrange if required.

Please also note that for any NHS employee who generates Intellectual Property in the normal course of their duties, it is recognised that the Intellectual Property Rights remain with the employer and not the employee.

Yours sincerely

Sean Scott
Research Management & Governance (RM&G) Manager

CC: Ms Carolyn Robinson, Finance Department, Chevrot Court, Freeman Hospital
Dr Stephen Sturgies, Clinical Director of Women’s Services, Royal Victoria Infirmary
Mrs Fiona Veloso-Parker, Research Team Lead, Royal Victoria Infirmary
Dr Salkaran Gopalakrishna, Researcher, Royal Victoria Infirmary
Appendix 1 - Study Entry Proforma

Section A: Enrolment

Questions A.1 and A.2 must be answered YES:
A.1 Is this infant's gestational age at birth less than 37 weeks? Yes No
A.2 Is this infant more than 5 days of age? Yes No
A.3 Infant’s date and time of birth: (use 24hr clock) D D M M Y Y H H m m
A.4 Infant’s expected date of delivery (EDD): D D M M Y Y
A.5 Infant’s birth weight: g
A.6 Infant’s current weight: g
A.7 Was the clinical condition stable over last 12 hours? Yes No
A.8 Is the clinician decision is to continue with NIV? Yes No
A.9 Does this infant have a congenital airway anomaly? Yes No
A.10 Has written informed parental consent been obtained? Yes No

If Yes, Please PRINT name of person who obtained consent:
A.11 What is this infant’s sex? Male Female Indeterminate
A.12 Infant’s NHS number: (if available)

Section B: Randomisation

B.1 Study number:
B.2 Group allocation: Group 1 (CPAP followed by HFNC) Group 2 (HFNC followed by CPAP)

Section C: Neonatal details

C.1 Was this infant delivered via caesarean section? Yes No
C.2 Were the membranes ruptured before labour? Yes No
C.3 Were the membranes ruptured >24 hours before delivery? Yes No
C.4 Was there oligohydramnios on any antenatal ultrasound scan? Yes No
C.5 Was the heart rate >100 at 5 minutes after birth? Yes No
C.6 How long was this infant ventilated via an endotracheal tube? Days Hrs
C.7 Received High frequency ventilation any time? Yes No
C.8 Received Nitric oxide anytime? Yes No
C.9 Episodes of sepsis with blood cultures positive? Yes No
C.10 Was the baby exposed to antenatal steroids? Yes No

Section D: Form details: Details of person completing form
Name: Role: Signature: Date: D D M M Y Y

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SG/MB/SH/ACF/CJ0 Version 6 29/04/2014