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A Prospective Observational Study of Nasal High Flow in a Cardiothoracic and Vascular Intensive Care and High Dependency Unit

The POSt NHF Study

Michelle Lesley Eccleston
Abstract

Introduction

There are three established respiratory support modalities routinely used in the management of acute respiratory failure (ARF). These include invasive mechanical ventilation (IMV), noninvasive ventilation (NIV) and oxygen therapy. In addition, a new modality called nasal high flow (NHF) has recently been introduced. However, there is little evidence available with which to guide the appropriate application of NHF in a given clinical scenario.

Aim

The aim of this research was to quantify the experience with NHF in a critical care environment where the therapy is now routinely used for selected patients with ARF. Based on this population and their subsequent therapy outcomes, the broad aim of this research was to begin to provide support for future clinical practice and research. In so doing, begin to understand when, why, how and on whom NHF should be appropriately applied.

Methods

In the context of normal clinical practice a prospective, observational study was conducted to describe one patient population receiving NHF.
Results

Data were collected and analysed from 120 consecutively enrolled patients, who required NHF for the management of ARF in the course of their critical care admission. Nasal high flow was considered to be successful for 78% of patients, in spite of significant hypoxemia (mean PaO₂:FiO₂ ratio, 190 [SD56]) and mild to moderate respiratory distress (mean respiratory rate, 20 [SD6]; mean PaCO₂ 5.5 [SD0.8]; mean pH 7.36 [SD0.06]). The population described was predominantly a post operative cardiac surgical group (52%) but also included patients following vascular (15%) and thoracic (11%) surgery. Nasal high flow was used principally as a step up from traditional forms of oxygen therapy (73%) or as a weaning step down from IMV (18%). Twenty two percent of patients experienced failure of NHF, requiring an escalation of respiratory support to either NIV or IMV. Generally NHF failure was associated with a more unstable physiological status. At baseline, a pH of less than 7.35 should specifically alert the clinical team to the higher probability of NHF failure (p = 0.04).

Conclusion

In a population of patients experiencing ARF following major surgery, NHF was associated with a high therapy success rate, in spite of significant hypoxemia. The addition of NHF, as a new respiratory support modality appears to be a promising advance the management of patients with ARF.
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Abbreviations

ARF: Acute Respiratory Failure

ICU: Intensive Care Unit

HDU: High Dependency Unit

ICU/HDU: Intensive Care Unit / High Dependency Unit (The Study Site)

L/min: Litres per Minute

HHHFNOT: Heated and Humidified High Flow Nasal Oxygen Therapy

NHF: Nasal High Flow

ECMO: Extra Corporeal Membrane Oxygenation

FiO₂: Fraction of Inspired Oxygen

CO₂: Carbon Dioxide

FRC: Functional Residual Capacity

IMV: Invasive Mechanical Ventilation

ALI: Acute Lung Injury

ARDS: Acute Respiratory Distress Syndrome

NIV: Noninvasive Ventilation

CPAP: Continuous Positive Airway Pressure

BiPAP: Bi-Phasic Airway Pressure

COPD: Chronic Obstructive Pulmonary Disease

BH: Bubble Humidifier

HH: Heated Humidifier
°C: Degrees Celsius

\( p = p \) value

mg/L: Milligrams per Litre

H₂O: Water

BTPS: Body Temperature Pressure Saturated

NICU: Neonatal Intensive Care Unit

USA: United States of America

FDA: Food and Drug Administration

PICU: Paediatric Intensive Care Unit

cmH₂O: Centimetres of Water

WHO: World Health Organisation

HHFM: Humidified High-Flow Face Mask

SD: Standard Deviation

EIT: Electrical Impedance Tomography

hr(s): Hour(s)

GCP: Good Clinical Practice

CRF: Coded Recording Form

APACHE II: Acute Physiology and Chronic Health Evaluation II

SOFA: Sequential Organ Failure Assessment

min(s): Minute(s)

SPSS: Statistical Package for the Social Sciences

CABG: Coronary Artery Bypass Graft

LFNC: Low Flow Nasal Cannulae
SFM: Simple Face Mask

FM: Face Mask

PI: Principle Investigator

pH: Measure of Acidity

Kg: Kilograms

BMI: Body Mass Index

Kg/m²: Kilograms per square metre

n: Sample

no.: Number

mmHg: Millimetres of Mercury

SpO₂: Pulse Oximeter Oxygen Saturation

PaCO₂: Partial Pressure of Carbon Dioxide

PaO₂: Partial Pressure of Oxygen

PaO₂:FiO₂ Ratio: Ratio of the Partial Pressure of Oxygen to the Fraction of Inspired Oxygen

MAP: Mean Arterial Pressure

Q1: Lower Quartile

Q2: Median

Q3: Upper Quartile

GCS: Glasgow Coma Score

SIGN: Scottish Intercollegiate Guideline Network
Chapter 1. Introduction

1.1. Context

This thesis is set within the context of acute respiratory failure (ARF) and the continuum of respiratory support therapies routinely used in its management. The environmental context for this study is a tertiary level cardiothoracic and vascular intensive care and high dependency unit (ICU/HDU).

Five years ago a novel technique for providing high flow oxygen therapy was introduced to this unit. The technique allowed up to 60 L/min of blended oxygen to be delivered directly into the nasal vestibule, via none occlusive nasal cannulae. At the time this seemed implausible, possibly even dangerous, to consider delivering such high flows of gas to a patient in this manner. However, with the addition of warmth and moisture to the gas flow, the clinical team learned that it was not only possible but also tolerable - although most of us needed to be convinced of this by trying it out on ourselves first!

At this stage only a small number of adult ICUs were using the technique which was initially referred to as ‘HHHFNOT’ (Heated and Humidified High Flow Nasal Oxygen Therapy). Over the last few years the abbreviations and names have changed. The manufacturer calls it Optiflow™ but for the purposes of this thesis, the therapy will be referred to as Nasal High Flow or NHF.
During the last five years, NHF has become a standard of care in this unit for selected patients with ARF (Parke, McGuinness, & Eccleston, 2011). This practice trend has been supported by a program of local clinical research, which continues to evaluate NHF both in terms of its mechanisms of action and clinical efficacy (Parke, McGuinness, & Eccleston, 2009; Parke, McGuinness, & Eccleston, in press; Parke et al, 2011). Support also comes from an observed reduction in noninvasive ventilation (NIV) rates, believed to be attributable to the introduction of NHF (Parke et al. 2011). Now, approximately 13% of the 2000 patients treated each year in the ICU/HDU receive the therapy.

Generally however, NHF is not well described in the clinical literature as a treatment modality for ARF in adults. Only a small number of published papers describe its application in this population. Therefore the role, scope and limitations of NHF are not widely understood.

1.2. The Clinical Issue

A learned professor once advised me that when selecting a respiratory support therapy, the clinician should always choose the simplest, most comfortable and efficacious therapy available, to meet the patient’s needs. The therapy should also be the most cost effective and should minimise complications as much as possible (personal communication. Professor R Haslam. Women’s and Children’s Hospital, Adelaide, South Australia. September 2009). However, the assessment of such criteria is relative. It is dependent on both the clinical scenario and the comparator in question.
The challenge therefore is to understand the degree and type of respiratory failure able to be managed with NHF, relative to the other respiratory support therapies available. Cost and complexity can be justified if a new therapy is shown to be more efficacious than its comparator. Equally, if the new therapy is shown to be of a similar efficacy, but is cheaper and simpler, then the cheaper, simpler therapy will surely take precedence. In the financial equation, the impact of therapy outcome must also be considered.

“All too frequently, application of new therapy is based on administrative decisions, without using research to guide clinical practice”

(Wattier & Ward, 2011, p. 356)

1.3. The Research Objective

Within this context, the primary objective of this research was to describe a ‘real world’ experience with NHF. The patient population treated with NHF in this ICU/HDU are therefore described. This description is then moderated by both therapy outcome and the degree and type of ARF exhibited by the population. These observations begin to guide where NHF might fit within the spectrum of respiratory support therapies currently available, helping to define appropriate comparators with which to evaluate the suitability of NHF in a given clinical scenario. This objective was set within the broader aim of beginning to understand when, why, how and on whom NHF should be used in the management of ARF.
1.4. Study Methodology

This study is a single centre, prospective observational study. A descriptive study design was selected as the most appropriate to achieve the aims and objectives of this research. It was imperative that the study reflected usual clinical practice and as much as possible, did not affect care delivery, hence its non-interventional nature. All patients receiving NHF in the unit could therefore be enrolled.

The rational for enrolling the whole population, was so that the results would be directly relevant to actual clinical practice (Vincent, 2010). Also, given the paucity of data in this field and the complexity of the issue, a descriptive study was considered necessary to generate new theories which could then be tested in future experimental studies (Closs & Cheater, 1999). This study design was therefore selected for its relevance to both clinical practice and future research.

1.5. Who Will Benefit From This Research?

Patients, care givers and researchers will benefit from this study. For patients, NHF may present an important advance in respiratory care. This study objectively evaluates NHF and begins to elucidate which patients could benefit from its application. For care givers, this research begins to guide and support clinical practice decisions with regards to NHF, thereby helping to improve care efficiency. Also, researchers will benefit from this work because it generates new hypotheses and begins to define appropriate inclusion and exclusion criteria for subsequent studies.
1.6. Study Limitations

This study, due to the methodology employed, cannot draw cause and effect conclusions. Therefore ‘answers’ are not provided. The degree to which questions are addressed is limited by the relatively small sample of data from a single centre. While the data set was reflective of the population to receive NHF in the ICU/HDU, the main subgroup analysis (NHF success versus NHF failure) produced a relatively small comparative group (NHF failure).

1.7. Thesis Overview

Chapter 2 describes ARF and the continuum of respiratory support therapies routinely used in its management. Nasal high flow is introduced in this chapter and the preliminary clinical literature is reviewed.

Chapter 3 presents the methodology for this research and defines the research aims and objectives. The evolution of the study protocol and the development of the data tools are discussed, followed by a description of the statistical methods employed.

Chapter 4 provides the results of this research.

Chapter 5 presents a discussion of the study results in the context of what is already known. Unexpected results are discussed and possible explanations presented. The limitations and challenges associated with this thesis are then covered, followed by a summary of the contribution and implications of this work. Finally, recommendations for future research are suggested.
1.8. Chapter Summary

The introduction of NHF to this ICU/HDU has led to a new standard of care in the unit for selected patients with ARF. However, relative to current respiratory support therapies, the role and scope of NHF is not widely documented or understood. The objective of this research is therefore to describe the patient population who receive NHF in this unit and their subsequent therapy outcomes. In so doing, begin to appropriately guide therapy selection in terms when, why, how and on whom NHF should be used in the management of ARF.
Chapter 2. Background and Literature Review

2.1. Introduction

This chapter describes ARF and the continuum of respiratory support therapies routinely used in its management. Each therapy in the continuum, ranging from invasive mechanical ventilation to low flow nasal cannulae, has its own inherent benefits, risks and limitations. The clinical team is tasked with matching the most appropriate therapy to the patient’s needs, while acknowledging the scope of each treatment modality. The degree and type of respiratory failure is usually the primary determinant of therapy selection, however patient comfort, tolerance and cost must also be important considerations. Critical appraisal of the literature is a vital step in this decision making process.

Nasal high flow is a new therapy and an addition to the continuum of respiratory support therapies available. However, the exact role of NHF in ARF has not yet delineated. This review describes the preliminary clinical research in this field and evaluates the available physiological data. An effort is made to establish the potential role of NHF as a respiratory support modality and the likely mechanisms of action.

The review of the NHF literature is set within the context of ARF and the plethora of respiratory support devices routinely used in its management. However, extra corporeal membrane oxygenation (ECMO) and advanced ventilation techniques are beyond the scope of this review.
2.2. Acute Respiratory Failure

The respiratory system comprises two functional components. These are the lung itself which performs gas exchange and the respiratory pump, which consists of the chest wall and the muscles and nerves of respiration (Palange & Simonds, 2010). Either or both of these components can fail acutely resulting in respiratory failure (Albert, Spiro & Jett, 2004; Elliot Aitken, & Chaboyer, 2007; Vander, Sherman, & Luciano, 1994). Failure of the lung itself usually manifests as a low partial pressure of oxygen in arterial blood (hypoxemic respiratory failure), whereas failure of the respiratory pump results in high partial pressures of carbon dioxide (hypercapnic respiratory failure) (Palange & Simonds, 2010).

2.3. Management of Acute Respiratory Failure

Acute hypoxemic respiratory failure, when present in isolation, can often be managed by simply increasing the concentration of oxygen delivered to ventilated and perfused regions of the lung (Albert et al. 2004; Fink, Abraham, Vincent & Kochanek, 2005). Arguably this can be achieved noninvasively, assuming the required fraction of inspired oxygen (FiO$_2$) can be delivered reliably and the patient is otherwise stable (Albert et al. 2004). Increasing the delivered FiO$_2$ however, does nothing to correct the underlying cause of hypoxemia, nor does it improve carbon dioxide (CO$_2$) clearance if a respiratory pump problem coexists (Palange & Simonds, 2010).

Patients with hypercapnic respiratory failure will initially make their own efforts to improve the bulk flow of gas into the lungs by increasing their minute ventilation. When these mechanisms are insufficient to return CO$_2$ levels to with an acceptable range, or when the
additional work of breathing begins to cause fatigue, mechanical ventilatory support must be provided (Fink et al., 2005).

2.4. Mechanical Ventilation

The goal of mechanical ventilation is to maintain gas exchange and to support respiratory pump function when impaired (Albert et al. 2004). This is achieved by improving both alveolar ventilation and functional residual capacity (FRC) (Albert et al. 2004). Mechanical ventilation can be provided either invasively or noninvasively, usually with positive pressure breaths (Elliot et al. 2007).

2.4.1 Invasive Mechanical Ventilation

Patients suffering from ARF frequently require endotracheal intubation and invasive mechanical ventilation (IMV) to sustain life (Burns, Adhikari, Keenan, & Meade, 2010). Indeed, ARF is the most common indication for IMV (Goligher & Ferguson 2009) and one of the most common reasons for intensive care admission (Fink et al., 2005). The decision to provide IMV is a clinical one, based on a number of factors including gas exchange, work of breathing, ability to clear secretions and the patient’s ability to protect their own airway (Fink et al., 2005). Invasive mechanical ventilation can be described as the highest level of respiratory support routinely used in the management of acute respiratory failure.

While IMV plays a life saving role, it is not without risks and complications. Excessive lung pressures and volumes associated with IMV can cause mechanical damage such as shear
stress, which leads to inflammation and leakage in the alveolar capillary bed (Parker, Hernandez & Peevy 1993). This damage is known to increase mortality and to reduce ventilator free days in subjects with severe respiratory failure, such as occurs in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (ARDSNET, 2000). In addition, IMV can cause ventilator associated pneumonia (Ambrosino & Vagheggini, 2008) which is known to increase hospital length of stay, mortality and healthcare costs (Rello, Lode, Cornaglia, & Masterton, 2010).

In an effort to avoid such complications, there has been a significant shift in clinical practice towards using noninvasive strategies to provide mechanical ventilatory support (Burns et al., 2010; Nava & Hill, 2009).

2.4.2 Noninvasive Ventilation

Noninvasive ventilation (NIV) offers the ability to provide mechanical ventilation to spontaneously breathing patients without the use of an endotracheal tube (Ambrosino & Vagheggini, 2008; Antonelli, Pennisi, & Conti, 2003; Masip, 2008; Nava & Hill, 2009). In so doing, the complications associated with IMV can often be avoided (Nava & Hill, 2009) while achieving a similar physiological response in terms of work of breathing and gas exchange (Vitacca et al., 2001).

Non invasive ventilation is usually performed with a fitted oronasal mask to create a seal with the patient’s airway. Two modes of NIV are typically used, namely, continuous positive airway pressure (CPAP) and bilevel ventilation (Masip, 2007).
2.4.2.1. CPAP

CPAP is the simpler of the two modalities and involves increasing airway pressure above atmospheric pressure during both inspiration and expiration (Zarbock et al., 2009). In some of the physiological research in this field, Duncan Negrin, Mihm, Guilleminault and Raffin (1987) showed that CPAP improves alveolar recruitment and FRC, while Lenique et al. (1997) demonstrated that CPAP eases work of breathing and reduces cardiac preload.

2.4.2.2. BiLevel / BiPAP

Bilevel ventilation on the other hand is slightly more complex. Inspiratory pressure assistance is provided as the patient breathes in. Then as the patient exhales the pressure is dropped to a lower but still positive level. This results in a bilevel ventilation technique (Masip, 2007) often referred to as BiPAP (Bi-Phasic Airway Pressure) (Respironics, 2011). BiPAP has been shown to augment tidal volume, reduce breathing frequency, rest the muscles of respiration and improve gas exchange (Nava & Hill, 2009). Both NIV techniques are therefore useful in supporting respiratory pump function and gas exchange.

Noninvasive ventilation, is now a main stream alternative to IMV for the management of ARF related to COPD exacerbation (Carrera et al., 2009; Keenan, Sinuff, Cook, & Hill, 2003; Lightowler, Wedzicha, Elliott, & Ram, 2003; Scala et al., 2007; Quadrone et al., 2004), cardiogenic pulmonary oedema (Masip et al., 2005; Peter, Moran, Phillips-Hughes, Graham, & Bersten, 2006; Winck, Azevedo, Costa-Pereira, Antonelli, & Wyatt, 2006) and for patients with immunocompromise (Antonelli et al., 2000; Hilbert et al., 2001; Principi et al., 2004; Rocco et al., 2004). High level evidence including systematic reviews and metanalyses
support these applications. There are many additional clinical scenarios where the application of NIV is supported by a smaller volume of positive data (Curtis et al., 2007; Ferreyra et al., 2008; Girault et al., 1999; Murase et al., 2010; Nava et al., 1998; Zarbock et al., 2009).

The scope of NIV in the management of ARF does however have its limitations. There are well recognised contraindications to NIV which include:

- **Absolute contraindications:**
  - Respiratory arrest
  - Inability to fit the mask

- **Relative contraindications:**
  - Medical instability
  - Inability to protect own airway
  - Swallowing impairment
  - Excessive secretions (not effectively managed with secretion clearance techniques)
  - Multiple organ failure
  - Agitation, inability to follow commands
  - Recent upper gastrointestinal surgery or airway surgery

  (Nava & Hill, 2009)

The scope of NIV is also defined by the aetiology and severity of the respiratory failure being treated. For example, the literature strongly cautions the use of NIV in the management of severe hypoxemic respiratory failure, severe community acquired pneumonia and ARDS
(Nava & Hill, 2009). Also, Demoule, Girou, Richard, Taille and Brochard (2006) showed that while successful application of NIV (to avoid intubation) reduces overall mortality, subsequent failure of NIV actually increases mortality risk in some populations but not others. To explain further, failure of NIV in the management of de novo respiratory failure is associated with a significant increase in mortality. By contrast, failure does not affect mortality risk when the aetiology of ARF is either cardiogenic shock or acute exacerbation of chronic respiratory disease (Demoule et al., 2006). The decision to try NIV, as a means to avoid intubation, therefore requires a complex decision making process to balance the potential benefits against the potential risks for a given clinical scenario.

Aside from very careful patient selection, NIV also has some inherent side effects. The literature frequently sites mask discomfort and claustrophobia as significant issues as well as oral dryness, eye irritation and pain in the sinuses and ears (Gay, 2009; Hill, 2000). It is not uncommon for patients to develop pressure sores related to the mask, especially at vulnerable points such as the bridge of nose (Gay, 2009; Hill, 1997; Racca et al., 2009). More serious but less frequent complications include aspiration and pneumothorax (Gay, 2009).

The balance of all the benefits, risk and limitations must be evaluated for an individual patient. The clinician needs to consider for whom NIV is suitable and for how long it is appropriate to persevere before intubation is indicated. Where there is any doubt, escalation to IMV should be immediately available (Ambrosino & Vaghegguni, 2008).
2.5. Oxygen Therapy

In the other direction, oxygen therapy represents a step down in the level of respiratory support compared with NIV. Irrespective of the device used, all oxygen therapies have the common purpose of correcting hypoxemia, rather than treating breathlessness or hypercapnia (Palange & Simonds, 2010). In other words they have no role in supporting respiratory pump function. There are a plethora of oxygen therapy devices available, which vary by the amount of oxygen and the nature of the flow they deliver (Waldau, Larsen, & Bonde, 1998).

2.5.1 Low Flow Nasal Cannulae

The first option for delivering low to moderate amounts of oxygen is low flow nasal cannulae (O'Driscoll, Howard, & Davison, 2008). Patients tend to tolerate nasal interfaces well, preferring them to face masks (Ayhan, Iyigun, Tastan, Orhan, & Ozturk 2009; Eastwood, Reeves, & Cowie, 2004; Kory, Bergmann, Sweet, & Smith, 1962; Tiruvoipati, Lewis, Haji, & Botha, 2010; Waugh & Granger, 2004). Presumably this is because of induced feelings of claustrophobia, impedance of oral intake and communication difficulties associated with face masks (Sasaki, Yamakage, & Iwasaki, 2003). Ayhan et al (2009) found that in a group of post op patients, nasal cannulae were more effective than facemasks in the early management of post operative hypoxemia. This was attributed to significantly more frequent device removals in the mask group compared to the nasal cannulae group (75% versus 3.8% p < 0.01). Forty percent of patients who removed their masks had low oxygen saturations (Ayhan et al., 2009). A previous investigation by Nolan, Winyard, & Goldhill (1993) also supports this finding. They too found that nasal cannulae remained in place more often than face masks and were more effective in avoiding oxygen desaturation as a result.
Low flow nasal cannulae are cheap and simple to use so they tend to be applied preferentially as a first line option for the management of hypoxemia (O'Driscoll et al., 2008). Low flow nasal cannulae are however limited to 4 – 6 L/min oxygen due to the cooling and drying effects on the airway mucosa (Kallstrom, 2002). Delivering more than 4 - 6 L/min via nasal cannulae is intolerable for this reason and can result in epistaxis, crustation, as well as septal and mucosal damage (Banerjee, Kumar, & Sethi, 2005; Kopelman & Holbert, 2003). Mucociliary function is also depressed by exposure to cold, dry oxygen (Capellier et al., 1997; Salah, Xuan, Fouilladieu, Lockhart, & Regnard, 1988; Tatkov, 2009; Williams, Rankin, Smith, Galler, & Seakins, 1996). Miyamoto and Nishimura (2008) assessed dry nasal oxygen versus humidified nasal oxygen in both healthy subjects and in patients with pulmonary disease. They found that as gas flow increased so too did the symptoms of nasal dryness and discomfort, with a marked increase related to the dry oxygen. At flows greater than or equal to 3 L/min, nasal dryness and discomfort were significantly worse in relation to dry oxygen compared with humidified.

As a general rule the FiO\textsubscript{2} range with low flow nasal cannulae is from 24% – 50% oxygen (Wettstein, Shelledy, & Peters, 2005). Every 1 litre increase in oxygen flow increases the FiO\textsubscript{2} by approximately 0.04% (Vines, 2010). Unfortunately this rule cannot be applied with any certainty due to variation in the patient’s breathing pattern resulting in a variable FiO\textsubscript{2} delivery. For example Bazuaye, Stone, Corris, & Gibson (1992) investigated the variability of FiO\textsubscript{2} with low flow nasal cannulae and concluded that low flow nasal cannulae are unsatisfactory if a precise control of FiO\textsubscript{2} is required. In this investigation, the FiO\textsubscript{2} achieved with 2 L/min oxygen varied from 0.24 to 0.35. The conclusion that low flow nasal cannulae are unable to provide an accurate FiO\textsubscript{2} is also supported in other investigations (Kory et al., 1962; Waldau et al, 1998; Wettstein et al., 2005).
Further limiting the scope of low flow nasal cannulae, it is believed that during oral breathing they become ineffective, in which case a simple face mask should be the next device employed (Chanques et al., 2009; O'Driscoll et al., 2008).

2.5.2 Simple Face Masks

As with low flow nasal cannulae, simple face masks are cheap and easy to use. They are applied routinely in the management of hypoxemia to deliver 5 – 10 L/min oxygen (Kallstrom, 2002; O'Driscoll et al., 2008), providing an approximate FiO$_2$ range of 0.35 – 0.50 (Kallstrom, 2002). As previously implied, simple face masks offer some advantages over low flow nasal cannulae during oral breathing (Chanques et al., 2009; O'Driscoll et al., 2008) but limitations include mask discomfort, more frequent device removal and subsequent oxygen desaturation (Ayhan et al., 2009; Kory et al., 1962; Nolan et al., 1993; Tiruvoipati et al., 2010; Waugh & Granger, 2004).

As with low flow nasal cannulae the FiO$_2$ achieved with simple face masks is dependent on a combination of the patient’s inspiratory flow, the amount of room air entrained and the flow of oxygen delivered through the device. As the patient’s respiratory pattern changes the amount of entrained room air is affected which alters the FiO$_2$ (Sim et al., 2008; Waldau et al, 1998).

This concept has been demonstrated in a study of healthy volunteers in which the performance of oxygen delivery systems was evaluated. In this study Sim et al. (2008) measured the FiO$_2$ achieved with different oxygen delivery systems both at rest and under simulated respiratory distress. They found that simple oxygen masks set to deliver 4, 12 and
24 L/min oxygen, resulted in a significant drop in the achieved FiO\textsubscript{2} during respiratory distress, compared with quiet breathing. Therefore neither low flow nasal cannulae nor simple face masks can provide a precise or consistent oxygen concentration.

### 2.5.3 Venturi Masks

Venturi masks on the other hand do offer some FiO\textsubscript{2} control, at least over the maximum oxygen concentration delivered (Wilkins, Stoller & Kacmarek, 2009). The nozzle of a venturi mask is designed so that a known flow of oxygen will draw a known amount of room air in through an aperture in the nozzle (by a mechanism known as the venturi effect) giving a known oxygen concentration (Wilkins, Stoller & Kacmarek, 2009). Dilution of delivered oxygen does still occur if the patient’s inspiratory flow exceeds the delivered flow. Never the less, the risk of delivering an undesirably high concentration of oxygen is reduced in this manner. Masks kits are available to give a range of set concentrations, typically from 24% - 50% oxygen (Vines, 2010).

### 2.5.4 High Flow Reservoir Masks

There are of course situations where delivering high concentration oxygen therapy is necessary and desirable. The device of choice in the short term situation is a high flow reservoir mask (O'Driscoll et al., 2008). This mask allows 10 – 15 L/min oxygen to be delivered and reduces room air entrainment by integrating an oxygen reservoir into the system (O'Driscoll et al., 2008; Vines, 2010).
In comparison to simple face masks and low flow nasal cannulae, the high flow reservoir mask is able to maintain a high delivered oxygen concentration even during respiratory distress (Sim et al., 2008). Interestingly however, Sim et al. (2008) found that the maximum FiO\textsubscript{2} achieved with this device is around 0.68. This is less than often quoted in the literature and by manufacturers (Sim et al., 2008; Vines, 2010). The principal limitation of the high flow reservoir mask is that when used for any length of time, there is a tendency for drying of the upper airway to occur (Chanques et al., 2009).

2.5.5 Humidified High-Flow Face Mask

Medical gas is very cold and dry (Barnes, 2000) so when high flow oxygen therapy is required for ongoing management of hypoxemia, the addition of humidity to the gas is required (O'Driscoll et al., 2008). Drying of the airway mucosa is a product of gas flow rate, temperature, humidity and exposure time (Ryan, Rankin, Meyer, & Williams, 2002; Williams et al., 1996). In other words, the higher the gas flow, the colder and dryer the gas, the longer the exposure time, the greater the amount of heat and moisture loss from the airway will be (Ryan et al., 2002; Williams et al., 1996). There is however debate about how much humidity should be added to be optimal (Ricard & Boyer, 2009).

A recent investigation by Chanques et al. (2009) has provided some insight into this problem. The investigators evaluated cold bubble humidifiers (BH) compared to heated humidifiers (HH) during the delivery of high flow face mask oxygen therapy. This study showed that the use of HH provided greater relief from mucosal dryness symptoms compared with BH. In a concurrent bench study Chanques et al. (2009) also found that HH generated a higher median
temperature (34.1 °C versus 26.7 °C, \( p < 0.05 \)), a higher median relative humidity (77.6 % versus 60.7 %, \( p < 0.05 \)) and higher median absolute humidity (29.7 mg/L versus 15.6 mg/L, \( p < 0.05 \)), compared with BH, irrespective of flow. The longer term clinical impact of HH for high flow oxygen therapy has not yet been evaluated, however the results from this study suggest HH is superior to BH in terms of alleviating dryness symptoms.

2.6. The Introduction of Nasal High Flow

The principle limitation of high flow humidified oxygen therapy has been that until recently a face mask was required to deliver it. Nasal high flow is a novel therapy which combines nasal cannulae and heated humidification, enabling high flow oxygen therapy to be delivered directly into the patient’s nose (Price, Plowright, Makowski, & Misztal, 2008; Tiruvoipati, et al., 2010). Non occlusive nasal cannulae connect to a heated humidifier and distal to that a flow source (See Figure 1). Flows of up to 60 L/min are possible with the full range of oxygen concentrations (21% - 100%) (Fisher & Paykel Healthcare, 2010).

![Figure 1. Nasal High Flow System (Optiflow™, Fisher & Paykel Healthcare)](image-url)
The early rationale for using NHF was to provide a comfortable and effective alternative to face mask oxygen therapies, particularly in high dependency settings (Elliot et al., 2007). The main advantage was thought to be that patients could continue to eat, drink, talk and receive oral care, without interface removal (Guerrero, Cuneo, Hnatiuk, & Shorr, 2003). In addition, the mucosal drying associated with high flow un-humidified oxygen therapy could also be prevented (Hoyling, 2006). However, the preliminary clinical evidence suggests that NHF may have additional advantages. It is now proposed for example, that NHF delivers some low level positive airway pressure (Fraser & Corley, in press; Groves & Tobin, 2007; Parke et al., 2009) which may differentiate it from traditional forms of oxygen therapy.

### 2.7. The History of Nasal High Flow

A concept similar to NHF was first described in the clinical literature in 1968 when Dr Neils Lomholt (1968) proposed an innovative system for delivering very high flows of pure oxygen directly into the nares. Lomholt discovered he could deliver 20 - 30 L/min oxygen into one nostril of a patient, comfortably "even without perception" (Lomholt, 1968, p. 1214), provided the gas was at body temperature (37 °C) and saturated with water vapour (44 mg/L H₂O). This gas condition is known as body temperature and pressure saturated (BTPS). Under normal physiological conditions this is the level of heat and humidification achieved in the airway by the time inspired gas reaches the second generation bronchi (Branson, Peterson, B. D., & Carson, K. D., 1998). Nasal high flow delivers gas at BTPS conditions (Fisher and Paykel Healthcare, 2010; Vapotherm, n.d.). This means in theory, the gas is physiologically neutral to the airway in terms of heat and moisture balance, preserving mucosal integrity and mucociliary function (Ryan et al., 2002; Williams et al., 1996).
In spite of the concept showing early promise, NHF didn’t gain acceptance as a respiratory support modality until fairly recently. It became popular in neonatal intensive care units (NICUs) between 2004 and 2006 when the American company Vapotherm Inc. (Stevensville, USA) gained FDA approval to market a device called the 2000i™. However in January 2006 the 2000i™ was subject to an FDA recall amid safety concerns over *Ralstonia spp.* colonisation and cross infection (de Klerk, 2008). In the mean time Fisher and Paykel Healthcare Ltd (East Tamaki, Auckland, New Zealand) introduced a disposable, single patient use system. Vapotherm have since returned to the market with their latest offering, Presicion Flow™ and both devices are now common place in NICUs around the world (de Klerk, 2008; Hochwald & Osiovich, 2010; Hough, Shearman, Jardine, & Davies, 2011).

More recently, both manufactures have released NHF systems designed for adult applications, quickly followed by a number of competitors (Smiths-medical, 2011; Teleflex, 2010).

An extensive review of the literature was performed in November 2010 to identify all relevant and available data pertaining to NHF. Full details of the literature search methodology can be found in Appendix A. The following sections in this chapter review the literature identified.

### 2.8. Neonatal and Infant Applications of Nasal High Flow

There have been several studies published describing the use of NHF in neonates and infants, where ‘high flows’ are generally considered to be 2 – 8 L/min (de Klerk, 2008). Interestingly however, there is a distinct lack of well designed randomised control trials assessing
clinically meaningful outcomes in this population. Much of the available data is observational or physiological in nature.

Firstly, McKiernan, Chua, Visintainer and Allen (2010) conducted a retrospective chart review of infants less than 24 months old, admitted to a paediatric intensive care unit (PICU) with bronchiolitis. They found that the introduction of NHF to the unit was associated with a significant reduction in the rate of intubation compared with a previous comparable period. They also found a reduction in the median length of PICU stay, also thought to be attributable to the introduction of NHF. McKiernan et al., (2010) hypothesised that reduced work of breathing, reduced respiratory rate and good patient tolerance to NHF led to the observed reduction in intubation rate.

While the results of this study may be compelling, the study design did not control for all of the confounding variables which could impact on patient outcome (such is the nature of observational research). However, adding strength to the conclusions of McKiernan et al. (2010), another recent observational study of a similar population, reported almost identical findings associated with the introduction of NHF (Schibler et al., 2011). This second research group (Schibler et al., 2011) agreed with McKiernan et al. (2010) as they also considered that an observed reduction in intubation rates in their unit, resulted from a reduced work of breathing associated with NHF. They went on to test this hypothesis in a physiological study. Schibler, Hough and Pham (2010) used an oesophageal pressure measuring technique to establish that NHF produces a similar physiological effect to CPAP of around 4 cmH₂O and that this significantly reduces work of breathing.
In the preterm neonatal population, physiological evidence also exists to support the concept that reduced work of breathing is attributable to NHF (Saslow et al., 2006). In addition, a retrospective review of 46 infants showed that NHF not only improved oxygenation but also affected lung recruitment due to the generation of a low level positive airway pressure, similar to CPAP (Spentzas, Minarik, Patters, Vinson, & Stidham, 2009).

The balance of evidence would suggest that the generation of a CPAP like effect is confirmed with multiple investigations showing similar results (Hasan & Habib, 2010; Kubicka, Limauro, & Darnall, 2008; Lampland, Plumm, Meyers, Worwa, & Mammel, 2008; Locke, Wolfson, Shaffer, Rubenstein, & Greenspan, 1993; Spentzas et al., 2009; Sreenan, Lemke, Hudson-Mason, & Osiovich, 2001; Wilkinson, Andersen, Smith, & Holberton, 2008). Only one study questions if the amount of pressure is clinically significant (Kubicka et al., 2008). The investigators of this study concluded that only when NHF is delivered to the smallest infants, using the highest flows, can clinically meaningful pressures be generated - and then only when the mouth is fully closed. Of note however, Kubicka et al. (2008) measured oral cavity pressure, whereas the other investigators measured either nasopharyngeal or oesophageal pressure. This perhaps indicates that the different methodologies employed are not comparable.

Most authors agree that the relationship between flow and pressure is positive and linear, although the exact amount of pressure generated with NHF is not easily predicted for the individual infant (Dani, Pratesi, Migliori, & Bertini, 2009; de Klerk, 2008; Lampland et al., 2008; Spence, Murphy, Kilian, McGonigle, & Kilani, 2007; Wilkinson et al., 2008). The inability to monitor the exact pressure delivered is cause for concern amongst a number of
key opinion leaders in the neonatal community. This is due to the risks associated with high uncontrolled airway pressure (de Klerk, 2008; Finer & Mannino, 2009; Walsh, Brooks, & Grenier, 2009).

In spite of some concern, NHF does offer some attractive and tangible advantages over nasal CPAP if used appropriately. For example, NHF has been found to be more easily tolerated than nasal CPAP as a form of respiratory support (Shoemaker, Pierce, Yoder, & Digeronimo, 2007). The equipment required is also cheaper, simpler and less bulky. The interface allows for feeding and parental interaction (de Klerk, 2008) which may also lead to improved growth and development (Holleman-Duray, Kaupie, & Weiss, 2007).

Cautioning the use of NHF as a replacement for nasal CPAP however, one small randomised study of 40 neonates failed to demonstrate any benefit from using NHF over nasal CPAP (Campbell, Shah, Shah, & Kelly, 2006). Indeed, NHF was unable to maintain extubation status as effectively as nasal CPAP in a group of neonates weighing less than 1250g.

To date, the predominant clinical application of NHF for infants and neonates has been as a bridge to or from nasal CPAP, with only a few neonatal units using it as a complete replacement for nasal CPAP (Hochwald & Osiovich, 2010). None the less, the use of NHF is now wide spread and growing rapidly in diverse neonatal and infant populations. This is in spite of a lack of large scale randomised control trials to assess long term safety and efficacy (Bouaram & Fernandes, 2008; de Klerk, 2008; Finer & Mannino, 2009; Walsh et al., 2009).
Encouragingly, it appears that a number of well designed studies are currently in progress, with the aim of addressing clinically meaningful outcomes in this population. These trials can be found by searching for “nasal high flow” and related terms on the World Health Organisation’s international clinical trial registry platform (WHO, 2011).

2.9. Adult Applications of Nasal High Flow

Only a small number of published studies describe the application of NHF in the management of adults with ARF (Lomas, Roca, Álvarez, & Masclans, 2009; Parke et al., 2011; Price et al., 2008; Roca, Riera, Torres, & Masclans, 2010; Tiruvoipati et al., 2010). Firstly, in a recent study conducted by Parke et al. (2011), 60 patients experiencing mild to moderate hypoxemic respiratory failure were randomised to receive either NHF oxygen therapy or heated and humidified high-flow face mask (HHFM) oxygen therapy. The study was conducted in a cardiothoracic and vascular ICU. The study population was predominantly a post operative, cardiac surgical group.

Randomised therapy was successful for more patients in the NHF group compared with the HHFM group (26/29 versus 15/27 respectively, \( p = 0.006 \)). Therapy failed for 12 patients allocated to receive HHFM. Seven of those patients were directly treated with NIV, however the other five were switched to NHF. Only one of whom required subsequent escalation to NIV (the remaining four patients were able to be managed with NHF). In the NHF group, therapy failed for three patients, all of whom were treated directly with NIV. The rate of NIV was therefore 3/29 in the NHF group (10%) compared with 8/27 (30%) in the HHFM group \( (p = 0.096) \). The study was not designed or powered to evaluate NIV rates but the trend towards a lower NIV rate in the NHF group may be useful data to inform future study design.
Parke et al. (2011) also showed that patients in the NHF group experienced significantly fewer episodes of oxygen desaturation over time compared with those in the HHFM group ($p = 0.009$). It is hypothesised that this result was due to more frequent interface removals in the HHFM group. This supports the findings of Nolan et al. (1993) and Ayhan et al. (2009) where oxygen masks were more likely to be removed than nasal cannula, leading to oxygen desaturation.

In addition to the cardiac surgical environment, NHF has also been evaluated in a general ICU setting. In this environment two cross over studies have been conducted comparing NHF against conventional oxygen therapy (Roca et al., 2010; Tiruvoipati et al., 2010).

Roca et al. (2010) compared NHF with conventional oxygen therapy in a sequential cross over study. This study showed NHF to be associated with improved oxygenation and a reduced respiratory rate, as well as a subjective improvement in the sensation of dyspnea and comfort when compared to standard oxygen therapy. Conversely, Tiruvoipati et al. (2010) failed to show any significant difference between NHF and HHFM in terms of oxygenation or respiratory rate. The authors concluded that NHF was as effective as HHFM, however a significant improvement in patient tolerance was demonstrated with NHF.

Returning to the post surgical area, an audit conducted in a surgical high dependency setting supported the findings of Roca et al. (2010) in terms of finding reduced respiratory rates and improved oxygenation associated with NHF (Price et al., 2008). Likewise, a published case report describing the use of NHF during fibroscopy also found it to be useful in the
management of a patient with severe hypoxemic respiratory failure (Lomas et al., 2009). They too concluded that NHF was effective in improving respiratory rate and oxygenation.

Two further studies on this subject have been published as conference proceedings recently. They are yet to be published as full journal articles in the peer reviewed literature. Firstly, Sztrymf et al. (2010) described a prospective observational study of 35 patients with ARF receiving NHF. Patients in this study were severely hypoxemic requiring 80±20% oxygen. In spite of the increased severity of the hypoxemia exhibited, the investigators were in agreement with Roca et al. (2010) in their findings. The investigators found that NHF was associated with a reduced respiratory rate, heart rate and dyspnea score as well as improved oxygenation.

The investigators also reported anecdotally that they considered that a number of intubations were avoided as a result of using NHF. It is important to note however that the study conducted by Sztrymf et al. (2010) was an observational study and so no cause and effect relationships have been demonstrated. Strong conclusions should therefore await a prospective randomised control trial in this population, evaluating this particular outcome.

The second study presented was a prospective randomised control trial which assessed the effect of NHF in a general ICU population, following endotracheal extubation (Idone et al., 2010). In this study hypoxemic patients ready for extubation were randomised to receive either NHF or venturi mask. Preliminary results were described and once again a treatment effect in favour of NHF was evident. Highly consistent results were observed compared with
previous studies in terms of oxygenation, respiratory rate and comfort (Sztrymf et al., 2010) (Roca et al., 2010). In addition, investigators also found less interface displacement and fewer oxygen desaturations with NHF compared with face mask. Again this is consistent with previous work (Ayhan et al., 2009; Nolan et al., 1993; Parke et al., 2011).

Some consensus is therefore evident in the early clinical literature which seems to suggest that NHF may be a promising new treatment modality for the management of adults with ARF, particularly hypoxemic respiratory failure. While the evidence is still preliminary, the balance of data suggests that NHF may be more effective than traditional oxygen therapy in this regard. What is less clear from the literature so far discussed is why NHF is associated with improved physiological effects and increased therapy success.

2.9.1 Proposed Mechanisms of Action

Limited published literature exists to describe the physiological effects of NHF in the adult patient population. Much of the evidence is generated from small numbers of patients and healthy volunteers. Some in vitro work is also available. The available data does however propose that there are some key mechanisms of action which differentiate NHF from traditional forms of oxygen therapy:

2.9.1.1. Positive Airway Pressure

Delivering very high flows of gas directly into the nose inevitably changes the flow and pressure dynamics in the upper airway. This effect has previously been described in neonates
and infants (Hasan & Habib, 2010; Lampland et al., 2008; Locke et al., 1993; Saslow et al., 2006; Spence et al., 2007; Spentzas et al., 2009; Sreenan et al., 2001; Wilkinson et al., 2008) and more recently it has been described in adults.

A number of studies in adults have now demonstrated that a low level of positive pressure is generated in the nasopharynx with NHF. This work was first conducted in healthy volunteers (Groves & Tobin, 2007; Williams, Ritchie, & Gerard, 2006) and then validated and in cardiac surgical patients (Parke et al., 2009; Parke et al., in press).

In the first in a series of studies conducted by Parke et al. (2009), 15 adult post operative cardiac surgical patients were enrolled. Pressure measurements were carried out with NHF and HHFM, both at a flow rate of 35 L/min. This study demonstrated that during mouth closed breathing the pressure generated with NHF was significantly higher than with HHFM (2.7 cmH₂O [SD 1.04] versus 0.2 cmH₂O [SD 0.63], p < 0.001), all be it with a reasonable degree of inter-patient variability. It was also evident that the pressure generated with mouth open breathing was significantly higher with NHF than with HHFM (1.2 cmH₂O [SD 0.76] versus 0.1 cmH₂O [SD 0.39] p < 0.001).

In a second study conducted by Parke et al. (in press), the relationship between flow and pressure was further investigated. In this study, patients were assessed with NHF at increasing gas flow rates of 30, 40 and 50 L/min. A positive linear relationship was described between flow and pressure, meaning that as flow increased, so too did pressure. Using the predictive linear regression model developed from this study every 10 L/min increase in gas
flow, results in an estimated pressure increase of 0.7 cmH₂O with mouth closed and 0.35 cmH₂O with mouth open. As with the first study by Parke et al.(2009) there was a degree of inter-patient variability, so results must be interpreted carefully when applying NHF to the individual patient. This pressure variability is likely to be affected by patient size, gender and anatomical variations as well as the relative size of the nasal prong to the nare, affecting resistance to expiration (Groves & Tobin, 2007; Parke et al., 2009).

The delivery of some pressure may present a mechanism to explain the observed improvements in clinical status previously described. It is known that conventional CPAP improves work of breathing, reduces cardiac preload (Lenique et al., 1997), increases alveolar recruitment and increases FRC (Duncan et al., 1987) but it is not known if these effects are also associated with NHF.

Until very recently techniques have not been available to assess at the bedside, whether the pressure generated by NHF in the upper airway translates into meaningful physiological changes for the patient. However, a new technology called Electrical Impedance Tomography (EIT) has been refined to the point where real time analysis of ventilation distribution in one cross sectional plane of the lungs can now be carried out. This technology has recently been employed to evaluate the effect of NHF on lung volumes, in particular FRC (Fraser & Corley, in press).

Electrical impedance tomography works by detecting and mapping the dynamic impedance change (electrical resistance) across the chest, caused by changes in lung volume during inspiration and expiration (Grant, Fraser, Dunster, & Schibler, 2009). Changes in lung
impedance correlate very well with changes in lung volume so assessing changes in FRC can be reliably evaluated with this technique (Fraser & Corley, in press).

Fraser & Corley (in press) used EIT to investigate the physiological effect of NHF. Similar to the studies performed by Parke et al. (2009; 2011; in press), the study population were predominantly patients with ARF following cardiac surgery. The investigators evaluated the effects of NHF in terms of both lung volume and airway pressure. The airway pressure measurements obtained were in concert with previous work (Groves & Tobin, 2007; Parke et al., 2009; Parke et al., in press; Williams et al., 2006). However by using EIT, Fraser & Corley (in press) were also able to demonstrate that as airway pressure increased, so too did end expiratory lung volume and FRC. This indicates that the elevated airway pressure associated with NHF does indeed translate into improved ventilation. These results suggest that unlike standard oxygen therapies, NHF may also be effective in improving the ventilation status of patients. Secondary outcomes were also assessed in this study in terms of respiratory rate, oxygenation and sensation of dyspnoea. Not surprisingly results were again consistent with much of the previous work described, with a significant treatment effect in favour of NHF (Idone et al., 2010; Roca et al., 2010; Sztrymf et al., 2010).

2.9.1.2. Controlled Oxygen Delivery

Nasal high flow can provide up to 60 L/min of blended oxygen with the full range of oxygen concentrations (21% - 100%). The delivered flow can therefore exceed the resting inspiratory flow of most adults by around 30 L/min (Lomholt, 1968; Williams et al., 2006). In this regard NHF can be considered as a fixed performance oxygen delivery device (Walsh et al, 2009). In order to meet this classification the delivered flow must be sufficient to meet or exceed the
patient’s inspiratory flow, thereby minimising room air entrainment, so the delivered oxygen concentration can be assumed to be the patient’s FiO$_2$ (Hill, Barnes, Hollway, & Tennant, 1984; Waldau et al., 1998). It must be acknowledged however that in severe respiratory distress, patients can generate inspiratory flows of up to 120 L/min (L'Her et al., 2005). In this scenario the clinician can be less certain of the FiO$_2$.

Unfortunately there is no clinical data specifically exploring this concept. Only two studies of healthy volunteers, using simulated conditions, have evaluated the performance of NHF in relation to achieved FiO$_2$. Firstly, Williams et al. (2006) used a hypopharyngeal catheter to assess the FiO$_2$ achieved with NHF in 10 healthy subjects, at rest and with exercise. Inspiratory flows of up to 30 L/min were measured in participants at rest. Then with exercise, inspiratory flows were actively increased to achieve greater than 100 L/min to simulate severe respiratory distress.

The investigation found that at rest the delivered oxygen concentration was very close to the FiO$_2$ providing that the delivered flow exceeded the participant’s inspiratory flow. With inspiratory flows of 100 L/min the delivered flows could not meet the participants’ inspiratory demand and room air dilution occurred. This resulted in some variability between the delivered oxygen concentration and the FiO$_2$.

The second study evaluated the performance of NHF in relation to standard oxygen therapies (Sim et al., 2008). Similar to Williams et al. (2006), healthy subjects ($n = 13$) were assessed at rest and then during simulated respiratory distress. This time respiratory distress was
induced by binding the subject’s chest until their forced expiratory volume over one second was reduced by more than 50%. The maximum achieved FiO2 was then compared between normal breathing and chest bound breathing.

In this study, there was no significant reduction in the FiO2 achieved with NHF during simulated respiratory distress, compared to normal breathing. This result differs from that of Williams et al. (2006) but of course their simulation methodologies were different. Of note, Sim et al. (2008) also demonstrated the maximal achieved FiO2 with NHF was higher than with any of the other oxygen therapies evaluated (mean FiO2 0.89 with NHF versus 0.69 with a high flow reservoir mask, for example). Unfortunately the statistical significance of this finding was not evaluated.

In summary the evidence indicates that NHF provides a flexibility of flow and oxygen concentration which exceeds the performance range of other oxygen therapy devices available. However this work still needs to be validated in a patient population.

2.9.1.3. Flushing of Anatomical Dead Space

It is suggested that flushing of CO2 from the upper airway is an important mechanism in terms of how NHF works (Dysart, Miller, Wolfson, & Shaffer, 2009; Walsh et al., 2009). At the end of a normal expiration the conducting airways are filled with expired, CO2 rich gas which is re-breathed at the beginning of the next inspiration (Vander et al., 1994). These conducting airways are termed ‘dead space’ because they do not take part in gas exchange. Their volume constitutes approximately one third of a resting breath, around 150mls (Vander
et al., 1994). Of this volume, the gas in the nasal passages, nasopharynx, larynx and trachea account for a significant proportion.

The delivery of high flow gas directly into the nasopharynx is believed to create additional turbulence in these conducting airways which flushes out some of the expired, CO$_2$ rich gas, in exchange for fresh oxygen (Dysart et al., 2009; Lomholt, 1968; Walsh et al., 2009). This may also create a reservoir of fresh gas in the upper airway which would increase the inspired concentration of oxygen (Dysart et al., 2009; Lomholt, 1968; Walsh et al., 2009). This opinion is essentially theoretical at present, with little substantive evidence. The best available data in support of the theory comes from highly sophisticated in vitro studies of upper airway flow dynamics (Spence, Buchmann, Jermy, & Moore, 2010). It appears that no investigators to date have been able to substantiate this concept with in vivo data.

There are some clinical indications that flushing of anatomical dead space may occur. For example, patients tend to slow down their respiratory rate when commenced on NHF without any associated rise in CO$_2$ (Fraser & Corley, in press; Roca et al., 2010). This indicates that CO$_2$ clearance may be more efficient. However teasing out whether the mechanism is due to a washout of anatomical dead space or improved ventilation remains to be elucidated.

2.9.1.4. Mucociliary Transport

While heated humidification is an essential component of NHF, it also appears that there are some inherent therapeutic benefits to delivering additional warmth and moisture to the airways. For example, Hasani et al. (2008) assessed the effect of NHF on mucociliary
clearance. The investigators delivered NHF to a group of patients with bronchiectasis for 3 hours per day for a seven day period. Mucociliary clearance was assessed using an inhaled radioaerosol technique, before and after the NHF intervention. The researchers concluded that delivering room air conditioned to BTPS conditions via the NHF system, significantly improved mucociliary clearance. However, Hasani et al. (2008) performed a ‘before and after’ comparison which is known to be subject to the Hawthorn effect (Cormack, 2000) and caution should be applied to strong conclusions. Never the less the results appear to be supported in a recent randomised control trial with a robust study design and important clinical endpoints (Rea et al., 2010).

In this large randomised control trial, participants with chronic lung disease were randomised to receive either standard care or domiciliary NHF for a period of 12 months (Rea et al., 2010). Humidification delivered in this manner significantly reduced the number of acute on chronic exacerbation days and also reduced the time to first exacerbation. Lung function and quality of life were also significantly improved in the treatment group compared to the control (Rea et al., 2010). The authors propose improved mucociliary clearance to be the primary mechanism affecting these important clinical outcomes. It seems reasonable to suggest that NHF may also affect mucociliary clearance in acute as well as chronic respiratory failure but more research is required to test this hypothesis.

2.9.2 Positioning of Nasal High Flow in the Continuum of Respiratory Care

The current evidence suggests that NHF is a novel technique for delivering high flow oxygen therapy in a comfortable and effective manner. It appears to have advantages over other oxygen therapy devices in terms of scope, flexibility, comfort and tolerance, as well as in
physiological response. Perhaps in combination, these benefits extend the role of NHF beyond that of traditional oxygen therapy.

It is not yet clear if NHF can significantly off load the respiratory muscles to support respiratory pump function, but it does seem evident that NHF modulates respiratory rate, lung volume and sensation of dyspnea to some beneficial extent. However, given the relatively low pressures generated with NHF, it appears unlikely that the level of mechanical support offered is equivalent to NIV. Perhaps, rather, the need for escalation of therapy may be averted in some cases if NHF is commenced early in the course of respiratory failure (Parke et al., 2011). Whether the principal mechanism of action is pressure delivery, control of FiO₂, flushing of anatomical dead space, mucociliary clearance or indeed comfort and compliance, remains to be elucidated.

This review leads to the hypothesis that NHF has an extended role, beyond that of traditional oxygen therapy in the management of ARF. However testing this hypothesis requires an extensive research process, to further define the benefits, risks and limitations of NHF. This process will need to be similar to the one undertaken in the NIV literature where large scale studies have investigated clinically meaningful outcomes in multiple patient populations.

In anticipation of such empirical evidence, the aim of this study is to provide insight from an experienced centre to inform future clinical decision making with regards to NHF. More specifically, addressing the questions of when, why, how and on whom to appropriately use NHF.
Chapter 3. Methodology

3.1. Introduction

This study was undertaken in a tertiary level ICU/HDU in a large teaching hospital in New Zealand. In the ICU a 1:1 nurse to patient ratio is usual. In the HDU area this ratio generally drops to 1:2. The clinical governance and day to day management across the whole unit is under the direction of the intensive care consultant team and the senior nursing leadership team. The HDU is a distinct area within the unit and is staffed by an appropriate skill mix of nurses, depending on patient acuity.

The unit predominantly receives patients following both elective and emergent cardiac, thoracic and vascular surgery. The ICU area also admits cardiology patients with critical illness following interventional procedures and community cardiac arrest. In addition to these core functions, a number of highly specialised services are provided to patients and their families. These include providing critical care facilities for the New Zealand heart and lung transplant service and the New Zealand ECMO service. In recent years the unit has also provided a left ventricular assist device service for appropriately selected patients with heart failure.

Approximately 2000 patients are admitted each year, with around 60% requiring ICU and 40% requiring HDU care. Patients with multiorgan failure organ failure and/or a requirement for IMV are nursed in the ICU. As general rule, patients with single organ failure and a requirement for some invasive monitoring or close observation are nursed in the HDU. Noninvasive ventilation (CPAP and BiPAP) can be provided for patients in the HDU,
providing the patient is otherwise stable. The HDU is occasionally used as a step down unit for the ICU but the majority of HDU patients are post operative patients who have undergone thoracic and vascular surgery. The majority of patients in the ICU are post operative patients following cardiac surgery.

Nasal high flow with the Optiflow™ system (Fisher and Paykel Healthcare, East Tamaki, Auckland, New Zealand) was introduced into the unit in 2006. Initially it was used to provide an alternative to high flow face mask oxygen therapy when patients found mask therapy difficult to tolerate. Since then, its application has been broadened significantly. The use of NIV in the unit over the intervening years has dropped dramatically. This drop correlates with the increase in the use of NHF. It is presumed by many of the nurses and doctors that NHF is responsible for the reduction in the need for NIV. Locally, NHF is now believed to be a simple, effective and comfortable means of delivering oxygen therapy and a valuable bridge to more aggressive forms of respiratory support (Parke et al., 2011).

3.2. Research Aims

The clinical literature has not yet delineated where NHF fits in the continuum of respiratory support. Therefore in anticipation of empirical evidence this project aimed to quantifying the NHF experience in this ICU/HDU. The aim was to describe this experience in a manner which could be shared with the wider clinical community and which would help to inform future clinical practice and research. It was hoped that this research would begin to provide valuable and pragmatic support as to; when, why, how and on whom to use NHF.
3.2.1 Primary Objective

In the context of usual clinical practice, the primary objective of this study was to describe the patient population receiving NHF and their subsequent therapy outcomes.

3.2.2 Secondary Objectives

A number of secondary objectives were also developed to achieve the broader aims of this study:

- To describe the clinical reasons for commencing NHF
- To describe the initial management of NHF in terms of therapy settings
- To evaluate the short term physiological impact of NHF
  - To look specifically at the oxygenation response by therapy outcome, to determine if there were ‘responders’ and ‘non responders’ to NHF therapy
- To describe the respiratory management of patients before and after NHF, with a view to establishing where NHF is used in the continuum of respiratory support
- To describe the typical reasons for NHF failure
- To begin to develop criteria to help predict future clinical responses in terms of when NHF is likely to be successful and when it is likely to fail.

To achieve these objectives, it was important to have criteria determined \textit{a priori} to define success and failure of NHF.
3.3. Defining Success and Failure of Nasal High Flow

Nasal high flow was considered to have been successful if one of the following criteria were reached:

- The patient was able to be weaned to low flow nasal cannulae, simple facemask oxygen therapy or room air within 48hrs
- The patient was transferred to the ward on NHF within 48hrs
- The patient was stable and still on NHF at 48hrs
- The patient received NHF for palliative care and did not require an escalation of respiratory support within 48hrs
- The patient was electively intubated and ventilated for a non respiratory reason within 48hrs. (i.e. for a procedure or surgery)

Providing none of the success criteria had been reached, NHF was considered to have failed if:

- The patient required an escalation of respiratory support within 48hrs -
  Escalation of respiratory support included NIV (mask CPAP and mask BiPAP) and IMV

3.4. Study Design

It was important that the study findings reflected usual clinical practice, therefore an observational, non interventional study was deemed to be appropriate. A retrospective chart review was considered, however this was discounted as some of the information required was not consistently documented in the medical notes. For example, the reasons for commencing
NHF were frequently missing from the notes and required specific questions to be asked of the nursing staff commencing the therapy. Therefore a prospective observational study was undertaken. This study is however considered research rather than audit due to its intended purpose.

“Research is concerned with discovering the right thing to do; audit with discovering that it is done right”

(Smith, 1992, p. 905)

A university statistician was consulted during study design and protocol development. This helped to ensure cohesion between the objectives of the study, the nature of the data being collected, the tools being used to collect the data and the statistical tests which would be used to describe relationships between and within the data. The study was also designed in accordance with Good Clinical Practice (GCP) Guidelines (European Medicines Agency, 2002).

3.5. The Scope of the Study

Describing cause and effect relationships is beyond the scope of observational research and it was not the aim of this study to imply causality. Rather, in anticipation of empirical evidence, to add richness and depth to what is known about NHF, and through careful observation, provide insight into likely future responses to inform clinical decision making.
It was beyond the scope of this project to conduct a definitive study in the form of a randomised control trial. The results of this research will however be useful to inform future trial designs by generating new hypotheses, demonstrating event rates and effect size, thereby informing power calculations etc.

3.6. Inclusion and Exclusion Criteria

All patients admitted to the ICU/HDU over the course of this study were screened for eligibility. Patients were deemed eligible if they met the following criteria:

- Patient received NHF in ICU/HDU
  - Using the Optiflow™ system
  - With flows >20 L/min

Patients were excluded from the study if:

- The patient was < 18 years old
- High flow therapy was delivered via face mask
- High flow therapy was delivered via a tracheostomy
- The patient had previously been observed in this study within the same ICU/HDU admission
The rational for excluding patients within the same ICU/HDU admission was based on wanting to avoid multiple data sets for the same patient. It was anticipated that patients who required an escalation of respiratory support beyond NHF could potentially receive NHF again during weaning. Once NHF was considered to have failed it would have been misleading for the same patient to be observed again within a short period of time. Indeed some patients were expected to be on and off NHF multiple times during their ICU stay. Patients were however eligible for re-enrolment if they received NHF during a previous ICU/HDU admission. The rational being, that ICU/HDU discharge, indicated a resolution of ARF. Readmission to ICU/HDU requiring NHF indicated a new episode of ARF. It was acknowledged that in some cases this ‘line in the sand’ would not always hold true but as long as the inclusion / exclusion criteria were applied rigorously and consistently this would not introduce any enrolment bias into the study.

3.7. Study Period and Sample Size

There were no available data on which to base a sample size calculation for this study. However, it was expected that at least 100 patients would receive NHF during a six month period. This rate was based on the rate of Optiflow™ cannulae used each month in the unit. A six month study period was considered both reasonable and pragmatic to capture a representative amount of data to describe current clinical practice trends in relation to NHF use. If more than 100 patients received NHF during the six month period they would be included in the study. Ethically this was deemed acceptable given the observational nature of the study, in so much as, including more patients wouldn’t alter the level of risk exposure.
The original clinical study protocol relating to the previous sections (3.2 – 3.7) can be found in Appendix B).

3.8. Data Collection and Data Management

In accordance with GCP (European Medicines Agency, 2002; Mathieu, 2008), coded recoding forms (CRFs) were developed by the Principle Investigator (PI) to facilitate the data collection required to achieve the specific objectives of the study. Three CRFs were required to collect the following data:

- Date and time NHF was initiated (Appendix C)
- Indications for commencing NHF (Appendix C)
- Respiratory support used prior to NHF (Appendix C)
- Demographic data including ethnicity (Appendix D)
- Clinical diagnosis, significant co-morbidities and smoking history (Appendix D)
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Wagner, Knaus, & Draper, 1983) and Sequential Organ Failure Assessment (SOFA) scores (Vincent et al., 1996) (Appendix D)
- Baseline clinical status (Appendix D)
- NHF therapy settings such as flow and FiO₂ (Appendix E)
- Clinical data one hour following NHF commencement (+/- 30 mins) (Appendix E)
- The most extreme variables and settings within the study period (Appendix E)
- NHF therapy outcome at 48hrs (Appendix E)

- Respiratory support used following discontinuation of NHF (Appendix E)

- A brief description of subsequent respiratory management captured in written notes, when NHF was considered to have failed (Appendix E)

### 3.8.1 Coded Recording Forms

The purpose of coding data the collection tools was to increase patient confidentiality while maintaining traceability (European Medicines Agency, 2002; Mathieu, 2008). As patients were enrolled in the study they were given a unique study number. Their traceable, personal information was recorded in an enrolment log which was linked to their study number. Health information could then be collected, stored, analysed and managed without traceable personal information being directly attached.

The CRFs also needed to be a tool to facilitate rigorous data collection and minimise the need for interpretation and therefore bias. They needed to be sufficiently in depth to capture all of the data required to achieve the study objectives, but concise enough to avoid redundancy. It was important to resist the temptation to collect more data than necessary which would risk diluting the quality of the data collected. A time factor was also taken into consideration. Hence the CRFs were designed so that the required data could be collected in around 30 minutes per patient.
As patients would be eligible for enrolment 24 hrs a day, it was necessary for the bedside nurses to complete the initial form to identify patients going onto NHF (CFR 1, Appendix C). So this form in particular needed to be very easy to interpret and it needed to be quick and simple to complete.

3.8.2 Pilot Phase

In order to test the data collection tools and to test the feasibility of the research protocol, the first 10 patients were treated as a pilot study. For these reasons, conducting a pilot study is generally recommended prior to entering into the main phase of a study (Cormack, 2000). The plan was to include the first 10 patients in the main study providing no major problems were encountered. This created an opportunity to review the data collection tools and make any modifications necessary. This proved to be a useful exercise and some small amendments to the CRFs were made. Of note, the order of the data collection points was rearranged to match the order in which those data points were recorded on the patients chart. This made data collection more time efficient and reduced the likelihood of transcription error. In addition, some extra notes were made on the CRFs to serve as a guideline for data collection. This was useful when there was potential for interpretation in how and when data were recorded.

3.8.3 Designing the Database

Following the pilot phase of 10 patients the database was created and tested by the PI. The database needed to reflect the CRF and facilitate data management and analysis. The database
was de-identified so no traceable, personal information was recorded, only the patients study number.

During the development of the database, the student version of SPSS (SPSS Statistics 17.0, Microsoft, 2008) was trialled. While the functionality of SPSS seemed well suited to this project it was discovered that the student version of this package was not going to be sufficient to cope with the volume of data being collected. A full licence was cost prohibitive so the database was created in excel (Microsoft Excel, 2003) and subsequently transferred to R statistical software before analysis (R Version 2.10.1) (R Core Development Team, 2009).

Codes were developed where possible to group data appropriately. This helped to keep the data clean and facilitated analysis. An example of one code created can be seen in Table 1.

Table 1. ICU/HDU Admission Reason Codes - Example

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CABG Surgery</td>
</tr>
<tr>
<td>2</td>
<td>Cardiac Valve Surgery</td>
</tr>
<tr>
<td>3</td>
<td>CABG and Valve Surgery</td>
</tr>
<tr>
<td>4</td>
<td>Thoracic Surgery</td>
</tr>
<tr>
<td>5</td>
<td>Vascular Surgery</td>
</tr>
<tr>
<td>6</td>
<td>Bilateral Lung Transplant</td>
</tr>
<tr>
<td>7</td>
<td>Respiratory Arrest</td>
</tr>
<tr>
<td>8</td>
<td>Post Operative Respiratory Failure</td>
</tr>
<tr>
<td>9</td>
<td>Other Sternotomy</td>
</tr>
<tr>
<td>10</td>
<td>Cardiac Arrest</td>
</tr>
<tr>
<td>11</td>
<td>Post Angiography</td>
</tr>
<tr>
<td>12</td>
<td>Heart Transplant</td>
</tr>
<tr>
<td>13</td>
<td>Myocardial Infarction</td>
</tr>
</tbody>
</table>
A binary 0 / 1 code was used for all binary data. (0 = No, 1 = Yes). An example of how the binary code worked can be seen in

Table 2.

<table>
<thead>
<tr>
<th>LFNC</th>
<th>SFM</th>
<th>HHFM</th>
<th>FM BiPAP</th>
<th>FM CPAP</th>
<th>IMV</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(LFNC= Low Flow Nasal Cannula; SFM = Simple Face Mask; HHFM = Heated Humidified Face Mask; FM BiPAP = Face Mask BiPAP; FM CPAP = Face Mask CPAP; IMV = Invasive Mechanical Ventilation).

Collating and storing the data in this manner not only made data transfer into the statistical package easier but it also kept the data clean and consistent, making it easier to analyse and interpret.

3.9. Ethical Approval

Ethical approval was obtained for a period of one year from the Northern X Regional Ethics Committee. (See Appendix F). This study was eligible for expedited review due to its non-interventional, low risk nature. Also, given that the study sought only to describe current
practice, the requirement for informed, written consent from patients was waived by the committee.

Studies eligible for expedited review are assessed by the ethics committee Chairperson (or their deputy), rather than the whole committee. The reviewer is tasked with assessing the level of risk to patients and providing protection for participants involved in the research (Ministry of Health, 2007). The Chairperson (or their deputy) will defer the application to the full committee if there are any concerns over the risk to patients. In this case approval was granted by the deputy Chairperson of the committee.

Approval to conduct the study within the District Health Board was also obtained through an expedited process with a hospital based research review committee. (See Appendix G). This process ensures local oversight of research and evaluates the resources required, including any financial impact on the organisation.

3.10. Implementing the Study Protocol

This study was heavily reliant on the ICU/HDU nursing staff identifying and screening patients 24 hours a day, 7 days a week, for a six month period. The nurse responsible for commencing NHF was also responsible for completing the first data collection form for each patient (CRF 1). This form needed to be given to the PI, who would then collect the remaining data required. This presented some logistical concerns.
3.10.1 Education

An intensive education and promotion period was therefore undertaken by the PI. This started with an email alert to all staff, informing them about the study and letting them know to expect some education in the coming weeks. A presentation was also created for the coffee room wall to promote and educate staff about the study. It was not practical to pull staff away from their patients in groups, so one on one training was carried out at the bedside for approximately 80% of Staff Nurses. All Clinical Charge Nurses, Nurse Educators, Clinical Coaches and Shift Coordinators received training and education. This involved evening and weekend sessions to ensure a good level of cover would be achieved. All of the ICU/HDU consultants were also briefed about the study. Training records were maintained to track who had received education. Buckwalter et al. (2009) recommend identifying and addressing any environmental and organisational barriers to research prior to embarking on recruitment. This helps to maintain internal and external validity in unstable research environments such as critical care (Buckwalter et al., 2009). They also recommend identifying the personnel who are vital to the success of the research. Presenting the benefits of the study, in terms of how it will benefit these key stakeholders, is an important aspect of research planning (Buckwalter et al., 2009). It was hoped that through good communication and education, the vast majority of staff in the unit would understand what the study was trying to achieve and would therefore be more motivated to support the rigorous completion of CRF 1. Providing one on one education to key stakeholders ensured any major issues or barriers could be addressed before recruitment commenced.
3.10.2 Logistics

The initial data collection forms were printed on pink paper, to differentiate them from other forms used in the unit and to try to prevent them from being filed in the patient’s notes. The ward clerks were asked to keep an eye out for any stray forms and were shown where to put them in the event they did find any. The forms themselves were made easily available in plastic pockets which were attached to the six Optiflow™ systems used in the unit. A collection box was made for the pink forms and this was left in a prominent place at the nurse’s station.

Three additional ‘study champions’ were identified to help pick up any missing patients and to help remind staff to fill in forms prospectively. The aim was to recruit 100% of patients receiving NHF during the six month period.

3.10.3 Recruitment Phase

Once a pink form (CRF 1) was completed by the bedside nurse and left in the collection box, the PI would follow up with the patient. Depending on the delay between form completion and collection, the patient could be discharged from ICU/HDU. So frequently this required patients to be followed up elsewhere in the hospital. Data collection was completed primarily from the patient’s notes, however occasionally when documentation was inconclusive or absent it was necessary to speak with the nurse who looked after the patient.
3.11. Data Entry, Data Cleaning and Source Data Verification

Data sets for each patient were compiled and filed securely in a locked office in the unit. Data entry was undertaken by the PI in blocks of 10 data sets. Prior to entering data into the database, each CRF was thoroughly checked for any missing or illegible data. Where necessary, source data verification was undertaken which involved retrieving the patient’s notes electronically and making any amendments required. The first 10 patients from the pilot phase were included in the study and where necessary missing data obtained to complete their data sets in line with subsequent data sets.

Once all of the data was entered for every patient in the study, a data cleaning exercise was undertaken by the PI. This involved coding data where possible (as previously described) to ensure consistency across and between data fields. All numeric variables were plotted as individual data to check for significant outliers and spurious data points. When data seemed implausible or unlikely, source data verification was undertaken. This process identified a number of transcription errors which were then appropriately corrected.

To further address the possibility of transcription errors, at the completion of data entry and data cleaning, a quality control audit was undertaken. A random sample of 12 data sets was retrieved and each data point checked against the source data. This process of source data verification is considered good research practice (Mathieu, 2008). No significant errors or omissions were identified at this point so the data was deemed to be complete, accurate and ready for analysis.
3.12. Statistical Methods

Together with the statistician the PI performed the data analysis using R statistical software (R Version 2.10.1) (R Core Development Team, 2009). R is a free statistical package developed to provide a platform to conduct statistical techniques. It enabled the following analysis:

- The data were first examined using descriptive statistical techniques including calculation of summary statistics. Tables, graphs and plots were generated to describe means, medians, standard deviations, percentages, ratios and counts where appropriate.

- The descriptive analysis served to determine the demographic data, physiological variables and therapy settings across the whole group, as well as by NHF success and NHF failure. Welch two sample t-tests, Pearson’s Chi-squared tests (with and without Yates’ continuity correction) and paired t tests were then carried out to describe differences between groups.

- To identify predictive risk factors, logistic regression was used to examine if there were any variables which affected the likelihood of NHF failure.

- Using the trends identified from the descriptive statistics and the logistic regression, further evaluation of variables thought to be associated with NHF failure was
undertaken. This involved splitting the study population into 2 groups by clinically meaningful assessment criteria (eg. group 1 = pH ≤ 7.35 versus group 2 = pH > 7.35). The probability of NHF failure was then evaluated by group and compared using two sample tests for equality of proportions with continuity correction.

- Where statistical tests were used p values of ≤ 0.05 were considered statistically significant.
Chapter 4. Results

4.1. Introduction

Between January and July 2010, there were 599 admissions to the ICU and 400 admissions to the HDU. During this six month period, 120 patients received NHF and all were eligible to participate in the study. One hundred and twenty patients were therefore enrolled. Data collection was complete for all patients with no patients lost to follow up.

Following the commencement of NHF, the therapy outcome (at 48hrs) divided the group by whether NHF was considered to have been successful or whether NHF was considered to have failed. Of the 120 patients to receive NHF, the therapy was successful for 94 patients (78%). Conversely, NHF was considered to have failed for 26 patients (22%). These two main subgroups provide a framework for comparison throughout this chapter.

4.2. The Patient Population

The patient population who received NHF in the ICU/HDU ranged from 24 to 84 years of age (median 65). Patients were predominantly male (69%) and New Zealand European (67%), with a mean weight of 87 Kg (SD 10) and a mean BMI of 30 Kg/m² (SD 6.3). Table 3 describes baseline demographic data and is separated by therapy outcome at 48hrs.
Table 3. Baseline Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>NHF Success</th>
<th>NHF Failure</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 94</td>
<td>n = 26</td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>65 (24-84)</td>
<td>62 (38–82)</td>
<td>0.26a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>63 (67)</td>
<td>20 (77)</td>
<td>0.47b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight in Kgs, mean (SD)</td>
<td>87 (21)</td>
<td>88 (20)</td>
<td>0.87a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI in Kg/m², mean (SD)</td>
<td>30 (7)</td>
<td>30 (5)</td>
<td>0.76a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand European</td>
<td>64 (68)</td>
<td>16 (62)</td>
<td>0.69c</td>
</tr>
<tr>
<td>Other European</td>
<td>7 (7)</td>
<td>4 (15)</td>
<td>0.39d</td>
</tr>
<tr>
<td>New Zealand Maori</td>
<td>7 (7)</td>
<td>1 (4)</td>
<td>0.84e</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>13 (14)</td>
<td>4 (15)</td>
<td>0.91f</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.49g</td>
</tr>
<tr>
<td>Indian</td>
<td>2 (2)</td>
<td>1 (4)</td>
<td>0.83h</td>
</tr>
<tr>
<td>Reason for ICU admission, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG Surgery</td>
<td>27 (29)</td>
<td>8 (31)</td>
<td>0.97a</td>
</tr>
<tr>
<td>Cardiac Valve Surgery</td>
<td>17 (18)</td>
<td>6 (23)</td>
<td>0.77b</td>
</tr>
<tr>
<td>CABG and Valve Surgery</td>
<td>5 (5)</td>
<td>2 (8)</td>
<td>0.99c</td>
</tr>
<tr>
<td>Thoracic Surgery</td>
<td>10 (11)</td>
<td>4 (15)</td>
<td>0.75d</td>
</tr>
<tr>
<td>Vascular Surgery</td>
<td>14 (15)</td>
<td>1 (4)</td>
<td>0.24e</td>
</tr>
<tr>
<td>Bilateral Lung Transplant</td>
<td>2 (2)</td>
<td>1 (4)</td>
<td>0.83f</td>
</tr>
<tr>
<td>Post Operative Respiratory Failure</td>
<td>7 (7)</td>
<td>2 (8)</td>
<td>0.71g</td>
</tr>
<tr>
<td>Other Sternotomy</td>
<td>5 (5)</td>
<td>1 (4)</td>
<td>0.84h</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>2 (2)</td>
<td>1 (4)</td>
<td>0.83h</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Smoking History, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>22 (23)</td>
<td>3 (11)</td>
<td>0.30b</td>
</tr>
<tr>
<td>Ex</td>
<td>43 (46)</td>
<td>15 (58)</td>
<td>0.39c</td>
</tr>
<tr>
<td>None</td>
<td>29 (30)</td>
<td>8 (31)</td>
<td>0.82d</td>
</tr>
</tbody>
</table>

Significant co-morbidities were also evident in this population. The predominant co-morbidities exhibited were hypertension, ischemic heart disease, type II diabetes mellitus, dislipidemia, renal and vascular disease. Of note, respiratory disease was also evident in approximately 26% of patients enrolled in the study. Of the patients with documented respiratory disease, asthma, COPD and emphysema were sited most frequently. A smoking history was recorded in 69% of all patients’ medical histories (21% current smokers, 48% ex-smokers).
As with the demographic data captured, the rate and nature of co-morbidities and smoking history was similar between groups (NHF success versus NHF failure).

4.3. Prior to Nasal High Flow

4.3.1 Baseline Physiological Status

To further describe the population, physiological status was captured immediately prior to NHF commencement. Table 4 describes baseline clinical variables and is again split by whether or not NHF was subsequently found to be successful.

Table 4. Baseline Physiological Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>NHF Success n = 94</th>
<th>NHF Failure n = 26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate / min</td>
<td>20 (6)</td>
<td>21 (7)</td>
<td>0.82a</td>
</tr>
<tr>
<td>Heart Rate / min</td>
<td>90 (17)</td>
<td>95 (17)</td>
<td>0.19a</td>
</tr>
<tr>
<td>Mean Arterial Pressure – mmHg</td>
<td>78 (14)</td>
<td>73 (8)</td>
<td>0.02b</td>
</tr>
<tr>
<td>SpO₂ %</td>
<td>94 (3.5)</td>
<td>94 (4)</td>
<td>0.88a</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (0.06)</td>
<td>7.36 (0.06)</td>
<td>0.13a</td>
</tr>
<tr>
<td>PaCO₂ – kPa</td>
<td>5.47 (0.8)</td>
<td>5.57 (0.8)</td>
<td>0.56a</td>
</tr>
<tr>
<td>PaO₂ – kPa</td>
<td>9.4 (1.96)</td>
<td>9.3 (1.95)</td>
<td>0.83a</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.5 (0.7)</td>
<td>1.6 (0.9)</td>
<td>0.66a</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.37 (0.07)</td>
<td>0.42 (0.14)</td>
<td>0.14b</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>195 (58)</td>
<td>173 (49)</td>
<td>0.07a</td>
</tr>
<tr>
<td>*APACHE II Score</td>
<td>12.11 (5.17)</td>
<td>13.38 (4.09)</td>
<td>0.19a</td>
</tr>
<tr>
<td>Cardiovascular *SOFA Score</td>
<td>1.71 (1.33)</td>
<td>2.12 (1.37)</td>
<td>0.54b</td>
</tr>
<tr>
<td>Respiratory *SOFA Score</td>
<td>2.70 (0.59)</td>
<td>2.96 (0.06)</td>
<td>0.04b</td>
</tr>
</tbody>
</table>

*SOFA = Sequential Organ Failure Assessment

*APACHE II = Acute Physiology And Chronic Health Evaluation

a Welch two sample t test

b Pearson’s Chi-squared test

4.3.1.1. Oxygenation Status

A striking observation of the population was the degree of hypoxemia exhibited, as evidenced by the PaO₂:FiO₂ ratios and the respiratory SOFA scores. Interestingly, there was a trend
towards lower baseline PaO$_2$:FiO$_2$ ratios in the NHF failure group compared with the NHF success group ($p = 0.07$). There was also a statistically significant difference in respiratory SOFA score (which is derived from the PaO$_2$:FiO$_2$ ratio) between groups ($p = 0.04$).

4.3.1.2. Ventilation Status

Of note, the CO$_2$ status of the study population at baseline tended to be in the mid to upper reference range. Respiratory rates tended to be slightly elevated but there were no significant differences in either respiratory rate or PaCO$_2$ between groups at baseline ($p = 0.82$ and $p = 0.56$, respectively).

4.3.1.3. Cardiovascular Status

On the whole, patients were cardiovascularly stable at baseline in terms of heart rate, blood pressure and cardiovascular SOFA score. There was a statistically significant difference in mean arterial pressure (MAP) between the two groups with MAP being lower in the group where NHF went on to fail ($p = 0.02$).

4.3.2 Assessment of Predictive Physiological Variables at Baseline

Logistic regression was performed to determine if any of the baseline physiological variables contributed strongly to the risk of therapy failure. A lower MAP and a lower pH showed the greatest risk contribution, with a strong relationship trend for both of these variables ($p = 0.06$ for both MAP and pH). Details of the complete logistic regression analysis can be found in
Appendix H. None of the baseline physiological variables had a statistically significant effect on the risk of therapy failure \((p \geq 0.05\) for all variables).

With a view to demonstrating the clinical relevance of the trends previously noted, variables which were thought to be the most influential were then selected for further assessment. The probability of therapy failure was evaluated using clinically relevant split points for MAP, pH and \(\text{PaO}_2: \text{FiO}_2\) ratio. A MAP of 70mmHg was selected as being a clinically relevant split point to indicate hypotension. For pH, a level of 7.35 was the indicator of acidosis and for \(\text{PaO}_2: \text{FiO}_2\) ratio, 180 was chosen as the split point for severe hypoxemia. Results are described in Table 5.

Table 5. Comparison of the Probability of NHF Failure at Baseline, by Clinically Important Indicators

<table>
<thead>
<tr>
<th></th>
<th>MAP ≤ 70</th>
<th>MAP &gt; 70</th>
<th>(p =)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHF Failure ((n=26))</td>
<td>11</td>
<td>15</td>
<td>0.51(^a)</td>
</tr>
<tr>
<td>NHF Success ((n=94))</td>
<td>31</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>NHF Failure ((n=25))(*)</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>NHF Success ((n=93))(*)</td>
<td>29</td>
<td>64</td>
<td>0.04(^a)</td>
</tr>
<tr>
<td>(\text{PaO}_2: \text{FiO}_2) ratio ≤ 180</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>(\text{PaO}_2: \text{FiO}_2) ratio &gt; 180</td>
<td>42</td>
<td>51</td>
<td>0.4(^a)</td>
</tr>
</tbody>
</table>

\(^a\) One missing data point
\(^*\) 2-sample test for equality of proportions with continuity correction

This analysis produced a significant result for pH ≤ 7.35 but not for MAP ≤ 70 or \(\text{PaO}_2: \text{FiO}_2\) ratio ≤ 180.
4.3.3 Reasons for Commencing Nasal High Flow

For each patient, the nurse was asked to record all of the contributing reasons why NHF was commenced. The frequency of each applicable reason was then collated. Multiple reasons could be identified for each patient. Figure 2 shows the frequency of each reason.

![Figure 2. Reasons for Commencing NHF](image)

It is clear that the primary reason for commencing NHF was due to hypoxemia as evidenced by arterial blood gas and/or oxygen saturations. This correlates well with mean PaO₂ measurements recorded at baseline. Weaning from IMV was the next most frequently sited
reason for commencing NHF (frequency = 34), where as weaning from NIV was not so common (frequency = 12). Increasing respiratory rate and increasing respiratory distress featured prominently, however other indicators of worsening respiratory pump failure, such as increasing PaCO₂, worsening dyspnoea and use of accessory muscles were not so evident.

4.3.4 Respiratory Support Prior to Nasal High Flow

The respiratory support therapy used immediately prior to NHF was then evaluated. This evaluation also took into account whether NHF was subsequently found to be successful or otherwise. Results are described in Table 6.

<table>
<thead>
<tr>
<th>Respiratory Support</th>
<th>NHF Success n = 94</th>
<th>NHF Failure n = 26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count (%)</td>
<td>Count (%)</td>
<td></td>
</tr>
<tr>
<td>Low Flow Nasal Cannulae</td>
<td>41 (44)</td>
<td>4 (15)</td>
<td>0.02a</td>
</tr>
<tr>
<td>Simple Face Mask</td>
<td>27 (29)</td>
<td>11 (42)</td>
<td>0.28a</td>
</tr>
<tr>
<td>HHFM</td>
<td>3 (3)</td>
<td>1 (4)</td>
<td>0.65a</td>
</tr>
<tr>
<td>Face Mask BiPAP</td>
<td>1 (1)</td>
<td>3 (12)</td>
<td>0.04a</td>
</tr>
<tr>
<td>Face Mask CPAP</td>
<td>5 (5)</td>
<td>1 (4)</td>
<td>0.84a</td>
</tr>
<tr>
<td>IMV</td>
<td>15 (16)</td>
<td>6 (23)</td>
<td>0.58a</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
</tbody>
</table>

a Pearson’s Chi-squared test with Yates’ continuity correction

There were some apparent differences between groups in terms of the respiratory support therapy used immediately prior to NHF. For example, the use of low flow nasal cannulae in the NHF success group was quite high (44%) but comparatively low in the NHF failure group (15%). This difference was statistically significant (p = 0.02). Face mask BiPAP also gave a significant result but the absolute numbers were very small. Across the group as a whole (n =
it was apparent that NHF was used most frequently following standard oxygen therapies (low flow nasal cannulae, simple face mask and HHFM: \( n = 87, 73\% \)). Nasal high flow was also used following IMV (\( n = 21, 18\% \)) and following NIV (mask CPAP and mask BiPAP: \( n = 10, 8\% \)).

### 4.3.5 Starting Nasal High Flow

To describe how NHF was commenced, the initial therapy settings were recorded. This data is described across the whole population and by group (NHF success versus NHF failure) in Table 7.

<table>
<thead>
<tr>
<th>Initial NHF Settings</th>
<th>Whole Population ( n = 120 )</th>
<th>NHF Success ( n = 94 )</th>
<th>NHF Failure ( n = 26 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Flow, L/min</td>
<td>40 (6)</td>
<td>40 (6)</td>
<td>41 (6)</td>
</tr>
<tr>
<td>( \text{FiO}_2 )</td>
<td>0.44 (0.09)</td>
<td>0.44 (0.09)</td>
<td>0.45 (0.09)</td>
</tr>
</tbody>
</table>

A mean flow of 40 L/min (SD 6) with a mean \( \text{FiO}_2 \) of 0.44 (SD 0.09) represented the average starting settings for the whole population receiving NHF in the ICU/HDU. The initial flow and \( \text{FiO}_2 \) settings were found to be almost identical between groups.
4.4. Following Nasal High Flow Commencement

4.4.1 Extremes of Nasal High Flow Use

To capture the extremes of use, the highest independent flow and FiO\textsubscript{2} settings were recorded for each patient during the study period. The lowest independent PaO\textsubscript{2}:FiO\textsubscript{2} ratio was also captured in conjunction with the corresponding gas flow rate at that time. Results are described in Table 8.

Table 8. Extreme Variables within the Study Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>NHF Success (n = 94)</th>
<th>NHF Failure (n = 26)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest Independent FiO\textsubscript{2}</td>
<td>0.49 (0.1)</td>
<td>0.53 (0.11)</td>
<td>0.06\textsuperscript{a}</td>
</tr>
<tr>
<td>Highest Independent Flow, L/min</td>
<td>44 (7)</td>
<td>46 (5)</td>
<td>0.1\textsuperscript{a}</td>
</tr>
<tr>
<td>Lowest PaO\textsubscript{2}:FiO\textsubscript{2}</td>
<td>158 (41)</td>
<td>134 (37)</td>
<td>&lt;0.01\textsuperscript{a}</td>
</tr>
<tr>
<td>Flow at Lowest PaO\textsubscript{2}:FiO\textsubscript{2}, L/min</td>
<td>42 (5.56)</td>
<td>45 (5)</td>
<td>&lt;0.01\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Welch two sample t test

There was a marked difference in the lowest PaO\textsubscript{2}: FiO\textsubscript{2} ratio exhibited during the study period between groups \((p < 0.01)\). The gas flow rate at the corresponding time also differed significantly by group \((p < 0.01)\).

4.4.2 Physiological Status Following Nasal High Flow Commencement

Once established on the therapy, physiological variables were again measured. Table 9 describes physiological status captured at one hour following NHF commencement.
Overall, the predominant feature of the population remained the degree of hypoxemia exhibited. Between groups, the snapshot evaluation of physiological status at one hour showed a number of trends. While none of these trends reached the level of statistical significance it is interesting to note that for most variables evaluated, the clinical picture was marginally better in the NHF success group compared with the NHF failure group.

### 4.4.3 Assessment of Predictive Physiological Variables at One Hour

Simple logistic regression was performed to determine if there were any physiological variables at one hour which strongly affected the risk of therapy failure. At this point, a lower pH appeared to be the strongest contributing risk factor, however this relationship was not statistically significant ($p = 0.08$). See Appendix I for full details of the logistic regression performed. Once again, the clinical relevance of the trends noted was further assessed and variables which were thought likely to be the most influential were selected.
The same variables assessed at baseline were also selected at one hour, therefore the same clinically relevant split points were chosen to reflect the presence of hypotension, acidosis and severe hypoxemia. The probability of NHF failure was compared by each criterion. Results are shown in Table 10.

Table 10. Comparison of the Probability of NHF Failure at One Hour, by Clinically Important Indicators

<table>
<thead>
<tr>
<th></th>
<th>MAP ≤ 70</th>
<th>MAP &gt; 70</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHF Failure (n=26)</td>
<td>13</td>
<td>13</td>
<td>0.45a</td>
</tr>
<tr>
<td>NHF Success (n=94)</td>
<td>37</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>pH ≤ 7.35</td>
<td></td>
<td></td>
<td>p =</td>
</tr>
<tr>
<td>NHF Failure (n=25)</td>
<td>9</td>
<td>16</td>
<td>0.34a</td>
</tr>
<tr>
<td>NHF Success (n=92)</td>
<td>22</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>PaO₂:FiO₂ ratio ≤ 180</td>
<td>22</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>PaO₂:FiO₂ ratio &gt; 180</td>
<td>18</td>
<td>7</td>
<td>0.32a</td>
</tr>
<tr>
<td>NHF Failure (n=25)</td>
<td>18</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>NHF Success (n=92)</td>
<td>54</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

# One missing data point
* Two missing data points
a 2-sample test for equality of proportions with continuity correction

At one hour post NHF commencement there were no statistically significant differences in the probability of NHF failure when evaluating therapy outcome by MAP ≤ 70, pH ≤ 7.35 or PaO₂:FiO₂ ratio ≤ 180.

4.4.4 Physiological Response to Nasal High Flow

To gain further insight into the overall physiological response to NHF, physiological status at one hour was then compared to the respective baseline variables. (See Table 11).
### Table 11. Physiological Response to NHF, Baseline to One Hour

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline n = 120</th>
<th>one hour n = 120</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate / min</td>
<td>20 (6)</td>
<td>21 (6)</td>
<td>0.78&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart Rate / min</td>
<td>91 (17)</td>
<td>90 (14)</td>
<td>0.20&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean Arterial Pressure – mmHg</td>
<td>77 (13)</td>
<td>77 (13)</td>
<td>0.96&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt; %</td>
<td>94 (4)</td>
<td>95 (3)</td>
<td>&lt;0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 (0.06)</td>
<td>7.38 (0.06)</td>
<td>&lt;0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PaCO&lt;sub&gt;2&lt;/sub&gt; – kPa</td>
<td>5.49 (0.8)</td>
<td>5.42 (0.78)</td>
<td>0.10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; – kPa</td>
<td>9.38 (1.95)</td>
<td>10.05 (2.32)</td>
<td>&lt;0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.54 (0.75)</td>
<td>1.55 (0.75)</td>
<td>0.72&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FiO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.38 (0.09)</td>
<td>0.45 (0.09)</td>
<td>&lt;0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;:FiO&lt;sub&gt;2&lt;/sub&gt; ratio</td>
<td>190 (56)</td>
<td>173 (53)</td>
<td>&lt;0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Welch two sample t test

Across the whole population (n = 120) there was no apparent change in mean respiratory rate, heart rate, blood pressure or lactate between time points. Oxygen saturation (SpO<sub>2</sub>) showed a trend towards improvement (p = 0.07) and there was a statistically significant improvement in PaO<sub>2</sub> following NHF commencement (p < 0.01). However, the improvement in PaO<sub>2</sub> would appear to have been associated with a significant increase in FiO<sub>2</sub> (p < 0.01) which translated to a significantly worse PaO<sub>2</sub>:FiO<sub>2</sub> ratio between time points (p < 0.01).

There was also a statistically significant increase in pH from baseline (p < 0.01) and a clinically relevant shift towards the mid reference range (away from respiratory acidosis) with regards to the combination of pH and PaCO<sub>2</sub>. The change in PaCO<sub>2</sub> was not statistically significant (p = 0.10).
4.4.4.1. Comparison of Oxygenation Response by Therapy Outcome

To determine if the oxygenation response differed between therapy outcome group, the change in PaO\(_2\):FiO\(_2\) ratio was further evaluated. Firstly, the change in PaO\(_2\):FiO\(_2\) ratio over time was compared by group. (See Figure 3).

![Figure 3. Change in PaO\(_2\):FiO\(_2\) Ratio from Baseline to One Hour](image)

Consistent with the group as a whole, both the NHF success group and the NHF failure group showed a drop in PaO\(_2\):FiO\(_2\) ratio after one hour of NHF therapy. This was a statistically significant drop for the NHF success group \((p < 0.01 \text{ Paired t-test})\) but not for the NHF failure group \((p = 0.1 \text{ Paired t-test})\).
Visually it appears as though the relative change in PaO₂:FIO₂ ratio between the two time points time is similar between groups. However, detailed analysis was undertaken to confirm if this was the case. The relative difference between PaO₂:FIO₂ ratio at one hour compared to baseline was therefore plotted as a ratio for each patient (see Figure 4).

![Ratio of PaO₂:FIO₂ at 1hr compared to baseline](image_url)

**Figure 4. Ratio of Change in PaO₂:FIO₂ Ratio at One Hour to Baseline - Individual Data and Box Plot**

(Explanation of Figure 4: Individual data are represented with closed circles. A ratio of 1.0 represents no change in PaO₂:FIO₂ ratio from baseline. A ratio of 0.8 represents a 20% reduction in PaO₂:FIO₂ ratio from baseline and a ratio of 1.2 represents a 20% increase in PaO₂:FIO₂ ratio from baseline. Figure 4 also shows the data represented as a box plot: The
smallest observation; the lower quartile (Q1); the median (Q2); the upper quartile (Q3); and the largest observation are indicated. Outliers are represented with open circles).

There was indeed no statistically significant difference in the ratio of the response between groups ($p = 0.92$ Welch two sample t test).

### 4.5. Therapy Outcomes

A primary objective of this study was to describe the therapy outcomes of the study population. Figure 5 describes the therapy outcome at 48 hours for all patients enrolled in the study.

![Patient therapy outcome (n = 120)](image)

Figure 5. Therapy Outcome at 48 Hours
Weaning to standard oxygen therapy was clearly the most common therapy outcome at 48 hours, with almost half of the population falling into this category \((n = 57)\). Nineteen percent of patients \((n = 23)\) were able to be transferred to the ward on NHF within the 48 hour observation period and 9% remained in ICU/HDU but were stable on NHF. These outcomes constituted successful therapy outcomes for NHF.

Patients who required an escalation of respiratory support made up another predominant group. Twenty two percent of the population fell into this category, also making up the population for whom NHF was considered to have failed \((n = 26)\).

### 4.5.1 Respiratory Support Strategies used Following Nasal High Flow

Figure 6 shows the breakdown of respiratory support strategies employed immediately after NHF, within the study period.
During the study period, low flow nasal cannulae was the most frequently applied therapy following NHF \((n = 55)\). Other therapies included Mask CPAP \((n = 14)\), mask BiPAP \((n = 7)\), IMV \((n = 7)\) and HHFM oxygen therapy \((n = 2)\). Interestingly, no patients were given simple face mask oxygen therapy and no patients were weaned to room air following NHF.

### 4.5.2 Failure of Nasal High Flow

Nasal high flow was considered to have failed for 26 patients (22%). All of those patients required an escalation of respiratory support due to a deteriorating clinical status. More detailed reasons contributing to NHF failure were also captured. These reasons are described in Figure 7.
Hypoxemia was the most frequently sited contributing cause of NHF failure, followed by hypercapnia and increasing respiratory distress. Cardiovascular instability, reduced Glasgow Coma Score (GCS) (Teasdale & Jennett, 1974) and inability to clear secretions were also recorded more than once. Other documented causes included a right lower lobe collapse, hypoventilation, acidosis, respiratory arrest and ARDS. Discomfort associated with NHF was not sited as a contributing factor in any of the cases.
4.5.3 Respiratory Management Following Nasal High Flow Failure

To complete this study, the subsequent respiratory management of patients following NHF failure was also monitored carefully. Themes were then identified, and described. Details can be found in Appendix J. Of particular note, 8 patients required intubation and mechanical ventilation following failure of NHF. Seven of whom were intubated quickly, with or without a short trial of NIV first. One patient was managed for four hours with BiPAP but struggled to tolerate the therapy. NHF was reinstituted for a further two hours before the patient was intubated. Two of the patients who required intubation were readmissions from the ward. Both were admitted in semi conscious states with severe respiratory compromise. In these cases NHF was used for preparation and pre-oxygenation, for a controlled intubation.

The remaining 18 patients (who did not require intubation) were managed with a period of NIV before eventually being weaned. Most \( n = 16 \) were treated with subsequent sessions of NHF before either being weaned to low flow nasal cannulae or transferred to the ward. In 9 cases, NHF was used effectively to ‘cycle’ with NIV to avoid intubation. These patients were managed by alternating (cycling) a session of NIV with a session of NHF for varying time periods, usually one to two hours on each therapy. Of note, four of these patients were already on NIV prior to NHF commencement. Finally, tolerance to NIV was a recurrent problem noted \( n = 8 \) and it appeared that NHF was used in a number of cases to facilitate NIV for this reason.
Chapter 5. Discussion

5.1. Introduction

The introduction of NHF to the continuum of respiratory care poses many questions around its potential role in the management of ARF. The clinical literature is yet to define this role, therefore this study sought to provide some preliminary insight into when, why, how and on whom to appropriately use NHF. This was achieved within the context of one population and was moderated by the therapy outcomes experienced by the patients of this ICU/HDU.

This chapter first characterises the patient population who received NHF in the ICU/HDU and in so doing a typical patient and therapy experience is described. Deviations from the typical scenario are also considered with particular emphasis on the circumstances where NHF failed to meet patients’ respiratory needs. This establishes two main subgroups within the population (NHF success and NHF failure), which facilitates the discussion of therapy outcome throughout the chapter.

The results from this research are then discussed within the framework of ARF and in context to previous NHF research. During this process the questions of when, why, how and on whom to use NHF, are specifically addressed. However, it must be acknowledged that the body of evidence in this field is still in its infancy. An important outcome of this research is therefore the new hypotheses which have been generated. The limitations, challenges, contributions and implications of this study are then discussed, before recommendations for future research are suggested.
5.2. Synopsis of Main Results

Data from 120 patients who received NHF in the ICU/HDU were collected and described. This process detailed both the demographic and physiological status of patients at the beginning of NHF therapy. An account of the short term physiological response to NHF was then provided, before therapy outcomes at 48 hours were determined.

The study population was predominantly a post operative cardiac surgical group (52%) but also included patients following vascular (15%) and thoracic (11%) surgery. Nasal high flow was considered to have been successful for 78% of patients, in spite of significant hypoxemia (mean PaO\textsubscript{2}:FiO\textsubscript{2} ratio, 190 [SD56]) and mild to moderate respiratory distress (mean respiratory rate, 20 [SD6]; mean PaCO\textsubscript{2} 5.5 [SD0.8]; mean pH 7.36 [SD0.06]). In general, the population did not therefore exhibit fulminate signs of hypercapnic respiratory failure.

Nasal high flow was used principally as a step up from traditional forms of oxygen therapy (73%) or as a weaning step down from IMV (18%). The rate of NIV usage prior to NHF was comparatively low (8%). The application of NHF resulted in an overall increase in PaO\textsubscript{2} (\(p < 0.01\)) but this was also associated with a significant increase in FiO\textsubscript{2} (\(p < 0.01\)) which translated to a significantly worse PaO\textsubscript{2}:FiO\textsubscript{2} ratio (\(p < 0.01\)). In addition there was a clinically relevant trend away from respiratory acidosis with regards to pH (\(p < 0.01\)) and PaCO\textsubscript{2}. However, this trend was not statistically significant for PaCO\textsubscript{2} (\(p = 0.1\)).

Twenty two percent of patients experienced a failure of NHF, requiring an escalation of respiratory support to either NIV or IMV. The most frequently sited reason for failure was
hypoxemia - but hypercapnia and respiratory distress also featured. Generally NHF failure was associated with a more unstable physiological status. At baseline, a pH of less than 7.35 resulted in a significantly higher probability of NHF failure (p = 0.04).

5.3. The Patient Population

In the context of usual clinical practice, the primary objective of this research was to describe the patient population receiving NHF in the ICU/HDU and then to examine patients’ subsequent therapy outcomes. This study has captured a representative sample of patients to describe this population but to give a framework for the data, a typical patient scenario is characterised.

5.3.1 A Typical Patient Scenario

The typical patient to receive NHF in the ICU/HDU would be a New Zealand European male aged approximately in his mid 60’s, following cardiac surgery. His BMI would be around 30 Kg/m² and he would probably have a smoking history as well as hypertension, dislipidaemia and ischaemic heart disease. In addition he may also have type II diabetes mellitus, renal impairment or vascular disease.

This typical patient would be experiencing ARF with moderate to severe hypoxemia prior to commencing NHF. He would be receiving either standard oxygen therapy, or he may have just been extubated. In spite of his hypoxemia, he would otherwise be fairly stable, although his respiratory rate may be slightly elevated and he may show signs of increasing respiratory
distress. In addition, a clinical clue that he may be at risk of respiratory pump failure would be a borderline low pH combined with a PaCO$_2$ in the mid to high reference range.

In terms of baseline physiological status, the typical patient who received NHF in this study was similar to the population described by Parke et al. (2011). However compared to the study population of Roca et al. (2010) this current population was marginally more hypoxemic, with a greater tendency towards respiratory acidosis (lower pH and higher PaCO$_2$). Unfortunately there is little other data available in the literature to allow for further population comparisons.

Returning to the typical scenario in this ICU/HDU, NHF would be commenced principally due to low PaO$_2$ and low oxygen saturation. A starting flow rate of around 40 L/min, blended to deliver around 45% oxygen would be usual. Over the next hour it could be reasonably expected that SpO$_2$ and PaO$_2$ would improve (albeit with a higher FiO$_2$ compared to pre NHF) and pH and PaCO$_2$ would trend back towards the mid reference range. Hypoxemia would still be the predominant feature in the clinical presentation and PaO$_2$:FiO$_2$ ratio may in fact be worse than it was at baseline.

It is likely that within 48 hours of commencing NHF, the typical patient would wean to low flow nasal cannula oxygen without further escalation of respiratory support. If not, he may either continue on NHF in the unit, or he may be transferred to the ward while still receiving the therapy.
5.3.2 Deviations from the Typical Scenario

Of course there are many deviations to be expected from this hypothetical scenario and the ‘typical’ experience described assumes a normal distribution of the data. The descriptive statistics previously reported show the variability and spread in the results obtained.

One deviation of particular interest was the scenario where NHF proved to be insufficient to meet the patient’s respiratory requirements and an escalation of respiratory support was required. This was the case for 22% of the population. By examining this population in more detail, it was apparent that this subgroup differed somewhat from the population for whom NHF was successful.

5.4. Analysis by Therapy Outcome

5.4.1 Physiological Status

More specifically, heart rate, MAP, pH, FiO₂, PaO₂:FiO₂ ratio, APACHEII score and respiratory SOFA score, all indicated a more unstable physiological picture for the NHF failure group at baseline. Then at one hour post therapy commencement MAP, SpO₂, pH, PaO₂, FiO₂ and PaO₂:FiO₂ ratio indicated a similar picture. While most of the individual trends were none significant, all of the trends did point in the same direction. This does therefore strongly suggest that the NHF failure group were more ‘unwell’ than the NHF success group.
5.4.2 Respiratory Support Prior to Nasal High Flow

In addition, the distribution of respiratory support therapies used prior to NHF also differs somewhat by therapy outcome. The use of low flow nasal cannulae for example, was weighted toward the NHF success group. This indicates that the degree of respiratory failure exhibited by this group was perhaps less than in the NHF failure group at baseline.

5.4.3 Extremes of Nasal High Flow Use

During NHF therapy, this observation was also echoed in the extreme variables noted within the study period. For example, the lowest PaO$_2$:FiO$_2$ ratios exhibited during the study period were significantly lower in the NHF failure group ($p < 0.01$). The corresponding gas flow rates used at that time were also significantly higher ($p < 0.01$). Again, this indicates that NHF failure group were experiencing more severe respiratory failure than the NHF success group.

5.4.4 Comparison of Oxygenation Response

In terms of response to NHF, only the change in PaO$_2$:FiO$_2$ ratio was evaluated by therapy outcome. This decision was made *a priori* due to a perception that this was likely to be a sensitive measure of NHF effectiveness. It was therefore surprising, that the group as a whole showed an overall drop in PaO$_2$:FiO$_2$ ratio, as this was inconsistent with previous research (Fraser & Corley, in press; Idone et al., 2010; Roca et al., 2010; Sztrymf et al., 2010). When this result was evaluated by therapy outcome, the analysis demonstrated that the response to NHF between groups was very similar in terms of both the absolute and the relative drop in PaO$_2$:FiO$_2$ ratio over one hour.
These were disappointing observations. It was expected that by looking at the oxygenation response, early in the course of NHF, therapy outcome could be predicted. This concept of ‘responders’ and ‘non-responders’ has been previously described in the NIV literature (Ambrosino et al., 1995; Antonelli et al., 2001). It does not however appear that the oxygenation response to NHF at one hour will be a useful criterion by which to anticipate a patient’s need for therapy escalation.

5.4.5 Failure of Nasal High Flow

At a certain point, a threshold was reached by some patients and the clinical team made a decision to escalate therapy beyond NHF. It is not clear from this or previous research exactly what that threshold should be but it is apparent that NHF has its limitations. Hypoxemia was the most frequently sited reason for NHF failure. This implies that in spite of its apparent success in this regard, there is a point where NHF is not able to meet the patient’s oxygenation needs. This assessment however is likely to be subjective given the absence of evidence in this area.

Looking back at the most extreme NHF variables within the study period, this may help to characterise the subjective thresholds at which point the clinical team were less comfortable persisting with NHF. Comparing the highest independent FiO₂ for example, the average setting in the NHF failure group was 0.53. In the success group it was 0.49. The difference did not reach the level of statistical significance but this finding may have clinical significance.
To explain, if a normal distribution of the data is assumed, then relatively more patients in the NHF failure group would have reached a setting of 50% oxygen or higher. This may represent a subjective threshold at which point the clinical team are more likely to escalate therapy. The same principle might be applied to a number of other variables which either in isolation or collectively inform clinical judgement. Since there isn’t hard evidence to suggest if these judgements are right or wrong this probably reflects the art rather than science of critical care.

5.5. Informing Future Clinical Decisions

In anticipation of empirical evidence, the broader aim of this research was to provide a local insight into; when, why, how and on whom to use NHF and to do this in a manner which could easily be shared with the wider clinical community. The following sections therefore begin to provide some pragmatic support to guide the application and management of NHF. This information builds on what is known from the early clinical literature, with what has been learned from this research. It is acknowledged that this is the beginning of a lengthy research process and many questions remain inconclusively answered.

5.5.1 When: Positioning of Nasal High Flow in the Continuum of Respiratory Support

It seems reasonable to support the argument that NHF is at least an effective alternative to traditional forms of oxygen therapy as suggested by Elliot et al. (2007) and Tiruvoipati et al. (2010). However the success rate of NHF demonstrated in this study, given the degree of
hypoxemia exhibited by the population, is impressive. It suggests that NHF may have a role beyond that of traditional oxygen therapy.

Previous research has proposed physiological mechanisms by which this assertion is also supported. To recap, NHF generates some low level positive airway pressure (Fraser & Corley, in press; Groves & Tobin, 2007; Parke et al., 2009; Parke et al., in press), it is associated with a more accurate oxygen delivery (Williams et al., 2006) and a higher maximal FiO$_2$ compared to standard oxygen therapies (Sim et al., 2008). In addition, a flushing mechanism in the upper airway is proposed, which may have a combined effect of both creating a reservoir for fresh oxygen and increasing CO$_2$ washout in the upper airway (Dysart et al., 2009; Spence et al., 2010). Lastly, mucociliary clearance may be improved (Hasani et al., 2008; Rea et al., 2010) due the delivery of heat and humidification at levels which are optimal for mucociliary transport (Ryan et al., 2002; Williams et al., 1996). However the degree to which each of these mechanisms contributes to extending the role of NHF, beyond traditional oxygen therapy, is unknown.

Certainly in this current study, it appears as though NHF was most frequently used as a step up from either low flow nasal cannulae or simple face mask oxygen therapy. One of the likely explanations for this relates to previous NHF research conducted in this ICU/HDU. For example, NHF has previously been identified as the preferred option for the management of hypoxemic respiratory failure in the unit and found to be more successful than high flow face mask oxygen therapy in this regard (Parke et al., 2011). In addition, it is likely that the clinical team in this unit understand that some low level positive pressure is generated with NHF, as this physiological effect was also described by the same authors (Parke et al., 2009;
Parke et al., in press). This translation of research into practice is likely to have influenced practice trends towards using NHF as a step up from traditional oxygen therapies.

Looking at the other therapies used immediately prior to NHF, it is also apparent that NHF was used fairly frequently as a weaning step, down from IMV. A number of patients were extubated directly onto NHF and although not captured formally, these patients were often perceived to be at risk of extubation failure. In many of these scenarios, extra hand written notes were left by the nursing staff on the pink data collection forms used. These often explained that NHF was commenced due to concerns around perceived reintubation risks factors, such as obesity, heavy smoking history, previous failed extubation and chronic lung disease. It might therefore be assumed that the rate of NHF failure would be significantly higher in this group. Interestingly however, NHF performed quite well. The NHF failure rate was slightly higher in this subgroup but not significantly so (23% versus 16%. $p = 0.58$).

The study presented by Idone et al. (2010) may provide more substantive evidence to advocate the use of NHF post extubation. Certainly a physiological benefit was demonstrated with NHF over standard oxygen therapy but as yet no therapy outcomes have been reported.

It is clear that the rate of NIV usage prior to NHF was quite low. It is presumed that this indicates that NHF is invariably used before NIV in the ICU/HDU. This is not specifically supported in the unit in terms of policy but on further discussion with the intensive care consultant team, it is generally agreed that this is likely to be the case (personal communication. Dr S McGuinness. March 14, 2011). Also, given some of the difficulties and
complications associated with NIV, as described by Gay (2009) and Hill (2000), this may represent a reluctance to start NIV if it can be avoided with NHF.

Due to the recognised absence of clinical practice guidelines in the unit, informed but none the less subjective decision making usually guides therapy selection and escalation (Parke., 2011). It is presumed that this experience is also shared by other units. Evidence based criteria do however exist for commencing NIV. For example, Nava and Hill (2009) suggest the following indications:

- Degree of breathlessness – moderate to severe
- Increased respiratory rate - >24 breaths per minute in obstructive lung disease, >30 breaths per minute in restrictive lung disease
- Signs of increased work of breathing – accessory muscle use, and abdominal paradox
- Acute or acute on chronic respiratory pump failure (best indication) - \( \text{PaCO}_2 > 5.9 \) with \( \text{pH} < 7.35 \)
- Hypoxemia (use with caution) - \( \frac{\text{PaO}_2}{\text{FiO}_2} \) ratio < 200

Broadly speaking, the population to receive NHF in this study would have met the hypoxemic criteria for commencing NIV. However, it is widely known that this indication for NIV is not so well supported in the literature (Antonelli et al., 2003; Nava & Hill, 2009). For the remaining NIV indications, the typical patient would not have met the other escalation criteria (notably, patients did not generally exhibit fulminate signs of respiratory pump failure). However, if a comparison is made between the indications for NIV and the typical
status of this study population, it can be surmised that many patients would have been close
to meeting the respiratory pump failure threshold for NIV:

- Typical status of the study population:
  
  o Degree of breathlessness – generally mild to moderate
  
  o Increased respiratory rate – average 20 breaths per minute (SD 6)
  
  o Signs of increased work of breathing – noted in some patients
  
  o Acute or acute on chronic respiratory pump failure – average PaCO$_2$ 5.49 (SD 0.8), average pH 7.36 (SD 0.06)
  
  o Hypoxemia – average PaO$_2$:FiO$_2$ ratio 190 (SD 56)

It seems logical that the indications for commencing NHF should indeed be different to those
for commencing NIV. The ability of each therapy to affect different facets of respiratory
failure differs by their respective mechanisms of action. For example, the physiological
evidence suggests that NHF may have some beneficial effect on ventilation (Fraser & Corley,
in press) but the extent to which it is able to off load respiratory muscles is unlikely to be
equivalent to NIV. This is due to the relatively low airway pressures generated (Groves &
Tobin, 2007; Parke et al., 2009; Parke et al., in press).

Perhaps what was observed in this current study reflects the use of NHF in patients who were
evidently hypoxemic but who were perceived to be at risk of requiring future therapy
escalation for hypercapnic / respiratory pump failure. In other words there may have been an
anticipated need for therapy escalation but the criteria (other than perhaps hypoxemia) for
commencing NIV or IMV were not yet reached. It remains to be seen in large scale randomised control trials as to whether this early application of NHF can avert the need for NIV or IMV in some cases. Differentiating between the type of respiratory failure (hypoxemic versus hypercapnic) is going to be an important consideration for future research.

In summary, the scope of NHF appears to cover that of traditional oxygen therapy but evidently it extends beyond it in term of the management of hypoxemia. How far beyond remains to be seen. As a prophylactic measure, it also seems justifiable to use NHF when there are concerns that the patient is showing early signs of respiratory pump failure. However, as yet there is no justification to use NHF as an alternative to either NIV or IMV for this indication. Once the accepted and evidence based indications for these therapies have been reached, escalation to NIV or IMV should occur without delay.

### 5.5.2 Why: Indications for Nasal High Flow

Defining the scope of NHF leads to the process of trying to distil down to define appropriate indications for its application. There are a number of possible indications which are supported by the preliminary evidence and further substantiated, to a greater or lesser extent in this study. These include:
5.5.2.1. To Correct Hypoxemia

- NHF appears to be more effective than traditional oxygen therapy in correcting hypoxemia (Fraser & Corley, in press; Idone et al., 2010; Roca et al., 2010) and seems to reduce the frequency of oxygen desaturation (Idone et al., 2010; Parke et al., 2011).

- This study showed NHF to be associated with a significant improvement in PaO₂ and to be highly successful in the management of moderate to severe hypoxemia. Nearly half of the patients in the NHF success group had a PaO₂:FiO₂ ratio of less than 200 at baseline. To put this further into context, a PaO₂:FiO₂ ratio of 200 or less is one of the defining criteria of ARDS (Fink et al., 2005). It is not yet clear what the exclusion criteria should be for NHF, with regards to a lower limit for PaO₂:FiO₂ ratio.

5.5.2.2. To Relieve Mild to Moderate Respiratory Distress

- NHF seems to relieve breathlessness and it has been shown to improve respiratory rate (Fraser & Corley, in press; Idone et al., 2010; Roca et al., 2010). It also delivers low level airway pressure which improves lung volume and ventilation to some extent (Fraser & Corley, in press; Groves & Tobin, 2007; Parke et al., 2009; Parke et al., in press).

- This study failed to show an improvement in respiratory rate but PaCO₂ and pH were positively affected. While neither of these variables were grossly deranged at baseline, both tended to shift away from hypercapnic respiratory failure and acidosis, towards the mid reference ranges (this was a significant change for pH \([p < 0.01]\) and a strong trend for PaCO₂ \([p = 0.1]\)). This finding warrants further investigation but it
does provide further evidence to support the assertion that NHF improves ventilation
to some beneficial extent (Fraser & Corley, in press).

- This study also showed that increasing respiratory rate and increasing respiratory
distress, were often contributing reasons for commencing NHF. While subjective, this
implies that the clinical staff believed that NHF would be of some benefit for patients
with these indications.

5.5.2.3. To Improve Patient Comfort

- NHF has been shown to be more comfortable and more easily tolerated than mask
therapies (Roca et al., 2010; Tiruvoipati et al., 2010) and generally patients tend to
prefer nasal interfaces to facemasks (Ayhan et al., 2009; Nolan et al., 1993).

- This study did not specifically evaluate patient comfort but it was evident that any
discomfort associated with NHF was not a contributing factor in NHF failure.

5.5.2.4. To Facilitate Secretion Clearance

- NHF improves secretion clearance (Hasani et al., 2008; Williams et al., 1996) and
improves markers of acute exacerbation frequency in chronic lung disease (Rea et al.,
2010).

- This study showed that a small number of patients were commenced on NHF to
facilitate secretion management but this outcome was not specifically measured.
5.5.2.5. To Provide a Bridge to and from Mechanical Ventilation

- NHF may be a useful bridge to and from NIV or IMV because it provides a noninvasive means of delivering low level respiratory support with comfort (Fraser & Corley, in press; Roca et al., 2010). It may be more effective than traditional oxygen therapies in this regard (Parke et al., 2011).

- This study has shown that NHF is used as a step up from traditional forms of oxygen therapy, as a step down from IMV and is often tried before NIV.

- In the management of hypoxemia, given the current equivocal evidence of benefit with NIV (Ambrosino & Vagheggini, 2008; Antonelli et al., 2003; Nava & Hill, 2009), this study indicates that there could be a significant overlap between the current hypoxemic indications for NIV and the potential role and scope of NHF. This may provide a stimulus to revise the current hypoxemic threshold for NIV (PaO$_2$:FiO$_2$ ratio < 200) due to the introduction of NHF. However, this hypothesis needs to be tested rigorously before strong recommendations can be made.

- In the management of respiratory pump failure and in the context of previous research conducted by Parke et al. (2011), this study also poses the hypothesis that the early application of NHF may avert the need for NIV in some cases.

5.5.3 Why Not: Contraindications

While it is clear that the evidence is building to define the indications for NHF, it is apparent that there is a no data to indicate when NHF should not be used. Due to the delivery of some positive pressure, it would however seem prudent to at least apply the same contraindications to NHF as for NIV, as described by Nava and Hill (2009). In addition, it also seems
reasonable to strongly caution the use of NHF when the recognised indications for either NIV or IMV have been reached. As more evidence comes to light this caution may soften for some specific applications and indications (eg. for hypoxemic respiratory failure).

5.5.4 Why Continued: Justification for Nasal High Flow

In the scheme of critical care complexity, NHF is relatively simple and seems acceptable to nurses and patients alike (Groves & Tobin, 2007; Roca et al., 2010). However NHF is significantly more complex and costly than a simple face mask or low flow nasal cannula. It is therefore difficult to justify NHF for patients who are experiencing mild or transient hypoxemia (Wattier & Ward, 2011). Nasal high flow would be unlikely to meet the criteria of being the simplest, most comfortable and cost effective option to meet the patient’s needs. On the other hand, patients who are going to be on oxygen therapy for a longer period of time, or who require high flow oxygen, are more at risk of suffering discomfort and complications (Chanques et al., 2009). For these patients it may be that the comfort and compliance achieved with NHF justifies the additional cost and complexity. The cost benefit argument will be further strengthened if NHF is shown to be effective in either preventing clinical deterioration requiring escalation of respiratory support, or facilitating faster discharge from the ICU or hospital.

On this theme, a number of patients in this study were able to be transferred out to the ward while receiving NHF. This observation may indicate that some patients were able to be discharged from ICU/HDU more quickly as a result of NHF. To explain further, normal practice would be to wean patients to standard oxygen therapy if possible, prior to ward transfer. Therefore if NHF was not available in both the unit and the ward it is conceivable
that some patients would stay in the ICU/HDU longer. This observation generates the hypothesis that NHF facilitates earlier discharge to the ward.

**5.5.5 How: Delivering and Titrating Nasal High Flow**

As noted, there is an absence of protocols and guidelines available to provide advice on how to deliver NHF. This study showed that a starting flow rate of 40 L/min was typical with an initial FiO$_2$ of 0.45. It also showed the highest typical flow and FiO$_2$ settings during the study period. It did not however describe how flow was increased or decreased incrementally, or how FiO$_2$ was titrated. It is clear that evidence based protocols and guidelines need to be published and disseminated to guide the management of NHF.

**5.5.6 Who: Generalisability**

This study has described a predominantly post operative surgical population (cardiac, thoracic and vascular) for whom NHF was generally associated with positive therapy outcomes. Indeed of the limited research available in this area, the surgical and cardiac surgical populations feature most frequently (Fraser & Corley, in press; Palange & Simonds, 2010; Parke et al., 2009; Parke et al., in press; Parke et al., 2011; Price et al., 2008). Some limited evidence exists to support the use of NHF in the general ICU (Idone et al., 2010; Roca et al., 2010; Sztrymf et al., 2010; Tiruvoipati et al., 2010) but no studies have looked specifically at the use of NHF in different aetiologies of ARF (e.g. pneumonia, atelectasis, acute exacerbation of COPD, etc). The common clinical presentation of all of the populations studied so far, including this one, is hypoxemic respiratory failure with no more than mild to moderate respiratory distress. All of clinical studies so far discussed, have shown clinical
benefit for this broad population. It does therefore seem reasonable to use NHF, within the scope previously described, for patients who present with this clinical picture of ARF.

5.5.7 Predicting Therapy Outcome

There has been no previous research which has attempted to look for predictors of NHF therapy outcome. This study therefore aimed to provide some novel insight into likely future responses to NHF and in so doing assist with clinical decision making. However, the process of identifying predictive variables is a challenging one that requires extensive study on large populations. Never the less this study may offer some preliminary suggestions as to what to look out for in clinical practice and also where to focus future research.

Firstly, it was evident that there were some physiological differences between patients who subsequently experience NHF failure versus patients who did not. As previously discussed, failure of NHF was generally associated with more unstable physiological status. Logistic regression was then performed with a view to identifying whether any of these factors were influential in determining therapy outcome. This process identified some strong but non significant trends. In particular, lower baseline MAP and pH were highlighted as variables which warrant further evaluation. In the mean time though, it seems reasonable to assess these variables carefully before commencing NHF and to be aware of the possible influence they may have on therapy outcome.

In an attempt to provide more pragmatic decision making support, an analysis of the probability of NHF failure was then performed using clinically relevant criteria. This aimed
to identify more specific measures by which to determine the suitability of NHF for a given patient. Based on trends previously noted, MAP, pH and PaO₂:FiO₂ ratio, were selected for further evaluation in this regard.

This leads to a strong conclusion that a pH of less than or equal to 7.35 should alert the clinical team to the higher probability of NHF failure. This is particularly relevant, given the accepted pH threshold for commencing NIV is less than 7.35 (Nava & Hill, 2009). A statement has already been made to suggest that (with the possible exception of the hypoxemic criteria) once the indications for NIV have been reached, then escalation of respiratory support should not be delayed. This result provides further evidence to support to this argument.

Once therapy had been commenced, it was less clear which variables posed risk factors for NHF failure. Following further logistic regression analysis, lower pH was again highlighted as a possible predictor. However, this was a non significant trend. Never the less, the presence of acidosis at one hour was further evaluated to determine if clinically meaningful criteria could be developed to predict therapy outcome. At this point though, the statistical signal was lost.

Reliably identifying risk factors associated with therapy failure proved to be very difficult. There are likely to be many factors which significantly influence therapy outcome but this study, with the exception of baseline pH, failed to detect them. This probably relates to two main factors. Firstly, the rate of NHF failure was quite low. Meaning the number of data
points to compare against was quite small. Due to the small sample size, other influencing factors may have been present but this study failed to detect them. In addition there are many confounding variables which affect a patient’s therapy outcome in the ICU/HDU environment. This will inevitably cause interference with the statistical signal (Devane, Begley, & Clarke, 2004). More epidemiological style research on larger populations needs to be conducted to better understand all of the influencing factors.

5.6. Unexpected Results

The most unexpected results were regarding the short term physiological impact of NHF. In particular, it was anticipated that respiratory rate and oxygenation status would improve from baseline to one hour post NHF commencement. This was especially so, given the consistency of this finding in previous research (Fraser & Corley, in press; Idone et al., 2010; Roca et al., 2010; Sztrymf et al., 2010). It was also expected that the oxygenation response to NHF would differ between the NHF success group and the NHF failure group.

There are a number of possible explanations as to why these effects were not observed in this study. Firstly, previous studies examining these variables were conducted in relatively controlled research environments with protocols in place for timing and accuracy of data collected. This study on the other hand was heavily reliant on what was routinely documented in the nursing charts. An effect could feasibly have been missed due to timing or inaccuracy of recordings. This may reflect the challenges of performing research in the ‘real world’ as opposed to in controlled experimental environments.
Secondly, it is likely that a number of patients were on a deteriorating clinical course when commenced on NHF. To explain further, the effect of NHF on an increasing respiratory rate might be to halt or slow deterioration, where as in a stable scenario, the effect might be to actively reduce respiratory rate. A similar phenomenon may also apply to PaO₂:FiO₂ ratio. If true, the results from this study would therefore be more realistic than previously observed because of their ‘real world’ nature.

With regards to the lack of improvement in PaO₂:FiO₂ ratio over time, it is also possible that the baseline FiO₂ was underestimated. There is known variability in the FiO₂ achieved with standard oxygen therapies due to room air dilution (Kory et al., 1962; Sim et al., 2008; Waldau et al., 1998; Wettstein et al., 2005) so inaccuracy of baseline measurement is plausible. However, if an underestimation did occur it would mean that the population were even more severely hypoxemic than documented.

In addition to the unexpected physiological response, some new and unexpected applications for NHF may have been identified. For example, two patients were readmitted to the ICU from the ward requiring rapid intubation and mechanical ventilation. These patients were treated with NHF in preparation for intubation. Both scenarios were classified as NHF failures however the therapy allowed the team to prepare for intubation in a controlled manner, while pre-oxygenating the patient with high concentration oxygen.

Also, NHF failure frequently resulted in the application of NIV which patients often found difficult to tolerate. It was not uncommon for NHF to be used subsequent to its ‘failure’ in
order to facilitate NIV therapy. It appeared that NHF was used to provide breaks from NIV and to cycle with NIV. It is also hypothesised that NHF may have allowed for shortened duration of NIV therapy by allowing weaning to occur more quickly than would otherwise be possible. These unexpected applications of NHF need to be specifically evaluated before any further discussion of their efficacy can be made.

5.7. Limitations and Challenges

Overall the research plan for this study was well executed. There were no major deviations required from the original protocol to achieve the objectives of this research (See Appendix B). To that end, the research process was a success. However, this study does have some limitations and there were certainly some challenges experienced along the way.

5.7.1 Limitations

There are naturally limitations to this study. For example, the chosen study design did not allow for cause and effect relationships to be determined. However, it was acknowledged from the start that this research was not going to provide definitive answers or imply causality. Rather, this research would add richness to the little that is known about NHF and would begin to provide some insight into its potential role in the management of ARF. While it is not a definitive study, given the paucity of data in this field, this research may represent a significant step forward in our knowledge and understanding.
A limitation within the study relates to the population sample. Data from only one ICU/HDU was collected and analysed. While the results may be pertinent to this unit, one of the broader aims of the study was to share the experience with the wider clinical community. The extent to which the results observed in this unit can be expected elsewhere is unknown. An important consideration when trying to generalise the results of this research is the relative expertise held at this site, which has evolved over five years of working with NHF. New users in different environments, with different patient populations, may have difficulty replicating the results obtained in this study.

Also, the sample size of this study is a limitation. Although a sample of 120 may be representative of the NHF population in the unit, the sub group analysis proved to be difficult. In particular the group of patients for whom NHF failed, only provided a sample of 26. This may explain why comparisons made between the NHF success and NHF failure groups, resulted in many trends which lacked statistical significance. The small sample size may have contributed to type II statistical errors or ‘false negative’ results (Devane et al., 2004). Also, there are many unknown or confounding variables which are likely to affect NHF therapy outcome. The only way to reliably account for these unknowns is to perform randomised control trials on sufficiently large populations (Devane et al., 2004). This filters out the confounding influence of these unknown variables. The observational nature of this research and the relatively small sub groups may therefore have contributed to the difficulties encountered in finding clear statistical signals.
5.7.2 Challenges

Broadly speaking, the principal challenge in this research process was the scarcity of relevant literature with which to inform study design and with which to compare results. This is a new field of research and as such, it presented both the opportunity and the challenge of choosing from a myriad of unexplored research paths. It was difficult but extremely important to limit the scope of this project, especially given time and resource constraints, in order to maintain the focus and the quality of this work. For example, this required difficult decisions to be made around what information ‘not’ to collect.

More specifically, the analysis phase of this study presented significant difficulties. The descriptive analysis was fairly straightforward but the process of identifying predictive variables and risk factors was complex. The output from this process needed to be clinically meaningful and needed to be presented in a manner which could help inform future clinical decision making. A number of different options were explored to achieve this goal but it came back to simple logistic regression and comparison of probabilities. Multiple analyses were trialled during this process but they were eventually excluded on the basis that they risked being misleading. It was more important to execute the research plan as determined \textit{a priori} than to explore trends in the data which were arguably beyond the original scope of the project. Indeed to examine the same data with many different techniques, risked generating type I statistical errors or ‘false positive’ results (Devane et al., 2004).

Setting up the database was also a big challenge. It took significant time and effort to achieve the desired functionality in order to achieve the aims of the project. It was however worth
spending this time to get it right. The database became an integral tool in the research process, facilitating data entry, data cleaning and data analysis.

5.8. Contribution and Implications of this Research

This study represents a significant advancement in our knowledge and understanding in a field where little evidence currently exists. In particular, this study has offered some novel insight into the potential role of NHF in the management of ARF. This preliminary understanding will also guide future clinical research because of the many new hypothesis generated as a result of this study.

Closs and Cheater (1999) identify that descriptive research, of a similar nature to this study, can be particularly valuable when exploring new or complex issues. The theories developed from such research can generate hypotheses to be specifically examined in experimental studies designed to test the effectiveness of an intervention (Closs & Cheater, 1999). More recently, Vincent (2010) argues that perhaps we should in fact abandon randomise control trials, at least temporarily in ICU research, in favour of gathering data from well designed observational studies. He explains that so many studies in critical care fail to show any clinical benefit because we have not truly understood how our interventions work or the effect they have on the population as a whole. In many cases this leads to inappropriately designed studies which inevitably fail to show an expected treatment effect (Vincent, 2010). This study therefore provides good quality ‘real world’ observational data on which to build our knowledge and understanding, prior to embarking on randomised control trials.


5.8.1 Implications for Clinical Practice

Invasive mechanical ventilation remains a cornerstone in the management of ARF (Jaber, Michelet, & Chanques, 2010). However there is a great motivation to avoid IMV and to reduce the duration of IMV by using noninvasive strategies (Burns et al., 2010). For the most part, the role of NIV in this strategy has been delineated in the clinical literature (Ambrosino & Vagheggini, 2008). However the potential role of NHF is only just beginning to be elucidated.

As a result of this research one patient population for whom NHF is generally associated with a good therapy outcome, has been described and characterised. Clinicians can now therefore compare their own patient population with the population of this study and make judgements as to whom to apply the results in the future. This should assist the clinical team’s decision making process when determining the suitability of NHF to meet the individual patient’s needs.

Principally, this research has shown that in a population of patients with ARF, NHF is an effective means of delivering oxygen therapy. However, the scope of NHF appears to extend beyond that of traditional oxygen therapy, covering moderate to severe hypoxemia as well as mild to moderate respiratory distress.

5.8.1.1. Development of Protocols and Guidelines

Possible indications for NHF were proposed during this research process. In the context of what is already known, this may be useful in the future development of evidence based
protocols and clinical practice guidelines. Such guidelines offer a systematic approach to assist practitioners and patients to make decisions about the appropriateness of healthcare options for specific clinical circumstances (SIGN, 2008). They should however arise from systematic reviews of the best available evidence (Rolls & Elliott, 2008). Such guidelines do not exist in relation to NHF. This study could provide an important contribution in their development.

5.8.1.2. Predicting Therapy Outcome

No previous research has evaluated predictors of NHF therapy outcome. While this research is by no means conclusive, it does contribute by providing a good basis for future clinical practice. In particular, it seems likely that acidosis at baseline (pH < 7.35) is a strong predictor of NHF failure. This finding should be used to assess the suitability of NHF for future patients.

5.8.2 Implications for Future Research

In the context of significant hypoxemia the success rate of NHF demonstrated in this study was impressive. This research may therefore provide a stimulus to re-evaluate the indications for NIV in relation to hypoxemic respiratory failure. This is especially relevant given the equivocal evidence of benefit with NIV in this population (Ambrosino & Vagheggini, 2008; Antonelli et al., 2003; Nava & Hill, 2009). The implication being that if NHF is shown to either be equivalent or superior to NIV in avoiding intubation, it could feasibly become a standard of care for the management of hypoxemic respiratory failure. Of course before this
can happen, well designed, appropriately powered randomised control trials need to evaluate long term and clinically meaningful outcomes.

This study could provide important data to help design such definitive studies. For example, to calculate the required sample size for a randomised control trial, researchers need to know the expected difference in the primary outcome between treatment groups. This is otherwise known as the effect size (Devane et al., 2004). This study provides a realistic estimation of the expected rate of therapy escalation for the NHF arm of such a study.

In addition, this study has indicated that NHF is often used before NIV and before the respiratory pump failure indications for NIV have been reached. In the context of the findings of Parke et al. (2011) it is hypothesised this represents the early application of NHF in the course of respiratory pump failure, which may avert the need for NIV in some cases. If substantiated in a definitive study, the implication is that NHF could become a standard of care for patients judged to be at risk of developing respiratory pump failure. Again, the data from this study may be useful in the design of such a trial, particularly to help define appropriate inclusion and exclusion criteria. For example, the presence of acidosis should perhaps be a specific exclusion criterion. This study indicates that a pH ≤ 7.35 is likely to reduce the overall treatment effect associated with NHF.
5.9. Specific Recommendations for Future Research

In the context of previous research, this study has helped to develop the following hypotheses which should be addressed in well designed and appropriately powered randomised control trials:

1. For the management of hypoxemic respiratory failure, in the absence of significant respiratory pump failure;
   a) NHF is superior to standard oxygen therapy in avoiding escalation of therapy to either NIV or IMV
   b) NHF is equivalent to NIV in avoiding IMV

2. For the prophylactic management of mild to moderate respiratory distress;
   a) NHF is superior to standard oxygen therapy in modulating the course of respiratory pump failure and averting the need for therapy escalation

Other applications and populations have also been touched on in this study, where clinical benefit associated with NHF is thought possible. These include:

1. Post extubation as a prophylactic measure to improve extubation success

2. To improve the success of NIV (avoiding intubation) by cycling with NHF and using NHF to provide breaks from NIV

3. To prepare patients for controlled intubation

These subgroups were too small to warrant further analysis in this study and therefore specific hypotheses have not been formulated. However they still offer opportunities for future research.
It is recommended that all of these hypotheses and research opportunities are tested in multiple studies, at multiple sites and in many different populations. It is also suggested that well defined inclusion and exclusion criteria need to be developed, to differentiate between the various aetiologies and types of respiratory failure. This is because the expected treatment effect with NHF is thought likely to differ by the nature of the pathophysiology being managed. Extensive physiological research is recommended to inform this process. Areas of particular interest include understanding the following mechanisms more thoroughly:

- the extent to which NHF can off load the respiratory pump
- the extent to which NHF can improve lung ventilation (aeration)
- the extent to which flushing in the upper airway improves the efficiency of gas exchange

In the longer term, there will inevitably be a cost benefit argument to justify. Therefore economic outcomes also need to be incorporated into the design of NHF studies. In particular, ICU, HDU and hospital length of stay will be important endpoints in this regard.

In addition to randomised control trials, larger scale observational studies are recommended in broad, heterogeneous populations. This study has made an initial attempt to inform this process for one population. Much broader epidemiological data will be needed to really understand the impact of NHF on the population as a whole.
“Although observational studies are often criticised, being considered only hypothesis generating, they have many advantages, one of the major being that the entire population can be enrolled; there are no exclusion criteria, making the study results more relevant to actual clinical practice”

(Vincent, 2010, p. S537)
Chapter 6. Conclusion

6.1. Thesis Purpose

Nasal high flow is a relatively new therapy in the spectrum of respiratory support modalities available. However, there is little published evidence to guide clinical decision making in relation to when, why, how and on whom NHF should be applied in the management of ARF. The purpose of this thesis was therefore to begin to understand the potential role, scope and limitations of NHF in this regard. The challenge identified, was the need to describe the degree and type of respiratory failure able to be effectively managed with NHF and to do this relative to existing therapies. A review of the literature led to the hypothesis that NHF has an extended role, beyond that of traditional oxygen therapy.

6.2. The Study

The introduction of NHF, to a tertiary level ICU/HDU, has changed the standard of care in the unit for selected patients with ARF. Nasal high flow is now seen as the preferred option for patients with hypoxemic respiratory failure and is attributed with reducing the use of NIV in the unit (Parke et al., 2011). The aim of the study was therefore to describe and quantify this local experience with NHF. The primary objective was to describe the patient population receiving NHF and the subsequent therapy outcomes achieved during normal clinical practice. In so doing, provide support for both future clinical practice and research.

A prospective observational study was carried out over a six month period which captured the application of NHF in 120 patients experiencing ARF. Nasal high flow was considered to
have failed if the patient required an escalation of respiratory support, within 48 hours of 
NHF commencement. The description of the study population was moderated throughout this 
thesis by therapy outcome.

6.3. The Main Results

The main results were:

- Nasal high flow was considered to have been successful for 78% of patients

- The patient population was significantly hypoxemia (mean PaO₂:FiO₂ ratio, 190 
  [SD56])

- The patient population also exhibited mild to moderate respiratory distress (mean 
  respiratory rate, 20 [SD6]; mean PaCO₂ 5.5 [SD0.8]; mean pH 7.36 [SD0.06]) but 
  they were not experiencing fulminate respiratory pump / hypercapnic respiratory 
  failure

- The population described was predominantly a post operative cardiac surgical group 
  (52%) but also included patients following vascular (15%) and thoracic (11%) surgery

- Nasal high flow was used principally as a step up from traditional forms of oxygen 
  therapy (73%) or as a weaning step down from IMV (18%). Nasal high flow appeared 
  to be used prior to NIV in many cases

- The application of NHF resulted in an overall increase in PaO₂ (p < 0.01) but this was 
  associated with a significant increase in FiO₂ (p < 0.01) which translated to a 
  significantly worse PaO₂:FiO₂ ratio. In addition, there was a clinically relevant trend
away from respiratory acidosis with regards to pH ($p < 0.01$) and PaCO$_2$. The trend was not statistically significant for PaCO$_2$ ($p = 0.1$)

- Twenty two percent of patients experienced a failure of NHF, requiring an escalation of respiratory support to either NIV or IMV. The most frequently sited reason for failure was hypoxemia - but hypercapnia and respiratory distress also featured.

- Generally NHF failure was associated with a more unstable physiological status. At baseline, a pH of less than 7.35 should specifically alert the clinical team to the higher probability of NHF failure ($p = 0.04$).

### 6.4. Future Considerations

Oxygen therapy has remained essentially unchanged for over 40 years (Anderson, 2010). It is certainly possible that NHF simply represents a technological advance its delivery. However, if the differentiating feature of oxygen therapy is its inability to treat breathlessness or improve ventilation (Palange & Simonds, 2010) then the preliminary physiological evidence (Fraser & Corley, in press) suggests that NHF is not just oxygen therapy. Indeed the results from this study indicate that NHF is already being used to treat increasing respiratory rate and respiratory distress with some impact on pH and possibly PaCO$_2$. In addition, using the current indications for NIV as a comparator, the degree of hypoxemia exhibited in this study population would normally necessitate an escalation of respiratory support beyond oxygen therapy (Nava & Hill, 2009). That said, this study also suggests that NHF has its limitations. In particular the clinical team should tread cautiously if considering NHF for the more unstable patient or if acidosis is a feature in the patient’s clinical presentation. Perhaps, what should be cautioned most strongly however, is that there are still many unknowns at this
stage. A great deal more research is required to truly understand the scope and limitations of NHF in the management of ARF.

The observations from this study do however begin to guide where NHF might fit within the spectrum of respiratory support therapies currently available. This has helped to define appropriate comparators with which to evaluate the suitability of NHF in a given clinical scenario. This process led to the evolution of some important new hypotheses which, if validated and substantiated, have the potential to challenge the standard of care for selected patients with ARF. In particular questioning whether, in the management of hypoxemic respiratory failure, NHF is more effective than standard oxygen therapy and equivalent to NIV in averting the need for intubation. Then in the evolution of hypercapnic respiratory failure, questioning whether NHF is more effective than standard oxygen therapy in averting the need for NIV.

To truly understand the ability of NHF to affect the different facets of respiratory failure (hypoxemia versus hypercapnic respiratory failure) an extensive research program is required. Well designed and appropriately powered randomised controlled trials, with clinically meaningful endpoints, need to be conducted to test the hypotheses generated from this study. However, given the acknowledged difficulties and costs associated with conducting such trials in critical care (Vincent, 2010) the evaluation of NHF should also take advantage of other research methodologies.
For example, extensive physiological research will help to determine the extent to which
NHF is able to off load the respiratory pump and will further elucidate the extent to which
NHF can support ventilation. Large scale observational research will also serve to provide a
real world understanding of the impact of NHF. This needs to be achieved outside of the
highly selective and controlled environment of experimental research.

In anticipation of an extensive evidence base, NHF appears to be a promising new respiratory
support modality (Roca et al., 2010) which provides a useful tool in the armourmentarium of
respiratory support therapies currently available (Wattier & Ward, 2011). As we learn more it
will become easier to match the most appropriate therapy to the patients needs while
balancing the risks, benefits and limitations of each therapy against one another. We should
expect to see the quantity and quality of NHF research grow exponentially in the coming
years.
APPENDICIES
Appendix A

Literature Search Methodology

The Principle Investigator performed an extensive literature search in November 2010. The following literature sources were used to identify the data:

- PubMed
  

- Medline
  

- The Cochrane Library
  
  http://www.thecochranelibrary.com/view/0/index.html

- Hand searching of conference proceedings, including but not limited to the scientific meetings of:
  
  - The American Thoracic Society
  
  - The American Association of Respiratory Care
  
  - The European Society of Intensive Care Medicine
  
  - The European Respiratory Society
  
  - The Australian and New Zealand Intensive Care Society
  
  - The Pediatric Academic Societies
The author’s endnote library

The following search strings were applied to online sources:

Search string 1:

(((nasal) AND high) AND flow) AND respiratory

Search string 2:

(((high) AND flow) AND oxygen) AND therapy) AND nasal

Search string 3:

(((high) AND flow) AND nasal) AND cannula

Search string 4:

(humid*) AND cannula

Search string 5:

((nasal) AND humid*) AND oxygen

The following limits were applied before including data in this review:

- English language
- Key terms, related terms or key concepts pertaining to NHF
- Use and performance of NHF a key factor in article
- High quality data offering insight into NHF as a respiratory support modality
Appendix B

Study Protocol

Clinical Study Protocol

A Prospective Observational Study of Nasal High Flow in a Cardiothoracic and Vascular Intensive Care and High Dependency Unit
Agreement.

This study will be conducted in accordance with all applicable regulations and Good Clinical Research Practice (GCP) Guidelines.

__Michelle Eccleston_______________________ Principle Investigator

_________________________________________________
(Signature of Principle Investigator) (Date)
Section 1 - Background.

Nasal High Flow (NHF) has been in use in the Cardiothoracic and Vascular Intensive Care Unit and High Dependency Unit (CVICU/CVHDU) at Auckland City Hospital for approximately 3 years. Use of the device has increased in that time and it is now seen as an effective means of delivering oxygen therapy and as a bridge to more aggressive forms of respiratory support.

Several other research projects have also been undertaken in the CVICU (Parke, McGuinness, & Eccleston, 2009; Parke et al., in press; Parke, McGuinness, & Eccleston, 2011) measuring airway pressure generated by the therapy and also comparing it to the standard of care (face mask oxygen therapy) for patients experiencing mild/moderate respiratory distress (Parke, McGuinness, & Eccleston, 2011).

The system used to deliver NHF is designed to deliver oxygen therapy at high flow rates (up to 60 L/min) via nasal cannula. The cannula itself is made of very soft, light weight material. A heated humidifier and heated delivery tube is used to enable the high flows of gas to be delivered directly into the nares without causing mucosal cooling or drying.

The patient population in this ICU is predominantly post operative, cardiac surgical. Patients receive post operative intensive care following cardiopulmonary bypass surgery for coronary artery bypass grafts as well as valve repair and replacement. Smaller but none the less important populations include medical cardiology patients requiring intensive care for cardiopulmonary support, patients with acute respiratory failure and patients with major vascular or thoracic problems, requiring surgical intervention and organ support post operatively.

The patient population in the HDU is also predominantly surgical. Patients cared for in the HDU require close observation with some invasive monitoring. The majority of patients here have undergone significant thoracic or vascular surgery. Some patients are “stepped down” from the ICU into the HDU and likewise some patients in HDU, who require a greater level of organ support, are “stepped up” to the ICU.

In spite of the local experience with NHF there is little evidence in the peer reviewed literature to guide clinicians as to when and how to use the therapy.
**Section 2 - Aims.**

Within the context of “usual care” the aim of this study is to identify key factors associated with successful therapy outcomes and importantly those factors associated with poor outcomes for patients receiving NHF in CVICU/HDU.

Factors will be assessed to determine whether predictive criteria can be developed to inform future practice decisions with regards to NHF.

**Section 3 – Outcomes.**

Primary outcome:

To describe the patients receiving NHF and their therapy outcomes within the context of “usual care” in the CVICU/HDU.

Secondary outcomes:

To identify key factors associated with both successful and unsuccessful NHF therapy outcomes; to identify the reasons for escalation of respiratory support (eg increased hypoxemic respiratory failure) and to describe the short term physiological effects of NHF on respiratory and cardiovascular status.

**Definitions of Successful vs Unsuccessful NHF Therapy Outcomes:**

A successful outcome following NHF is considered to be one of the following:

- Weaned to low flow nasal cannula, simple facemask oxygen therapy or room air within 48hrs.
- Transferred to ward on NHF within 48hrs
- Still on NHF at 48hrs
- Patient receives NHF for palliative care and dies within 48hrs (physiological variables will be discounted once “not for escalation”)
- Electively intubated and ventilated for a procedure or surgery within 48hrs
- Other

An unsuccessful outcome following NHF is considered to be:

- Requirement for escalation of respiratory support within 48hrs. Escalation includes formal CPAP, NIV, IMV.
Reason for escalation will be captured and classified as one or more of the following:

- Increased hypoxemic respiratory failure
- Increased hypercapnic respiratory failure
- Increased respiratory distress
- Discomfort / intolerance
- CVS instability / arrest
- Respiratory arrest or peri arrest
- Secretion retention
- Other

Section 4 - Study Design.

This is a single centre, prospective, observational study.

Section 5 – Methodology.

The study will commence after ethical approval has been obtained and will continue for twelve months. It is anticipated that 160 patients will receive NHF in CVICU/HDU over a twelve month period. This is based on the utilisation of NHF captured over a three month period within the unit.

Given that there is no suitable literature on which to base a sample size calculation, it was felt that this timeframe is both feasible and sensible for obtaining a representative amount of information while capturing seasonal variation.

Patients meeting the inclusion criteria will be identified by the CVICU/HDU nurses when NHF is commenced. The Research Nurse will be informed and will then collect the study data from the CVICU/HDU charts, based on what is routinely documented by the medical, nursing and allied health team.

Inclusion / Exclusion criteria

All patients admitted to the CVICU/HDU over the course of this study will be screened for eligibility for this study.

Patients will be deemed eligible if they meet the following criteria:

- Patient receives Nasal High Flow in CVICU/HDU
  - Using the Optiflow™ system
  - With flows >20 L/min
Patients will be excluded from the study if:

- < 18 years old
- High flow therapy is delivered via face mask
- High flow therapy is delivered via a tracheostomy
- Previously observed in this study within the same ICU admission

Section 6 - Measurements and Data Collection.

The Research Nurse will collect data that is routinely documented on the patient charts.

Data will be collected to describe:

- Date and time NHF initiated (CRF 1)
- Indications for NHF (CRF 1)
- Respiratory support used prior to NHF (CRF 1)
- Demographic data including ethnicity (CRF 2)
- Clinical diagnosis, significant co-morbidities and smoking history (CRF2)
- APACHE II and SOFA score (CRF 2)
- Baseline clinical status (CRF 2)
- NHF therapy settings such as flow, FiO2 (CRF 3)
- Clinical data one hour post commencing NHF (+/- 30 mins) (CRF 3)
- Most deranged clinical variables whilst on NHF within 48hrs (CRF3)
- NHF therapy outcome at 48hrs (CRF 3)
- Respiratory support used following discontinuation of NHF (CRF 3)

Section 7 - Analysis.

The data will be managed using SPSS.

The data will first be examined using descriptive statistical techniques including calculation of summary statistics and drawing of plots. The descriptive analysis will serve to determine the baseline demographics and guide further analysis. Variables which affect successful or unsuccessful NHF therapy will be investigated using logistic regression. Physiological effects pre- and post-NHF will be examined using plots and either t-tests or Wilcoxon tests depending on the nature of the observations.

Statistical analysis aims to investigate relationships between

- T”0”hr Baseline clinical data and successful / unsuccessful outcome
- T”1”hr hour clinical data and successful / unsuccessful outcome
- Most severe physiological variables during 48hrs and successful / unsuccessful outcome

119
- Baseline demographics including co morbidities and successful / unsuccessful outcome
- Short term physiological effects, pre and post NHF (T"0"hr: T"1"hr)

**Section 8 - Patient Identification and Privacy.**

Participants will each be allocated a unique study number at the time of enrolment which will be recorded on each of their respective data sets.

The Research Nurse will retain a list of participants in the study which will match their given study numbers. This list will be stored in a locked office in the CVICU/HDU at Auckland City Hospital, accessible only by Research Staff.

**Section 9 - Data Management and Security.**

**Data forms**

Coded recording forms will be used for data collection

**Identification of data**

All data collected will be linked by a unique patient study number

**Data Accuracy**

All data will be double checked by the Research Nurse. Coded recording forms will be used to ensure clean and accurate data. The Research Nurse will compare with patient notes if any discrepancy occurs.

**Data Storage**

Data will be stored for 10 years and then disposed of in an appropriate manner.

**Section 10 - Publication of Data.**

This project will be reported in a Masters thesis through the University of Auckland.

Results will be presented at an international conference and in a peer reviewed journal.
Appendix C

Coded Recording Form 1

Prospetic Observational Study of Nasal High Flow (Optiflow™) in CVICU/HDU

Please complete for all patients receiving Nasal High Flow (Optiflow™) in CVICU/HDU

Step 1. Stick Patient Identification Label Here

Step 2. Date and time of commencing Nasal High Flow. Cannula size.

Date: ________________________ Time: ________________________ Cannula Size: S N L

Step 3. State reason(s) for commencing Nasal High Flow (Optiflow™) (Tick if all which apply)

- ↓ SpO2 (finger probe saturation)
- ↓ PaCO2 (From ABG)
- Tolerance to previous therapy
- ↓ pH
- ↑ Respiratory Distress
- ↑ Respiratory Rate
- Use of Accessory Muscles
- ↑ Dyspnoea
- ↑ Discomfort associated with previous therapy
- ↑ PaCO2
- To facilitate a procedure
- To facilitate weaning from NIV / BiPAP or CPAP
- To facilitate weaning from invasive ventilation
- To facilitate sedation management

Other (please state): _______________________________________________________

Other (please state): _______________________________________________________

Step 4. Describe respiratory support / therapy immediately prior to commencing Nasal High Flow (Optiflow™) (Select most appropriate)

- Low flow nasal cannula
- Simple face mask
- Humidified face mask
- Face mask BiPAP
- Face mask CPAP
- Invasive ventilation

Other (please state): _______________________________________________________

Step 5. Return this form to the front desk to be collected by the Research Nurse
Thank You!

Contact for enquiries: Michelle Eccleston 021 461 165
Appendix D

Coded Recording Form 2

<table>
<thead>
<tr>
<th>Baseline Data</th>
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<tbody>
<tr>
<td>Patient Study Number</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immediately Prior to NHF Therapy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Data</td>
</tr>
<tr>
<td>DEU / Age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Diagnosis and Significant Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for admission</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute Physiology Scores (24hr period prior to study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>(All variables to be recorded from the same time points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>HR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Therapy / Support (cross ref CRF1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
</tr>
</tbody>
</table>

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Appendix E

Coded Recording Form 3

POST NHF (Optiflow™) in CVICU/HDU

Outcome Data

| Patient Study Number |

Initial NHF Therapy Settings:

<table>
<thead>
<tr>
<th>Flow Rate</th>
<th>FiO2</th>
<th>Cannula Size</th>
</tr>
</thead>
</table>

Clinical Status 1 Hour Post Commencing NHF (+/- 30mins)

<table>
<thead>
<tr>
<th>RR</th>
<th>HR</th>
<th>NBP</th>
<th>SpO2</th>
<th>pH</th>
<th>PAO2</th>
<th>LACr</th>
<th>FiO2</th>
<th>PACO2</th>
<th>RED</th>
<th>SOFA</th>
</tr>
</thead>
</table>

Most Deranged Clinical Variables whilst on NHF during 48hr period:

<table>
<thead>
<tr>
<th>RR</th>
<th>HR</th>
<th>NBP</th>
<th>SpO2</th>
<th>pH</th>
<th>PAO2</th>
<th>LACr</th>
<th>FiO2</th>
<th>PACO2</th>
<th>RED</th>
<th>SOFA</th>
</tr>
</thead>
</table>

NHF Therapy Outcome at 48hrs post commencement of NHF (if applicable):

<table>
<thead>
<tr>
<th>Wanted to lower renal cannula, change mask, oxygen therapy or room air</th>
<th>Tranferred to ward on NHF</th>
<th>Still on NHF</th>
<th>NHL for patient care and the patinet had been treated during the procedure or surgery</th>
<th>Electrally initiated ventilator used for a procedure or surgery</th>
<th>Required escalation of respiratory support / therapy</th>
</tr>
</thead>
</table>

Respiratory Support / Therapy used immediately following NHF:

<table>
<thead>
<tr>
<th>Low Flow nasal cannula</th>
<th>Simple face mask</th>
<th>High Flow humidified face mask</th>
<th>Heated CPAP</th>
<th>Bi-level Bi-level</th>
<th>Positive End Expiratory Pressure</th>
<th>Room air</th>
<th>HH remained on NHF with other equipment</th>
</tr>
</thead>
</table>

For patients who required an escalation of respiratory support use the space below to briefly record subsequent respiratory management:
Appendix F

Ethical Approval

15 December 2009

Ms Michelle Ercolani
Cath. P.O. Box 92315
Auckland 1142

Dear Michelle

Northern X Regional Ethics Committee
Health select
Disability
Ethics
Committees

Email: eth@min.govt.nz

Prospective observational study of rural high flow practice - predictors of success: Prof 2011/09

Principal Investigator
Ms Michelle Ercolani

Supporting
 Locality
Radiology. Auckland District, University of Auckland

Thank you for your application for expedited review. The above study has been given ethical approval by the Deputy Chairperson of the Northern X Regional Ethics Committee.

Approved Documents

• Protocol dated 23 November 2009
• Gated Recording Form 1
• Gated Recording Form 2
• Gated Recording Form 3

Accreditation

The Committee involved in the approval of this study is controlled by the Health Research Council and is conducted and operates in accordance with the Operations Standard for Ethics Committees, April 2006.

Final Report

The study is approved until 15 December 2010. A final report is required at the end of the study and a form to deposit this is available at http://www.ethicscommittee.health.govt.nz/form.htm - progress report. At the end of the study the study will be assessed by the Ethics Committee for the production of a final report and this report must be sent to the Ethics Committee.

Amendments

It should be noted that Ethics Committee approval does not imply any request comments or administrative facilitation by any health service provider within whose facility the investigation is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

We wish you well with your study.

Yours sincerely

Ron Chalmers
Administrator
Northern X Regional Ethics Committee
Appendix G

Institutional Approval

Research Office
Level 14, Support Bldg
Auckland City Hospital
P.O. Box 93034, Grafton, Auckland
Phone: 64 9 307 4849 Ext. 23854
Email: Samantha@sdhb.govt.nz
Website: www.sdhb.govt.nz/ResearchOffice

21 December 2009

Ms Michelle Eccleston
Cardiothoracic & Vascular ICU
Lvl 4 Auckland City Hospital

Dear Michelle

RE: Research project A+4617 (Ethics # NTX/09/169/EXP) - Prospective Observational Study of Nasal High Flow Practice - Predictors of success

The Auckland DHB Research Review Committee (ADHB-RRC) would like to thank you for the opportunity to review your study and has given approval for your research project.

Your institutional approval is dependent on the Research Office having up-to-date information and documentation relating to your research and being kept informed of any changes to your study. It is your responsibility to ensure you have kept Ethics and the Research Office up to date and have the appropriate approvals. ADHB approval may be withdrawn for your study if you do not keep the Research Office informed of the following:

- Any communication from Ethics Committees, including confirmation of annual ethics renewal
- Any amendment to study documentation
- Study completion, suspension or cancellation

More detailed information is included on the following page. If you have any questions please do not hesitate to contact the Research Office.

Yours sincerely

[Signature]

On behalf of the Research Review Committee
Dr Samantha Jones
Manager, Research Office
Auckland DHB
Appendix H

Complete Logistic Regression Analysis of Baseline Physiological Variables

Call:
glm(formula = Required.Escalation ~ RR + HR + MAP + SpO2.1 + PaO2.1 + PaO2.FiO2 + PaCO2.1 + pH.1 + Lactate + FiO2 + APACHEII + SOFA.CVS + SOFA.Resp, family = binomial, data = NHF)

Deviance Residuals:
          Min       1Q   Median       3Q      Max
-1.3207  -0.6776  -0.4007  -0.1574   2.2055

Coefficients:
                          Estimate Std. Error   z value  Pr(>|z|)
(Intercept)              114.50901   61.70382   1.856   0.0635 .
RR                       -0.03352    0.04588  -0.731   0.4650
HR                       0.01173    0.01656   0.708   0.4789
MAP                      -0.06069    0.03232  -1.878   0.0604 .
SpO2.1                   0.04696    0.08948   0.525   0.5997
PaO2.1                   0.12661    0.31588   0.401   0.6886
PaO2.FiO2                -0.01450    0.01471  -0.986   0.3241
PaCO2.1                  -0.93283    0.56714  -1.645   0.1000
pH.1                     -15.34676   8.07725  -1.900   0.0574 .
Lactate                  0.14037    0.35108   0.400   0.6893
FiO2                     1.05756    5.85842   0.181   0.8567
APACHEII                 -0.03212    0.06800  -0.472   0.6367
SOFA.CVS                 0.04848    0.27225   0.178   0.8587
SOFA.Resp                1.10988    0.80791   1.374   0.1695

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 110.533  on 110  degrees of freedom
Residual deviance:  90.019  on  97  degrees of freedom
(9 observations deleted due to missingness)
AIC: 118.02

Number of Fisher Scoring iterations: 6
Appendix I

Complete Logistic Regression Analysis of Physiological Variables at One Hour

Call:
glm(formula = Required.Escalation ~ RR.1 + HR.1 + MAP.1 + SpO2.2 +
       pH.2 + PaCo2 + PaO2.2 + Lactate.1 + FiO2.2 + PaO2.FiO2.1,
       family = binomial, data = NHF)

Deviance Residuals:
    Min        1Q  Median        3Q       Max
-1.1164   -0.7145   -0.5205   -0.3807    2.6786

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    89.6321   50.6851    1.77     0.077
RR.1           0.0068    0.0406    0.17     0.866
HR.1           0.0087    0.0201    0.43     0.666
MAP.1          -0.0198    0.0225   -0.88     0.379
SpO2.2         -0.0443    0.1021   -0.43     0.665
pH.2           -1.4399    6.5291   -0.22     0.830
PaCO2          -0.6149    0.5074   -1.21     0.226
PaO2.2         -0.2050    0.3347   -0.61     0.540
Lactate.1      0.2627    0.3210    0.82     0.413
FiO2.2         4.7940    5.8600    0.82     0.413
PaO2.FiO2.1    0.0056    0.0180    0.31     0.757

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 112.80  on 109  degrees of freedom
Residual deviance: 102.34  on  99  degrees of freedom
(10 observations deleted due to missingness)
AIC: 124.34

Number of Fisher Scoring iterations: 5
Appendix J

Respiratory Management Following NHF Failure
<table>
<thead>
<tr>
<th>Study number</th>
<th>Prior to NHF</th>
<th>NHF</th>
<th>Event 1</th>
<th>Event 2</th>
<th>Event 3</th>
<th>Event 4</th>
<th>Event 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>HMF → NHF</td>
<td>NHF</td>
<td>CPAP 2 hrs ∈</td>
<td>Not able to tolerate CPAP →</td>
<td>NHF 3 days →</td>
<td>Transferred to ward on NHF</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP 4 hrs →</td>
<td>Difficulty tolerating CPAP →</td>
<td>CPAP cycled with NHF 9 hrs →</td>
<td>NHF 37 hrs →</td>
<td>Transferred to ward on NHF</td>
</tr>
<tr>
<td>113</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP 6 hrs →</td>
<td>Not able to tolerate CPAP →</td>
<td>CPAP and BIPAP cycled with NHF for 60 hrs →</td>
<td>NHF 14 hrs →</td>
<td>Weaned to LFNC</td>
</tr>
<tr>
<td>14</td>
<td>BIPAP → NHF</td>
<td>NHF</td>
<td>BIPAP cycled with NHF 8 hrs due to BIPAP intolerance →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>BIPAP cycled with NHF 16 hrs due to NIV intolerance →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>CPAP → NHF</td>
<td>NHF</td>
<td>CPAP cycled with NHF 8 hrs →</td>
<td>NHF 30 hrs →</td>
<td>Transferred to ward on NHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>119</td>
<td>BIPAP → NHF</td>
<td>NHF</td>
<td>CPAP and BIPAP cycled with NHF 4 hrs →</td>
<td>NHF 14 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>IMV → NHF</td>
<td>NHF</td>
<td>BIPAP 8 hrs →</td>
<td>Difficulty tolerating BIPAP →</td>
<td>CPAP cycled with NHF 24 hrs →</td>
<td>Weaned to LFNC</td>
<td>(Developed nasal bridge sore from mask)</td>
</tr>
<tr>
<td>63</td>
<td>IMV → NHF</td>
<td>NHF</td>
<td>BIPAP 1 hr →</td>
<td>Not able to tolerate BIPAP →</td>
<td>NHF 26 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>IMV → NHF</td>
<td>NHF</td>
<td>CPAP 11 hrs →</td>
<td>NHF 16 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>IMV → NHF</td>
<td>NHF</td>
<td>CPAP 2 hrs →</td>
<td>HMF →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP cycled with NHF 12 hrs →</td>
<td>NHF 4 days →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>BIPAP → NHF</td>
<td>NHF</td>
<td>BIPAP cycled with NHF 9 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>LFNC → NHF</td>
<td>NHF</td>
<td>BIPAP 24 hrs →</td>
<td>CPAP 4 hrs →</td>
<td>NHF 29 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP and BIPAP 17 hrs →</td>
<td>NHF 12 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP 10 hrs →</td>
<td>NHF 18 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>BIPAP 6 hrs →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP 10 hrs →</td>
<td>NHF 21 hours →</td>
<td>Weaned to LFNC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>IMV → NHF</td>
<td>NHF</td>
<td>Failed extubation within 1 hr →</td>
<td>Intubated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>IMV → NHF</td>
<td>NHF</td>
<td>Failed extubation within 1 hr →</td>
<td>Intubated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>NHF for 30 mins while preparing for intubation →</td>
<td>Intubated</td>
<td>(4GCS on readmission from the ward)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>NHF for 30 mins while preparing for intubation →</td>
<td>Intubated</td>
<td>(4GCS on readmission from the ward)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>LFNC → NHF</td>
<td>NHF</td>
<td>BIPAP 4 hrs →</td>
<td>Not able to tolerate BIPAP →</td>
<td>NHF 2 hrs →</td>
<td>Intubated</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>LFNC → NHF</td>
<td>NHF</td>
<td>CPAP 2 hrs →</td>
<td>NHF 1 hr →</td>
<td>Intubated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>LFNC → NHF</td>
<td>NHF</td>
<td>Intubated</td>
<td>(Previous failed extubation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>SFM → NHF</td>
<td>NHF</td>
<td>CPAP 2 hours →</td>
<td>Intubated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- NHF cycled with NIV
- Subsequent use of NHF after a period of NIV
- Tolerance to NIV identified as a problem
- Weaned to LFNC or transferred to the ward on NHF
- Intubated


Vincent, J-L., Moreno, R., Takala, J., Willatts, S., De Mendonça, A., Bruining, H., et al. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of


