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High Flow Nasal Oxygen Therapy in Patients After Cardiac Surgery

Rachael Louise Parke

Abstract

Background: Following cardiac surgery, patients are admitted routinely to the Intensive Care Unit (ICU). They are mechanically ventilated until ready for extubation following which oxygen therapy is administered until adequate oxygenation is maintained. There are many devices available to the clinician by which oxygen may be administered. One therapy, nasal high flow oxygen therapy, has been shown to improve oxygenation and be better tolerated when compared to other methods. However, there is little evidence to describe the mechanisms of action of nasal high flow or to demonstrate efficacy.

Aims: To investigate the effect of nasal high flow oxygen therapy on patients after cardiac surgery.

Methods

1. Review of the literature – Pubmed, Medline and CINAHL were searched for all descriptions and reports of nasal high flow oxygen therapy use in patients. This included case reports, observational studies and randomised controlled trials. Nasopharyngeal pressure measurements were performed using nasal high flow oxygen therapy and continuous positive airway pressure (CPAP) delivered via a sealed facemask. Pressures generated over the whole of the respiratory cycle were determined.

2. An evaluation study assessed anonymised chest x-rays of 50 consecutive patients which were scored by a blinded radiologist using both an existing and a modified scoring system. Chest x-ray (CXR) scores were also compared with oxygenation indices at the time of CXR. Scores were assessed for their ability to predict day 3 oxygenation indices.

3. A prospective randomised controlled trial was undertaken in adult patients undergoing cardiac surgery. Participants were assigned to receive either nasal high flow or standard oxygen therapy from the time of extubation through until 0900 hours day 2 postoperative. The primary outcome was number of patients with a ratio of peripheral oxygen saturation to fraction of inspired oxygen (SpO₂/FiO₂) > 445 on post-operative day 3.

4. A multi-centric, point prevalence study was undertaken to describe the current practices with regards oxygen therapy in non-intubated patients in 40 ICUs in Australia and New Zealand.
Results

There was no evidence available to guide clinicians providing care to patients following cardiac surgery as to whether or not the use of routine nasal high flow oxygen therapy would lead to improved outcomes and reduced incidence of pulmonary complications.

Mean (SD) nasopharyngeal airway pressures of 1.4 (0.6), 2.2 (0.8) and 3.0 (1.0) were recorded at 30, 40 and 50 L/min using nasal high flow. Analyses also determined the mean peak expiratory and mean expiratory plateau pressures. Expiratory pressures during NHF were significantly higher than the mean pressures previously reported for this therapy.

When evaluating two x-ray scoring systems it was found that the modified score demonstrated better ability to detect atelectasis on chest x-ray and better specificity than the existing score when comparing the CXR findings with the clinical oxygenation status of the patients. This modified scoring method performed better as an outcome measure for atelectasis in studies of patients following cardiac surgery. The routine use of NHF following cardiac surgery was not associated with an increase in SpO₂/FiO₂ ratio on day 3 post-operative but it may be associated with a reduction in escalation of respiratory therapy and a significantly lower partial pressure of carbon dioxide (PaCO₂).

It was found that oxygen was administered to 86% of non-intubated adult patients in 40 ICUs surveyed. The most common method of oxygen delivery on the day was simple nasal cannulae. Only 24.4% of patients had a documented prescription for oxygen therapy, of which only 7% would be considered complete and comprehensive.

Conclusion Nasal high flow oxygen therapy delivers positive airway pressure across the whole of the respiratory cycle but is not associated with an increase in SpO₂/FiO₂ ratio on day 3 following cardiac surgery when compared to routine care.
Acknowledgements

I would like to express my special thanks to the following, truly amazing people without whom this thesis would never have been possible or completed. I would also like to apologise to anyone else who may not find their name here. Please forgive my addled, tired brain and do not think that your contribution has gone unnoticed or was not truly appreciated.

To Dave, Jake and Cullen thank you all so much for your love, understanding, patience and support. I hope that in some way you have been inspired by what you have seen take shape over the last few years and that it may encourage you to greatness one day too. Thank you for filling up endless hours playing cricket, golf, sailing, walking dogs or going out to allow me the time to sit and write. You can now have the man cave back!! I must also acknowledge my extended family and friends for their love and support and putting up with my self-centredness for the last few years!!

I have been truly lucky to have had two such wonderful supervisors as Associate Professors Andrew Jull and Robyn Dixon. I remember back to the very beginning of this journey and feeling as though I was interviewing them for these roles. I guess in a way I did, as I knew I required a strong team to get me over the finishing line in a strong position and still standing! Andrew and Robyn both bring unique but complementary skills and views to this role and I am eternally grateful to them for the way in which they have challenged me and for their support and encouragement along the way.

I must also thank my clinical advisor Dr Shay McGuinness, Intensive Care Consultant, Cardiothoracic and Vascular ICU, Auckland City Hospital for his unwavering support and belief in both me and these projects. Never one to hold back on suggestions and advice, Shay please know that it is always appreciated (even though sometimes it may be accompanied by the odd “eye roll” and sceptical look!).

To the HOT-AS research nurses involved in this project– Lianne McCarthy, Charlotte Firth, Eileen Gilder, Jodi Brown and Anna Whitley. What a team ladies. Thank you all so very much for your commitment to the HOT-AS study and its completion and integrity. You all worked so hard to get the study completed quickly and efficiently and to ensure that not only was the data collected to a high standard but that our participants and their families were treated with the utmost respect and regard. I am truly lucky to work with such dedicated
people and also to have such wonderful supportive friends. Thanks for the endless cups of tea, laughs and the odd tissue and mojito when things got “challenging”!

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I was supported through this journey by a very generous PhD scholarship and project funding from the Green Lane Research and Education Fund and also by a Clinical Research Training Fellowship from the Health Research Council of New Zealand. I owe a huge debt of gratitude to Jan Ruygrok (GLREF) and Dr Mary-Anne Woodnorth, Research Manager, Auckland District Health Board, for their assistance and support in obtaining this financial assistance.

Finally, I pay tribute to the trial participants, their families, friends and whānau members. As researchers we are totally reliant on these kind and generous folk who agree to participate in our trials. After 8 years undertaking clinical research, it still amazes me at how willing people are to listen to a complete stranger explain a research study to them and then consent to be involved for no reward. The most common response I hear when talking with a potential study participant is “If it will help someone else…” I find this so refreshing and altruistic in this day and age, and truly reaffirms my faith in humanity and the goodness of others.
Personal Interest

My background as a senior Staff Nurse and senior Research Coordinator in the Cardiothoracic and Vascular Intensive Care Unit (CVICU) at Auckland City Hospital contributes greatly to the ideas represented and investigated as part of this thesis. Never could I have imagined when I commenced employment as a Staff Nurse in 1993, in the then Intensive Care Room at the former Green Lane Hospital that my experiences and ideas would culminate in this body of work. Perhaps it was better I didn’t know!

In 2003, Green Lane Hospital closed and all inpatient cardiac services were moved to the newly opened Auckland City Hospital. In 2004 I was appointed to the position of Research Nurse within CVICU and so commenced a new journey. A year later, while away at a research meeting, I heard surprising stories of how one ICU delivered high flows of oxygen directly into the nares and how well, surprisingly, patients tolerated this therapy. So began my journey with nasal high flow oxygen therapy (NHF). Frequently it would seem that as clinicians we are swayed by the “bells and whistles”, the flashing lights, or the free pens when purchasing and introducing new therapies into our practice. Often there has been little clinical research undertaken to demonstrate clinical utility and efficacy prior to marketing of a new device. NHF is to some extent a testament to people power. First designed for use in neonates and paediatrics, it moved slowly into the adult market. Initially manufacturers marketed NHF as a ward based therapy for adult patients; however it did not take long for it to be used in higher acuity patients. As anecdotal evidence spread to “prove” that the therapy worked in a wide range of patients and conditions manufacturers did not have to undertake research in order to encourage its adoption into practice - the product seemed to sell itself. However I wanted to know more about how this therapy worked – not just that it worked - we could see that.

This thesis is a labour of love which I hope will not only elucidate the nature of NHF but will also lead to the development of evidence to determine the most appropriate oxygen therapy for patients following routine cardiac surgery.
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Chapter 6. Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

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Chapter 7. A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for Cardiac Surgery

| Nature of contribution by PhD candidate | Rachael Parke was responsible for the study concept; study design; data collection; data analysis; manuscript preparation and submission; management of reviewers comments and rebuttals. |
| Extent of contribution by PhD candidate (%) | 94 |

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Chapter 8. Protocol for a randomised controlled trial of high flow nasal oxygen therapy compared to standard care in patients following cardiac surgery. The HOT-AS study.

Nature of contribution by PhD candidate: Rachael Parke was responsible for the original study concept and design of the study; obtained ethical approvals and local institutional approval; recruited and trained research nurses to assist with study procedures and data collection; recruited patients; undertook data collection and study procedures; undertook data analysis; prepared the manuscript; managed submission and review of the manuscript and rebuttal to reviewers comments. She was also responsible for obtaining full funding for the study.

Extent of contribution by PhD candidate (%): 94

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Publications


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Presentations


The University of Auckland, School of Nursing Seminar, June 2011, High flow nasal oxygen therapy in patients after cardiac surgery. Oral presentation.


The University of Auckland, HealthEx, September 2011. A New System for Assessing Atelectasis on Chest X-rays after Sternotomy for Cardiac Surgery. Poster presentation


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Abbreviations and Terms

ABG - arterial blood gas
ALI - acute lung injury
ANZICS - Australian and New Zealand Intensive Care Society
ANZICS CTG - Australian and New Zealand Intensive Care Society Clinical Trials Group
APACHE - acute physiologic and chronic health evaluation
ARDS - acute respiratory distress syndrome
ARF - acute respiratory failure
BiPAP - bi-level positive airway pressure
BMI - body mass index
BP - blood pressure
CABG - coronary artery bypass graft
cm H₂O - centimetres of water
CO₂ - carbon dioxide
COPD - chronic obstructive pulmonary disease
CPAP - continuous positive airway pressure
CPB - cardiopulmonary bypass
CRF - case report form
CT - computerised tomography
CVD - cardiovascular disease
CVICU - Cardiothoracic and Vascular Intensive Care Unit
CVS - Cardiovascular system
CXR - chest x-ray
DVT - deep vein thrombosis
EELI - end expiratory lung impedance
EELV - end expiratory lung volume
EIT - electrical impedance tomography
EPAP - expiratory positive airway pressure
FEV₁ – forced expiratory volume in one second
FiO₂ - fraction of inspired oxygen
FRC - functional residual capacity
FVC - forced vital capacity
HOT-AS - high flow oxygen therapy after cardiac surgery
HDU - high dependency unit
HFFM - high flow face mask
HFNC - high flow nasal cannulae
HHFNC - humidified high flow nasal cannulae
HR - heart rate
ICU - intensive care unit
IHD - ischaemic heart disease
IMAG - internal mammary artery graft
IPAP - inspiratory positive airway pressure
IQR - inter-quartile range
ITT - intention to treat analysis
kPa - kilopascal
L/min - litres per minute

LR - likelihood ratio

mmHg - millimetres of mercury

m-RAS - modified radiological atelectasis score

nCPAP - nasal continuous positive airway pressure

NHF - nasal high flow oxygen therapy

NICU - neonatal intensive care unit

NIV - non-invasive ventilation

NPAP - nasopharyngeal airway pressure

NRS - non-invasive respiratory support

O₂ - oxygen

OSA - obstructive sleep apnoea

PCI - percutaneous coronary intervention

PaCO₂ - partial pressure of carbon dioxide in arterial blood

PaO₂ - partial pressure of oxygen in arterial blood

PEEP - positive end expiratory pressure

PICU - paediatric intensive care unit

RAS - radiological atelectasis score

RCT - randomised controlled trial

RR - respiratory rate

SaO₂ - arterial oxygen saturation

SD - standard deviation

SPIV - stereoscopic particle imaging velocimetry
SpO₂ - peripheral oxygen saturation

SpO₂/FiO₂ ratio - ratio of peripheral oxygen saturation to fraction of inspired oxygen

SOFA - sequential organ failure assessment

TAVI - transcatheter aortic-valve implantation

VAS - visual analogue scale

VNS - visual numeric scale
Glossary of Terms

The following is a list of terms and definitions as used throughout this thesis:

**Acute respiratory failure (ARF)** A syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. Acute respiratory failure is characterised by life threatening derangements in arterial blood gases and acid-base status.

**Concentration of inspired oxygen** The proportion of oxygen in the air that is inspired expressed as a decimal expressed as a percentage e.g. 21%

**Continuous positive airway pressure (CPAP)** A technique of respiratory therapy in which airway pressure is maintained above atmospheric pressure throughout the respiratory cycle by pressurization of the ventilatory circuit.

**Deadspace** The space in the trachea, bronchi, and other airways which contains air that does not reach the alveoli during respiration.

**Delivered oxygen concentration** The concentration of oxygen at the site of the oxygen delivery device.

**Dyspnoea** Shortness of breath, difficulty breathing.

**Flow rate** The rate at which oxygen enters an oxygen delivery device in litres per minute.

**Forced expiratory volume in one second (FEV₁)** The volume of air, measured in litres, that can be exhaled during the first second of a forced exhalation.

**Forced vital capacity (FVC)** The amount of air, measured in litres, that can be forcibly expired from the lungs after a maximal, inspiratory effort.

**Fraction of inspired oxygen (FiO₂)** The proportion of oxygen in the air that is inspired expressed as a decimal e.g. 0.21.

**Functional residual capacity (FRC)** The amount of air left in the lungs at the end of normal, passive expiration.
Heated humidifier A device that actively adds heat and water vapour to the inspired gas

High flow face mask (HFFM) A full face mask that is used to deliver high flows of oxygen and air to patients

High flow nasal cannula (HFNC) A device used to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support delivered via a nasal interface

Hyperoxaemia A state of above normal oxygen levels in the arterial blood

Hyperoxia A state of oxygen excess at the tissue or cellular level

Hypoxaemia A state of oxygen deficiency in arterial blood

Hypoxia A state of oxygen deficiency at the tissue or cellular level

Inspired oxygen concentration The concentration of oxygen actually inspired by the patient

Intensive care nurse A registered nurse employed in an intensive care unit who is accountable and responsible for the care of an intensive care patient

Intensive care patient A patient admitted to an intensive care unit

Intensive Care Unit (ICU) A dedicated hospital ward specialising in the care and management of patients experiencing or likely to experience serious illness

Mechanical Ventilation The use of an invasive artificial airway to mechanically assist or replace spontaneous breathing, when patients cannot do so on their own

Minute volume Volume in millilitres of gas inhaled over a one minute period

Nasal high flow (NHF) A technique to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through a nasal interface

Nasal high flow oxygen therapy (NHF) A technique to provide a high flow of heated, humidified oxygen and air to patients requiring respiratory support, delivered through a nasal interface

Nasal cannula A small, plastic tube used to deliver oxygen to the patient via the nares
Non invasive ventilation (NIV) The delivery of ventilatory support without the need for an invasive endotracheal or tracheostomy tube, usually by way of a sealed facemask

Oxygen flow rate The rate at which oxygen enters an oxygen delivery device in litres per minute

Oxygen therapy The therapeutic administration of supplemental oxygen by way of a delivery device such as nasal cannula, face mask or invasive artificial airway

Respiratory dysfunction For the purposes of this thesis respiratory dysfunction is defined as alterations in respiratory function to the point that levels of oxygen or carbon dioxide cannot be maintained within normal range. In this thesis the following have been used to reflect dysfunction: bradypnoea (less than eight breaths per minute), tachypnoea (greater than 24 breaths per minute) and/or hypoxaemia (oxygen saturation of less than 95% measured by pulse oximetry)

Tidal volume (TV) Volume in millilitres of gas inhaled during one breath

Visual analogue scale (VAS) A technique to assess subjective levels of pain or discomfort on an increasing scale using visual cues for the patient that are related to a numerical value

Work of breathing The force required to expand the lung against its elastic properties
Learn from yesterday, live for today, hope for tomorrow.

The important thing is not to stop questioning.

Albert Einstein
Chapter 1. Introduction

Exemplar

Florence, a 68 year old woman, was admitted to the Intensive Care Unit (ICU) for post-operative management following coronary artery bypass graft surgery. On admission to the ICU her condition was stable and she remained sedated and ventilated for three hours post admission then sedation was discontinued. Once fully awake and able to follow instructions, she was extubated and commenced on low flow oxygen at 2 L/min via standard nasal cannulae. Four hours later her gas exchange worsened, she started to tire and was taking only rapid, shallow breaths. Florence was started on non-invasive ventilation (NIV) - providing continuous positive airway pressure (CPAP) via a close fitting facemask. Humidified CPAP was commenced at 50% fraction of inspired oxygen (FiO₂) with pressure of 6cmH₂O.

An hour later Florence complained that the mask was “unbearable”. She tried to remove it frequently as she also wanted to drink and to talk. Her nurse - Sarah - spent much time talking with her, reassuring her with regards the aims of and the necessity for the NIV. Sarah removed and replaced the mask so Florence could drink water. Ten minutes later the mask was removed and replaced again so Florence could take her tablets. Ten minutes later, the mask was removed again to allow Florence to clean her teeth and freshen her mouth. She complained about the heat and stated that she found the mask “claustrophobic”. Sarah spoke with the registrar on duty and detailed the continuous manipulation of the mask and Florence’s discomfort. Further arterial blood gas (ABG) analysis determined that the oxygen level had not improved significantly – most probably due to the frequent removal of the mask and interruption of the positive pressure and oxygen that it was there to deliver.

Sarah suggested that Florence may be suited to nasal high flow oxygen therapy (NHF), and this was trialled at 45 L/min with 55% FiO₂. Over the following four hours, Florence’s oxygen levels slowly improved, her respiratory rate (RR) decreased and importantly she showed reduced effort of breathing and slept for long periods. She was also able to drink and talk when awake.

The following day, Florence was weaned to low flow oxygen at 3 L/min prior to being transferred to the post-operative ward.
Chapter 1 – Introduction

This thesis presents a programme of research the purpose of which was to investigate the effects of nasal high flow oxygen therapy (NHF) in patients following cardiac surgery. With over one million operations a year, cardiac surgery utilising cardiopulmonary bypass (CPB) remains one of the most commonly performed major surgical procedures worldwide. Following cardiac surgery patients are routinely admitted to the Intensive Care Unit (ICU), where they spend a period of time intubated and mechanically ventilated until such time as they are deemed ready for extubation. Once extubated, patients receive oxygen therapy via a range of devices to maintain adequate oxygenation and avoid re-intubation. Postoperative respiratory complications increase morbidity and mortality and can lead to prolonged ICU and hospital length of stay. Atelectasis, a major contributing mechanism of postoperative respiratory complications, may be present in up to 90% of cardiac surgical patients and may prove resistant to simple techniques employed to improve lung function such as patient positioning and incentive spirometry. Although alveolar recruitment and positive airway pressure may reduce atelectasis formation this effect is seemingly lost at extubation. Recently NHF has been demonstrated to deliver a low level, flow dependent positive airway pressure. There are few randomised controlled trials assessing the clinical utility of NHF in adult patients and these studies have enrolled patients with either mild to moderate hypoxaemic respiratory failure or acute respiratory failure (ARF). To date no study has been undertaken to assess the routine use of NHF in the perioperative period.

1.1. Research Aims

This programme of research was designed to investigate the effects of NHF on pulmonary function in patients after cardiac surgery.

The main aims of this research were:

1. To investigate the pressure effect created by nasal high flow
2. To evaluate the routine use of nasal high flow oxygen in a patient population following cardiac surgery
3. To describe current practice with regards oxygen therapy in non-intubated patients in ICUs in New Zealand and Australia
Chapter 1 – Introduction

These aims were achieved by undertaking:

- An observational study to measure airway pressures generated by NHF in patients following cardiac surgery
- An evaluation study of two methods for assessing atelectasis on chest x-rays
- A randomised controlled trial (RCT) of routine NHF compared to usual care in patients following cardiac surgery
- An observational study of oxygen therapy administered to non-intubated adult patients in ICUs in New Zealand and Australia

1.2. Overview of Thesis

This thesis consists of 11 chapters as follows:

- Chapter 1 - provides an introduction to the thesis
- Chapter 2 - provides an overview of cardiovascular disease in New Zealand and discusses cardiac surgery and its complications
- Chapter 3 - provides an overview of methods of oxygen therapy
- Chapter 4 - provides an overview of the literature regarding nasal high flow oxygen therapy
- Chapter 5 - presents and discusses the methodology underpinning the thesis.

Chapters 6 – 10 present the manuscripts published for the studies undertaken as follows:

- Chapter 6 - describes the methods and results of an observational study performed to measure the airway pressure generated by NHF in patients following cardiac surgery
- Chapter 7 - describes the methods and results of an observational study undertaken to assess the ability of two radiological atelectasis scoring systems to accurately determine the degree of atelectasis present on chest x-ray
- Chapter 8 - describes the protocol for a randomised controlled trial undertaken to determine efficacy of prophylactic NHF in patients following cardiac surgery
- Chapter 9 - presents the findings of the randomised controlled trial undertaken to determine efficacy of prophylactic NHF in patients following cardiac surgery
Chapter 1 – Introduction

- Chapter 10 - describes the methods and results of a point prevalence investigation undertaken to describe current practice of delivery of oxygen therapy to non-intubated adult patients in ICUs in New Zealand and Australia
- Chapter 11 - summarises the key findings of the research described in this thesis, presents the strengths and limitations of the work presented and discusses the implications of this work for both clinical practice and future research.

The manuscripts included in each chapter are presented exactly as published or as submitted for consideration for publication. All pages, tables and figures have been numbered consecutively throughout the thesis for continuity. References are included as stand-alone sections for each manuscript i.e. not linked to the final reference list. Appendices provide supporting documents such as evidence of ethical and local approvals, information and consent forms for participants, examples of data collection forms, data dictionaries and manuals of procedures used in each study.
Chapter 2. Cardiovascular Disease and Surgical Treatment in New Zealand

The purpose of this chapter is to outline the prevalence of cardiovascular disease, its causes and prevalence, and to describe cardiac surgery in New Zealand – surgical approaches, challenges and complications with particular reference to respiratory complications encountered following surgery.

2.1. Cardiovascular Disease in New Zealand

Ischaemic heart disease (IHD) (also known as coronary heart disease or coronary artery disease) is a major cause of cardiovascular deaths – accounting for 19% of all deaths in New Zealand in 2008. On average 16 New Zealanders die each day as a result of IHD. IHD is caused by atherosclerotic plaques developing in the intima of the coronary arteries. Growth of the plaque may lead to interruption of blood supply to the myocardium with resultant myocardial ischaemia - patients may experience this as angina or “chest pain”. If the plaque ruptures, thrombus is formed at the site of rupture which may in turn cause microvascular obstruction, ischaemia and result in clinically significant myocardial infarction. Complications of myocardial infarction include arrhythmias, acute heart failure, cardiac arrest, and rupture of heart structures. Therapy objectives aim to re-establish blood supply to the myocardium and support cardiac function. Reperfusion can be achieved using either primary percutaneous coronary intervention (PCI) or fibrinolysis with antifibrinolytic drugs such as streptokinase or alteplase. In some instances, surgical revascularisation with coronary artery bypass grafting (CABG) may be the only option. It has been shown that New Zealand has a high incidence of IHD - above the 75th percentile for male and female deaths from IHD when compared to other OECD countries - which accounts for around two thirds of cardiac surgery.

Rheumatic valvular heart disease seen in adult patients is the legacy of rheumatic fever in childhood and develops due to scar tissue formation which impedes valve function. Chronic rheumatic heart disease is a significant cause of premature death in New Zealand accounting for over 200 deaths each year. Rheumatic valvular heart disease can result in the requirement for either heart valve repair or replacement in childhood or adulthood. One study reports 36 children admitted to the paediatric cardiac ward at New Zealand’s Starship
Children’s Hospital with rheumatic fever, 25 of whom underwent cardiac surgery. Ten required single heart valve surgery, 14 had double heart valve surgery and one had triple heart valve surgery. The mean length of stay for the cohort was 54 days ±16, range 36 – 78 days. The authors suggest an average cost of $90,157 ± $6,388 (range $66,500 – 113,300) for this group and have hypothesised an annual cost to New Zealand of $9.5 – 10.5 million per year. In New Zealand, most rheumatic fever occurs in people of either Maori or Pacific ethnicity. Maori are 20 times more likely and Pacific people 37 times more likely to be hospitalised with acute rheumatic fever, compared to people of non-Maori/other ethnicity. Rheumatic fever is a disease closely associated with low socioeconomic status and in New Zealand, four areas (Counties Manukau; Flaxmere; Porirua and Northland) experience the highest rates of rheumatic fever hospitalisation. The Ministry of Health has invested $24 million in a 5-year programme, and developed a multi-faceted programme to address rheumatic fever aimed at strengthening primary health care services; raising community awareness; improving surveillance and addressing other factors such as housing which can contribute to development of sore throats and rheumatic fever.

2.1.1 Impact of Ethnicity on Cardiovascular Disease in New Zealand

Maori and Pacific peoples have a greater risk of experiencing cardiovascular events compared to other ethnicities. A cross-sectional study of patients admitted to a coronary care unit in South Auckland found that 13% of admissions were Maori, 15.2% Pacific peoples, 10.3% South Asian and that Maori and Pacific patients were younger than the European group admitted and more likely to live in areas of deprivation. They were also more likely to smoke and have higher levels of risk factors associated with metabolic syndrome such as Type 2 diabetes and obesity and more likely to reside in decile 9 and 10 areas - classified as the most deprived in New Zealand. Over time, cardiovascular mortality has declined in New Zealand in general; however the decline in Maori has occurred more slowly than in other ethnic groups. Death rates for Maori males are the same as for Pacific males but almost twice as high as other groups. Mortality from all cardiovascular disease is higher among Maori than among the general population. IHD is the leading cause of death for Maori, with Maori men 1.8 times more likely to die from IHD than non-Maori males (221/100,000 compared to 122/100,000). It has been proposed that the requirement for addressing historical, political, social and economic processes and barriers that underpin healthcare
provision and service within New Zealand is vital in order to try and address issues of marginalisation and deprivation amongst our most needy and most vulnerable citizens.\textsuperscript{21,23}

2.2. Cardiac Surgery in New Zealand

Cardiac surgery was first undertaken in New Zealand in the 1940s by a group of general surgeons at Wellington Hospital who, with little or no training, performed pericardectomies and ligation of the ductus arteriosus.\textsuperscript{24} At the time, surgeons at both Green Lane and Dunedin Hospitals were also attempting similar operations with limited success. Cardiac surgery developed primarily at Green Lane Hospital in the 1950s when cardiac surgeon Brian Barratt-Boyes performed the first operation utilising a heart and lung bypass machine in 1958. A pioneer of cardiac surgery, Barratt-Boyes developed the homograft aortic valve for aortic valve replacement and went on to advance surgery for congenital heart disease, proving that many complex conditions could be safely corrected in infancy.\textsuperscript{25} Green Lane Hospital continued to develop cardiac surgery and train cardiac surgeons and nurses and with these developments, demand for services grew. Currently in New Zealand there are five main public centres where cardiac surgery is undertaken: Dunedin, Christchurch, Wellington, Waikato and Auckland - cardiac surgery moved from Green Lane Hospital to Auckland City Hospital in 2003. Private hospitals in each of the main centres carry out approximately 25\% of all cardiac surgery undertaken.\textsuperscript{15} Starship Children’s Hospital provides congenital and paediatric cardiac surgery while Auckland City Hospital provides the national cardiothoracic heart and lung transplant service.

Demand for cardiac surgery has increased with improved results and decreased mortality. Simultaneously case mix complexity has increased and demand for services frequently exceeds availability of resources.\textsuperscript{15} Waiting times are a persistent problem nationally with New Zealand experiencing lower rates of cardiac surgery compared to international rates. In 2002/03 rates of isolated bypass surgery varied between 47.3:100,000 in the United Kingdom and 59.3:100,000 in Canada and 83.7:100,000 in Australia compared with just 34:100,000 in New Zealand.\textsuperscript{26} Concurrently, more patients were being referred for surgery earlier as research emerged showing that early surgical intervention and revascularisation may improve outcomes for some patient groups.\textsuperscript{27} A quality improvement plan for care for people with cardiovascular disease was developed jointly in 2008 by the Ministry of Health, District Health Boards, clinicians and consumers.\textsuperscript{15} The plan aimed to reduce waiting times and cancellations and improve theatre utilisation, thus enabling greater and more efficient
provision of cardiac surgical service. Around 2493 patients are discharged annually from New Zealand hospitals following cardiac surgery – 54 per 100,000 people.\textsuperscript{15} A national working group on cardiac surgical services in New Zealand, recommended however that the rate be increased by 35\% to 73 per 100,000 people within the subsequent two years.\textsuperscript{15}

Cardiac surgical services in New Zealand may be impacted upon by limited availability of critical resources such as operating room time, number of surgeons, perfusionists and intensive care beds for post-operative care. One report identified that ICUs were working to their individual resourced capacity but that:

\begin{quote}
the most significant issue identified consistently across all cardiac units in New Zealand is the high rate of cancellation of cardiac cases due to ICU shortages; either because of a lack of access to beds and/or shortage of ICU nurses''\end{quote}\textsuperscript{15}

A further report by the Ministry of Health published in 2011 suggested that there had been some improvement in the provision of cardiac services in New Zealand as seen by reductions in both waiting times and waiting list numbers, increases in the volume of operations, improved equity in geographical provision of services and enhanced prioritisation.\textsuperscript{28} Balancing the requirements of performing surgery for those incapacitated and emergently unwell in hospital with those experiencing discomfort and lifestyle restrictions while still waiting at home is a constant challenge for cardiac surgery providers as waiting for cardiac surgery is not ideal. Death rates of between 0.4\% and 11.2\% were reported in a study of patients awaiting coronary artery bypass surgery in Canada, Sweden, Germany, Brazil, the Netherlands and New Zealand.\textsuperscript{26} Risk factors associated with dying on the waiting list have been shown to include impaired left ventricular function, increased age, concomitant aortic valve disease, male gender, unstable angina and length of time on the waiting list.\textsuperscript{29-31} Other cardiac events such as myocardial infarction and angina may also occur while waiting, and anxiety, depression and reduced quality of life have also been reported along with significant decreases in physical and social functioning.\textsuperscript{32-34}

\section*{2.3. Types of Cardiac Surgery Performed in New Zealand}

\subsection*{2.3.1 Coronary Artery Bypass Grafting}

Coronary artery bypass grafting (CABG) provides symptom control for angina by grafting conduits to bypass blocked or narrowed coronary arteries thereby restoring blood flow to the
heart. These conduits may include saphenous vein, internal mammary arteries and radial arteries. The aortocoronary grafts are sutured proximally to the ascending aorta and distally to the affected coronary artery. CABG surgery requires a full sternotomy and traditionally the use of cardiopulmonary bypass (CPB). Over the past decade, “off-pump” techniques have been developed that allow CABG to be performed without the use of CPB. There is increasing evidence to support the use of off-pump CABG procedures and minimally invasive procedures where possible, with reports of reduced transfusion rates, perioperative bleeding, acute kidney injury, respiratory complications and shorter ventilation times.\textsuperscript{35-37} However, some studies report worse composite outcomes including poorer graft patency in the off-pump group.\textsuperscript{38}

Techniques to allow for minimally invasive CABG (mini-CABG) surgery have also been developed in an attempt to reduce the effect of cardiac surgery on the patient and on cost. Mini-CABG shortens recovery time, minimises risk of major adverse cardiac and cerebrovascular events and has shown superior outcome metrics when compared to standard CABG in one study including shorter intubation time, ICU and hospital length of stay.\textsuperscript{39}

Because of advances in interventional cardiology such as PCI and changing social demographics and expectations, the type of patient presenting for CABG surgery has changed. Patients are older, have more extensive coronary disease and are more likely to have impaired ventricular function.\textsuperscript{40} The overall mortality risk for patients undergoing CABG surgery is around 3.5%.\textsuperscript{41}

### 2.3.2 Cardiac Valvular Surgery

Since the 1960s heart valve surgery has been commonly performed to correct valvular heart disease,\textsuperscript{40} which if left untreated can cause severe heart failure due to the added pressure and volume load on the heart. Valve repair operations may not be possible for all valvular lesions, and in these instances the valve may require replacement. In New Zealand, rheumatic heart disease resulting from rheumatic fever is the leading cause of valvular defects though other causes of valvular heart disease such as bicuspid aortic valve, calcification and stenosis of the valve leaflets are seen also. Infective endocarditis with resultant valvular involvement due to growth of vegetations, can cause valvular incompetence also.

Valve replacement is traditionally undertaken on CPB, although in some selected high risk cases, peripherally inserted devices may now be an option. Transcatheter aortic-valve
implantation (TAVI) is performed in the catheter laboratory for patients with severe aortic stenosis and coexisting conditions, such as extreme age, that rule them ineligible for surgical replacement of the aortic valve. One RCT comparing TAVI to standard care showed the 1 year all-cause mortality was significantly lower with TAVI (30.7%) when compared to standard care (50.7%).

2.4. Standard Management of Patients Following Cardiac Surgery

Routinely, patients are admitted directly to the ICU from the cardiothoracic operating rooms, where they have been sedated, intubated and mechanically ventilated for their surgery. The ICU is staffed on a 1:1 nurse-patient ratio for all ventilated patients to ensure a high level of patient monitoring and intervention. The patient’s vital signs and adequacy of ventilation are checked and recorded by the attending ICU consultant, registrar and bedside nurse. Arterial blood gas (ABG) analysis is undertaken to assess oxygenation and a supine portable post-operative chest x-ray (CXR) is taken to assess line placement and lung pathology such as atelectasis, pneumothorax and pulmonary oedema. A full patient assessment is made including of the respiratory system involving auscultation of the chest to ensure adequate air entry, measurement of the peripheral oxygen saturation (SpO2) and ABG, inspection of the endotracheal tube to ensure accurate placement and observation of ventilator parameters. Mechanical ventilation is commenced on arrival according to an established protocol and adjusted based on results of ABG analysis, the aim being to maintain oxygenation and acid-base variables within normal parameters. Once the patient is haemodynamically stable, is warm, has adequate gas exchange and is not bleeding excessively, sedation is discontinued, the patient allowed to wake, ventilation weaned and the patient extubated. Once extubated, oxygen therapy at 2 – 6 L/min is commenced by way of a simple facemask or standard nasal cannulae. Supplemental oxygen is routinely administered for up to 48 hours as hypoxaemia may compromise cardiac function and because of the risks posed by nocturnal desaturations shown to be present up to 4 days following major surgery. Following extubation, patients are mobilised into a bedside chair and commence an oral diet – usually the morning of post-operative day 1. As long as their condition allows, patients are transferred to the cardiothoracic surgical ward on day 1 and by day 3 patients are off oxygen, have lines removed and are mobilising independently. They are discharged home from post-operative day 5 onwards. However, due to a variety of reasons, some patients may not progress as planned and may require a protracted stay in the ICU.
2.5. Respiratory Complications Following Cardiac Surgery

Respiratory complications are a leading cause of post cardiac surgery morbidity and can prolong hospital stay and increase costs.\(^{45}\) Forty to 90% of patients undergoing cardiac surgery develop pulmonary complications,\(^{46}\) while lung vascular injury is reported in 30-50% of patients, the pathogenesis of which is multi-factorial and complex.\(^{47,48}\) Respiratory complications may necessitate antibiotic therapy if the cause is suspected or proven to be infective, an escalation in oxygen therapy for example the requirement for NIV or if severe disturbances in oxygenation result, re-intubation and reinstitution of mechanical ventilation. Development of post-operative respiratory dysfunction can add to increased mortality and morbidity and may lead to prolonged mechanical ventilation; development of infectious sequelae; prolonged ICU and hospital length of stay.

Postoperative lung dysfunction may be related to pre-operative, intra-operative or post-operative factors. Pre-operative factors can include age; high body mass index (BMI), history of smoking, degree of heart failure present, presence of diabetes or chronic obstructive pulmonary disease (COPD) and previous cardiac surgery.\(^{47,49}\) Intra-operatively cardiopulmonary bypass, hypothermia, operative and anaesthetic techniques, along with medications and transfusion requirements, can cause lung trauma and injury.\(^{50,51}\) Other intra-operative factors include use of median sternotomy incision, topical cooling for myocardial protection, exposure to the extracorporeal circuit, anaesthesia and prolonged supine positioning all of which cause a general inflammatory response, atelectasis and surfactant damage.\(^{47,49,52}\) In addition apnoea ventilation during bypass may activate lysosomal enzymes which have been shown to be related to conditions such as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Haemodilution, due to mixing of the bypass prime with the patient’s own blood, reduces haematocrit and can contribute to increased interstitial oedema and ischaemia-reperfusion injury which increases production of some pro-inflammatory markers.\(^{48,53}\) Atelectasis superimposed on lung vascular injury has been shown to be a major determinant of oxygen impairment and airway pressure requirements post operatively, irrespective of whether cardiac surgery is performed using CPB or without CPB. In one prospective cohort study, lung vascular injury occurred in approximately half of all patients undergoing both off-pump and on-pump cardiac surgery due to trauma necessitating red blood cell transfusion rather than the CPB itself.\(^{48}\) Lack of ventilation during CPB leads to collapse of alveoli and development of atelectasis which contributes to postoperative pulmonary dysfunction and can predispose to infection. It has been shown that atelectasis
may in fact begin developing from the induction of anaesthesia prior to surgery. One study found that following induction of anaesthesia 46% of patients had developed atelectasis on computerised tomography (CT) scanning. Two hours postoperatively, 85% had atelectasis and the mean atelectatic area had increased from 1.0% to 1.8%. The use of internal mammary artery grafts (IMAG) for CABG surgery and resultant interruption of pleural integrity has been found to increase the incidence rate of postoperative pulmonary complications. One study demonstrated a large reduction in pulmonary function when IMAGs were used as conduits with a 65% drop in vital capacity and forced expiratory volume in one second (FEV₁) recorded on the first postoperative day.

Postoperative factors involved in the development of respiratory complications may include alterations in respiratory pattern with changes in vital capacity and functional residual capacity (FRC), increased airway resistance, postoperative pain due to surgical incisions, or the presence of pleural and mediastinal drains, possible dysfunction of the phrenic nerve or diaphragm, fluid imbalance, reduced mobility, impaired mucociliary clearance and ineffective cough and pulmonary oedema.

Clinical manifestations of post-operative respiratory complications may range from arterial hypoxaemia to ARDS and can be seen at the bedside as short shallow respirations, changes on CXR, increased respiratory rate and work of breathing, additional breath sounds and a productive cough.

A major cause of post-operative respiratory complications is atelectasis - collapse of alveoli with loss of aeration. Atelectasis is reversible and may be reflected by radiographic changes and/or the need for greater levels respiratory support in self-ventilating patients in order to maintain and improve oxygenation. The development of atelectasis in patients after general anaesthesia is almost inevitable and can extend for weeks. Atelectasis has been described as being present in most patients following cardiac surgery with reports involving up to 90% of patients. Atelectasis occurs more in both the bases and dependent areas of the lungs, and leads to high intrapulmonary shunt, reduced FRC, increased alveolar-arterial oxygenation gradient and retention of secretions in the deflated alveoli.

While the exact cause of atelectasis is not entirely known several mechanisms may lead to its development including inhibition of surfactant, gas reabsorption or compression of regional lung area. Under normal conditions surfactant covers and stabilises the alveolar surface and prevents its collapse, however this ability is reduced under the conditions of anaesthesia.
Furthermore, ventilation of healthy lungs that have developed atelectasis, for example after surgery, may lead to lung injury due to the reopening of the collapsed alveoli.\textsuperscript{62} Gas reabsorption may occur for two reasons. Firstly, when a ventilation perfusion mismatch develops as FiO\textsubscript{2} is increased the alveolar oxygen tension increases and any increased absorption of oxygen results in loss of alveolar volume. Secondly gas may become trapped in the lung unit distal to the obstruction causing collapse of the alveoli.\textsuperscript{54} Compression atelectasis “… results when the forces causing the alveoli to collapse are exceeded by the transmural pressure that distends and maintains the alveoli in the open state” (pg. 38),\textsuperscript{62} and is believed to be related to chest geometry as well as diaphragm position and motion.\textsuperscript{62,67} This may occur due to displacement of the diaphragm following the administration of muscle relaxants and positioning of the patient. It has been demonstrated that FRC can be reduced by 0.8 - 1 Litre simply by changing body position from upright to supine and that there may be a further decrease of 0.4 - 0.5 Litre following induction of anaesthesia.\textsuperscript{68} It has been demonstrated that morbidly obese patients i.e. those with a BMI > 35 kg/m\textsuperscript{2} may develop significantly more atelectasis when compared to non-obese patients persisting 24 hours after the end of surgery (9.7% vs. 1.9% respectively).\textsuperscript{64}

Factors that influence the formation of atelectasis include high FiO\textsubscript{2}, obesity and the presence of COPD.\textsuperscript{67,68} Preoxygenation with high concentrations of oxygen is standard practice amongst anaesthetists prior to intubation however the breathing of pure oxygen may increase the shunt by promoting alveolar collapse. During CPB oxygen levels are often maintained at supra-normal values which can result in hyperoxaemia and may mediate inflammatory processes contributing to pulmonary dysfunction.

Prevention of atelectasis formation is not straightforward. Two studies have shown that in mechanically ventilated patients a vital capacity or recruitment manoeuvre may reduce atelectasis although airway pressures of 30 - 40 cmH\textsubscript{2}O have been required to show a difference.\textsuperscript{69,70} The application of positive end expiratory pressure (PEEP) has been tested and shown to reopen some collapsed areas and may be applied on induction of anaesthesia and during positive pressure ventilation. This positive effect though is often lost on discontinuation of the PEEP, for example at the time of extubation or disconnection from mechanical ventilation for procedures such as suctioning of endotracheal secretions, thus losing any advantage.\textsuperscript{6} Atelectasis may also prove resistant to simple techniques traditionally employed at the bedside to improve lung function such as deep-breathing exercises, patient positioning and incentive spirometry.\textsuperscript{6} Reversing atelectasis with CPAP delivered non-
invasively as compared to standard oxygen therapy may reduce the need for re-intubation and recommencement of mechanical ventilation, and may result in a lower incidence of pneumonia and sepsis.\textsuperscript{71} Patients treated with CPAP in one study were shown to have a shorter length of stay in the ICU.\textsuperscript{71} A recent study in patients following cardiac surgery employed prophylactic nasal CPAP (nCPAP) of 10 cm H\textsubscript{2}O for at least 6 hours and reported a reduced incidence of respiratory complications - which the authors attributed to the development of atelectasis.\textsuperscript{3}

2.6. Summary

Oxygen therapy is necessary to support patients who develop atelectasis and other respiratory complications following cardiac surgery. The next chapter will provide background on oxygen therapies in general and provide information with regards oxygen therapy devices available for use.
Chapter 3 – Oxygen Therapy

Chapter 3. Oxygen Therapy

The feeling of it to my lungs was not sensibly different from that of common air; but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that, in time, this pure air may become a fashionable article in luxury. Hitherto only two mice and myself have had the privilege of breathing it.

Jason Priestley, Experiments and Observations on Different Kinds of Air (1775), Vol. 2, 102

Oxygen is a chemical element making up approximately 21% of the atmosphere and is necessary to support mammalian life. The two main functions of the heart and lungs are the adequate delivery of oxygen and nutrients to the tissues to sustain aerobic metabolism and to remove the waste products of metabolism. The normal range of arterial oxygen saturation ($\text{SaO}_2$) for adults aged < 70 years, is approximately 94 – 98% with a partial pressure of oxygen in arterial blood ($\text{PaO}_2$) range of 10.8 – 13.3 kPa at sea level. The mean $\text{SaO}_2$ may be lower in older people than in younger people, although this association is not fully understood and may be representative of the effect of diseases that become more common in old age.

Oxygen therapy is “the therapeutic administration of oxygen to patients for the treatment or prevention of hypoxaemia (low-blood oxygen levels) or hypoxia (inadequate oxygen at the cellular level)” (pg. 27). Oxygen is one of the most widely available and prescribed therapeutic drugs in medicine, and the majority of ICU patients receive supplemental oxygen as part of their therapy either because they are known to be hypoxaemic or because oxygen is indicated as part of routine post-operative care such as following cardiac surgery. Optimisation of oxygen delivery remains the cornerstone of treatment for common ICU syndromes such as sepsis, multiorgan dysfunction, ARDS and ALI. When administered correctly it may be lifesaving, but oxygen is often given without careful consideration of its potential benefits and side effects. The administration of oxygen is not without risk as inappropriate use may be hazardous due to either inadequate use or from toxic effects of delivering supranormal doses of oxygen. Hyperoxaemia should be avoided as much as
hypoxaemia, as oxygen in high doses may be toxic. It is plausible that hyperoxaemia may impair cell repair processes and delay recovery of organ function in critically ill patients,\textsuperscript{79} and it has been shown that a high FiO\textsubscript{2} can cause damage to the lungs.\textsuperscript{80,81} Often though oxygen is administered due to perceived need rather than documented hypoxia.\textsuperscript{80,82} Oxygen is poorly prescribed by medical staff.\textsuperscript{78,83-85} For instance one study found that only 8\% of patients receiving oxygen therapy in a medical ward had an oxygen prescription.\textsuperscript{84} To ensure the safe and effective administration of oxygen, a prescription detailing the flow rate, concentration, delivery method and method of assessing treatment should be available.\textsuperscript{75,84}

3.1. Evidence to Guide Oxygen Therapy

There is little published evidence to guide clinicians in the objective selection and use of delivery devices when prescribing oxygen therapy for non-intubated patients,\textsuperscript{86} and scant evidence to describe oxygen therapy delivered to intensive care patients in general. Nurses’ decision making with regards oxygen delivery devices used and the management of oxygen therapy is complex and influenced by a number of factors such as their knowledge and expertise, patient preferences and patient care activities.\textsuperscript{74} An observational study undertaken in Canada described the attitudes, beliefs and practices of clinicians in 52 ICUs in relation to oxygen use and concluded that considerable variation exists.\textsuperscript{87} Two Australian surveys have evaluated the attitudes of intensive care physicians and nurses to oxygen therapy.\textsuperscript{88,89} The first survey suggested that variability in oxygen therapy practice amongst intensivists was likely to continue until there was evidence from clinical trials to support clinical practice guidelines and concluded that there was a need to further explore factors that influence clinical decisions around oxygen therapy.\textsuperscript{88} The second survey by the same authors reported an on-line questionnaire of 542 critical care nurses undertaken to establish if there was variability in oxygen therapy practices and to attempt to quantify the degree of variability. This study reported practice and concerns regarding oxygen therapy were highly variable and that these factors were not associated with experience of the nurse or location of the hospital.\textsuperscript{89} A large multicenter, international observational study has provided information regarding the characteristics and outcomes of 15,757 adult patients in receiving mechanical ventilation.\textsuperscript{90} This study showed that survival depended not only on factors present at institution of mechanical ventilation but predominantly on the development of complications and patient management in the ICU.\textsuperscript{90} These studies have surveyed opinion and practice only
with regards oxygen therapy practices in patients who are receiving mechanical ventilation and oxygen therapy but have not included non-intubated, self-ventilating patients.

Two Australian studies have documented oxygen use in non-intubated patients following cardiac surgery. The first retrospectively audited the records of 245 patients and showed that the most common oxygen delivery device used was the simple face mask (87%). It was found that on average patients used two different oxygen delivery devices over the 24 hour study period, that 9% of patients required NIV or high-flow oxygen therapy and that 60% of patients experienced one or more episodes of hypoxaemia or abnormal respiratory rate during the first 24 hours of ICU care despite receiving supplemental oxygen suggesting that the ICU environment does not protect patients from suboptimal oxygen delivery. The second study aimed to observe how ICU nurses managed low-flow oxygen therapy. This descriptive exploratory study involved observations of a convenience sample of 16 patients and 16 ICU nurses. In this study most patients were admitted to the ICU following cardiac surgery. This study reported three key findings: First, that there were few changes made to oxygen therapy in response to deteriorating vital signs. Second, that there were discrepancies between measured SpO₂ and respiratory rate and those that were recorded. Third, that there was a failure to record abnormal values that did not coincide with the “on-the-hour” recording of patient vital signs. The authors concluded that ICU nurses’ management of low-flow oxygen therapy was suboptimal and documentation inaccurate.
3.2. Methods for the Administration of Oxygen Therapy

There are many varied methods available to the clinician to deliver oxygen therapy dependant on patient need and condition. Figure 1 presents a schematic of devices available for the administration of oxygen therapy in the ICU.

![Figure 1. Methods for the administration of oxygen therapy.](image)

3.2.1 Invasive Methods of Oxygen Delivery

Invasive ventilation provides positive pressure ventilation through an endotracheal tube or tracheostomy, and may be required as an adjunct to anaesthesia or as a curative support therapy whilst organ function recovers. The primary aims of invasive ventilation are to maintain gas exchange and support respiratory function. In normal breathing, a negative pressure is created within the thorax during inspiration and air is drawn into the lungs. With invasive ventilation, respiratory mechanics are altered and positive pressure delivered via a mechanical ventilator is required to “blow” air into the lungs.
Chapter 3 – Oxygen Therapy

Traditionally cardiac surgery patients have been ventilated for up to 24 hours after surgery while they re-warm, emerge from anaesthesia, stabilize haemodynamically and while bleeding settles. More recently however, the practice has been to wean the patient from mechanical ventilation and extubate early after surgery – often within 4 to 6 hours. This practice has emerged following evidence to suggest that earlier extubation reduced nosocomial infection rates associated with prolonged ventilation, and reduced ICU and hospital length of stay. Some centres practice “fast-tracking” of patients following cardiac surgery whereby the patient is rapidly weaned and may even be extubated in the operating theatre prior to transfer to the ICU/HDU. Patient that are extubated soon after surgery may have significantly less atelectasis, improved vital capacity and FEV₁/FVC ratio, and reduced rates of nosocomial pneumonia when compared to those extubated later.

3.2.2 Non-invasive Methods of Oxygen Delivery

Non-invasive methods of delivering oxygen to patients include both fixed performance and variable performance systems.

3.2.2.i. Fixed Performance Systems

Fixed performance systems provide a constant FiO₂ independent of the patients’ peak inspiratory flow rate, which is achieved either because the system has a high flow rate or a large-capacity reservoir.

3.2.2.i.a Venturi Mask

Masks containing Venturi valves employ the principle of jet mixing – the Bernoulli Effect. When oxygen passes through a narrow orifice it provides a high velocity stream that draws a constant proportion of room air through the base of the Venturi valve - the amount of entrainment is determined by the size of the jet and the size of the valve ports. These masks may be useful for delivering, more accurately, low concentrations of oxygen, reducing the risk of carbon dioxide retention and improving hypoxaemia. Venturi masks are available which can deliver oxygen concentrations of 24%, 28%, 35%, 40% and 60%. Re-breathing of carbon dioxide (CO₂) does not occur as the mask is constantly flushed by the high flow rates of fresh gas so they are suitable for patients with COPD who may be at risk of CO₂ retention.
3.2.2.i.b Nasal High Flow Oxygen

Developed initially for use in neonatal and paediatric populations and more recently introduced into the adult intensive care arena, NHF systems have been commercially available for use in adults for approximately 10 years and have rapidly gained popularity amongst the armamentarium of respiratory support devices and oxygen administration systems available to clinicians. Advances in the design of heated delivery tubing and the development of uniquely designed nasal interfaces have allowed the development of systems capable of delivering high flow rates of heated and humidified blended air and oxygen directly into the nares, allowing delivery of optimally conditioned gas. It was first reported in 1968 that a simple, easily portable system had been devised allowing high flow rates of gases to be administered via the nose provided they were delivered at body temperature and were fully saturated with water vapour. The delivery of high flows of gas and humidity via a commercially manufactured nasal cannula was first introduced by Vapotherm Inc. in 2002 after receiving U.S. Food and Drug Administration approval. Currently there are two principal manufacturers of nasal high flow systems - Fisher and Paykel Healthcare (New Zealand) manufacture both adult and infant devices and Vapotherm Inc. (USA) manufacture the Vapotherm2000i® and Precision Flow® devices (Figure 2).

![Figure 2. Nasal High Flow systems. a. Vapotherm 2000i®  b. Vapotherm Precision Flow®  c. Optiflow™](image-url)
Chapter 3 – Oxygen Therapy

Only one system (Optiflow™, Fisher and Paykel Healthcare) is currently available in New Zealand. The Optiflow™ system allows delivery of blended air and oxygen, heated to 37°C and optimally humidified to 44 mg/L water vapour. The system comprises an air-oxygen blender (capable of delivering 21 – 100% FiO₂), an active heated humidifier chamber, a single limb heated inspiratory delivery tube (which avoids heat loss and development of condensate in the circuit) and a large bore nasal interface.

Proposed mechanisms of action and advantages of NHF include improved levels of comfort and compliance, delivery of an accurate FiO₂, washout of the nasopharyngeal dead space, reduction of work of breathing, optimisation of the mucociliary transport system, and provision of low level positive airway pressure. Optiflow™ has also been shown to be as effective as and significantly better tolerated when compared to a high flow humidified face mask (HFFM) oxygen. NHF has been suggested as an intermediate form of respiratory support positioned between traditional methods of oxygen delivery such as low flow nasal cannulae and non-invasive ventilation. It can be used as part of a continuum of respiratory support either as a tool for escalation of respiratory support in the acute phase of illness, or as a means of moving from higher support to lower support and eventual discontinuation when used during the weaning phase (Figure 3).

![Figure 3. Continuum of respiratory support therapies.](image-url)
Chapter 3 – Oxygen Therapy

NHF has been used in the cardiothoracic ICU of the metropolitan hospital in which the current study was conducted for seven years now. Anecdotally, clinicians within the ICU have reported satisfaction with the system and it appears well tolerated by patients. Two recent observational studies have described the patient population utilising NHF in this ICU/HDU.111,112 The first studied 38 patients, over a 3 month period, who were commenced on NHF primarily for hypoxaemia. Of those enrolled only five (13%) went on to require NIV further supporting the hypothesis that the use of NHF may reduce the requirement for NIV. This descriptive study concluded that NHF was straightforward to initiate, could be employed for a relatively short period of time and was often discontinued before transfer of the patient to the ward.112 The second study conducted 18 months later, collected data over a 6 month period and enrolled 120 patients who required NHF for ARF. It was found that NHF was considered successful in 78% of patients and furthermore identified that a baseline pH of less than 7.35 was an predictor of subsequent failure of therapy in this group.111

3.2.2.i.c Non-invasive Ventilation

Non-invasive ventilation (NIV) provides the spontaneously breathing patient with positive pressure ventilation without the requirement for an endotracheal tube and partially compensate for changes in respiratory function by reducing work of breathing, recruiting alveoli and improving gas exchange while also reducing cardiac workload. NIV decreases cardiac preload by reducing venous return, decreases cardiac afterload by reducing transmural pressure and increases cardiac output and improves haemodynamics.40,49,113 The main aim of NIV is to provide the benefits of ventilatory support and oxygen therapy provided by mechanical ventilation whilst avoiding the disadvantages of endotracheal intubation such as the need for sedation and increased risk of nosocomial pneumonia.40 NIV is a well-established therapy for COPD, ARF, cardiogenic pulmonary oedema, and postoperative respiratory failure.114-117 NIV is delivered via a closely fitting mask – either nasal or oronasal, while in some countries a full facemask or a helmet device is used.

NIV can be applied as either a prophylactic or curative therapy. RCTs have compared prophylactic NIV to standard oxygen therapy and chest physiotherapy for a period of 1 – 12 hours and found significant improvement in gas exchange3,46,59 but no difference in degree of atelectasis46,118 or in measurements of lung function using spirometry.46,118 Conversely other studies have found lower atelectasis scores and better pulmonary function when using prophylactic NIV with or without recruitment manoeuvres after cardiac surgery.5,49,50,119
Overall the literature supports NIV as an adjunctive respiratory support therapy for patients following cardiac surgery.\textsuperscript{3,120}

NIV is not without challenges - success often depends on the fit and tolerability of the interface, patient cooperation, the absence of haemodynamic instability and the ability of the patient to protect their airway.\textsuperscript{119} Masks, and their fitting, may cause pressure area formation particularly across the bridge of the nose, dryness of the face, mouth and oral mucosa, eye irritation and sinus discomfort,\textsuperscript{121-123} and interfere with the ability of the patient to eat, drink and communicate. Furthermore, NIV can only be applied in an ICU or HDU setting requiring appropriate monitoring and clinicians skilled in its use. The application of NIV involves careful consideration of risks and benefits to the patient by the bedside clinician. Contraindications to the use of NIV include respiratory arrest, copious secretions, uncontrolled vomiting, severe agitation, inability to protect airway, facial trauma and haemodynamic instability.\textsuperscript{119,124}

Two modes of NIV can be delivered to the patient, continuous positive airway pressure (CPAP) and bi-level positive airway pressure ventilation (BiPAP). No clear advantage of either CPAP or BiPAP is identified in the literature however as a simple rule of thumb, CPAP is used to treat isolated hypoxaemia, while BiPAP is used to treat hypoxaemia with hypercapnia.\textsuperscript{40}

\subsection{Continuous Positive Airway Pressure (CPAP)}

CPAP is a breathing mode whereby the patient spontaneously breathes through a pressurised circuit against a threshold resistor that maintains a positive airway pressure during both inspiration and expiration.\textsuperscript{71,119} CPAP prevents airway and alveolar collapse and atelectasis, maintains FRC, reduces left ventricular workload and increases cardiac output.\textsuperscript{119} Commonly CPAP starts at 10 cm H\(_2\)O with Fi\textsubscript{O2} set as required to correct hypoxaemia. Both CPAP and Fi\textsubscript{O2} are then titrated to clinical effect. Recently a prospective RCT of 500 patients, all of whom had undergone cardiac surgery, compared intermittent nasal CPAP (nCPAP) at 10 cm H\(_2\)O every 4 hours (standard care) to prophylactic nCPAP at 10 cm H\(_2\)O for at least 6 hours per day following surgery (intervention). This intervention improved arterial oxygenation, reduced pulmonary complications including pneumonia, reduced re-intubation rates and reduced readmission rates to the ICU or HDU.\textsuperscript{3}
3.2.2.i.c.2 Bi-level Positive Airway Pressure Ventilation (BiPAP)

This therapy provides pressure assistance as the patient inspires and ensures that a positive airway pressure is maintained during the expiratory phase of the respiratory cycle. BiPAP involves two pressure settings – the expiratory positive airway pressure (EPAP) and the inspiratory positive airway pressure (IPAP). Standard initial settings are an EPAP of 4 to 8 cm H₂O and an IPAP of 8 to 12 cm H₂O with an FiO₂ set to maintain oxygenation. As with CPAP, EPAP and IPAP are subsequently titrated according to patient tolerance and clinical effect. The level of IPAP includes the set EPAP. One study suggests that a greater improvement in pulmonary function is found with the prophylactic use of BiPAP compared to CPAP due to improved alveolar opening and a greater reduction in work of breathing, although the authors do caution that inspiratory pressure should be adapted individually according to patients’ compliance and comfort levels.

3.2.2.ii. Variable Performance Systems

Variable (or low-flow) systems deliver a variable FiO₂, as delivered flow is usually less than the patients’ peak inspiratory flow thus causing entrainment of room air which in turn dilutes the inspired gas. Changes in respiratory pattern such as alterations in tidal volume, respiratory rate and peak inspiratory flow rate as well as device-related characteristics such as the shape of the device and the flow it can generate may also affect delivered FiO₂.

3.2.2.ii.a Low Flow Nasal Cannulae

Nasal cannulae are widely used to deliver low oxygen concentrations to self-ventilating patients of all ages. Nasal prongs are simple to apply, on the whole well tolerated and allow the patient to eat, drink, expectorate and communicate without having to remove the cannulae and there is no risk of rebreathing carbon dioxide. Studies have demonstrated increased levels of patient satisfaction when using nasal cannulae when compared to a facemask. Nasal cannulae can deliver oxygen flows of 0.5 - 6 L/min which equates to approximately 0.22 - 0.44 FiO₂. The exact concentration of delivered oxygen though is difficult to quantify as wide variations in respiratory pattern affect air entrainment and therefore delivered FiO₂. Nasal cannulae though deliver variable, low level oxygen concentrations; can be easily dislodged and can irritate the nasal mucosa, the nares and the skin around the ears. Biological evidence of on-going nasal inflammation following administration of nasal oxygen at 4 L/min for 5 hours has been demonstrated. Some centres have devised methods of
delivering oxygen and/or positive pressure directly into the nares in an attempt to improve gas exchange and to avoid mechanical ventilation and its associated risks.\textsuperscript{126,132}

3.2.2.ii.b Face Mask Oxygen Therapy

Face masks are useful for short periods and can provide a higher $\text{FiO}_2$ than nasal cannulae. On the other hand patients may find face masks uncomfortable at higher oxygen flow rates or when used to deliver humidified oxygen; therapy may be frequently interrupted by removal of the mask e.g. vomiting, nutrition, hygiene needs; face masks can engender feelings of claustrophobia in some patients and can lead to reduced compliance with oxygen therapy.\textsuperscript{128} Masks also entrain room air as patients’ inspiratory demand increases thus diluting the $\text{FiO}_2$ delivered to the patient. Patients may report reduced levels of comfort with a facemask and are often agitated and poorly compliant removing the mask frequently leading to a greater incidence of hypoxaemia and increased nursing workload.\textsuperscript{2,127,133,134} One study of 20 patients receiving 4 L/min oxygen via a simple face mask, used video surveillance technology to demonstrate that patients did not receive prescribed oxygen due to mask dislodgement.\textsuperscript{134} In this study only one mask remained on continuously and positioned correctly over an 8 hour study period. In the other 19 patients it was removed 64 times (range 1 – 10 per patient) – 45 times for nursing tasks such as mouth care. Other reasons cited for removal were nausea, vomiting and removal by the patient. The mask remained off for a median of 6 mins 55 secs per episode and 1 hour 6 mins 48 secs per patient. Mask removal resulted in an average decrease in oxygen saturation of 4%.\textsuperscript{134}

3.2.2.ii.b.1 Simple Face Masks

Simple face masks made of rigid plastic are cheap, widely available and used frequently to deliver oxygen therapy. Face masks deliver oxygen flows of 5 – 10 L/min (concentrations of up to approximately 0.6 $\text{FiO}_2$) and are worn over the mouth and nose. They are predominantly used for type I respiratory failure and at low oxygen flow rates significant rebreathing may occur as the exhaled air, rich in carbon dioxide, is not adequately flushed out of the mask. Rebreathing may lead to retention of carbon dioxide within the mask and therefore simple face masks not suitable for patients with type II (hypercapnic) respiratory failure.\textsuperscript{72,75} Delivered oxygen concentration is variable due to air entrainment and thus difficult to accurately quantify when a simple face mask is utilised.
3.2.2.ii.b.2 Humidified High-Flow Face Mask

During normal inspiration the upper airways condition inspired gases with heat and humidity from the upper airway mucosa to body temperature (37°C), 100% relative humidity with 44 mg/L of absolute humidity.\(^{135}\) This process, occurring mainly in the nares where inspired gases are exposed to a large surface area of highly vascular mucosa, assists the lungs in maintaining the physiological balance of heat and moisture necessary for optimal airway defence and gas exchange and promotes mucociliary function. Normal mucociliary function of the airways relies on adequate humidification otherwise cytologic damage occurs leading to accumulation of tenacious secretions and microatelectasis.\(^{40}\) When oxygen therapy is delivered from an artificial source such as the piped oxygen that is available in hospitals, it is delivered cold and extremely dry at a temperature of around 15°C with an absolute humidity of just 0.3 mg/L. This can lead to patient discomfort as well as damage to the airway mucosa and the mucociliary transport system. Optimal humidity is required to maintain the rheology of airway secretions, optimise secretion clearance, and may reduce inflammatory actions.\(^{102,131,135}\)

High flow oxygen therapy is described as flow rates that exceed patient inspiratory flow rates,\(^{136}\) and has traditionally been delivered via a face mask at flows of up to 15 L/min. The set-up for this therapy typically includes a humidifier capable of warming the oxygen to 32°C and a simple facemask. For spontaneously breathing patients, the humidifier temperature is set at 32°C, delivering 32 mg/L water vapour. However, patients may find them claustrophobic and hot complaining of the warm, moist air circulating around their face, frequently removing masks for nutrition and hygiene cares.\(^{2,9}\) Poor patient compliance and refractory hypoxaemia may result. A randomised cross-over trial of 30 patients measured discomfort and hygrometric properties of patients receiving high-flow oxygen therapy humidified with either a bubble or heated humidifier.\(^{137}\) This study demonstrated that compared to bubble humidifiers, heated humidifiers delivered increased levels of humidity and were associated with decreased dryness symptoms in patients, with mouth and throat dryness significantly lower with heated humidification when compared with bubble humidification (median 5.0 vs. 7.8 and 4.3 vs. 5.8 respectively). The absolute humidity measured at an ambient temperature of 26°C was almost double in the heated humidifier group compared to the bubble humidifier regardless of flow rate (median 30 vs. 16 mg/L).
3.3. Summary

This chapter has shown that there are many devices available to deliver oxygen therapy to patients though little evidence to assist clinicians in this decision making.

While NHF has been researched for this period, the current body of literature has not been summarised, therefore the next chapter provides an overview of the literature with regards NHF.
Chapter 4. Overview of the Literature Regarding Nasal High Flow Oxygen Therapy.

4.1. Introduction

The purpose of this review is to summarise the available literature available regarding nasal high flow oxygen therapy. This review will present and discuss evidence available in bench and animal models, in neonates, paediatrics and in adults.

4.2. Search Strategy

A literature search was conducted covering the period January 1980 to April 2013 utilising the following medical and nursing databases: PubMed, CINAHL, EMBASE and the Cochrane Database of Systematic Reviews were searched using the following search terms: “nasal high flow therapy”; “humidified high flow nasal cannulae”; “Optiflow™”; “Vapotherm™”; “high flow nasal oxygen”; “high flow nasal oxygen therapy” and all repeated for “high-flow....”. In addition, hand searching of reference lists, conference proceedings and manufacturers brochures produced some inclusions. An electronic search of conference proceedings using the search engines Google and Google Scholar was also completed. Regular automatic email up-dates also allowed frequent notification and appraisal of the literature. All types of studies were considered for inclusion: interventional, observational and case reports. All languages were included.

4.3. Evidence in Bench and Animal Models

Several bench studies have been performed assessing all commercially available high flow delivery devices. Two high flow devices – Salter Labs non-heated high flow nasal cannula and Vapotherm 2000i - were tested using a digital psychrometer to measure relative humidity and temperature of gas delivered by each device. Both devices met minimum humidification standards and offered practical new treatment options. Another bench study, using the Vapotherm 2000i and a simulated lung with a variable leak, demonstrated that CPAP of 0.5 – 4.5 cm H₂O was generated at flow rates of up to 8 L/min. Two further papers report bench studies performed prior to undertaking infant measurements. In one, both the Vapotherm neonatal cannulae and Fisher and Paykel devices were inserted into the port of an
anaesthesia bag which was used to simulate an infant’s lung. For any given leak size there was an almost linear relationship between flow rate delivered and pressure generated with the highest pressure achieved being 4.5 cm H2O (Vapotherm cannula at a flow rate of 8 L/min and leak of 3 mm).\textsuperscript{139} Measurements obtained with the Fisher and Paykel device generally corresponded to the Vapotherm measurements. In the second study, pressure and flow were measured using varying degrees of leak and also with and without the use of a pressure limiting valve.\textsuperscript{140} In the absence of leaks, pressure was limited by the pressure-limiting valve only at flows $\geq 2$ L/min and that with leaks of 30% and 50% pressure generated was always $< 3$ cm H2O. The authors suggested the need for a pressure-limiting valve to be present in high flow circuits in order to minimise the potential for excess pressure delivery to the patient. Stereoscopic particle imaging velocimetry (SPIV) has been used to describe the distribution and velocity of the airflow in the nasal cavity with and without NHF to try and understand the airflow characteristics within the nasal cavity.\textsuperscript{141} An anatomically correct, scaled model of the complete nasal cavity was constructed from CT images and airflow simulated to demonstrate that NHF modifies nasal cavity flow patterns altering the proportion of inspiration and expiration through each passageway and producing jets with in vivo velocities of up to 17.0 ms$^{-1}$ with 30 L/min cannula flow. In a second study, the same group used SPIV to map velocities in the nasal cavity across the entire respiratory cycle during natural breathing and with NHF.\textsuperscript{142} The flow pattern in the nasal cavity with NHF was found to differ significantly from natural breathing. Velocities of 2.4 and 3.3 ms$^{-1}$ occurred at peak expiration and inspiration respectively in the nasal valve area during natural breathing however on expiration a maximum velocity of 3.8 ms$^{-1}$ occurred in the nasopharynx. When using NHF, maximal velocities of 13.6 and 16.5 ms$^{-1}$ were recorded in the nasal valve area during expiration and inspiration respectively. These results suggest that a steady flow assumption within the nasal cavity is invalid during natural breathing however it appears valid with NHF. This may add to the argument that NHF continuously flushes the nasopharyngeal dead space which may enhance washout of carbon dioxide. The relationship between the device, intraprong and proximal airway pressures and the flow values in a test lung has been assessed using both the Vapotherm 2000i and Fisher & Paykel humidified nasal cannulae.\textsuperscript{143} All three pressures increased with increasing flow with both devices, irrespective of leak but the authors cautioned that NHF systems may deliver uncontrolled CPAP to infants which, along with potential leak effects, renders the CPAP generated unpredictable.\textsuperscript{143}
Chapter 4 – Overview of the literature regarding nasal high flow oxygen therapy

The effect of gas flow on temperature, humidity, pressure and airway resistance profiles of three different respiratory support systems - nasal cannulae, NHF and CPAP – under well controlled in vitro conditions has been tested.\textsuperscript{144} NHF provided significantly higher levels of humidity than either nasal cannula or CPAP (83 ± 3.1\% vs. 76 ± 0.81\%, \(p < 0.01\)) and also recorded higher pressure (56 cm H\(_2\)O vs. 14 cm H\(_2\)O) and resistance (783 cm H\(_2\)O/L/sec vs. 280 cm H\(_2\)O/L/sec) when compared to CPAP. Furthermore it has been demonstrated in an experimental paediatric model, that high-flow oxygen therapy systems produce only a low-level CPAP even with the use of very high flow rates.\textsuperscript{145} Linear regression analyses showed a linear relationship between flow and pressure measured both in the pharynx and in the distal airway.\textsuperscript{145} The relationship between the pressure generated at the airway opening and flow through a nasal cannula has been described using a simulated infant model.\textsuperscript{146} This study demonstrated that nasal cannula size correlated with the pressure generated, further substantiating the belief that minimising the leak around the nares is important. The premature size cannula had the greatest effect on tidal volume and pressure change when compared to the infant and paediatric cannulae.

Only one study has looked at the effects of NHF in an animal model.\textsuperscript{103} The investigators state that airway pressure results to date are confounded by several limitations as all have been collected by nasopharyngeal, oral cavity or oesophageal pressure monitoring and although these methods are minimally invasive, they only provide an estimate of actual airway pressure. To address these perceived limitations, this study used a tracheal pressure monitoring device placed mid-trachea into 13 neonatal piglets and found a direct linear relationship between flow rate and tracheal pressure measured (\(p = 0.04\)) as well as a flow-dependant increase in Pao\(_2\) (\(p = 0.03\)).

\textbf{4.4. Evidence in Neonates, Infants and Children}

The concept of high flows of oxygen being delivered intra-nasally originated in neonatal and paediatric practice as an alternative to nasal CPAP. Although definitions of “high flow” vary, recent reviews have used flows of over 1 - 2 L/min as describing nasal high flow in neonates and flows of > 6 L/min in older children.\textsuperscript{147-150} NHF has been described as being used in the treatment of apnoea of prematurity, respiratory distress syndrome, post extubation support and to wean from nasal CPAP in neonatal intensive care units (NICUs) in the USA, UK, Australia and New Zealand. The interfaces are easy to apply and allow better access to the infant encouraging feeding and bonding. During 2005, the Centre for Disease Control and
Prevention was notified of an outbreak of *Ralstonia* species - a waterborne bacilli - amongst paediatric patients using the Vapotherm 2000i.\textsuperscript{151} This outbreak resulted in the NHF system being recalled, redevelopment of the product and development of new disinfection and infection control guidelines. Following withdrawal of this product, the only available NHF product on the market at the time, there were widespread anecdotal reports of centres devising their own systems for delivering high flow humidified oxygen. Subsequently, Fisher and Paykel Healthcare (Auckland, New Zealand) manufactured the RT329 Infant Oxygen Delivery System designed to deliver humidified gas (37°C, 44 mg/L) via nasal cannulae at flow rates between 0.3 and 8 L/min.\textsuperscript{152}

Available evidence regarding NHF use in neonates is not strong with few randomised controlled trials to assess efficacy and determine appropriate patients selection. Out of 8 publications, only 3 observational studies report primary physiological outcome measurements such as respiratory rate, airway pressures and work of breathing.\textsuperscript{140,153,154} The two largest studies undertaken in this population were retrospective, observational studies.\textsuperscript{155,156} Of 3 prospective RCTs involving 137 neonates one compared NHF (5-6 L/min) to nasal CPAP (5-6 cm H\textsubscript{2}O) and found that NHF failed to maintain extubation status as effectively as nasal CPAP.\textsuperscript{157} The second compared two methods of delivering high-flow gas therapy by nasal cannula which was commenced at extubation and used a cross-over study design.\textsuperscript{158} In this study, Group 1 received Vapotherm for the first 24 hours after extubation then standard high flow for the next 24 hours while Group 2 received standard NHF for the first 24 hours then Vapotherm for the next 24 hours. Mean gas flow during use of Vapotherm was significantly higher (3.1 ± 0.6 L/min compared to 1.8 ± 0.4 L/min, \(p = 0.001\)) when using standard NHF and it was also shown that neonates treated with Vapotherm maintained a significantly more normal appearing nasal mucosa (\(p < 0.001\)), a lower respiratory effort (\(p < 0.05\)) and had lower reintubation rates (Group 1 \(n = 0\); Group 2 \(n = 2\)). The third study compared two forms of NHF (Fisher and Paykel compared to Vapotherm) and found that there was no difference in extubation success up to 7 days after extubation.\textsuperscript{159}

Most studies in neonates have focussed on the use of NHF as respiratory support in the period following extubation.\textsuperscript{149} One study assessed the frequency of use, safety and utility of NHF in two tertiary care hospitals and compared it to a historical group of premature infants who had received nCPAP.\textsuperscript{155} This retrospective review of 101 preterm infants determined that NHF was well tolerated and that there had been no adverse outcomes subsequent to the
introduction of this therapy. More infants required re-intubation for failing nCPAP compared to those who received NHF (40% vs. 18% p = 0.03).

A further study retrospectively reviewed 114 premature infants both prior to and following the introduction of Vapotherm 2000i NHF into one NICU. Infants treated with NHF were extubated from a significantly higher ventilator breath rate (32.6 ± 8.5 vs. 28 ±7.5, p = 0.003) and spent fewer days on the ventilator (11.4 ± 12.8 vs. 18.5 ± 21, p = 0.028) when compared to historic controls. It was also found that rates of ventilator associated pneumonia were significantly higher in the control group (p = 0.018) and that discharge weights were significantly higher in the NHF group (p = 0.016) despite a similar hospital length of stay and gestational age at discharge. The investigators speculated that the improved levels of comfort and respiratory support provided by NHF reduced energy demands which in turn resulted in improved growth. This study had no pre-determined criteria for selecting post-extubation respiratory support and an early extubation protocol was introduced into the unit at the same time as NHF was introduced, which may have confounded the results therefore the true impact of NHF was uncertain.

Recently an RCT of 132 infants less than 32 weeks gestation compared the effect of Vapotherm humidified high flow nasal cannulae (HHFNC) to nCPAP following extubation. This single centre RCT found no difference in rates of extubation failure between the two groups (22% vs. 34% respectively, p = 0.14) but did find that infants who received HHFNC had significantly less nasal trauma (recorded 3 times a day for 7 days post extubation) than those who received nCPAP (p < 0.001). Limitations of this study included the sample size which had been calculated using retrospective extubation data and a concurrent change of delivery device for the nCPAP arm.

Observational studies of NHF use in neonatal and paediatric populations have been undertaken. One study hypothesised that clinical improvements associated with the gas flow delivered by nasal cannula could be related to changes in breathing pattern in response to a positive end-distending pressure. By measuring oesophageal pressure and thoraco-abdominal motion in preterm neonates, the investigators showed a positive end-distending pressure was generated with gas flows of 1 and 2 L/min using a 0.3 cm nasal cannula - a mean pressure of 9.8 cm H_2O was generated at 2 L/min of flow. This study also found that breathing patterns were altered by the use of higher gas flows, resulting in improved thoraco-abdominal synchrony. These effects were believed to be related to the size of the nasal
cannula but did not correlate to baseline pulmonary function values. Another study demonstrated that a positive intra-pharyngeal pressure was delivered when utilising NHF in infants with respiratory distress, and that the system was well-tolerated in this patient group.\textsuperscript{154} A further study measured airway pressure in infants using NHF utilising both the Vapotherm 2000i and the Fisher and Paykel RT329 devices.\textsuperscript{139} The pressure recorded was found to be flow and weight dependent but it was also found that no pressure was generated when infants breathed with mouth open. A subsequent study, using the Fisher and Paykel RT329, has confirmed the presence of end expiratory oesophageal pressure which increased with increases in flow when the patient was breathing with the mouth closed.\textsuperscript{140} Both inter-patient (range 51 – 180%) and intra-patient (range 161 – 1885%) coefficients of variation were high for end expiratory oesophageal pressure at each flow rate measured.

An early study compared ventilator generated nCPAP to high flow nasal cannulae in an RCT of 40 premature infants.\textsuperscript{161} This study showed that high flow nasal cannulae were as effective as nCPAP in managing apnoea of prematurity and determined that the flow required to generate a comparable positive distending pressure with nasal cannulae varied with the infant’s weight. No difference was found in the work of breathing in a study of 18 premature neonates weighing < 2 kg when comparing NHF to nCPAP.\textsuperscript{153} The authors concluded that the two systems were comparable in preterm infants with mild respiratory illness. It has also been demonstrated that NHF is associated with increased pharyngeal pressures and that the pharyngeal pressure measured related directly to flow but inversely to infant size.\textsuperscript{162} This study confirmed that preterm infants receiving NHF at flows of 2 – 8 L/min received transmitted pharyngeal pressures similar to those observed in infants receiving nCPAP. The authors postulated that the differences in results between this study and others may be due to different measuring techniques employed (oesophageal vs. nasopharyngeal) or due to the cannula size used relative to the size of the nares.

A randomised cross over trial of 30 preterm infants found that 47% of infants who received “standard care” (an unspecified form of high-flow oxygen) after extubation required re-intubation whilst no patients extubated to the Vapotherm 2000i required re-intubation (p < 0.005).\textsuperscript{158} However it was found in another RCT that 60% of infants randomised to NHF required re-intubation compared to 15% using nCPAP.\textsuperscript{157} It was also found in this study that the group randomised to NHF had an increased oxygen requirement and post extubation they experienced more apnoeas and bradycardias. These two studies also investigated the local effect of NHF on nasal mucosa. By evaluating nasal mucosa after 24 hours of treatment it
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was found that NHF performed better than standard nasal cannulae in maintaining nasal mucosa integrity.\textsuperscript{158} The authors speculated that the improved nasal mucosa condition was the result of higher humidity and body temperature of gas. The first study reported no nasal damage in any infants as assessed by digital photography at 1, 7 and 30 days post-extubation.\textsuperscript{157}

A narrative review of NHF attempted to answer the question “\textit{Is Humidified High-Flow Nasal Cannula the new and improved CPAP?}”\textsuperscript{152} This review concluded that HHFNC and CPAP are not one and the same and that the positive airway pressure generated when using HHFNC was inconsistent, unreliable and unpredictable. The author suggested the following recommendations: that HHFNC should not be used routinely in neonatal care until adequate evidence for safety and efficacy was made available; that use should be limited to well-designed clinical trials to produce evidence; and that the use of HHFNC outside of said studies be limited to larger neonates and to more moderate flows while paying close attention to any potential adverse outcomes. In a subsequent review of NHF therapy in preterm infants, 9 studies were reviewed the authors concluding that HHFNC devices were preferable to high flow nasal cannulae because the delivery of humidified and warmed gas could offer significant benefits.\textsuperscript{163} It was also suggested that NHF be considered an alternative to nCPAP in clinical practice only after large RCTs were completed comparing efficacy, safety and cost-benefit of NHF to nCPAP. It has been suggested that NHF could be used as an alternative to either nCPAP or an oxygen hood in order to prevent skin breakdown due to nasal cannulae, promote parental bonding or as a device to deliver higher $\text{FiO}_2$.\textsuperscript{99} In practice, the adoption of this therapy has been slow due to a lack of evidence to support its use and cost, and it has been noted that cost may be a particularly relevant factor in the United States of America as NHF is reimbursed at the same level as low flow nasal cannulae but with a substantially higher cost in terms of units and consumables and can cost a department $\text{US18 -80 per patient.}$.\textsuperscript{99} A neonatal unit may even risk losing justification for their respiratory therapy staffing model if the unit switched to NHF rather than nCPAP.

A retrospective review of 46 paediatric patients with respiratory distress syndrome treated with NHF, demonstrated that NHF improved respiratory distress scale score, oxygenation saturation and the patient’s COMFORT score.\textsuperscript{164} This study was limited though by a lack of comparator. Much of the literature with regards NHF in paediatrics has assessed its utility in children with bronchiolitis despite a lack of evidence with regards the physiological mechanisms of action of NHF in children. One study demonstrated a decrease in intubation
rates in infants suffering from bronchiolitis who were treated with NHF. In a retrospective chart review of 115 infants admitted to the paediatric intensive care unit (PICU) with bronchiolitis (median age 3 months) it was found that the requirement for intubation and mechanical ventilation had significantly fallen from 23% to 9% (p = 0.043) since the introduction of NHF. The authors also reported a decreased respiratory rate and PICU length of stay in the group treated with NHF. A second retrospective chart review reported on 298 infants < 24 months of age who received NHF therapy over a five year period, 56% of whom had a primary diagnosis of viral bronchiolitis. Overall 12% (n = 36) of those treated with NHF required escalation to invasive ventilation while only 4% (n = 6) of those in the viral bronchiolitis subgroup required intubation and ventilation. The rate of intubation in the bronchiolitis subgroup had fallen from 37% to 7% after the introduction of NHF. Importantly, no adverse events were identified with the use of NHF in this population.

While evidence of clinical effect exists in infants with bronchiolitis, efficacy of NHF has not been demonstrated in other respiratory conditions of childhood such as asthma and pneumonia, thus generalisability of results to these conditions is difficult.

**4.5. Evidence in Adults**

Reports of NHF use in adults involve diverse patient populations including those experiencing acute respiratory failure, acute lung-graft rejection, exacerbation of COPD and asthma, and pulmonary oedema.

**4.5.1 Case reports and case series**

The first report of NHF use in adults reported a prospective evaluation of 33 patients receiving NHF or conventional supplemental oxygen therapy. This study showed that when receiving Vapotherm NHF the mean RR was significantly lower when compared to conventional oxygen therapy (23 breaths per minute vs. 27 breaths per minute respectively, p <0.001) and also that mean SaO₂ was significantly higher with NHF compared to conventional oxygen therapy (96% vs. 90.9%, p < 0.001). An audit undertaken in a surgical HDU describes the use of NHF to improve oxygenation and deliver high humidification to enhance secretion mobilisation in patients experiencing hypoxaemia due to atelectasis. In this centre, NHF was used as a weaning aid to reduce the incidence of re-intubation and also used in conjunction with face mask CPAP when patients had difficulty tolerating CPAP for long periods. Reduced RR and improved oxygenation were reported over
the 2 year audit period which saw 72 patients receiving NHF. The authors also report that the “vast majority of patients are satisfied during the treatment and it is a system that staff find relatively easy to use with few complications” (pg303). Patients were also asked “Overall are you satisfied/dissatisfied with your experience with Vapotherm therapy?” Ninety percent stated that they were satisfied. The use of the Vapotherm 2000i NHF system in a 92 year old patient with delirium and dementia in ICU who required a high FiO\textsubscript{2} for multi-lobar pneumonia and severe hypoxemia who could not tolerate a nasal or facial mask has been described. This case report showed that NHF reduced agitation and improved dyspnoea, oxygenation, tolerance of therapy and comfort at end of life. Reductions in RR, heart rate (HR) and blood pressure (BP) six hours after institution of therapy were also reported. Another study reports the use of NHF in three ICU patients. The first patient, a 57 year old male was admitted with pneumonia and systemic sepsis, the second a 79 year old female was admitted with pneumonia and had a long history of COPD. Both patients were treated successfully with NHF without requiring any escalation in therapy. The third patient, a 70 year old male was admitted with pneumonia complicated with pulmonary fibrosis and was severely hypoxic. He was initially treated with face mask CPAP but was unable to tolerate the mask. To ease discomfort a humidified high-flow oxygen system was employed, however his condition was such that the decision was made to palliate care. The author suggests that NHF augmented palliation and prevented agitation and confusion allowing the patient a dignified and comfortable death. Lastly, Lomas reports a patient with myaesthenia gravis and severe ARF who underwent fibre optic bronchoscopy with oxygen administration via NHF. In this patient, the use of NHF was subjectively associated with an improvement in RR, dyspnoea symptoms and oxygenation and allowed the bronchoscopy procedure to take place without the need for intubation and mechanical ventilation.

While these reports of NHF use are all descriptive, they provide a valuable resource in terms of the diverse range of patient groups that NHF may prove appropriate for. There is no definitive evidence to determine who should or who should not be given a trial of NHF and so these studies may give clinicians some degree of reassurance when treating patients in their care with NHF and extending its use beyond that of simple delivery of oxygen therapy to hypoxaemic patients.
4.5.2 Reviews of NHF therapy

There has been increasing evidence published with regards NHF - both observational and interventional. Several systematic and narrative reviews have now been published reporting on NHF. A conclusion that “further research is required to determine how the therapy can be incorporated into clinical practice” (pg.68), while the other concluded that while NHF offers theoretical benefits over standard oxygen therapy, there was insufficient evidence to definitively demonstrate superiority to other methods of respiratory support and pointed to the large number of ongoing trials which may help address the issue of efficacy of NHF with regards clinical outcomes such as intubation rates, mortality and morbidity. The most recent review notes that widespread patient use of NHF preceded in-depth testing and clinical trials, but that there had been an effort to both address this and evaluate efficacy and to identify clinical uses for NHF. The authors conclude by stating that:

Randomised controlled trials have become the cornerstone of evidence based practice. However, in the process of controlling variables such as patient cohorts and precise protocols, findings may lose the ability to be generalisable to clinical realities of the real worlds of ED, ICU or neonatal ICU. As physicians, nurses, and respiratory therapists incorporate the HFNC in their clinical practice, they should be encouraged to conduct research or carefully record their observations as they apply this medical gas interface within the “realities” of their clinical settings and the individual patient’s need (pg. 118).

A second review of the literature regarding NHF in critically ill infants, children and adults concluded that:

While theoretical advantages exist over standard nasal cannula and face mask oxygen, current evidence does not definitively demonstrate superiority to other methods of respiratory support ……….. few studies have focused on clinical outcomes beyond common respiratory parameters (pg. 255).

A systematic review included 8 reports of NHF use. At the time the review was undertaken there were no published papers and the authors included abstracts and poster presentations from scientific meetings. The authors concluded that there was “…emerging preliminary evidence…” (pg. 68) suggesting clinical benefit with NHF in terms of improved oxygenation when compared to standard oxygen therapy. However they determined that “…further
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research is required to determine how the therapy can be incorporated into clinical practice” (pg. 68).\textsuperscript{172} It was suggested that future research address issues such as determination of the effect of NHF whilst therapy is in progress, with particular focus on NHF use in patients with Type II respiratory failure, an evaluation of NHF to prevent re-intubation as well as assessment of long term outcomes such as mortality and morbidity and the development of a tool for more accurately assessing dyspnoea and comfort in patients utilising NHF in the ICU.

The literature regarding NHF in adults will now be reviewed in terms of proposed mechanisms of action and clinical effects.

4.5.3 Provision of a flow dependent positive airway pressure effect

The first study to demonstrate that a pressure effect was generated by NHF involved 10 healthy volunteers.\textsuperscript{107} This study demonstrated that expiratory pressures were significantly higher at 20, 40 and 60 L/min compared to no flow at baseline (p < 0.001) and that the pressure effect was enhanced when participants breathed with mouth closed as compared to mouth open (p < 0.001). In addition, inspiratory pressures were found to be significantly different in males when compared to females when breathing with mouth open (p = 0.05) but not when breathing with mouth closed. The reason for this discrepancy is unclear. A second study enrolled 15 cardiac surgical patients and measured nasopharyngeal airway pressure (NPAP) at 35 L/min delivered by NHF compared to 35 L/min delivered via a standard face mask.\textsuperscript{8} A low level positive airway pressure was generated with NHF which was significantly higher when compared to a standard face mask (p = 0.001) and that the pressure was higher again when the participant breathed with mouth closed as opposed to mouth open (p = 0.001) (Table 1).\textsuperscript{8}

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Further studies have now described the presence of a positive airway pressure when NHF is used in both patient populations and healthy volunteers.\textsuperscript{7,12,103,108} A study undertaken in healthy volunteers measured hypopharyngeal pressure by way of a 10 French catheter inserted into the hypopharynx via the nose, in 10 subjects using the Optiflow\textsuperscript{TM} system and found that pressure rose significantly with flow rate during nasal breathing.\textsuperscript{108} Mean airway pressure rose from a mean (SD) of 0.51 (± 0.35) cm H\textsubscript{2}O at 10 L/min to 5.13 (± 0.1.32) cm H\textsubscript{2}O at 50 L/min. This observational study also measured FiO\textsubscript{2} and end tidal CO\textsubscript{2} at different flow rates and demonstrated that the calculated FiO\textsubscript{2} delivered by the Optiflow\textsuperscript{TM} system approached that prescribed when the delivered flow rates exceeded participant peak inspiratory flow rate. This small study enrolled 10 healthy volunteers, 2 of which were female. The methods by which airway pressures were calculated are not described. This study is one of the few to note that the peak pressures are noticeably higher at higher gas flow rates and when breathing with mouth closed. Subsequently it has been shown that the pressure generated by NHF increases as flow is increased.\textsuperscript{7} Mean (SD) airway pressures of 1.93 (± 1.25), 2.58 (± 1.54) and 3.31 (± 1.05) cm H\textsubscript{2}O were generated when patients breathed with their mouth closed whilst receiving 30, 40 and 50 L/min of NHF respectively. Furthermore a positive linear relationship was found between the flow delivered and the airway pressure generated.\textsuperscript{7} Regression analysis of the mean NPAP (Figure 4) demonstrated that in the mouth closed position, for every 10 L/min increase in flow the mean NPAP increased by 0.69 cm H\textsubscript{2}O and by 0.35 cm H\textsubscript{2}O in the mouth open position.
In order to further describe the effect that positive pressure may have on changes in lung volume, two studies have now used electrical impedance tomography (EIT) to provide real-time images and data regarding regional lung ventilation and lung volumes.\textsuperscript{12,173} The first study found that NHF increased both the end-expiratory lung volume (EELV) and tidal volume in 20 patients studied following cardiac surgery. Increases in end-expiratory lung impedance (EELI) were significantly influenced by BMI, with larger increases associated with higher BMIs. The authors postulate that increases in EELV may result in a reduction in the work of breathing, assist in prevention of small airway closure and lead to improved oxygenation due to reduced shunting. More recently, in a study of 20 healthy volunteers the use of NHF was found to increase global EELI in both the prone and supine position and it was suggested that this represented an increase in FRC.\textsuperscript{173} Although a small study, enrolling only healthy volunteers, it is the first to report the effect of body position on impedance distribution when using NHF. Both studies are limited by the limitations inherent to using EIT, including but not restricted to the fact that this technique reflects only a portion of the lung and not thorax shape and that EELI is a calculated value. Also, the positioning and placement of the electrode belts may prove difficult in some participants and thus may
provide inconsistent or incorrect data. Nevertheless these studies provide further evidence that NHF delivers a low level, flow dependent positive airway pressure which provides a distending effect to the lung units. Although small studies they include both healthy volunteers and patients following surgery, males and females and a range of body sizes and may thus be generalisable to various patient groups. There is no evidence currently available to demonstrate the pressures generated by NHF over the whole of the respiratory cycle.

### 4.5.4 Effect on oxygenation

Significant improvements in both PaO$_2$ and SpO$_2$ have been associated with the use of NHF. In one study PaO$_2$ improved significantly from a median (IQR) 77 mmHg (64 – 88) to 127 mmHg (83 – 191) and SpO$_2$ from 95% (91 – 97) to 98% (96 – 99), $p = 0.002$. Another study compared NHF to HFFM and found no significant difference in mean PaO$_2$ [NHF 102.1 (SD±40.3) vs. HFFM 98.4 (SD±38.5, $p = 0.38$)] and SpO$_2$ [NHF 95.3 (SD±6.1) vs. HFFM 95.6 (SD±5.3), $p = 0.36$] after thirty minutes of therapy. The improvement in oxygenation seen with NHF may in part be due to less dilution of delivered oxygen. As higher flows are achieved with NHF, meeting or exceeding patient inspiratory demand, less entrainment of room air and resultant dilution of oxygen concentration is seen. By measuring the delivered FiO$_2$ in the pharynx during both low-flow (1 - 6 L/min) and high-flow (6 – 15 L/min) nasal cannulae use in 10 healthy volunteers, it has been demonstrated that NHF delivers an accurate FiO$_2$. This study found a progressive increase in pharyngeal FiO$_2$ with each increase in oxygen flow with higher values achieved when participants breathed with mouth open compared to mouth closed. A number of limitations may affect the generalisability of these results. This study was undertaken in healthy volunteers, all of whom were relatively young, no tracheal gas sampling was undertaken, respiratory variables such as tidal volume and inspiratory flow were not reported and the presence of the measuring tube itself may have added to the resistance to oxygen flow from the nasal cannulae.

A significant difference in the PaO$_2$/FiO$_2$ ratio has been reported in one study, $p < 0.001$. The PaO$_2$/FiO$_2$ ratio was improved by 30.6% (95% CI 17.9, 43.3) in patients using NHF even though 95% of patients received an equal or lower FiO$_2$ while on NHF than on low-flow oxygen. This was attributed in part to the increase in EELV and improved alveolar ventilation as well as reduced air entrainment and oxygen dilution when using NHF. Increased SpO$_2$ 15 minutes after commencement of NHF is described in one study, as well as an improvement lasting throughout the 48 hour study period with a mean PaO$_2$ significantly higher an hour
after institution of NHF – 141 vs. 95 mmHg, p = 0.009.\textsuperscript{11} The PaO\textsubscript{2}/FiO\textsubscript{2} ratio also significantly improved one hour after commencement of therapy from a mean (SD) of 102 (± 23) to 169 (± 108) mmHg and then further at 24 hours to a mean of 187 mmHg (± 86). Another study describes a significant increase in both mean SpO\textsubscript{2} from 93.5\% vs. 98.5\% (p < 0.001) and in mean PaO\textsubscript{2} from 8.73 to 15.27 kPa (p = 0.001) after one hour of NHF therapy.\textsuperscript{174} One RCT enrolled 75 critically ill patients, who were allocated to receive oxygen by way of either NHF or Venturi mask at extubation.\textsuperscript{175} It was found that the PaO\textsubscript{2}/FiO\textsubscript{2} ratio was higher in the NHF group, being statistically significant at 1, 3, 24, and 36 hours (317 ± 78 vs. 253 ± 84, p < 0.01 at 24 hours). The only study undertaken in healthy volunteers to report oxygenation variables, used oximetry to demonstrate a significant upward trend for calculated FiO\textsubscript{2} with increasing flow rate for all breathing patterns when subjects were using NHF (p < 0.001).\textsuperscript{108}

\textbf{4.5.5 Effect on CO\textsubscript{2} clearance}

Recent reports on the efficacy of NHF with regards carbon dioxide (CO\textsubscript{2}) clearance differ. Two studies have reported no significant difference in partial pressure of CO\textsubscript{2} (PaCO\textsubscript{2}).\textsuperscript{2,10} One study found no difference in mean (SD) PaCO\textsubscript{2} at baseline or after 1 and 24 hours of NHF (38 ± 11, 37 ± 11 and 38 ± 10 mmHg respectively),\textsuperscript{11} while in another study it was found that a modest increase in PaCO\textsubscript{2} existed from a median 5.26 (range 4.33 – 5.66) to 5.73 (4.8 – 6.2) kPa (p = 0.005).\textsuperscript{174} It is difficult to infer from these results the true effect of NHF on CO\textsubscript{2} as neither of these studies was undertaken using a randomised controlled design and both included patients suffering hypoxaemic respiratory failure. Perhaps also, any effect due to NHF may have been difficult to detect given the small sample size and the comparator used. It is difficult to accurately determine how much flow or oxygen was being delivered via the non-rebreather mask used to deliver conventional oxygen therapy, and thus its effects on tidal respiration remains unclear. Measuring, reporting and determining the effect that NHF may have on CO\textsubscript{2} clearance is difficult and studies still need to be undertaken to elucidate the exact mechanism by which this occurs.

\textbf{4.5.6 Effect on respiratory rate}

Studies have reported a significantly reduced RR when NHF is used. A prospective comparative study of sequential interventions compared NHF to a standard facemask and found a significant reduction in RR when using NHF in patients without concurrent
hypercapnia or acidosis.\textsuperscript{10} A median (IQR) RR with facemask of 28 (25 – 32) and with NHF of 21 (18 – 27), \( p < 0.001 \) was reported.\textsuperscript{10} A reduced average (SD) RR was also reported in 72 patients utilising Vapotherm\textsuperscript{TM} NHF (baseline 26.3 ± 7.1, 1 hour after 22.6 ± 6.1, day 2 21.9 ± 6.3).\textsuperscript{168} Conversely, another study reported no difference in RR in a randomised crossover trial of NHF vs. high-flow face mask oxygen therapy (18.7 ± 5.5 vs. 19.7 ± 6.5, \( p = 0.18 \)).\textsuperscript{2} In a study of 17 patients presenting with ARF to the emergency department a reduction in median (IQR) RR was found from 28 (25 – 32) to 25 (21 – 28), \( p < 0.001 \) when comparing a non-rebreathing mask to NHF.\textsuperscript{176} A study of 20 patients post-cardiac surgery also found a significant reduction in mean RR (\( p < 0.001 \)) and it was hypothesised that this may reflect a reduced work of breathing due to NHF.\textsuperscript{12} The authors also suggested that the improvement in lung compliance, as evidenced by an increased EELI and improved FRC may be partially responsible for the reduced RR.\textsuperscript{12} A study of 38 patients with ARF found a significant reduction in RR (\( p = 0.009 \)) though the actual RRs observed are not reported.\textsuperscript{11} In a further prospective observational pilot study, a reduction in RR from 28 to 24.5 breaths per minute (\( p = 0.06 \)) one hour after initiation of NHF in patients with ARF was reported.\textsuperscript{174}

\subsection*{4.5.7 Effect on heart rate}

A trend towards decreased heart rate (HR) in patients receiving NHF was shown in one study,\textsuperscript{10} which found a non-significant difference in median HR between the two groups studied with a median of 94 beats per minute in the facemask group compared to median 85 beats per minute in the NHF group, \( p > 0.99 \). Another study reports significant reductions in heart rate 6, 12, 24 and 48 hours after commencement of NHF (\( p < 0.05 \)) from around 104 to 98 beats per minute,\textsuperscript{11} while another reports a non-significant trend to decreased heart rate over the study period with NHF median 105 vs. 100 beats per minute (\( p = 0.11 \)).\textsuperscript{174} It is assumed that while NHF has no direct effect on the HR itself, the reduction seen may be a result of reduced work of breathing and a reflection of improved oxygenation in hypoxaemic patients.

\subsection*{4.5.8 Effect on comfort}

Results of subjective assessment using a visual analogue scale (VAS) showed a significant improvement in comfort scores with the use of NHF.\textsuperscript{10} When using a standard facemask patients reported a median (IQR) comfort score of 5 (2.3 - 6.8) and with NHF 9 (8 – 10). Participants also reported perceived mouth dryness was significantly improved when using
NHF with the median score improving from 9.5 to 5 (p < 0.001). When asked which of the two oxygen systems the participants would like to continue with at the end of the study, all chose NHF. However this study was not randomised or blinded and so participants were aware of not only which oxygen delivery system they were using but also able to choose which one they received which may have affected results. In a randomised crossover trial comparing NHF to HFFM, a VAS using the WongBaker faces scale allowed bedside nurses to assess the comfort and tolerance of patients to both NHF and high-flow facemask oxygen delivery devices. A significant difference in terms of tolerance was found with NHF being better tolerated than HFFM (p = 0.01) although there was no significant difference in comfort scores (p = 0.09). Both tolerance and comfort scores were subjective and recorded by the bedside nurse and thus may have been influenced by personal preference. In a study of 30 patients with acute hypoxaemic respiratory failure, a significantly lower nasal dryness score was reported in the NHF group at 4 hours (2 vs. 7, p = 0.007) and 24 hours (1 vs. 7, p = 0.004) after initiation of therapy. In this study 16 patients (53%) preferred NHF as compared to standard oxygen therapy, particularly those who required a higher flow of oxygen at time of admission to the ICU. A cross over design was used to minimise bias and ensure comparability between the two groups. Limitations of this study include the subjective dryness scale used and self-reporting by participants. In an observational study of 38 patients a visual numeric scale (VNS) of 0 to 10 was used to report nasal discomfort and noise disturbances associated with NHF. When evaluated with the VNS, scores did not change between the beginning and the end of the study with average (SD) values of 3 (± 3) and 4 (± 3) respectively. Intolerance to the therapy was never the cause of NHF cessation. Participants in a prospective RCT of 75 patients experiencing poor gas exchange following extubation reported significantly less discomfort due to the interface when using NHF at 12, 24, 36 and 48 hours (p < 0.01) and less discomfort related to dryness of the upper airways when using NHF as compared to Venturi mask at all time points (p < 0.01). This study also found that interface displacements occurred less frequently in patients who were treated with NHF when compared to a Venturi mask (30% vs. 71% respectively, p < 0.01).

4.5.9 Effect on dyspnoea

One study asked patients to self-report feelings of dyspnoea using a VAS where 0 = lowest and 10 = highest degree of dyspnoea. A significant improvement was found when patients used NHF - median score facemask = 6.8 with NHF = 3.8 (p = 0.001). This result should be
interpreted cautiously as subjective rating scales can be prone to misinterpretation especially when used in an unblinded study where patients know which device they are assessing. Significant decreases in dyspnoea scores after 60 minutes of therapy have been shown - using both the Borg scale median (IQR) 6 (5 – 7) vs. 3 (2 – 4) p < 0.001 and a VAS 7 (5-8) vs. 3 (1.5) p = 0.002. Significant reduction in dyspnoea after 30 minutes of NHF therapy has also been demonstrated using a VNS. In that study the improvement in dyspnoea symptoms was significant over the entire 48 hour study period. A modified Borg scale was used in another study which asked patients to self-report dyspnoea levels. Scores were lowered by 0.8 points in patients using NHF as compared to those using low-flow oxygen therapy (95% CI 0.1, 1.4; p = 0.023).

4.5.10 Success of therapy

A success rate - defined as avoidance of intubation - of over 75% has been reported with Optiflow™. Meanwhile, another study reports 86.2% of patients treated with NHF did not require intubation and ventilation while on the Vapotherm 2000i system and 83.3% of patients who received NHF in this audit survived and were discharged from hospital. One RCT assessing the utility of NHF in patients experiencing mild to moderate hypoxaemia found that significantly more patients allocated to NHF succeeded on their allocated therapy when compared to those allocated to a high flow humidified face mask (26/29 vs. 15/27 respectively, p = 0.006). Reduced use of NIV was also reported in the NHF group (10% vs. 30%, p = 0.1) in this study. Although not statistically significant, the authors described this finding as clinically significant.

4.5.11 Failure of therapy and predicting failure

In a post hoc analysis of patients treated with NHF during the H1N1 Influenza pandemic it was found that baseline characteristics such as the presence of shock and high organ failure scores at ICU admission were associated with failure of NHF. A prospective observational study of 38 patients with acute hypoxaemic respiratory failure reported 9 patients (23.7%) requiring intubation and mechanical ventilation. Interestingly all patients were intubated while still utilising NHF in order to provide both pre-oxygenation and maintain oxygenation during the procedure. Respiratory parameters of the patients requiring intubation were compared to those of the remaining study population to try and identify predictors of NHF failure. Patients who “failed” NHF had a higher RR 30 and 45 minutes after beginning NHF;
a lower SpO₂ 15, 30 and 60 min after beginning NHF and a lower PaO₂ and PaO₂/FiO₂ ratio one hour after beginning NHF. The proportion of patients showing signs of respiratory distress such as thoraco-abdominal asynchrony was significantly higher at 15 (43.7% vs. 9%, p = 0.04), 30 (50% vs. 11.5%, p = 0.02), 60 (75% vs. 10%, p = 0.04) and 120 minutes (80% vs. 15.6%, p = 0.009) post commencement of NHF. A further study reports a 30% “failure” rate - 6/20 patients required intubation and mechanical ventilation. The authors suggested that this figure compared similarly with the failure rate for NIV in other French ICUs. Again this study was not randomised and the possible intubation rate had a randomised trial been undertaken is unknown. An observational study undertaken in a tertiary cardiothoracic ICU described the patient population receiving NHF and their subsequent therapy outcomes. Data was collected on 120 patients over a 6 month period and demonstrated that 22% of patients were considered to have failed NHF therapy - failure was defined as a requirement for an escalation of respiratory support to NIV or invasive mechanical ventilation within 48 hours of commencing NHF. Logistic regression analysis was used to determine if any baseline physiological variables collected contributed strongly to the risk of failure of therapy. It was found that a lower mean arterial pressure (≤ 70 mmHg) and a lower pH (≤ 7.35) at study enrolment showed the greatest risk contribution with a strong relationship trend for both. On further analysis it was found that a baseline a pH of ≤ 7.35 resulted in a significantly higher probability of NHF failure. One of the limitations of all studies aiming to quantify failure or success of NHF therapy so far is that none have published definitive guidelines as to when patients require an escalation in respiratory support and what constitutes “failure of therapy”. This is left to clinician discretion and local practice. While pragmatic in terms of study design, this does make results difficult to interpret and extrapolate.

4.5.12 Patient populations utilising NHF

NHF has been used in diverse patient groups for a wide range of conditions. A recent retrospective observational study described the use of NHF in 50 patients with a do-not-intubate order and respiratory failure. This study showed that NHF significantly reduced mean RR from 30.6 to 24.7 breaths/minute (p < 0.001), improved oxygen saturation from 89.1 to 94.7% (p < 0.001) and was well tolerated with no reports of epistaxis or skin breakdown. Another study described providing oxygenation by way of NHF to patients undergoing bronchoscopy. The authors studied 45 patients undergoing fibreoptic
bronchoscopy who were randomly assigned to one of three groups: group one received FiO\textsubscript{2} 50\% at 40 L/min via a Venturi mask; group two received FiO\textsubscript{2} 50\% at 40 L/min via NHF; group three received FiO\textsubscript{2} 50\% at 60 L/min via NHF. At the end of bronchoscopy, patients randomised to receive 60 L/min via NHF had significantly higher arterial/alveolar PaO\textsubscript{2} ratio, PaO\textsubscript{2}/FiO\textsubscript{2} ratio and SpO\textsubscript{2} when compared to those randomised to either 40 L/min via Venturi mask or 40 L/min via NHF. Ten minutes after completion of bronchoscopy there remained a difference in SpO\textsubscript{2} only. There was no difference in comfort levels between the groups (p = 0.57). NHF has been used in patients diagnosed with infective respiratory failure and included immunosuppressed patients such as HIV patients, those with pandemic H1N1 influenza pneumonia and in do-not-intubate patients,\textsuperscript{11} while a further study reported the successful treatment with NHF of 5 patients with acute heart failure due to acute pulmonary oedema.\textsuperscript{181}

A single-centre retrospective review of 183 patients reports the use of NHF in adult oncology patients,\textsuperscript{182} and eloquently describes the physiologic and quality-of-life benefits offered by NHF when compared to standard oxygen delivery devices such as obviating the need for either ICU admission or invasive mechanical ventilation. Although this study was retrospective in nature and therefore it is not possible to draw any strong conclusions between the use of NHF and outcomes such as comfort or dyspnoea in this patient group, anecdotal evidence presented by the investigators points to increased ability to eat and talk amongst NHF users and reduced feelings of confinement due to a mask - crucial patient centred outcomes in the terminally ill. The use of NHF in a patient with pulmonary fibrosis complicated by ARF has been described.\textsuperscript{183} Initially the patient was treated with NIV and HFFM which were both poorly tolerated. So poor was the prognosis for this patient, that mechanical ventilation was not deemed appropriate and thus palliative care using NHF was initiated. However, after 10 days of NHF therapy both the PaO\textsubscript{2}/FiO\textsubscript{2} ratio and radiographic infiltrates had improved so dramatically that the limitation of therapy order was cancelled. Better tolerance of the NHF interface and fewer interruptions of oxygen delivery are believed to have contributed to the improvement seen in this patient.

Several studies now report the use of NHF in cardiac surgical patients.\textsuperscript{7-9,12,184,185} Predominantly these studies have been observational in nature with some undertaking measurement of nasopharyngeal airway pressure and lung volume using pressure transducers and/or EIT. One preliminary RCT has been undertaken in an ICU which enrolled participants with mild to moderate hypoxaemic respiratory failure, some of whom were admitted
following cardiac surgery. This study compared NHF to HFFM oxygen therapy and found those treated with NHF were more likely to succeed on their allocated therapy and less likely to experience desaturations than those allocated to HFFM. A French study evaluated the use of NHF for treatment of severe postoperative hypoxaemia in adult patients following cardiac surgery. This study compared NHF to HFFM in 40 patients and found no significant differences in duration of hypoxaemia, duration of ICU length of stay, occurrence of postoperative pneumonia or requirement for non-invasive ventilation, re-intubation or catecholamine use. Patient satisfaction with oxygen therapy and mouth dryness was significantly improved with the use of NHF (p < 0.001 for both).

One study reports the efficacy and convenience of NHF used when intubating patients and states that NHF provides exceptional intubation conditions as the same device is used all the way through from initial management of respiratory failure and can provide continuous oxygenation during the time of endotracheal intubation. The authors also hypothesise that the high constant flow may indeed provide sufficient oxygen to the alveoli during apnoea. In a study reporting the use of NHF in patients with 2009 Influenza H1N1 it is reported that NHF was not associated with any complications such as pneumonia or barotrauma and neither was it associated with secondary infections among health care workers. This may help ameliorate some concern over potential for droplet spread amongst health care professionals when caring for patients with respiratory infections who are utilising NHF.

4.5.13 Adverse events

There have been few adverse events connected with the use of NHF. Mild adverse events were reported in 5 (25%) participants in one study, including a sensation of cervical-thoracic discomfort related to flow level; complaints of gas temperature being too high; and a complaint of nasal discomfort. It has also been reported that some patients experience rhinorrhea (runny nose) because of the high humidity. Only one patient in that study (n = 72) refused to continue with the system because of this issue, while others managed with a supply of tissues. It was also suggested that the nasal cannulae used with the system in the study may cause soreness around the nares and over the ears, particularly in patients using the system for more than 3-4 days.
4.6. Summary of the Literature

These studies add to the growing body of evidence surrounding NHF in diverse clinical settings and patient conditions. When the initial literature review was conducted in January 2010, 26 citations were identified that fulfilled the search criteria. Now some 90 studies can be identified - 55 of them published in the last 3 and a half years. Some are experimental studies however these remain few, with most evidence being observational. The majority of papers involve paediatric and neonatal patients rather than adults. There have been no prospective RCTs of patients scheduled for elective surgery and enrolled prior to ICU admission and there is no data to support the concept of NHF being used as a routine therapy at extubation. There remains no experimental evidence of NHF use in cardiac surgical patients other than those who have already failed conventional oxygen therapy and are now considered to have respiratory dysfunction.

4.7. Identified Gaps in the Literature

There is a paucity of high quality evidence regarding NHF oxygen therapy. There are few RCTs, most of the literature having been generated by way of case reports and observational studies. Initially much of the literature arose from paediatric and neonatal populations however now there exists an increasing body of literature with regards NHF in adults, reflecting the natural progression in the use of NHF which was first used in the neonatal and paediatric arena and then became popular in adult services.

There is little to describe the use of NHF in cardiac surgical patients and no reports of NHF being used prophylactically at extubation in patient populations not deemed to be hypoxaemic and who have had a routine post-operative course. There is little evidence to describe exactly the mechanisms of action of NHF and how each contributes to the improvement in patient condition that is seen.

One further question that remains unanswered is where in the continuum of respiratory support therapies nasal high flow therapy sits. It has been suggested that NHF may be considered as an intermediate step between conventional oxygen therapy and non-invasive ventilation.186

Relatively loose criteria for determining success or failure and requirement for escalation of therapy have been used in each study and there is no consistent standard for reporting or
determining what constitutes respiratory failure or hypoxaemia. Furthermore, varying comparators have been used in evaluations of NHF. The question remains should NHF be compared to conventional oxygen therapy and conventional oxygen therapy devices or should it be compared to NIV? This question is difficult to answer while uncertainty remains as to NHF’s place in supportive management of oxygenation and its position in the continuum of oxygen support therapies. No analysis has been undertaken to assess the cost of delivery of NHF. This therapy currently can only be delivered in a hospital setting as it requires high flow rates that cannot be generated by available flow generators in a home setting. Capital outlay is required to provide the heated humidifier, blender and flow meters necessary and consumables including the heated delivery tubing and nasal interface must be purchased for each patient. When compared to prolonged mechanical ventilation NHF would seem cheaper however, in some areas cost may prove prohibitive in terms of devices and consumables but also in terms of the increased oxygen consumed in delivery.

4.8. On-going Clinical Trials Involving NHF

A search of all registered clinical trials was last performed in June 2013 and it was found that there were currently around 45 trials underway in infants, children and adults examining NHF. These studies were registered on the following databases: the Australia New Zealand Clinical Trials Registry (http://www.anzctr.org.au/), U.S. National Institutes of Health (http://clinicaltrials.gov), and World Health Organisation International Clinical trials registry platform (www.who.int/ictrp). Trials are now focussing on clinical outcomes such as intubation rates; extubation failure rates; morbidity and mortality.

4.9. Conclusion

This overview demonstrates that the available literature surrounding NHF has increased latterly, though much of it is low grade evidence. While theoretical advantages exist over standard nasal cannulae and face mask oxygen therapy devices, current evidence is lacking with regards either superiority or equivalence of NHF. Few studies have produced evidence describing clinical outcomes beyond common respiratory parameters.

There is no higher level evidence available to guide clinicians providing care to patients following cardiac surgery as to whether or not the use of prophylactic nasal high flow oxygen therapy will lead to improved outcomes and reduced incidence of pulmonary complications.
Chapter 5. Methodology

_In much of society, research means to investigate something you do not know or understand_

_Neil Armstrong_

Research is a systematic investigation whereby data is collected, analysed and interpreted in an effort to understand, and is vital in order that we may examine, and continue to improve, practice and patient care. Nursing and health research use numerous methodologies, arising from differing political or ideological positions, and methods to develop knowledge and answer questions. Since the time of Florence Nightingale, nursing and nurses have been involved in and concerned with acquiring theoretical knowledge for application in clinical practice. This approach has aided nursing in developing as a professional discipline separate to medicine and has led to the distinction of nursing as a profession as opposed to a “calling”. Nurses and nurse-researchers are keen to develop new ways of working and to assist in the generation of new knowledge and evidence in order to respond to changes in society such as an ever increasing demand for and use of technology and the ever changing scope of nursing practice.

This section gives a broad overview of research paradigms underpinning this thesis and the implications of that for knowledge production. It will also describe which research methods were chosen for the works undertaken during the course of this study and why.

5.1. Research Paradigms

A paradigm is a “broad intellectual framework or set of assumptions used to analyse a scientific issue or field of scientific inquiry” pg. 179. A researchers’ paradigmatic position relates to their understanding of the nature of their knowledge and of their reality, and the paradigm chosen not only reflects the researchers’ approach but also guides the direction and conduct of the research. Broadly speaking there are two dominant research paradigms: quantitative and qualitative research, although in reality there may exist multiple paradigms within these and researchers may employ methods from differing paradigms to generate
Determining the most appropriate paradigm and resulting trial design depends on the purpose of the research, the nature of the issue being investigated, the background of the investigator and the need for generalisability of trial findings. Research paradigms can be further classified as positivist, critical or interpretive. When designing research, the researcher must appreciate how differing research methods and approaches have emerged over time from differing practices and how different understandings of the world are produced. It has been suggested that nursing research may fall within the two broad worldviews of positivism and naturalistic paradigms. A pragmatic approach to conducting research has been proposed which advocates integrating strategies that clarify the theoretical perspective most needed to aid in knowledge development. The dominant paradigms represented in nursing research are positivist, post positivist, interpretive and critical social theory. For the purposes of this thesis I will concentrate on positivist and post positivist paradigm both of which assume that observations can be made objectively and are either value-free or value neutral with the goals of control and prediction.

5.2. Positivism and Post Positivism

A positivist paradigm, based on the ideas of French philosopher Auguste Comte, maintains that reality is fixed and that objective knowledge can be produced only through use of rigorous methodology. Positivism is rooted in 19th century thought and is a reflection of a broader school of thought referred to as modernism which stresses the rational and the scientific. Features of a positivist paradigm include determinism, objectivity, quantification, reliability and generalisability. Positivists seek to be objective holding personal beliefs and biases in check while undertaking research to avoid contaminating the investigation. This approach involves orderly, disciplined procedures designed to test the researchers’ hypotheses with regards the events being studied and relationships among them. Positivists believe that observation and measurement are at the core of scientific endeavour, and that the key scientific method is the experiment. It has been suggested that within the positivist framework there are various methods for advancing knowledge of health and illness through research, while the key aim is to construct evidence on which to base practice. Using a positivist approach, empirical testing is used to test and prove or disprove questions and/or hypotheses while potential confounders are carefully controlled for to prevent outcomes being influenced. Methods such as the RCT, cohort studies, survey research, content analysis, structured interviewing and systematic review employ a positivist
paradigm. Criticism of the positivist approach is aimed at its seeming disregard for the subjective state of participants as human behaviour may be seen as passive, controlled and dehumanised and reduced to scores and percentages. While designs such as the RCT have much to offer in terms of knowledge development, not all questions are amenable to this design. For instance an RCT cannot explore what is happening in a person’s life and relationships.

Science and clinical research have now moved to an era of post-positivism. Post-positivists recognise that the way in which scientists think and work is not that different to how we think and work in everyday life and it has been suggested that scientific reasoning and common sense reasoning are essentially the same process. Critical realism is one of the more common variants of post-positivism and suggests that there is a reality independent of our thinking about it that science can study. Post-positivist critical realists recognise that all observation is fallible and may be open to error which may affect our observations. Post positivism methodology aims to address perceived issues by using a modified experimental design in a more natural environment, while collecting more situational information and may include qualitative methods also. The move towards post-positivism is also reflected in the need for pragmatic trials that may more accurately generate information about intervention effects in clinical practice.

5.3. Role of Clinical Epidemiology

Clinical epidemiology is the “application, by a physician who provides direct patient care, of epidemiologic and biostatistical methods to the study of diagnostic and therapeutic processes in order to effect an improvement in health” (pg125). Clinical epidemiologists may provide more advantage than clinical researchers as they combine principles and methods developed in both clinical medicine, epidemiology and biostatistics and assist greatly in explaining disease and cure. Clinical epidemiology is a basic science relied on by clinicians in their care of patients, which develops and applies methods of observation that lead to conclusions by avoiding systematic error and chance. Clinical epidemiology provides evidence to guide clinicians in determining care of their patients by fostering methods of clinical observation and interpretation. This is done by asking and answering questions with regards abnormality, diagnosis, frequency, risk, prognosis, treatment, prevention and cause. Questions may be distinguished as background or foreground. Background questions are general and broad thereby producing a wide range of evidence for review. For instance,
answer the question of how best to manage a patient's pain may require synthesising evidence related to not only prescribing and administering pharmacological interventions but also alternative and/or behavioural therapies. A *foreground question* is focussed and includes a specific comparator. For instance “Is orally administered Morphine more effective than intravenous Morphine in patients following abdominal surgery?” Background questions can be complex but may produce evidence that may lead to formulation of a foreground question.

Epidemiological studies may be classified as either observational or experimental.

### 5.4. Observational and Experimental Study Design

In research the study design and methods employed are guided and determined by the purpose and research question underpinning the inquiry, the context of the study and the nature of the question being asked. A continuum of quantitative research describes three major categories used in quantitative research – observational, quasi-experimental and experimental.

#### 5.4.1 Observational Design

Observational (non-experimental) designs are utilised when the researcher wishes to answer the question of “what is this?” These studies describe variables, examine relationships, and retrace or follow participants over time to establish causal relationships. There is no manipulation of variables in an observational study. Often observational designs are used when there is little available information or evidence on the topic or the phenomena of interest are not suitable to be studied using an experimental design. Observational studies are limited in their ability to infer causality and include:

- Descriptive Studies e.g. survey, questionnaire, direct observation designed to collect large amounts of information from a large population
- Correlational studies that aim to investigate relationships among variables and may be useful to gather data to develop future interventional studies
- Cross-sectional studies that may infer a causal relationship between two or more variables
Chapter 5 – Methodology

- Retrospective studies which link present outcomes to past events, such as case-control studies which examine participants on the basis of an exposure
- Cohort studies that assess the development of disease or outcome of interest in a population over time

5.4.2 Quasi-experimental Design

*Quasi-experimental* studies involve manipulation and intervention to examine causality, but may lack randomisation or may not exert control over which participants receive treatment or intervention. Quasi-experimental designs can be practical and feasible and may be the only design possible in some clinical settings and include:197,202

- Non-equivalent control group studies - pretest data allowing comparison of two groups prior to intervention
- After-only non-equivalent control group studies - assumes that the groups were equivalent prior to the intervention being delivered
- One group pre-test post-test studies - may be used to evaluate the impact of training programmes
- Time-series studies - useful if only one group is available and may distinguish between changes occurring over time from the effects of the intervention.202

5.4.3 Experimental Design

Experimental studies involve a scientific investigation which includes a period of observation and data collection according to a predefined and specific protocol. Experimental designs all use control groups and random allocation. Types of experimental studies include RCTs, cluster RCTs, parallel group and factorial design, adaptive and cross-over trials.

The RCT is one of the most commonly used designs in medical research. Retrospective cohort and cross-sectional designs may also be employed to study aetiology, prognosis and prevalence of a disease as well as report factors that may influence health outcomes or behaviours. However, these methods are not routinely used for interventional studies as, due to their nonrandomised nature, it is often difficult to determine whether the outcome is due to the intervention or some other confounding factor. In addition, these studies may be more
susceptible to issues such as selection bias and contamination due to use of the intervention in the control arm or through Hawthorne effects over time. Observational studies have important limitations such as a tendency to overestimate treatment effect and can only demonstrate association.\(^{204}\)

RCTs are employed to provide conclusive evidence to answer questions regarding effectiveness of treatments or interventions on outcomes.\(^{205}\) The history of clinical trials dates back to around 600BC when Daniel of Judah purportedly conducted a clinical trial to compare the effects on health of a vegetarian diet compared to those of a royal Babylonian diet, using a control group and an independent outcome assessor.\(^{206}\) Sir Austin Bradford Hill is recognised as the innovator of the modern RCT for his work on streptomycin for pulmonary tuberculosis in 1948.\(^{207,208}\) Over time two fundamentals of the RCT have developed which provide surety around study results and outcomes - blinding and randomisation. RCTs rank as Level II evidence in the hierarchy of evidence due to the minimal amount of bias that is present in a well-designed study.\(^{205}\)

An RCT

“sets out to evaluate the effects of a particular treatment or management strategy in a population where an intervention is introduced, by comparing the outcome with a control group where no intervention has been made” (pg. 224).\(^{209}\)

In an RCT, participants are randomly allocated to one of the study arms which prevents researchers, clinicians and patients from predicting and influencing the group they are assigned to. Randomisation and allocation concealment reduce the chance of confounding while strengthening internal validity and have been described as the most straightforward and accessible method of maintaining allocation.\(^{205,210}\)

5.5. Error in Study Design

Error can be defined as “a false or mistaken result of measurement” pg 85.\(^{190}\) The error may be either due to random - due to chance - or may be a systematic error - due to bias. The goal for researchers is to produce studies and study tools that minimise error and bias, thus strengthening the internal validity of the study.

Validity describes the credibility and accuracy of the study,\(^{211}\) and may be categorised as internal and external validity. Internal validity is a measure of accuracy of the study and study
results while external validity is the extent to which the study and its results are generalisable to other populations or settings. The challenge for researchers is in balancing a desire for strong internal validity whilst still producing results with a high degree of external validity and generalisability. Studies show internal validity when, apart from the effect of random error, the observed difference in study endpoint between the intervention and control groups is solely attributable to the intervention. Systematic errors, also called “bias”, are due to errors in study design and may invalidate results of a clinical trial by introducing alternative explanations for the observed difference.

5.6. Types of Error

Bias may be systematic or random and on occasion intentional.212 There are several ways of describing and classifying bias.

5.6.1 Random Error

Random error is “the portion of variation in a measurement that has no apparent connection to any other measurement or variable, generally regarded as due to chance” (pg. 85).190 Random error may occur due to variations in the instruments used to collect the data or in measuring techniques e.g. different clinicians may obtain different blood pressure measurements on the same patient when no intervention has occurred. Random error adds variability to the data collected but may not necessarily affect average performance for the group and is often referred to as “noise”.195

5.6.2 Systematic Error

Systematic error is “error that is consistently wrong in a particular direction; it often has a recognizable source” (pg. 85).190 Systematic error is constant and may be due to error in study design or implementation, analysis and interpretation, reporting or publication leading to results that are systematically at odds to the truth.190 Although many types of bias have been identified, they can be broadly categorised as selection, measurement and confounding bias. These three main categories are described next.

5.6.2.i. Selection bias

Selection bias creates the absence of comparability of the groups being studied and may occur in both interventional and observational studies and is the systematic difference
between participants in how they are allocated to treatment. That is, the intervention group and the control group differ in an important aspect aside from the intervention and systematic differences may be seen in baseline characteristics of the groups randomised. For example, if all overweight participants were to be enrolled into the intervention arm of a study to determine whether a reduced calorie intake diet leads to weight reduction whilst normal weight participants were enrolled into the control arm.

5.6.2.ii. Measurement bias

*Performance bias* refers to those factors related to the intervention that might have an effect on the outcome. For example using an unblinded assessor in a diagnostic study, the ability of a surgeon in a surgical trial, compliance with interventional therapy by a participant, an unexpectedly high rate of dropout or loss to follow-up of study participants which may all affect the outcome and results.

*Measurement bias*, also called observation, classification or information bias results from incorrect assessment of exposure or outcome or both and is the systematic distortion of the assessment of outcome measures by the investigator or study participants if they are aware of treatment allocation.

*Detection bias or ascertainment bias* refers to “systematic differences in the outcome assessment between groups in ascertainment, assessment, diagnosis or verification of outcomes” pg. 64. That is to say there are systematic differences in how outcomes are determined.

*Attrition bias* may occur when the number of participant withdrawals from the study distorts the balance of the initial selection process and therefore the results. Different rates of loss to follow-up in each group may alter the characteristics of these groups irrespective of the intervention, therefore there should be detailed reporting of those who withdraw in order to avoid distortion of results.

*Spectrum bias* “may affect a study of diagnostic accuracy when it fails to account for the variation of heterogeneity of the test performance across population subgroups” (pg. 233). Spectrum bias may occur when a diagnostic test performs differently across subgroups however the study has not been adequately performed in those subgroups. It may be due to a change in case-mix of patients with or without the disease of interest or due to a change in prevalence and may affect both sensitivity and specificity of a diagnostic test.
5.6.2.iii. Confounding bias

Confounding occurs when there is an association between exposure to an intervention and the outcome as a consequence of an intervening variable – a third unknown factor. Confounding is a “mixing or blurring of events” (pg. 250). When testing a hypothesis a researcher attempts to make a link between exposure to an intervention and the outcome of interest. Confounding variables may be related to the intervention and may affect the outcome either directly or indirectly. For example early studies demonstrated strong links between oral contraceptive pill use and myocardial infarction. It was later found that these links were unclear due to a high number of cigarette smokers among contraceptive pill users.

5.7. Why Error is Important

Without fair and unbiased evaluations, useless or even harmful treatments may be prescribed because they are thought to be better than current therapy. The literature is littered with examples of therapies that have been instituted on the basis, perhaps, of one published trial of questionable quality. One example of this was the worldwide uptake of intensive insulin therapy, or intensive blood glucose control, in intensive care patients following a study of 1548 patients undertaken at a single, surgical intensive care in Belgium. The main finding of this study was a 32% adjusted relative reduction in mortality with intensive insulin therapy vs. conventional insulin therapy (4.6% vs. 8% respectively p < 0.04). Following publication and presentation of study findings, many ICUs worldwide adopted the practice of intensive insulin therapy for many critically ill patients. In 2009 a study was commenced to address perceived methodological issues in the original study such as complexity of the intervention delivered, post-hoc subgroup analyses and concern about the generalisability of the results. The NICE-SUGAR study was a multicentre study of 6104 patients undertaken in three countries which found that using intensive insulin therapy actually increased mortality. Possible reasons for the disparities in results of the two studies may be due to study design and methodological differences between the two studies. Analysis and reporting bias may also have been introduced into the Belgian study due to the use of post-hoc subgroup analysis and selective reporting of study results. The subsequent NICE-SUGAR study addressed issues of statistical power, internal and external validity and provided compelling evidence that intensive insulin therapy should not be used in critically ill patients.

Studies with observational designs are open to bias also. Selection bias creates an absence of comparability between the groups being studies, whilst information bias may result from an
incorrect determination of the intervention, the outcome or both. The effect of information bias depends on the type of information gathered and the way in which it is gathered. For example an observational study of 5133 Finnish men and women reported that an inverse relationship was observed between dietary intake of Vitamin E and coronary mortality in both sexes. However, a subsequent large RCT of 14,641 patients at risk of cardiovascular events failed to demonstrate any effect of Vitamin E on cardiac mortality.

The aim of a diagnostic test is to determine whether the given test is able to distinguish between those with the disease and those without as defined by a gold standard test. When assessing the potential applicability of a diagnostic test for a patient group it is important to know whether the results of the study are valid; what the results of the study are and will the results help in the care of the patient in question. At the same time, the test should be simple and safe. In order to determine if the results of the study are valid one may ask if there was an independent, blind comparison with a reference standard. The person evaluating the reference standard test should be blinded to the results of the diagnostic test under evaluation so as to provide an impartial evaluation. Assessors should seek to determine if there was a comparison of the diagnostic test to a gold standard which identified those with the disease compared to those without. Lack of blinding may cause overestimation of sensitivity and specificity. Whether or not the results of the test being evaluated influenced the decision to perform the reference standard or not may be distorted if the test results influence whether or not the patient undergoes confirmation by the reference standard. This is known as verification bias or work-up bias. For example, a patient who exhibits a normal treadmill exercise test may be less likely to undergo an invasive coronary angiogram (the gold standard) when cardiovascular heart disease is suspected.

Likelihood ratios associated with the range of possible test results are a useful when assessing results of a diagnostic test. Likelihood ratios (LR) indicate by how much a given diagnostic test result will raise or lower the pre-test possibility of the target disorder. A LR of 1.0 means that the post-test probability is exactly the same as the pre-test probability while a LR > 1.0 increases the probability that the disorder of interest is present and LR < 1.0 decreases the probability that the disorder is present. The value of a diagnostic test rests on the ability of the test to reproduce the same results when applied to a range of patients. Lack of reproducibility may be inherently due to the test itself or due to interpretation of the test results.
5.8. Minimisation of Error

5.8.1 Random Error

Random error relies on chance and can be minimised principally by ensuring an adequate sample size is calculated, then by subsequently ensuring that the population of interest is enrolled and has primary outcome assessed. In order to design a study to test a hypothesis definitively, the investigator must determine the correct number of patients that will be enrolled in order to have the most power to determine a treatment effect. A study has adequate power if it can reliably detect a true difference in outcome between the groups if a clinically important difference actually exists.226

5.8.1.i. Sample size

Sample size calculations ensure that the investigator has chosen an appropriate number of patients in the study to be able to detect a difference in the chosen outcome. Sample size calculation depends on three factors: the size of the effect estimated to be found between the treatment groups; the type of data that will be collected and the degree of probability of finding a Type I or Type II error that the investigator is willing to accept.197 A Type I error occurs when the null hypothesis is rejected when it is in fact true (a false positive) and a Type II error occurs when the null hypothesis is accepted when in fact it is false (a false negative).199

5.8.1.ii. Level of significance

Determining a level of significance helps researchers control the risk of a Type I error by indicating the probability of incorrectly rejecting the null hypothesis. The significance level - commonly called alpha or $\alpha$ - is commonly set at 0.05 (5%) or 0.10 (1%).199 That is to say that there is a 5% chance of a Type I error.

5.8.1.iii. Statistical Power

Statistical power indicates the ability to detect true relationships between variables,199 or the probability that a trial will find a statistically significant difference should a difference actually exist.197 Power analysis reduces the risk of Type II errors and estimates how large a sample is needed. Commonly in clinical trials statistical power is set at 80% or 90%. With power set at 80% the researcher accepts that there is a 20% chance of not showing a
statistically significant difference between two treatments when an effect exists in reality. That is to say there is a 20% chance of a Type II error.

5.8.2 Systematic Error

5.8.2.i. Diagnostic Studies

Diagnostic tests help clinicians determine the diagnosis and develop a treatment plan for patients based on the results of the test. These may include blood tests; radiological tests and scans and psychological and physical functioning tests. The accuracy of the test influences the diagnosis. When a new test is developed, it may be compared to the existing reference test or gold standard. Reducing systematic error in diagnostic studies focuses on the following areas:

5.8.2.i.a Spectrum bias

Ideally studies of diagnostic tests should enrol consecutive patients who meet defined inclusion and exclusion criteria that are suspected of having the disease of interest. However, it is nearly impossible to run a study 24 hours a day, so patients may have to be selected according to availability of investigators or equipment. If this is the case it may be possible to collect some data from patients who would have been eligible but were not recruited and to collect basic demographic data and presenting characteristics from the whole study population, so it can be determined whether or not a highly selected cohort has been used. By enrolling consecutive patients, investigators avoid the bias of selecting patients who may appear suitable for the test whilst excluding patients with co-morbidities who may not and may lead to over-estimation of sensitivity and specificity.

5.8.2.i.b Measurement bias

The reference standard is the “gold standard” test to which the new diagnostic test is being compared to. Ideally all patients should receive the test and the reference standard i.e. if patients undergoing an exercise stress test to aid in diagnosis of ischaemic heart disease returned a positive test and were referred for cardiac angiography, while those who returned a negative exercise test received follow-up with their GP but no angiography, then a measurement bias could be anticipated. It has been suggested that it is not surprising that this happens as clinicians may be less likely to subject patients with a low probability of the disease of interest to more invasive diagnostic testing if less invasive diagnostic tests prove negative.
5.8.2.i.c Performance bias

Blinding of assessors is vital in studies designed to evaluate the performance of a diagnostic test,228 so as to provide an objective assessment of outcome. Assessors should be blind to the true diagnosis of the participant and in studies undertaken to evaluate the reproducibility of the diagnostic tool, observers should be unaware of their previous measurement on the same individual. The same is true if more than one blinded assessor is involved; both should remain unaware of the other’s measurement.199

5.8.2.ii. Randomised Controlled Trials

5.8.2.ii.a Confounding

Randomisation is an effective means of reducing systematic error as it guarantees – as long as it is undertaken correctly - that treatment assignment is not based on patient characteristics. Randomisation controls for both known and unknown confounders thus ensuring that they are equally distributed between the groups and any imbalance minimised. In its simplest form randomisation can be achieved through tossing a coin – allocation is then based on whether the coin shows heads or tails and ensures a chance event. While this is simple, cheap and easy to do it may result in uneven numbers allocated to intervention and control. Other methods involve telephone or computer-generated randomisation methods. Block randomisation further minimises the risk of uneven groups by randomising participants in blocks of 4, 6, 8, 12 etc. and ensures that at the end of the block there are even numbers in each group. Randomisation involves not only generating an unpredictable sequence of treatment allocation but also concealing that sequence until allocation occurs as inadequate concealment may lead to introduction of bias, on occasion due to deliberate intent/subversion and sometimes subconsciously.229 Random allocation minimises the effect of systematic differences as these should be evenly spread between the two groups. Therefore, any difference found in outcome can be attributed to the intervention being studied and not to differences in participant characteristics at baseline.

Intention to treat (ITT) analysis involves analysing all study participants in the treatment group to which they were originally randomly allocated to, regardless of whether or not they actually received that allocation, withdrew from the study early, withdrew from the allocation early or received a different therapy from that allocated.230 By analysing participants in the groups to which they were allocated, the investigator ensures that confounding factors present at baseline remain evenly balanced between the two groups. ITT analysis recognises and
accepts that protocol deviations and noncompliance are likely to happen in the real world of clinical practice.\textsuperscript{231} Per-protocol analysis, an alternative to ITT analysis, involves only analysing the subset of patients who completed the study according to the study protocol and without any major protocol deviations or violations, and is now largely discredited as it may introduce bias by excluding participants from analysis.\textsuperscript{231,232} Proponents of per protocol analysis propose that only patients who have fully or sufficiently complied with the study protocol be considered in the final analysis as they are truly representative of the intervention or control.\textsuperscript{231} Per protocol analysis shows the effect in compliant patients only, but may be useful as a secondary analysis, not as a primary analysis. A third approach would be a treatment received analysis whereby patients are analysed according to the treatment they actually received rather than that to which they were allocated, though this then reduces the impact of random allocation.

Another approach that may be employed to minimise confounding is that of stratification which ensures equal allocation of subgroups at randomisation. Stratification can occur either at the time of randomisation - to ensure balance of the confounding variable across groups or post hoc during data analysis whereby data is analysed and results presented according to subgroup or strata.\textsuperscript{197}

\textbf{5.8.2.ii.b Selection bias}

Allocation concealment seeks to eliminate selection bias and protects the randomisation sequence up to allocation.\textsuperscript{229,233} Allocation concealment is possible in all trials though reportedly is not undertaken or reported well in many, leading to poor methodological quality.\textsuperscript{229,210} Allocation concealment can be achieved in several ways: by ensuring that the investigator who enrolls participants is not the person who generated the allocation sequence; involving people independent of the trial in the generation of the sequence and the method of allocation e.g. an independent statistician who generates the sequence, a centralised voice response system to determine allocation, web-based allocation systems, serially numbered containers of equal appearance for intervention drug and placebo or sequentially numbered, opaque, sealed envelopes.\textsuperscript{210} When blinding is not practicable and an open-label design necessary, larger block sizes or blocks of variable sizes may be used so as to prevent those involved in enrolment and assignment predicting to which arm of the study the next participant may be allocated. Schulz and colleagues conclude that “Without proper
application of measures to achieve concealment, the whole point of randomization vanishes and bias is likely to distort results” (pg. 412).\textsuperscript{229}

5.8.2.ii.c Ascertainment bias

If subjects withdraw from a study or are lost to follow-up, there is no way of knowing what happened to them and what their outcome was. For data analysis and outcome determination it cannot be assumed that they behaved and therefore responded in the same way as those who were retained in the study.\textsuperscript{212} Failing to account for all individuals who participated in a study can affect the validity of the study results. Loss to follow-up has been described as a “quality indicator” in RCTs.\textsuperscript{234}

There are many reasons that a participant may be deemed lost to follow-up. They may have withdrawn or be withdrawn from the study prior to study end, they may have not complied with the study protocol or they may have moved location and are not able to be contacted. Well-designed, well-executed studies may have to devote significant time and expense to following up study participants to ascertain outcome particularly as some studies track patients for many years. Research coordinators or study investigators may have to track patients either electronically or via telephone to determine and evaluate study outcomes and minimise loss to follow-up rates over time. Requirements for study follow-up should always be included in a thorough information and consent process to ensure that study participants are aware of the time and effort this may involve and any reimbursement or incentives offered for completing these visits and assessments.

5.8.2.iii. Detection Bias

Blinding eliminates bias due to the awareness of treatment allocation and assists in minimising performance bias, expectation bias and detection bias.\textsuperscript{199} Blinding may involve concealing information with regards allocation of therapy from participants, clinicians, and data collectors and analysts and ensures protection of the allocation sequence after allocation.\textsuperscript{229} RCTs that have not used blinding tend to show a much larger treatment effect than blinded studies.\textsuperscript{229} Blinding allows for continuing equipoise as subjects and clinicians remain blinded to intervention and effect in clinical practice and thus cannot affect outcome measures. While it may be fairly easy to blind a study medication with the use of a placebo, blinding may prove difficult in a surgical intervention or an intervention involving a device or physical treatment such as oxygen therapy. Detection bias can be minimised by blinding of outcome assessors who therefore have no knowledge of the intervention received. This is
especially important if the outcome measure is subjectively measured e.g. wound healing. Blinding minimises detection bias which may also be reduced by formulating a study manual of procedures or data dictionary that is strictly followed to ensure that data is collected and study procedures undertaken in the same manner by all involved. In observational studies reliance on participant reporting of an event as an outcome may lead to recall and detection bias.

5.9. Other Considerations Important to Study Design

5.9.1 Equipoise

Equipoise is a state of genuine uncertainty on the part of the clinical investigator or scientific community regarding the comparative therapeutic merits of each arm in a trial. That is to say that the investigator has no preference for therapy throughout the whole trial. The concept of equipoise suggests that ethically we should only conduct clinical trials in areas of uncertainty and only for as long as uncertainty remains. The latter may prove difficult in a long running trial where contemporaneous data and publications may lead to investigators altering their preference for therapy as the trial continues and as new information comes to light regarding the intervention or outcomes of interest.

5.9.2 Comparator

When designing an RCT the investigator must determine to what the intervention of interest will be compared. There are several options depending on whether the trial aims to determine equivalence, non-inferiority or superiority. The intervention arm may be compared to a routine care arm (where participants randomised to this group receive all treatment as they usually would) or a placebo comparison (whereby the new therapy is compared to a dummy therapy with no active ingredients). In some cross-over design studies, patients may move between the two study arms over a period of time thus experiencing both intervention and control arms at some point in the study period.

5.9.3 Pragmatism in Study Design

One criticism of RCTs has been that due to the rigid design employed in these trials in order to ensure internal validity there is a subsequent reduction in relevance to real-life applications and generalisability. This has led to the development of pragmatic clinical
trials, which aim to maximise external validity while having little or no effect on internal validity.\textsuperscript{237} Previously, results of some clinical trials have had little relevance once completed as the patient population may vary greatly and thus not include relevant patient groups or where studies have been conducted in different settings. It has been argued that a pragmatic study should enrol patient groups that include a broad and representative sample from a variety of practice settings.\textsuperscript{237} Generalisability can be achieved through the use of minimal exclusion criteria and by providing data on participation rates and demographics of participants and study settings.

Pragmatic studies answer questions that arise out of clinical practice and may seek to answer questions not only of benefit and risk of an intervention, but also of cost.\textsuperscript{199} Often, pragmatic studies compare two clinically relevant interventions rather than comparing an intervention to a placebo and in this way, the current standard of care is assessed against the proposed new intervention. Because of this, data collected in a pragmatic study may include a combination of quantitative and qualitative variables to provide information on the whole trial and interventions such as characteristics of the setting in which the study was performed; details on the implementation of the study protocol, feasibility of intervention, barriers to implementation, measures of quality of life, cost and behavior change in participants and staff.\textsuperscript{237} It is possible that collecting a myriad of data such as this may prove time consuming and costly to investigators, however it provides rich data for key stakeholders and could well increase applicability and generalisability of the research undertaken and its results. Two significant factors in pragmatic studies involve who delivers the intervention arm care and who delivers the control arm care. Rather than having the intervention delivered by an investigator, in a pragmatic study intervention can be delivered by normal staff that have been trained in the procedure under investigation. Also, care of participants outside of the intervention being studied is often left to the discretion of the treating clinician, not dictated entirely by the study protocol.

\textbf{5.9.4 Choice of Outcome Measures}

Determining the primary and secondary outcome measures for any study can present a challenge to investigators in the study design phase. Choosing which is most appropriate can be difficult and may be influenced by a number of factors such as the intervention or disease of interest and the stage at which the trial is set. Outcomes may be a direct reflection of how a patient feels, functions and survives or may be an indirect measure such as a biomarker of
disease, radiological tests or other measures considered to be a surrogate for clinically meaningful outcomes. In some instances the outcome may combine more than one outcome of interest. It is argued that the most important consideration when determining the primary endpoint in a definitive clinical trial is that it provides reliable evidence about whether or not an intervention provides clinically meaningful benefit.\textsuperscript{238}

5.9.4.i. Clinically Meaningful Outcomes.

Clinically meaningful outcomes report a clinical event relevant to the patient or the intervention or an endpoint that measures directly how a patient feels, functions or survives,\textsuperscript{238} and may include death, pain, or loss of function. While investigators may have to rely on subjective measurements such as self-report, trial design may be strengthened and made less open to bias if an objective outcome measure can be chosen. Disease or treatment centered outcomes include mortality, hospital length of stay and resolution of disease symptoms. Recently, there has been a move towards inclusion of more patient centred outcomes in clinical trials as opposed to disease or treatment oriented outcomes. Patient centred outcomes include outcomes that patients value such as quality of life assessments which may measure the impact of the intervention or disease under study rather than the intervention or disease itself.

5.9.4.ii. Surrogate Measures.

In many studies, the rate of occurrence of the endpoint of interest may be extremely low and thus a large sample size is required to obtain sufficient data. One way of circumnavigating this issue is to use surrogate outcomes that occur more frequently than the endpoint of interest but may predict its occurrence. Benefits of using surrogate outcomes include a possible reduction in sample size or trial duration, reduction in trial costs, avoidance of an invasive endpoint measure, and the ability to measure a surrogate endpoint event close to the time of intervention rather than having to wait for distant endpoints such as death which may be confounded by secondary or competing treatments or risks.\textsuperscript{239} For instance, a series of blood pressure measurements may be used as a surrogate outcome measure for the incidence of ischaemic heart disease when comparing different types of anti-hypertensive medications; serum biomarkers may be measured to reflect changes in kidney function in a trial to determine the best intervention to prevent cardiac surgery associated acute kidney injury.

Surrogate outcome measures are particularly useful in phase I and II clinical trials that examine the effect of new therapies and help determine whether or not a large phase III trial
Chapter 5 – Methodology

is warranted. However it must be recognised that surrogate endpoints are only a substitute for clinical endpoints, and as such do not truly reflect the true outcome of the intervention.\textsuperscript{240} A recent meta-epidemiological study concluded that studies reporting surrogate outcomes were more likely to report larger treatment effects estimates of on average up to 47% when compared to studies reporting patient centered outcomes.\textsuperscript{241}

5.9.4.iii. Role of Phase of Clinical Trials in Selecting Outcomes

A clinical trial is defined as “a prospective scientific experiment that involves human subjects in whom treatment is initiated for the evaluation of a therapeutic intervention” (pg.1164).\textsuperscript{236} As is shown in Table 2 clinical trials may be classified by phase.\textsuperscript{226,236}

<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective</th>
<th>Approximate Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Investigate the effects of and tolerance to the intervention e.g. new medication. Often called “first in human” studies.</td>
<td>10 to 30 Usually healthy volunteers</td>
</tr>
<tr>
<td>Phase IIa</td>
<td>Pilot trial to investigate efficacy and safety in selected populations. May focus on dose-response.</td>
<td>100</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>Well controlled trials evaluate efficacy and safety in patients with disease of interest.</td>
<td>100</td>
</tr>
<tr>
<td>Phase III</td>
<td>Compare new treatment to the standard therapy or control or placebo.</td>
<td>100s to 1000s</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Conducted after the medicine or device is marketed to establish long-term morbidity and efficacy. Often referred to as “post marketing surveillance”.</td>
<td>1000s</td>
</tr>
</tbody>
</table>

Testing of a new drug or intervention usually commences with a Phase I trial and then, if this proves positive and no undue safety concerns exist, progresses to Phase II or Phase III trials. Phase II studies, undertaken to determine if the intervention works or not, may also serve as pilot or feasibility studies to determine whether or not it would be prudent to progress to a Phase III trial. After licensing, a Phase IV trial may be undertaken to determine long-term efficacy or morbidity that may have not been apparent in the earlier studies.

Often progression through the phases is not well differentiated. Indeed many non-pharmaceutical products and devices get to market with only Phase I and perhaps Phase II studies having been undertaken. Medical devices often seem to get to market with little
objective research having been undertaken. Device companies are concerned with establishing safety of the product but often leave the task of providing evidence as to their efficacy up to clinicians in the field. Trials may be designed to show superiority, equivalence or non-inferiority of the intervention being studied, and thus this informs the outcome measures under investigation.

In clinical research of the critically ill, a stepwise approach as shown in Figure 5 is often employed as a means of efficiently and effectively generating evidence required to support a large scale phase III clinical trial in this population.\textsuperscript{204}

Figure 5. A stepwise approach to the development of a Phase III clinical trial.

Biological plausibility and possible mechanisms of action may be established or inferred through in vitro experiments initially. There should then if possible be supportive data generated from animal studies. Observational studies may either support a potential clinical effect in patients with the disease of interest or may be undertaken to provide further information about the disease or population of interest which can then be utilised to inform study design. Human models of critical illness can be used to determine whether or not an intervention of interest may affect mechanisms of action and can provide information of safety. Proof of concept data obtained through a pilot study provides information on feasibility of the intervention and proposed study as well as data to determine sample-size calculations and estimates of treatment effect. A phase II trial should be adequately powered to confirm efficacy, determine effect size and to inform sample size. Finally, the large, definitive phase III trial is undertaken. Although using this stepwise approach to trials in the critically ill may increase the time taken for a therapy to be proven or disproved, it may ensure that more phase III studies succeed.\textsuperscript{204}
5.9.5 External Validity

External validity refers to the ability of the study findings to be generalised to other populations or settings. The sample chosen and inclusion and exclusion criteria used should reflect the population of interest and to which the findings will be generalised to. A study is only generalisable to patients similar to those included in the study. Often it is hard to answer the question with one definitive study only and therefore large scale, multi centre studies may be required to reduce and where possible eliminate possible bias and ensure replication of study results. In order to ensure the highest degree of external validity, the investigator must ensure that the study population of interest are enrolled; that the study population is carefully described and that unusual patients who are outside the norm are avoided.\(^\text{197}\) This is done through formulating inclusion and exclusion criteria which captures the population of interest and will reduce bias. Using “real world” or pragmatic study designs aids in ensuring that the study is conducted in as close to a normal practice environment as possible and not in an artificial setting that is not representative of daily life.

5.9.6 Subgroup Analysis

Subgroup analysis may be undertaken if the investigator considers that the intervention under investigation may have alternative effects on subgroups as opposed to the whole population being studied.\(^\text{199}\) For example, if studying the effect of oxygen therapy in patients it may be of interest to determine whether or not current smokers receive any additional benefit from the therapy as compared to non-smokers or ex-smokers. However, the sample enrolled must be of sufficient size to allow subgroup analysis as splitting the sample will reduce the effect size causing subgroup analyses to be underpowered and therefore must be solely exploratory in nature. It is also possible to examine for heterogeneity by undertaking subgroup analysis, but this should be undertaken with caution should the intervention effect prove negative.

While tempting to undertake subgroup analysis to further examine trial results in particular reference to some groups of patients, the investigator may risk being misled as there is an increased chance of finding effects in a subgroup that may not be present in the whole population.\(^\text{197}\) This may be seen as a subgroup of patients being denied an effective treatment (a “false-negative” conclusion) or a subgroup of patients being given an ineffective or potentially harmful treatment ( a “false positive” conclusion).\(^\text{242}\) Therefore any planned subgroup analysis should be determined \textit{a priori} and not arise out of post hoc analysis or data dredging in order to try and discover a result. Similarly, consumers of evidence must be
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adroit in evaluating the literature in relationship to subgroup analysis and in determining whether or not the effects discovered are real and applicable to the groups analysed. The question should always be “why should I not use these findings ….” Rather than one of “why should I use these findings” when appraising research and translating research findings into practice.

5.10. Where Does this Thesis and its Contents Fit into the World of Research?

One of the difficulties for any researcher is in defining the methodology most appropriate for the research to be undertaken. I believe that this is especially so for nurses who undertake research and nursing research. For how does one truly define what nursing research is? One may argue that “nursing research” is a rather nebulous term/phenomenon/discipline as it has been used to describe a myriad of possibilities. So what is nursing research in 2023 and how should it be defined? Is nursing research defined by the subject of the research for instance a study investigating the effects of shift work on nurses? Is it defined by who undertakes the research i.e. the principal investigator is a nurse, the methods chosen e.g. a hermeneutic approach or is it only nursing research if it is solely to be used by nurses in clinical practice?

The landscape of nursing research has changed dramatically in the last 30 years. Previously nursing research was predominantly undertaken by academics teaching in universities, but now much of the research is led by nurses practicing in the clinical area and seeking answers to everyday practice questions. More nurses are now involved in diverse research activities such as journal club presentations, involvement in development of evidence based practice guidelines, undertaking study procedures for clinical trials, while others undertake and lead research projects of their own possibly as part of post-graduate study. Involvement of nurses in research can only enhance both the research itself and the experience and utility of research for nurses. Nurses though must feel comfortable and confident in what they contribute to the research team in whatever role they assume. In New Zealand and Australia there exists a unique environment whereby multi-disciplinary research is undertaken by highly skilled and trained research teams often lead by a nurse but also involving medical doctors, physiotherapists, dieticians and biostatisticians aiming to answer real-world questions with patient centred outcomes. This approach is unique around the world and involves nurses at all phases of the trial process including involvement in governance roles.
such as on study management committees. Nurses in particular are often seen as the vital link between the research and the trial participants.

Personally I struggle to define what “nursing research” is and how it relates to just one dimension of research. The same could be said for “medical research” too. Can that only be undertaken by, read by, used by medical doctors? I prefer to conclude the most meaningful, all-encompassing term is “health research” and that this thesis and the studies contained within it contribute to health research by presenting a body of work undertaken by a nurse, using appropriate methodologies and concerned with generating new knowledge surrounding practices to improve patient care. This notion also fits comfortably with me in terms of developing a multi-disciplinary approach to research involving the most appropriately skilled team to answer the question posed. The way forward must surely involve multi-disciplinary, collaborative work across traditional professional boundaries, while recognising, respecting and celebrating professional diversities and attributes.

With regards to selecting the methodologies employed in this thesis, I have taken a post-positivist approach in order to prove or disprove the theory that NHF was able to improve oxygenation following cardiac surgery. There was no evidence available to answer this question so it was vital to develop a robust study protocol for an RCT that would allow this question to be answered definitively and thus provide further evidence and contribute to the body of knowledge surrounding this novel therapy. When planning the RCT described in chapters 8 and 9, it became apparent that a robust system to assess atelectasis on chest x-ray was required if it was to be used as an outcome measure. This involved the assessment of two differing systems to assess atelectasis on chest x-ray by way of an observational study. It was also important to further establish the mechanisms of action of NHF therapy and any effects on the whole of the respiratory cycle hence the descriptive study undertaken into airway pressure generated by the therapy. By undertaking these two observational studies and developing this programme of research the resulting RCT was appropriately designed and robust to test the hypothesis that was posed. Not only was the study designed to answer the clinical question, it was also designed pragmatically so that it would work in a real-life setting and not be open to bias and failure.
5.11. Conclusion

Developing a programme of research requires the investigator to slowly work through steps to try and outline the mechanisms of action of the therapy prior to establishing its efficacy in clinical practice. Few research projects stand on their own and are better developed I believe through a structured programme which may prove more valuable than individual projects when seeking to explain a new therapy. It is important to not only want to know if a therapy works but how it works. A programme of research may start with basic observational and descriptive work undertaken to inform a large scale interventional study.

This thesis and its associated programme of research, was undertaken to address the question of whether or not NHF could prevent respiratory complications following cardiac surgery using a post positivist approach. Study 1 (Chapter 6) looked at the airway pressure generated across the whole of the respiratory cycle using NHF using a descriptive study in order to further describe and understand the mechanisms of action of NHF. Study 2 (Chapter 7) assessed two systems used to report atelectasis on chest x-ray by way of an observational study to determine which system would prove more reliable as a secondary outcome measure in the planned RCT. Study 3 (Chapter 8 and 9) undertaken using a randomised controlled trial design answered the question of whether the use of routine NHF improved oxygenation on day 3 following cardiac surgery. Study 4 (Chapter 10) used a point prevalence survey design to collect data with regards administration of oxygen therapy to non-intubated patients in ICUs in Australia and New Zealand.
Chapter 6. Study 1: Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

Preamble

Delivery of positive airway pressure may lead to a reduction in atelectasis, an improvement in ventilation-perfusion ratio, and decrease the work of breathing. Prior to commencing this thesis and its associated programme of research, two studies had quantified the degree to which pressure was generated in the naso-pharynx by nasal high flow oxygen therapy in an attempt to describe perceived mechanisms of action. However, all previous investigations had reported the mean pressure delivered by NHF over a specified time period e.g. from the beginning of the first breath to the beginning of the last breath over a one minute period. The pressures previously reported were low and not considered to be truly clinically significant but discussion ensued as to whether or not these low pressures were responsible or not for the degree of clinical improvement that was seen when NHF was used in patients deemed to be suffering from respiratory failure. Doubt was raised as to the clinical relevance of low level positive pressure as a proposed mechanism of effect of NHF. Previously published studies had reported the mean airway pressure generated over one minute, however it was hypothesised that there may be a different pressure effect at different points of the respiratory cycle depending on what was occurring physiologically in the airway as the patient breathed in or out. In order to establish what pressures were generated across the whole of the respiratory cycle and address concerns at the low level pressure generated by the therapy, unpublished data obtained in a previous study was reanalysed for the purposes of this thesis and the inspiratory, plateau and expiratory pressures calculated in an attempt to further describe the physiological effects of NHF and how it may prove effective.

This chapter consists of the article published to report these study findings. The article is published in Respiratory Care the Journal of the American Association for Respiratory Care.

See Appendix A for study related materials and approvals.
Chapter 6 – Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

**Pressures delivered by Nasal High Flow Therapy During all Phases of the Respiratory Cycle**

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Australian Clinical Trials Registry www.anzctr.org.au ACTRN12609000305224

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**Conflict of Interests**

Fisher and Paykel Healthcare Limited provide some funding to the Auckland District Health Board by way of an unrestricted grant which in part pays for the salary of the research nurse employed in the Cardiothoracic and Vascular Intensive Care Unit. Rachael Parke received a travel grant from Fisher and Paykel Healthcare, New Zealand which covered some costs of presenting these results at the American Thoracic Society scientific meeting, May 2012.
Abstract

Nasal high flow oxygen therapy (NHF) and continuous positive airway pressure (CPAP) are modes of non-invasive respiratory support used to improve respiratory function in multiple patient groups. Both therapies provide positive pressure although this varies during the respiratory cycle. The purpose of this study was to measure and compare the airway pressure generated during different phases of the respiratory cycle in patients receiving NHF at various gas flows.

Methods: Patients scheduled for elective cardiac surgery were approached and invited to participate in this study. Nasopharyngeal pressure measurements were performed using nasal high flow with gas flow rates of 30, 40, and 50 L/min. All measurements were performed in random order, with the subjects breathing with mouth closed.

Results: During NHF the mean ± SD nasopharyngeal airway pressures were 1.4±0.6, 2.2±0.8 and 3.0±1.0 were recorded at 30, 40 and 50 L/min using nasal high flow. Analyses also determined the mean peak expiratory and mean expiratory plateau pressures.

Conclusion: This study describes the airway pressures generated by NHF. The expiratory pressures during NHF were higher than the mean pressures previously reported for NHF therapy. This may account in part for the disproportional clinical effects seen with NHF.

Keywords: Airway pressure; Nasal high flow oxygen therapy; non-invasive ventilation; Optiflow™; oxygen

Introduction

Respiratory complications, including hypoxia, sputum retention, and basal lung atelectasis, remain a leading cause of post-cardiac surgery morbidity and can prolong hospital stay and increase costs.¹ Traditionally, therapy has consisted of the administration of supplemental oxygen and non-invasive ventilation via oronasal mask CPAP to maintain adequate oxygenation in patients with inadequate postoperative respiratory function. A recent novel therapy that is gaining widespread use in both the intensive care unit (ICU) and post-operative ward is nasal high flow oxygen therapy (NHF), in which heated and humidified blended oxygen and air is administered at flows of up to 60L/min delivered, via a specially designed nasal interface.²⁻⁶ NHF has been demonstrated to be easy to institute and comfortable for the patient, with excellent adherence to the therapy.⁶ ⁷ A recent randomized
controlled trial comparing NHF to high flow facemask oxygen therapy (HFFM) found that more patients allocated to NHF were considered to be successful on their treatment \((p = 0.006)\), and there was less use of NIV in the NHF group \((p=0.1)\) was also described.\(^2\) However, until recently there was little evidence explaining the likely mechanisms of action attributed to NHF, namely the provision of positive airway pressure, active humidification and naso-pharyngeal washout.\(^8\) It has previously been demonstrated that NHF provides a low level, flow dependent positive airway pressure,\(^5,9,10\) however the clinical effect often appears to be disproportional to the low pressures described. A common feature of all these studies is that the airway pressure reported at different NHF flow rates has been the mean pressure recorded over the whole of the respiratory cycle; however observation of the pressure waveform demonstrates significant variation in pressure during inspiration and expiration. It is plausible that the predominant benefits of positive pressure occur during expiration, particularly in patients who are at risk of, or have established, atelectasis. It could be assumed that mean expiratory pressures may be responsible for preventing atelectasis and peak and mean expiratory pressures responsible for the re-expansion of collapsed areas.

This study aimed to quantify the pressures produced during the different parts of the respiratory cycle with NHF using various gas flows.

**Methods**

This study was approved by the Northern X Regional Ethics Committee and registered with the Australian Clinical Trials Registry (www.anzctr.org.au ACTRN12609000305224). Adult patients scheduled for elective cardiac surgery were invited to participate and written informed consent gained pre-operatively. Patients were excluded if contraindications to either NHF or NIV were present. Following surgery, and whilst still sedated and ventilated in the ICU post-operatively, a 10 French catheter was inserted into the nasopharynx via the nose. The catheter was secured in place and remained in situ overnight. Pressure measurements were performed once the participant was awake, extubated and sitting up in a chair the day after surgery. Placement of the pressure measuring catheter was first confirmed with a visual check to ensure the tip was positioned just below the uvula, and then also checked using end tidal \(\text{CO}_2\) monitoring. If necessary the catheter was adjusted or suctioned to obtain a clear trace. The catheter was then connected to the Honeywell precision pressure transducer (PPT-0001 DWWW2VA-B, Honeywell International Ltd, NJ, USA) using a laptop computer interface. This methodology has previously been reported.\(^9, 10\) The Optiflow™ system
(MR880 heated humidifier, RT241 heated delivery tube, RT033/034 Optiflow™ nasal cannula, Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) was used to deliver humidified nasal oxygen and measurements were performed with gas flow rates of 30, 40 and 50 L/min (Figure 6). Measurements were performed in random order with patients breathing with mouth closed. The order of measurement was determined by Latin square, constructed in a Williams design, so that each treatment occurred once per patient. This ensured random treatment allocation to each measurement and sequences were randomly allocated to patients square by square. A washout period was allowed between each treatment to ensure no carry over effect. At the end of the investigation, the nasopharyngeal catheter was removed and the patient continued on their original oxygen therapy. Nasopharyngeal pressure at each flow was recorded over one minute of breathing. Actual pressure was recorded in an Excel spreadsheet at a resolution of 120Hz and waveforms of the pressure trace reconstructed from the data.

The mean nasopharyngeal airway pressure was determined by averaging the pressure over one minute – from the peak of inspiration of the first breath to the peak of inspiration of the last breath. This allowed the entire pressure profile of each breath within that minute to be included within the mean airway pressure calculation. Analysis of the inflection points of the airway pressure recordings allowed determination of the start of inspiration and expiration enabling the calculation of peak expiratory pressure, average expiratory pressure, average inspiratory pressure and average plateau pressure.

All data analysis was performed using Microsoft® Office Excel 2003. Data are presented as mean (SD).

Figure 6. Pressure measuring set-up with Optiflow™ nasal high flow.
Chapter 6 – Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

Results

15 patients scheduled for elective cardiac surgery participated in this study. Patient characteristics are described in Table 3. Thirteen patients had coronary artery bypass surgery while 2 patients had valvular surgery. All surgery was performed through a median sternotomy and involved cardiopulmonary bypass.

Table 3. Patient Characteristics

\[ n=15 \]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - mean (years)</td>
<td>59.5</td>
</tr>
<tr>
<td>SD</td>
<td>10.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Height - mean (cms)</td>
<td>173</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
</tr>
<tr>
<td>Weight - mean (kgs)</td>
<td>85.1</td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
</tr>
<tr>
<td>BMI - mean</td>
<td>29</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>10</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>3</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4 presents the mean (± standard deviation) nasopharyngeal airway, expiratory plateau, peak expiratory, mean expiratory and mean inspiratory pressures recorded with nasal high flow. Mean (SD) nasopharyngeal airway pressures of 1.52 (0.6), 2.21 (0.8) and 3.1 (1.2) were recorded at 30, 40 and 50 L/min using nasal high flow. Analysis of the pressure generated during different parts of the respiratory cycle demonstrated that higher pressures are obtained during expiration as compared to other parts of the respiratory cycle, and that both the expiratory plateau and peak expiratory pressures are flow dependent (Table 4).
Table 4. Airway pressures delivered with nasal high flow

<table>
<thead>
<tr>
<th>Flow</th>
<th>Mean airway pressure (cmH\textsubscript{2}O)</th>
<th>SD</th>
<th>Average plateau pressure (cmH\textsubscript{2}O)</th>
<th>SD</th>
<th>Peak Expiratory pressure (cmH\textsubscript{2}O)</th>
<th>SD</th>
<th>Average expiratory pressure (cmH\textsubscript{2}O)</th>
<th>SD</th>
<th>Average inspiratory pressure (cmH\textsubscript{2}O)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 L/min</td>
<td>1.52</td>
<td>0.6</td>
<td>1.71</td>
<td>0.73</td>
<td>3.01</td>
<td>1.18</td>
<td>2.1</td>
<td>0.83</td>
<td>0.55</td>
<td>0.38</td>
</tr>
<tr>
<td>40 L/min</td>
<td>2.21</td>
<td>0.8</td>
<td>2.48</td>
<td>0.94</td>
<td>3.81</td>
<td>1.45</td>
<td>2.88</td>
<td>1.04</td>
<td>1.11</td>
<td>0.51</td>
</tr>
<tr>
<td>50 L/min</td>
<td>3.10</td>
<td>1.2</td>
<td>3.41</td>
<td>1.24</td>
<td>4.86</td>
<td>1.79</td>
<td>3.81</td>
<td>1.33</td>
<td>1.77</td>
<td>0.69</td>
</tr>
</tbody>
</table>

All individual patient measurements and mean nasopharyngeal pressures delivered are shown in Figure 7. Typical pressure profiles from one patient at increasing gas flows (NHF) are shown in Figure 8.

Figure 7. Individual and mean nasopharyngeal airway pressures delivered by nasal high flow.
Chapter 6 – Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

Discussion

This study describes the airway pressures generated at three flow rates in patients receiving NHF and reports for the first time the pressure delivered during different phases of the respiratory cycle by NHF.

Previous work\textsuperscript{9, 10} has reported the mean pressure delivered by NHF across the whole of the respiratory cycle, however because these pressures are low (mean 2 - 4 cm H\textsubscript{2}O) doubt has been raised about the clinical relevance of positive pressure as a proposed mechanism of effect of NHF.

Observation of the airway pressure waveforms produced during different phases of the respiratory cycle demonstrates variability with NHF, with higher pressures measured during the expiratory phases. It has been hypothesised that the provision of positive end expiratory pressure (PEEP) by NHF contributes to the reduction in work of breathing and improvement in oxygenation that has been found in other studies\textsuperscript{5, 6, 12}

This study has shown that both the peak and expiratory plateau pressures generated during NHF therapy are higher than the mean airway pressures previously reported and we suggest that this may help explain the clinical benefits seen with these devices.
Chapter 6 – Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

NHF at flows up to 50 L/min provides PEEP and peak expiratory pressures at significantly higher levels than the recorded mean pressure but these are still less than that recorded and delivered with facemask CPAP. We would suggest that in patients who require an escalation in respiratory support therapy NHF should be seen as a logical step between traditional oxygen therapy and facemask CPAP. Similarly NHF is a logical intermediary step when weaning patients from higher positive airway pressure systems to low flow oxygen therapy.13

It has also been proposed that the high flows generated by NHF act as a resistance to exhalation and result in a clinically significant positive airway pressure when the patient breathes with mouth closed.14 This pressure effect may then be transmitted down the airways to the alveoli assisting in re-expansion of atelectatic areas. This increased resistance during expiration creates an expiratory positive airway pressure (EPAP) not dissimilar to that employed in devices for the management of obstructive sleep apnoea.15 This increased positive airway pressure may be responsible for the improved results seen when NHF is employed for hypoxaemic respiratory distress.2, 12

Limitations

This study was designed to measure respiratory pressures not physiological outcomes so no data was collected to show changes in respiratory rate, SpO₂, minute ventilation or lung volumes. There were a small number of females recruited into this study due to the convenience sampling technique employed. Therefore these results may not be entirely applicable to female patients and we were unable to test for gender differences, however it has been noted before that female subjects experience significantly higher airway pressure than males using Optiflow™.16 Also, due to the nature of the patient population available, the cohort only involved adult patients following cardiac surgery so the results of this study may not be generalisable to all patients such as paediatrics.

Conclusion

This study describes the airway pressures generated by NHF over the whole of the respiratory cycle and demonstrates that the pressure generated with NHF during expiration is higher than the mean airway pressure recorded over the whole respiratory cycle. Although NHF is unable to provide pressures similar to CPAP this study has demonstrated that both the mean and peak expiratory pressures are in a range that is likely to have a clinical effect and thus we believe that the provision of positive airway pressure is one of the mechanisms of action
Chapter 6 – Pressures delivered by nasal high flow therapy during all phases of the respiratory cycle

responsible for the clinical benefits seen with NHF. This study adds to the body of evidence relating to this novel respiratory support therapy, however further work is required to elucidate further the mechanisms of action of NHF including its effects on work of breathing, changes in lung volumes, oxygenation and intrathoracic pressure to truly support that NHF provides some form of lung recruitment.

References


Chapter 7. Study 2: A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for Cardiac Surgery

Preamble

This chapter describes the methods used and results of an observational study undertaken to assess the ability of two radiological atelectasis scoring systems to accurately determine the degree of atelectasis present on chest x-ray. Having now demonstrated that NHF delivers a flow dependant positive airway pressure over the whole of the respiratory cycle, the next planned step in the research programme was to undertake an RCT to see whether the routine application of NHF could improve oxygenation by the re-expansion of collapsed alveoli due to the pressure effect of NHF.

Whilst designing the RCT of routine nasal high flow oxygen therapy following cardiac surgery (the HOT-AS study Chapters 8 and 9), it was necessary to determine appropriate endpoints for the study. One of the endpoints I wished to consider was the incidence of atelectasis on chest x-ray, to see whether NHF could reduce this incidence. As described previously, reported incidence of atelectasis is up to 90% in patients following surgery. Determining appropriate endpoints for a randomised controlled trial involves consideration of many factors in order to choose robust and meaningful primary and secondary outcomes. This determination is especially important in a Phase II study where there is often not a lot known about the treatment under investigation and its effects on the population of interest. Preferably the chosen outcome measure is precise, specific to the intervention under investigation, objective and clinically meaningful. Reduction in atelectasis may make a difference to patients by reducing development of respiratory complications following surgery. It also seemed plausible that NHF could reduce the amount of atelectasis due to the positive pressure effect, which has been shown in Chapter 6, by recruiting atelectatic alveoli. Positive end expiratory pressure can prevent and reduce both the formation of atelectasis and development of respiratory complications and therefore the hypothesis was that NHF could do the same. The original study proposal was first presented to the ANZICS CTG Research Development Day for discussion and peer review. Commentary included that changes in atelectasis on chest x-ray were not a robust enough primary outcome measure due
Chapter 7. A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for cardiac Surgery

to logistics with chest x-ray measurement and interpretation. Therefore it was decided to include atelectasis on chest x-ray as a secondary outcome measure only. Chest x-rays are part of routine care for cardiac surgical patients; they all have one prior to surgery to establish a baseline recording and then all have further x-rays on return to the ICU following surgery, on the morning of day 1 following surgery and again on day 3.

As I have no expertise in reading chest radiographs or assessing atelectasis I approached the Clinical Director of the Department of Radiology for advice with this project. Regarding atelectasis scores on routine post-operative chest radiographs, he raised the possibility of a modified x-ray scoring system. It was his view that previously published atelectasis scoring systems did not account for significant subtotal atelectasis in both lower lobes and would not attribute any extra score if both upper lobes were collapsed as well. A modified radiological atelectasis scoring system (m-RAS) would need to be evaluated by comparing it to the existing radiological atelectasis scoring system (RAS)\(^{244}\) that has been previously used in trials reporting atelectasis to achieve the following:

- Determine the incidence of atelectasis in patients recovering from cardiac surgery in the study ICU
- Validate the proposed atelectasis scoring system in a group of patients following cardiac surgery.

The results could then be used to inform study design of a large randomised controlled trial of oxygen therapy aimed at reducing the degree of atelectasis seen after cardiac surgery.

See Appendix B for study related materials and approvals.
A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for Cardiac Surgery

Rachael L. Parke RN, MHSc (Hons), Shay P. McGuinness MBChB, FANZCA, FRCA, David Milne MBChB, FRANZCR, Associate Professor Andrew Jull RN PhD

First submitted: 27/09/2012; Revision submitted: 05/06/2013; Accepted: 21/02/2014


Abstract

Introduction

Pulmonary atelectasis is common following sternotomy for cardiac surgery. The degree of atelectasis present on chest x-ray (CXR) has been used to assess efficacy of interventions designed to reduce atelectasis, however radiological atelectasis scoring systems used may exaggerate the clinical effect of atelectasis in these patients. We have produced an alternative scoring system that seeks to correct this problem and this study aimed to evaluate this.

Methods

Following ethics approval we retrospectively selected 50 consecutive patients admitted to the intensive care unit (ICU) following cardiac surgery. Electronic copies of CXR taken on return to the ICU, on day 1 and day 3 postoperative were obtained and corresponding details of oxygenation were collected from patient records. Anonymised CXRs were scored, using both the old and new scoring system, by a radiologist blinded to the clinical data. CXR scores were compared with oxygenation indices at the time of CXR. Day 1 scores were also assessed for their ability to reflect day 3 oxygenation indices and supplemental oxygen requirement.

Results

The new score demonstrated better ability to detect atelectasis on chest x-ray and better specificity than the old score when comparing the CXR findings with the clinical
oxygenation status of the patients. The new score also performed better at predicting day 3 oxygenation status from the day 1 CXR.

Conclusions

This new scoring method performed better as an outcome measure for atelectasis in studies of patients following cardiac surgery. It may also better identify patients who require ongoing administration of supplemental oxygen on postoperative day 3.

Keywords

Atelectasis; cardiac surgery; cardiopulmonary bypass; chest x-ray; outcome measures

Introduction

Postoperative complications following cardiac surgery increase mortality, morbidity and costs.\textsuperscript{(1)} One major cause of postoperative respiratory complications is atelectasis.\textsuperscript{(2)} The development of atelectasis following general anaesthesia and cardiac surgery is almost inevitable\textsuperscript{(2, 3)} and has been described as present in most patients with an incidence of around 90% of cardiac surgical patients.\textsuperscript{(4, 5)} Atelectasis impairs oxygenation, worsens lung compliance, augments the development of lung injury and increases pulmonary vascular resistance.\textsuperscript{(6)} It may also be associated with postoperative infective complications such as pneumonia,\textsuperscript{(7)} and may be resistant to simple techniques employed to improve lung function such as patient positioning, physiotherapy and incentive spirometry.\textsuperscript{(3)} Ensuring adequate oxygenation and respiratory support is vital in the postoperative period; however there is little published evidence to guide clinicians in the objective selection and use of oxygen delivery devices.\textsuperscript{(8)} We are conducting a large scale randomised controlled trial to assess the effect of prophylactic nasal high flow oxygen therapy (NHF) using the Optiflow\textsuperscript{TM} system (Fisher & Paykel Healthcare, New Zealand) on postoperative oxygenation in cardiac surgical patients.\textsuperscript{(9)} In order to evaluate the hypothesis that NHF can improve pulmonary function and reduce atelectasis we required a validated atelectasis scoring system. Currently there are few scoring systems for reporting atelectasis from chest x-rays.\textsuperscript{(10-12)} The Radiological Atelectasis Score (RAS) has been used to describe the degree of atelectasis in postoperative patients.\textsuperscript{(10)} We felt this score may over-emphasise subtotal atelectasis in the lower lobes and furthermore it does
not attribute any extra weight if there is additional atelectasis in the middle or upper lobes. Therefore we have designed a new scoring system to differentiate the severity of atelectasis in patients with multi-lobar involvement.

The aims of this study were to evaluate a proposed atelectasis scoring system against a previously published scoring system in a group of patients following cardiac surgery; to assess the ability of the two scores to reflect the oxygenation at the time the CXR was taken; and to assess the ability of the two scoring systems to reflect oxygenation indices on subsequent days.

**Methods**

Fifty consecutive patients’ clinical records were selected for retrospective review. These patients were selected by the principal investigator and were admitted to the ICU during the month of January 2010. Inclusion criteria were: aged 18 years or more, received median sternotomy for cardiac surgery with cardiac bypass, weaned from mechanical ventilation and extubated within eight hours post-op, length of stay in intensive care (ICU) less than 24 hours, and only required simple nasal prongs or face mask for oxygen delivery following extubation. Ethical approval for the study was obtained from the Northern X Regional Ethics committee. Due to the retrospective observational nature of the study, the need for informed consent was waived.

**Oxygenation indices**

Clinical details of oxygenation on post-operative day 1 and 3 were obtained from the patients’ records and electronic copies of anteroposterior chest x-ray (CXR) taken on return to ICU (baseline), day 1 (d1) post-operative and day 3 (d3) post-operative were downloaded and stored on compact disc for review by the radiologist.

On day 1 all patients had arterial blood gas measurements available and the partial pressure of oxygen (PaO$_2$) and fraction of inspired oxygen (FiO$_2$) closest to the time the CXR was taken were recorded, along with pulse oximetry readings. Arterial blood gas measurements were not available on patients on day 3, so pulse oximetry was used to measure peripheral oxygen saturation (SpO$_2$) value. Oxygen requirement at time of CXR was recorded. From these data the PaO$_2$/FiO$_2$ (P/F) and SpO$_2$/FiO$_2$ (S/F) ratios were calculated. An S/F ratio of 445 was selected as a binomial outcome to distinguish patients either requiring oxygen or with SaO$_2$ or SpO$_2$ <94% versus those with an SaO$_2$ or SpO$_2$ ≥ 94% on air.
Atelectasis Scoring

The x-rays were scored using both the radiological atelectasis score (RAS) and a modified radiological atelectasis score (m-RAS) system by a single radiologist (Author DM) who was blinded to the oxygenation data and to the order in which the x-rays were taken by obscuring the date the CXR was taken (see box 1).

<table>
<thead>
<tr>
<th>The radiological atelectasis score (RAS): the presence of atelectasis is expressed by a 5-point score.(^{(10)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = clear lung fields</td>
</tr>
<tr>
<td>1 = plate-like atelectasis or slight infiltration</td>
</tr>
<tr>
<td>2 = partial atelectasis</td>
</tr>
<tr>
<td>3 = lobar atelectasis</td>
</tr>
<tr>
<td>4 = bilateral atelectasis</td>
</tr>
</tbody>
</table>

The modified radiological atelectasis score (m-RAS): each lobe (including the lingula) is scored 0-3 as shown below. The scores of the six lobes are then summed to give a 19-point score (0-18).

<table>
<thead>
<tr>
<th>The modified radiological atelectasis score (m-RAS): each lobe (including the lingula) is scored 0-3 as shown below. The scores of the six lobes are then summed to give a 19-point score (0-18).</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Normal</td>
</tr>
<tr>
<td>1 = Plate or minor infiltrate</td>
</tr>
<tr>
<td>2 = Moderate atelectasis</td>
</tr>
<tr>
<td>3 = Total atelectasis</td>
</tr>
</tbody>
</table>

Data analysis

Data analysis was undertaken using STATA12 (StataCorp LP, Texas, USA) and Statistical Package R (R Development Core Team (2010). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/). For both the old and new scores the day 1 and day 3 CXR scores were also compared with oxygenation indices (P/F or S/F ratio) at the time of CXR. Day 1 scores were also assessed for their ability to characterize day 3 S/F ratios below 445 (An S/F ratio of < 445 equates to any requirement for supplemental oxygen or SpO\(_2\) < 94% on air).
Chapter 7. A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for cardiac Surgery

Results

Fifty patients were included in this study. Baseline demographic data is presented in Table 5.

Table 5. Baseline demographics

<table>
<thead>
<tr>
<th>Gender n (%)</th>
<th>Male</th>
<th>35 (70)</th>
<th>Female</th>
<th>15 (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td>Male</td>
<td>35 (70)</td>
<td>Female</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Age, yrs - mean (SD)</td>
<td>60.54 (14.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>50</td>
<td>99</td>
<td>1.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Patients on room air</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S/F &lt;445 and FiO2 &gt;21%</td>
<td>50</td>
<td>99</td>
<td>1.3</td>
<td>0.45</td>
</tr>
<tr>
<td>S/F &lt;445 and SpO2 &lt; 93%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>50</td>
<td>97</td>
<td>2</td>
<td>0.29</td>
</tr>
<tr>
<td>Patients on room air</td>
<td>3</td>
<td>98</td>
<td>2</td>
<td>0.21</td>
</tr>
<tr>
<td>S/F &lt;445 and FiO2 &gt;21%</td>
<td>44</td>
<td>97</td>
<td>2</td>
<td>0.30</td>
</tr>
<tr>
<td>S/F &lt;445 and SpO2 &lt; 93%</td>
<td>3</td>
<td>92</td>
<td>1.7</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>49*</td>
<td>95</td>
<td>2.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Patients on room air</td>
<td>39</td>
<td>95</td>
<td>2.9</td>
<td>0.21</td>
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<tr>
<td>S/F &lt;445 and FiO2 &gt;21%</td>
<td>10</td>
<td>94</td>
<td>1.7</td>
<td>0.29</td>
</tr>
<tr>
<td>S/F &lt;445 and SpO2 &lt; 93%</td>
<td>10</td>
<td>91</td>
<td>2.2</td>
<td>0.21</td>
</tr>
</tbody>
</table>

On post-operative return to the ICU, 43 patients (86%) were determined to have some degree of atelectasis using both scoring systems. By day 1 the overall incidence of atelectasis was 86% using RAS and 98% using m-RAS. The incidence on day 3 was 98% using RAS compared with 96% using m-RAS. Figure 9 shows the degree of atelectasis at return to ICU, day 1 and day 3 for the group. There was an approximately linear relationship between the RAS and m-RAS scores, but with m-RAS demonstrating a greater range of scores.
When comparing the scoring systems’ ability to predict oxygenation status at day 3 from the changes seen on the CXR taken on day 1, the m-RAS performed better than the RAS; both scoring systems were more accurate in reflecting day 3 oxygenation status from changes seen on the day 1 CXR than on the day 3 CXR. The ability of day 1 x-ray to predict day 3 oxygenation is shown in Table 6. This was the only significant result with a likelihood ratio of 0.1 for an m-RAS of 3.
Table 6. Ability of Day 1 m-RAS to predict S/F ratio <445 on day 3

<table>
<thead>
<tr>
<th>m-RAS &gt;=</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td>0%</td>
<td>0.41</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>100%</td>
<td>3.45%</td>
<td>0.42</td>
<td>1.0</td>
<td>1.031</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>100%</td>
<td>13.8%</td>
<td>0.44</td>
<td>1.00</td>
<td>1.1</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>95%</td>
<td>41.4%</td>
<td>0.53</td>
<td>0.92</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>&gt;=4</td>
<td>75%</td>
<td>62%</td>
<td>0.58</td>
<td>0.78</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt;=5</td>
<td>45%</td>
<td>93%</td>
<td>0.82</td>
<td>0.71</td>
<td>6.4</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt;=6</td>
<td>30%</td>
<td>100%</td>
<td>1.0</td>
<td>0.67</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>&gt;=7</td>
<td>15%</td>
<td>100%</td>
<td>1.0</td>
<td>0.63</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>&gt;=8</td>
<td>10%</td>
<td>100%</td>
<td>1.0</td>
<td>0.62</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>&gt;=9</td>
<td>5%</td>
<td>100%</td>
<td>1.0</td>
<td>0.6</td>
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<tr>
<td>&gt;9</td>
<td>0%</td>
<td>100%</td>
<td>0.59</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

Figure 10 shows the receiver operating characteristic (ROC) curves for using the two scores to predict whether the S/F ratio would be below 445 on day 3 using the baseline x-ray. The area under the curve for m-RAS is 0.62 and for RAS is 0.55.

Figure 10. ROC curve for predicting day 3 S/F ratio of <445 using baseline x-ray scores
Chapter 7. A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for cardiac Surgery

Figure 11 shows the ROC curves for using RAS and m-RAS on day 1 to predict an S/F ratio <445 on day 3. The area under the curve for m-RAS is 0.79 and for RAS is 0.71.

![Figure 11. ROC curve for predicting day 3 S/F ratio of <445 using day 1 x-ray scores](image)

When analyzing the oxygenation indices it was found that on day 3 41% of patients had an S/F ratio below 445, indicating either an ongoing requirement for supplemental oxygen therapy (n=10) or a measured SpO$_2$ of $\leq$ 93% on room air (n=10). In the group still requiring supplemental oxygen, the average SpO$_2$ was 94.3% (range 91-96%), while receiving an average FiO$_2$ of 0.28 (giving an average S/F ratio of 330). Other data for the group not requiring oxygen but with SpO$_2$ $< 94\%$ is shown in Table 5.

**Discussion**

This study has evaluated a new system for assessing atelectasis on chest x-ray of patients following cardiac surgery. The overall incidence of atelectasis on return to ICU following cardiac surgery was found to be 86%. This is comparable with other studies in this population which have reported an incidence of 64% to 100%.\(^{(13-15)}\)

The m-RAS was developed to address perceived deficiencies when scoring atelectasis on CXRs of patients undergoing cardiac surgery. This study has demonstrated that day 1 m-RAS
is more accurate than day 1 RAS in predicting poor oxygenation in postoperative cardiac surgical patients from their routine CXRs. We hypothesise that this improved predictive ability is due to the ability of m-RAS to better differentiate subtotal lobar atelectasis.

The selection of appropriate end-points for Phase II clinical trials is essential to robust study design but may prove problematic. Defining a clinically important end point in studies of critically ill patients is an important consideration in order to avoid poorly conceived clinical trials. Whilst designing a study to investigate the effects of nasal high flow oxygen therapy on atelectasis in patients following cardiac surgery, we were tasked with finding a suitable tool to measure, accurately, atelectasis on chest x-ray at various time points postoperatively. It was felt that published scoring systems may over-estimate the severity of subtotal bilateral basal atelectasis frequently seen following cardiac surgery, thus reducing the specificity of the scores ability to predict clinically important indices. Therefore, a system was designed to more accurately describe the degree of atelectasis formation recognizing changes throughout the whole lung and with the ability to differentiate between patients with bilateral changes affecting the lower lobes only and patients with more extensive changes. Other published trials have faced this problem too, describing inconsistencies in the way atelectasis is reported and the apparent lack of an adequately validated scoring system for assessment and reporting of atelectasis.

Previous studies differ in how atelectasis is perceived to affect oxygenation. One study found that hypoxaemia was not present in most patients who had demonstrated atelectasis, with only 4% being unable to maintain an arterial oxygen tension of 13.3 kPa while another reports that the presence of atelectasis coincided with a requirement for higher positive end expiratory pressure (PEEP) and FiO2 necessary to maintain oxygenation. In this study it was found that the day 1 m-RAS was a good predictor of an S/F ratio of below 445 which would identify patients on supplemental oxygen therapy or those who had an SpO2 < 94% on day 3. This is a relevant and pragmatic clinical outcome for this group and reflects guidelines in the management of oxygen therapy in critically ill adults.

This study also demonstrated a difference in the temporal relationship between clinical signs (e.g. respiratory rate and oxygen saturations) and the changes seen on chest x-ray. This concept of a time-lag between clinical changes and CXR changes is well described. Clinical examination has been found to under-estimate the frequency of atelectasis and changes in temperature, heart rate and respirations are poorly correlated with atelectasis post
cardiopulmonary bypass.\textsuperscript{(14, 19)} Changes in lung function have been described previously with evidence showing that pulmonary complications persist for around a week after cardiac surgery, with the most severe symptoms observed around the second post-operative day.\textsuperscript{(20-22)} Increased elastance parameters following cardiac surgery with peak changes occurring around day two to three have also been demonstrated.\textsuperscript{(22)}

Limitations of this Study

No assessment of atelectasis was performed on the pre-operative chest x-ray, therefore the assumption is that there was no pre-operative atelectasis. Pre-operative CXR assessment has not been routinely performed in previously published studies either. One study took pre-operative x-rays and compared them to post-operative and found none at baseline but 8/35 had atelectasis post-operatively.\textsuperscript{(22)}

No other demographic or clinical data was collected. This study was performed purely to assess the degree of atelectasis on chest x-ray and to determine how this might predict oxygenation status post-operatively.

This study was designed as a retrospective study, thus potentially suffering from selection bias. However to minimize selection bias the protocol required the enrolment of 50 consecutive patients who met the inclusion and exclusion criteria chosen for this study who received routine post-operative oxygen therapy. They should therefore reflect the group that will be enrolled into the planned randomized controlled trial.

Conclusion

This new scoring method appears to be better suited as an outcome measure of atelectasis in studies of patients following cardiac surgery. It may also have some utility in discriminating patients who require ongoing supplemental oxygen on postoperative day 3, however further prospective studies are required to confirm this. We propose to use this modified scoring system as a secondary outcome in a randomised controlled trial investigating the use of prophylactic nasal high flow oxygen therapy after cardiac surgery (www.ANZCTR.org.au/ACTRN12610000973011).\textsuperscript{(9)}
Acknowledgements

With thanks to Professor Chris Triggs and Kai Xiong, Department of Statistics, The University of Auckland. This study is part of a programme of research partly funded by the Health Research Council of New Zealand and the Green Lane Research and Education Fund. Research in the CVICU is partially funded by an unrestricted grant from Fisher and Paykel Healthcare, New Zealand.

References


Chapter 7. A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for cardiac Surgery


Chapter 7. A New System for Assessing Atelectasis on Chest X-ray after Sternotomy for cardiac Surgery


Chapter 8. Study 3: Protocol for a randomised controlled trial of high flow nasal oxygen therapy compared to standard care in patients following cardiac surgery. The HOT-AS study

Preamble

Once the observational study described in Chapter 7 had been completed I had available to me data with which to design the planned RCT. The x-ray study had provided a unique insight not only into the incidence of atelectasis in the study ICU but also had identified a group of patients with poor oxygenation 3 days following surgery.

This chapter contains the article describing the protocol for an RCT undertaken to determine if the routine use of NHF could improve pulmonary function in patients following cardiac surgery. This article was published in the International Journal for Nursing Studies. After undertaking the literature review presented in Chapter 4, it was clear that there existed no current evidence regarding the use of routine nasal high flow oxygen therapy in patients following extubation after cardiac surgery. Therefore an RCT was designed to answer the question “Does routine nasal high flow improve pulmonary function after cardiac surgery?” This trial was designed to not only test the hypothesis but also to explore a range of secondary outcomes as befitting a Phase II trial. This RCT was designed as a superiority trial - that is the hypothesis was that routine NHF was superior to routine care in terms of the primary outcome.

All authors read and approved the manuscript.

See Appendix C for study related materials and approvals.
Chapter 8. Protocol for a randomised controlled trial. The HOT-AS study

Protocol for a randomised controlled trial of high flow nasal oxygen therapy compared to standard care in patients following cardiac surgery. The HOT-AS study

Rachael Parke, Shay McGuinness, Robyn Dixon, Andrew Jull.

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Abstract

Background: Postoperative respiratory complications following cardiac surgery may increase morbidity, mortality and length of stay. Non-invasive respiratory support therapies can be used prophylactically or curatively to reduce respiratory complications. One system, nasal high flow oxygen therapy, is in use in many intensive care units (ICUs) however there is a lack of information regarding its clinical utility and efficacy.

Objectives: This paper outlines the study protocol and methodology for a study designed to determine if the prophylactic use of nasal high flow oxygen therapy can improve pulmonary function in patients following cardiac surgery.

Methods/Design: A prospective randomised controlled trial will be conducted of adult patients scheduled for cardiac surgery and admitted to the Cardithoracic Intensive Care Unit of a tertiary hospital. Study participants will be assigned to receive either nasal high flow or standard oxygen therapy (oxygen therapy at 2 - 4 L/min via either simple facemask or nasal cannulae) at extubation. The primary outcome measure is improved pulmonary function demonstrated by SpO2/FiO2 ratio > 445 on post-operative day 3. Secondary outcome measures include atelectasis score on chest x-ray; spirometry; readmission to ICU for respiratory causes; ICU and hospital length of stay; mortality and incidence of respiratory complications at day 28; oxygenation variables; use of adjunctive respiratory support
therapies; escalation of respiratory support; adverse events and patient comfort during administration of oxygen therapy.

Sample Size: It was calculated that 340 patients will be required – 170 per arm of study – to give a 90% power to detect a 15% treatment effect.

Results: This study started recruiting in March 2011. It is anticipated that enrolment will be complete in April 2012 and results available towards the end of 2012.

Conclusion: This study will provide evidence of any benefits in the use of prophylactic nasal high flow therapy in post-operative cardiac surgical patients.

Trial Registration

This trial is registered with the Australian New Zealand Clinical Trials Registry www.anzctr.org.au (ACTRN12610000973011).

Keywords: atelectasis; cardiac surgery; intensive care; nasal high flow therapy; oxygen; randomised controlled trial

What is already known about the topic?

- Nasal high flow oxygen delivers flow dependent positive airway pressure
- Positive pressure can reduce pulmonary complications following cardiac surgery

What this paper adds

- This paper describes a protocol for a randomised controlled trial of prophylactic nasal high flow oxygen in cardiac surgery
Background

Cardiac surgery patients are routinely admitted to Intensive Care Units (ICU) where they are intubated and mechanically ventilated prior to extubation. Oxygen delivery after extubation is critical to maintain adequate oxygenation and avoid reintubation (Tiruvoipati et al., 2010). Postoperative complications increase mortality, morbidity and costs due to prolonged ICU and hospital stays (Zarbock et al., 2009). A major cause of postoperative respiratory complications is atelectasis (Sidebotham et al., 2007). Atelectasis is present in most patients, with an incidence of 90% of cardiac patients (Joshi et al., 2005; Pasquina et al., 2003) and is resistant to simple techniques employed to improve lung function such as patient positioning and incentive spirometry (Lumb et al., 2010). Lung recruitment and positive airway pressure may reduce atelectasis formation, but positive airway pressure is usually lost after extubation (Lumb et al., 2010).

Prophylactic non-invasive respiratory support (NRS) therapies, such as facemask continuous positive airway pressure (CPAP), reduce atelectasis in patients following cardiac surgery (Pasquina et al., 2003; Pelosi and Jaber, 2010). NRS therapies partially compensate for changes in respiratory function by reducing work of breathing, recruiting alveoli and improving gas exchange while also reducing cardiac workload, increasing cardiac output and improving haemodynamics (Pelosi and Jaber, 2010). However, NRS therapies are not without their difficulties. They require an ICU/HDU setting and success often depends on the fit of the interface and patient tolerance of the therapy. Patients report reduced levels of comfort with a facemask and are often agitated and non-compliant, sometimes removing their facemask leading to a greater incidence of hypoxaemia and increased nursing workload (Ayhan et al., 2009; Tiruvoipati et al., 2010). Facemasks also impede the ability of the patient to eat, drink and communicate.

Patient satisfaction may be increased when using nasal cannulae when compared to a facemask (Eastwood et al., 2004; Sasaki et al., 2003; Tiruvoipati et al., 2010). Nasal high flow oxygen therapy (NHF) is being used increasingly in adult intensive care settings, following successful use in paediatric populations (Lampland et al., 2009; Shoemaker et al., 2007). There have only been two randomised controlled trials assessing the clinical utility of NHF in adult patients, but they are small or have recruited patients with respiratory failure. One trial assessed comfort and oxygenation in 20 patients with acute respiratory failure defined as an oxygen saturation of < 96% while receiving humidified oxygen via a face mask.
Chapter 8. Protocol for a randomised controlled trial. The HOT-AS study

(Roca et al., 2010). The study showed that NHF was better tolerated than the facemask and also resulted in better oxygenation and a lower respiratory rate. The second study of 60 patients with mild to moderate hypoxaemic respiratory failure found that significantly more patients allocated to NHF were considered successful with their therapy than those allocated to receive high-flow humidified oxygen delivered via a facemask (Parke et al., 2011a). This study also demonstrated a reduction in non-invasive ventilation (NIV) rates and fewer episodes of oxygen desaturation in the NHF group. No previous trial has assessed the prophylactic use of NHF in the perioperative period. The aim of this study is, therefore, to determine whether the administration of prophylactic NHF improves pulmonary function after cardiac surgery. This study will add to the limited body of knowledge surrounding NHF, and better inform debate on the clinical utility of NHF and its impact on respiratory complications.

Methods

A prospective, open label, single centre, randomised controlled trial will be undertaken. A total of 340 patients will be randomised into this study - 170 patients each arm. Recruitment is anticipated to take 12 months. Ethical approval has been granted by the Northern X Regional Ethics Committee (NTX/10/12/131). Written informed consent will be obtained from all study participants prior to enrolment.

Study Participants

All participants will be consented pre-operatively. Any adult patient scheduled for elective cardiac surgery will be eligible for inclusion in this study if they are aged 18 years or over, are to have a surgical approach involving full median sternotomy. Exclusion criteria include a contraindication to NHF, such as a severe nasal septal defect, previous recruitment in this study and if - due to the type of surgery - they will be intubated for > 24hrs after the surgery.

Patients who have consented to the study, but do not meet extubation criteria by 1000 hours day 1 due to their clinical condition will not be randomised. This criterion ensures that patients receive at least 23 hours of allocated therapy. This group will have baseline demographic data collected and reason for continued mechanical ventilation recorded. Research staff will explain to patients why they were not randomised.
Randomisation

Stratified randomisation by computer-generated random numbers in blocks of 12 will ensure even distribution of sample size between the two study arms for body mass index (BMI) < 35 or BMI ≥ 35. Allocation concealment will be maintained by using opaque, sealed, sequentially numbered envelopes. Envelopes will be prepared by a person completely independent of the study. Each envelope will contain the unique patient identifier code and allocated study therapy details. Participants will be randomised to treatment just prior to extubation and allocated therapy will be commenced as soon as participant is extubated. Randomisation will be performed by the bedside nurse at the time of extubation.

Study Treatments

This study will compare NHF to standard oxygen therapy following extubation after cardiac surgery. NHF will be delivered via the Optiflow™ system (Fisher and Paykel Healthcare, NZ Ltd) using the AIRVO™ humidifier (Fisher and Paykel Healthcare, NZ Ltd). NHF delivers high flows of heated and humidified gas via a nasal interface. The system allows the delivery of accurate concentrations of inspired oxygen (Williams et al., 2006), delivers flow dependent continuous positive airway pressure (CPAP) (Groves and Tobin, 2007; Parke et al., 2009, 2011a, b). The AIRVO™ humidifier has been fitted with an uninterruptable power supply to ensure treatment will not be discontinued during transfer of patients to the post-operative ward and allows mobilisation to occur whilst still on therapy (Figure 12).

Figure 12. AIRVO™ humidifier fitted with uninterruptable power supply
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Once the patient is deemed clinically “ready for extubation” in accordance with the CVICU protocol for mechanical ventilation, the patient will be screened by research staff or bedside clinicians to ensure continued participation. The randomisation envelope will then be opened and patient allocation revealed. The patient will then be extubated and allocated therapy commenced immediately as follows:

- **Intervention group:** If patient is randomised to the intervention group then they will receive NHF at a flow rate of 45 L/min – $\text{FiO}_2$ (fraction of inspired oxygen) as determined by bedside clinician to maintain $\text{SpO}_2 > 93\%$.

- **Control group:** If the patient is randomised to the control group then they will receive standard care, which may include oxygen therapy at 2 - 4 L/min via either simple facemask or nasal prongs titrated by the bedside clinician to maintain $\text{SpO}_2 > 93\%$.

Allocated therapy will continue until 0900 hours day 2 at which point study therapy will be discontinued in conjunction with the research nurses and ongoing requirement for oxygen therapy assessed. All other therapy will remain unchanged.

**Escalation of therapy**

Whilst on the study, a patient may be deemed to have increasing requirements for respiratory support when one or more of the following criteria are met (Nava and Hill, 2009):

- Increased dyspnoea – moderate or severe
- Respiratory rate $\geq$ 35 breaths per minute
- Oxygen saturation $\leq 90\%$
- Heart rate $\geq$ 120 beats per minute or $> 30\%$ increase above baseline
- Mean arterial pressure $> 30\%$ above baseline
- Signs of increased work of breathing as seen by use of accessory muscles and abdominal paradox
- Ratio of $\text{PaO}_2 / \text{FiO}_2 < 200 \text{ mmHg}$.
Oxygen therapy would then be escalated as outlined in Figure 13. At all times, the decision to escalate therapy and what therapy will be deemed most appropriate for the patient will be left to the clinician responsible for the patient.

Figure 13. Respiratory support escalation strategies for patients treated with either Nasal High Flow or standard care.
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Data Collection, Measurements and Outcomes

The primary outcome will be improved pulmonary function demonstrated by \(\text{SpO}_2/\text{FiO}_2\) ratio > 445 on post-operative day 3. Secondary outcomes will include atelectasis score on chest x-ray; spirometry; readmission to ICU for respiratory causes; ICU and hospital length of stay; mortality and incidence of respiratory complications at day 28; respiratory rate; oxygenation variables (measured \(\text{PaO}_2/\text{FiO}_2\), \(\text{PaO}_2\) and \(\text{PaCO}_2\)); use of adjunctive respiratory support therapies; escalation of respiratory support; adverse events and patient comfort during administration of oxygen therapy (Table 7).

Table 7. Schedule of data collection

<table>
<thead>
<tr>
<th>Period of Study</th>
<th>Data Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Information</td>
<td>Patient demographics; BMI; medical history; EUROSCORE; medications – diuretics; inhalers; steroids; (\text{SpO}_2); HR; MAP; RR; (\text{FEV}_1); FVC.</td>
</tr>
<tr>
<td>Day 0 – 3</td>
<td>APACHE II and SOFA score; arterial blood gas measures; weight; method of (\text{O}_2) delivery; escalation of (\text{O}_2) therapy; diuretic therapy; physiotherapy sessions; patient comfort score; spirometry; chest x-ray</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Ongoing (\text{O}_2) therapy after day 3; spirometry; respiratory complications</td>
</tr>
<tr>
<td>Day 28</td>
<td>Mortality; length of stay in ICU; length of stay in hospital; readmission to ICU; date and cause of death; incidence of respiratory illness post discharge</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Description of any serious or non-serious adverse reactions thought to be study related will be collected from the time of randomisation through to discharge from hospital.</td>
</tr>
<tr>
<td>Non-randomised patients</td>
<td>APACHE II and SOFA scores; reason for continued ventilation</td>
</tr>
</tbody>
</table>
Data will be collected by trained research staff and entered into an electronic database. Baseline demographic data will be collected at study enrolment and will include ethnicity data; weight and height to calculate BMI; EUROSCORE and medication history. Post-randomisation, data will be collected daily for physiological parameters including heart rate, mean arterial pressure, respiratory rate and oxygen saturation. Daily record of weight, physiotherapy, diuretic therapy and requirement for adjunctive respiratory support will also be collected. Spirometry measures will be taken at baseline; day 2 and day 3 post-operative and then at discharge. Chest x-rays will be performed as per clinical pathway for cardiac surgical patients on return to the ICU, day 1 and day 3. X-rays will be assessed for atelectasis score by a radiologist blind to study intervention using both a published and a modified atelectasis score (Parke and McGuinness, 2011; Richter Larsen et al., 1995). All patients will be contacted at 28 days following randomisation to assess mortality and incidence of respiratory illness post hospital discharge. This will be defined as having visited their general practitioner for complaints of respiratory type illness and the requirement for antibiotic therapy. Patient comfort for both arms of the study will be assessed four hours post extubation, day 1 and day 2 by asking the patient “On a scale of 0 – 10, how comfortable do you find the oxygen mask/prongs that you are wearing? 0 = not comfortable at all; 10 = extremely comfortable”.

Sample Size

A recent audit of patients at study site found the incidence of patients recording a SpO₂/FiO₂ < 445 on day 3 post-operative was 40% and we assume there will be no difference in failure rate in high BMI versus low BMI patients. However, the evidence on the effect of BMI with nasal high flow is contradictory (Groves and Tobin, 2007). Hence we have stratified for BMI in the randomisation process to ensure balance between the treatment groups for this possible prognostic indicator. Based on preliminary work, we believed that NHF will reduce the treatment failure rate to 25% (Parke et al., 2011 a,b). Assuming an α = 0.05 a sample size of 332 (166 per arm) will give a 90% power to a treatment effect of 15%. We plan to randomise a total of 340 patients (170 per arm) in order to allow for a 3% loss to follow-up rate. Although our past experience suggests that actual follow-up rate is likely to be 100%, we believed it to be good practice to allow for some loss. Achieving 100% follow up will also allow us to detect a slightly smaller treatment effect should the effect be lower than we have anticipated.
Statistical Analysis

Data from the trial will be entered into an Excel spreadsheet, and then extracted into STATA for analysis. All analyses will be carried out on an intention-to-treat basis. Incidence rates and absolute differences (with corresponding NNTs) and 95% CIs will be obtained for binary variables in the first instance with subsequent multiple logistic regression adjusted for stratification factors. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow-up or death on the primary outcome. If important imbalances exist, these factors will also be entered into the regression analysis. Time to event data will be analysed using Cox regression modelling thereby taking into account known covariates and the varying times since randomisation. The proportionality assumption will be checked using standard graphical techniques. However, prior to undertaking any Cox regression modelling, the effectiveness of the interventions on time to outcome will be analysed using Kaplan-Meier curves to compare the differences between the two groups using the log rank test. Continuous data will be analysed using the appropriate parametric or non-parametric analysis after testing for normality.

Discussion

A systematic review concluded that NHF could be used as an intermediate therapy to improve oxygenation in adult critical care patients. However, the authors determined that further research was required to determine the effect of the therapy, identify the patient population for whom it is most beneficial and evaluate long-term outcomes and to enable definitive recommendations for practice to be made (Kernick and Magarey, 2010). Health care is littered with examples where practices have been implemented in advance of good quality evidence, and which the randomised evidence has demonstrated to have little effect or even harmful effects on patient outcomes. Honey dressings to increase venous ulcer healing (Jull et al., 2008), hormone and anti-oxidants for cardiovascular risk (Sesso et al., 2008), prone positioning for mortality in ventilated patients (Sud et al., 2008) and intensive blood glucose management in the critically ill, are but a few examples (The NICE-SUGAR study investigators, 2009). It is imperative where evidence gaps are identified in clinical practice that randomised evidence is provided to guide decision-making and reduce wasteful use of scarce health care resources.
Currently, there is only a limited body of evidence to guide choice of non-invasive respiratory support therapies in intensive care settings and much of it is non-randomised evidence. Where randomised evidence exists, it is not directly generalisable to adult populations having elective cardiac surgery, either because paediatric participants have been used, or because participants had acute respiratory failure on recruitment. Cardiovascular heart disease is the leading cause of death in New Zealand accounting for approximately 40% of all deaths annually (Hay, 2004). One in 20 adults have been diagnosed with cardiovascular heart disease – approximately 161,000 adults. Recent figures showed that around 2493 patients are discharged annually from New Zealand hospitals following cardiac surgery – 54 per 100,000 people (Ministry of Health, 2008). A national working group on cardiac surgical services in New Zealand, recommends however that the rate should be increased by 35% to 73 per 100,000 people within the next two years (Ministry of Health, 2008). Even without the anticipated increases in cardiac surgery, the current rates of surgery make it imperative that a randomised controlled trial be conducted to determine whether NHF improve pulmonary function and reduce pulmonary complications on an elective cardiac surgical population before NHF is widely implemented. If significant physiological improvement in pulmonary function and patient oriented outcome benefits are demonstrated by this study, these findings will influence practice on both a national and international scale. However, even if the anticipated benefits to patient oriented outcomes are not found, estimates of potential patient oriented benefits obtained from this trial will be used to investigate sample size requirements for a future definitive randomised controlled trial.

Conflicts of interest. Rachael Parke is employed as a research nurse in the Cardiothoracic and Vascular Intensive Care Unit. Fisher and Paykel Health care, NZ Ltd provide some funding to the unit by way of an unrestricted grant. Fisher and Paykel Healthcare, NZ Ltd are providing the consumables for the intervention arm of this study free of cost.

Funding

This study has been funded by grants and support from the following sponsors: a PhD scholarship and project grant from the Green Lane Research and Education Fund and a Clinical Research Training Fellowship from the Health Research Council of New Zealand. Fisher and Paykel Healthcare, NZ Ltd are providing the consumables for the intervention arm. The sponsors have had no input into the study design and will have no access to trial
Chapter 8. Protocol for a randomised controlled trial. The HOT-AS study

data. All analysis, reporting and decisions to publish will be made independently of the
sponsors.

References

Ayhan H, Iyigun E, Tastan S, Orhan ME, Ozturk E., 2009. Comparison of two different
oxygen delivery methods in the early postoperative period: randomized trial. Journal of
Advanced Nursing 65 (6), 1237 - 47.

Eastwood GM, Reeves JH, Cowie BS., 2004. Nasopharyngeal oxygen in adult intensive care-
lower flows and increased comfort. Anaesthesia & Intensive Care 32 (5), 670 - 671.

Groves N, Tobin A., 2007. High flow nasal oxygen generates positive airway pressure in

information. Auckland: National Heart Foundation.

Anaesthesia & Critical Care 16 (6), 369 - 383.


Kernick J, Magarey J., 2010. What is the evidence for the use of high flow nasal cannula
oxygen in adult patients admitted to critical care units? A systematic review. Australian
Critical Care 23 (2), 53 - 70.

Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC., 2009. Observational study
of humidified high-flow nasal cannula compared with nasal continuous positive airway

Lumb AB, Greenhill SJ, Simpson MP, Stewart J., 2010. Lung recruitment and positive
airway pressure before extubation does not improve oxygenation in the post-anaesthesia care

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Chapter 8. Protocol for a randomised controlled trial. The HOT-AS study


Chapter 8. Protocol for a randomised controlled trial. The HOT-AS study


Chapter 9. Study 3: An Open Label, Phase II study of Routine High Flow Nasal Oxygen Therapy in Cardiac Surgical Patients

Preamble

This chapter reports the results of the HOT-AS trial, a randomised controlled trial comparing nasal high flow to usual care following extubation in patients following cardiac surgery. The protocol for the study is described in detail in Chapter 8.

Prior to undertaking the trial, a preliminary vanguard study was undertaken to assess usability of study documentation and procedures and to refine study tools. Ten participants were enrolled in this study which was conducted immediately prior to commencement of the main RCT. This ensured that final adjustments were made to the study tools, protocol, data dictionary and manual of procedures prior to commencing the RCT. Vanguard studies, also called pilot or feasibility studies, are employed to assess safety of interventions, recruitment potential, and assist with experience of the study intervention and study tools. Undertaking the vanguard study also helped to assess time and budgetary considerations e.g. time taken to collect data and undertake study procedures. During the RCT itself, it was seen that some patients found the heat of the AIRVO™ humidifier system too intolerable and so using an adaptive approach, the protocol was amended to allow bedside staff to reduce the temperature from the default setting of 37° C to 31° C if patient comfort necessitated this. This was a pragmatic decision and allowed patients receiving NHF to remain on the allocated period of study intervention by reducing the temperature. A small trade-off for improved participant retention. Optimising enrolment procedures and ensuring that only eligible patients were screened and enrolled was also a benefit of the vanguard study and may have assisted in improving subsequent adherence to inclusion and exclusion criteria and identification of study patients for a randomised controlled trial. Inappropriate enrolment may cause harm for those patients leading to serious adverse events attributable to the use of the study interventions and alter study results due to dilution of the study effect. A recent systematic review of techniques and interventions for improving adherence to inclusion and exclusion criteria found only one abstract evaluating the effect of a dummy enrolment run-in phase on preventing enrolment errors in a multi-centre RCT. This abstract concluded that a formal run-in phase improved familiarity with trial eligibility criteria and reduced recruitment errors.
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By undertaking the vanguard study it was possible to determine that study recruitment of 8 patients a week, of which on average 6 would be randomised, was feasible. I also gained experience with obtaining informed consent from participants, undertaking the study procedures such as spirometry and with completing data collection and finally data entry into the database. This ensured that on completion of the vanguard study a comprehensive and accurate data dictionary and manual of study procedures was complete and available for training of the research nurses who were to work on this study, thus guaranteeing that all working on the RCT were collecting the same data and in the same way.

When undertaking the RCT, BMI was a stratification factor as it was not known whether or not BMI would have an effect on the primary outcome and I wished to balance any possible effect between the two groups. There are some advantages in stratifying and in ensuring that such variables are balanced between groups in single centre studies where certain variables may predict or influence outcome. In this study, there was a concern that BMI may influence the response of the participant to NHF based on literature showing that expiratory pharyngeal pressure decreased by 0.5 cm H\textsubscript{2}O for every 10 cm increase in participant height. An association with BMI has also been reported in a subsequent study which showed that increases in end expiratory lung impedance (EELI) were significantly associated with higher BMIs (p < 0.001). A recent report finds no association between BMI and EELI, though the authors do point out that the BMI of all patients in that study were all within normal range for BMI. In order to prevent imbalance based on BMI, study participants were stratified into two groups at enrolment – those with a BMI < 35 and those with BMI ≥ 35.

See Appendix C for study related materials and approvals.
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An Open Label, Phase II study of Routine High Flow Nasal Oxygen Therapy in Cardiac Surgical Patients

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Abstract

Background: Respiratory complications following cardiac surgery increase morbidity, mortality and length of stay. Studies suggest that routine delivery of positive airway pressure following extubation may be beneficial. We sought to determine whether the routine administration of nasal high flow oxygen therapy (NHF) improved pulmonary function after cardiac surgery.

Methods: A pragmatic randomised controlled trial; participants received either NHF (45 L min\(^{-1}\)) or usual care from extubation to day 2 after surgery. Primary outcome was number of patients with SpO\(_2\)/FiO\(_2\) ratio \(\geq 445\) on day 3 after surgery. Secondary outcomes included atelectasis score on chest x-ray; spirometry; intensive care and hospital length of stay; mortality at day 28; oxygenation indices; escalation of respiratory support; and patient comfort.

Results: We randomised 340 patients over 14 months. The number of patients with a SpO\(_2\)/FiO\(_2\) ratio \(\geq 445\) on day 3 was 78 (46.4%) in the NHF group versus 72 (42.4%) standard care (Odds Ratio (OR) 1.18 95% CI 0.77 - 1.81, \(p = 0.45\)). PaCO\(_2\) was significantly reduced at both 4 hours post-extubation and at 0900 hours day 1 in the NHF group (5.3 vs. 5.4 kPa \(p = 0.03\) and 5.1 vs. 5.3 kPa \(p = 0.03\) respectively). Escalation in respiratory support
occurred in 47 patients (27.8%) allocated to NHF compared to 77 (45%) standard care (OR 0.47 95% CI 0.29 – 0.7, p = 0.001).

Conclusions: Routine use of NHF did not increase SpO₂/FiO₂ ratio on day 3 but did reduce requirement for escalation of therapy and PaCO₂.

**Word Count:** 237

**Keywords:** surgery, cardiovascular; intensive care cvs; nasal high flow oxygen therapy; oxygen - therapy; clinical trial

**Trial Registration:** Australia New Zealand Clinical Trials Registry www.anzctr.org.au (ACTRN12610000973011).

**Introduction**

With over one million operations a year, cardiac surgery with cardiopulmonary bypass is one of the most common major surgical procedures worldwide.¹ Patients are admitted to intensive care units (ICUs) following cardiac surgery, where they often spend a period of time mechanically ventilated until deemed ready for extubation, whereupon they then receive oxygen therapy via a range of devices.² Postoperative complications increase morbidity and mortality and lead to prolonged ICU and hospital length of stay.³ A contributing mechanism of postoperative respiratory complications is atelectasis, which may be present in up to 90% of cardiac surgical patients.⁴,⁵ Atelectasis is resistant to simple techniques such as patient positioning and incentive spirometry.⁶ Lung recruitment manoeuvres and positive airway pressure may reduce atelectasis formation, but this effect is lost after extubation.⁷ Prophylactic nasal continuous positive airway pressure has been shown to reduce respiratory complications following cardiac surgery.³ Nasal high flow oxygen therapy (NHF) delivers low level, flow dependent positive airway pressure, may be better tolerated than non-invasive ventilation and enhance washout of nasopharyngeal dead space improving oxygenation.⁸-¹² There have only been a few randomised controlled trials assessing the clinical utility of NHF oxygen therapy in adult patients following cardiac surgery – all in patients who have respiratory failure prior to commencing the therapy.¹³-¹⁵ No study has assessed the prophylactic use of NHF in the postoperative period. The hypothesis that this phase 2 study set out to test was that the routine administration of NHF lead to improved oxygenation after cardiac surgery when compared to usual care oxygen therapy.
Methods

A pragmatic, open label randomised controlled trial was undertaken at a single study centre in a large metropolitan hospital. The study was approved by the Regional Ethics Committee (NTX/10/12/131). Written informed consent was obtained from all study participants prior to enrolment. The study was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12610000973011) and the protocol has been published previously (see supplementary material).16

Study Participants

All patients scheduled for elective cardiac surgery utilising cardiopulmonary bypass were eligible for inclusion in this study if aged 18 years or over and scheduled to have surgery involving full median sternotomy. Exclusion criteria were contraindication to NHF e.g. presence of a nasal septal defect, and previous recruitment. Patients were consented to the study and baseline observations made pre-operatively. If participants had not met extubation criteria by 10:00 am the day after surgery (day 1), they were not randomised. This approach ensured participants with a typical post-operative trajectory were randomised.

Randomisation

Randomisation was by computer-generated random numbers in blocks of 12, with the sequence generated by an independent statistician, stratified by body mass index (BMI) < 35 or BMI ≥ 35. Allocation concealment was maintained by using opaque, sealed, sequentially numbered envelopes prepared by a person not involved with study.

Study Treatments

Once the participant was deemed clinically “ready for extubation” (in accordance with unit protocol), allocation was revealed, the participant extubated and allocated therapy commenced. Patients were cared for in the ICU and then, if condition allowed, transferred to the post-operative ward the day following surgery. Study therapy for both groups continued until 0900 hours on day 2.

Intervention group: NHF oxygen therapy delivered at a flow rate of 45 L min⁻¹ – FiO₂ (fraction of inspired oxygen) as determined by bedside clinician to maintain a SpO₂ > 93%. NHF delivered via the Optiflow™ system (Fisher and Paykel Healthcare, NZ Ltd) using the AIRVO™ humidifier (Fisher and Paykel Healthcare, NZ Ltd). The AIRVO™ humidifier was
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fitted with an uninterrupted power supply to ensure treatment would not be discontinued during transfer of patients to the post-operative ward and to allow mobilisation to occur whilst still on therapy.

Usual care group: oxygen therapy at 2 - 4 L min$^{-1}$ via either simple facemask or nasal prongs titrated by the bedside clinician to maintain SpO$_2$ > 93%.

An algorithm guided clinicians when study participants required an escalation of respiratory support (Figure 14).

Data Collection, Measurements and Outcomes

Primary outcome was the number of patients with SpO$_2$/FiO$_2$ ratio ≥ 445 on day 3 after surgery - reflecting a SpO$_2$ on air of > 93%. This outcome reflects the current pathway for cardiac surgical patients at this hospital and current recommendations for oxygenation.  

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16 Figure 14. Respiratory support escalation strategies for study patients.

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Accurate measurement of the FiO\(_2\) in participants receiving low flow oxygen is difficult. We used established clinical tools for oxygen estimation to estimate FiO\(_2\) in participants in the usual care group. This approach may have introduced some inaccuracy in measuring FiO\(_2\) in the control group, but reflects the practice reality whereby estimates of FiO\(_2\) are used to assess oxygenation of patients. Secondary outcomes included atelectasis score of chest x-rays (assessed by a blinded radiologist), spirometry, readmission to ICU for respiratory causes, ICU and hospital length of stay, mortality and incidence of respiratory complications at day 28, respiratory rate, oxygenation variables were collected serially at 30mins, 4hours and day 1 and day 2 post-operatively, use of adjunctive respiratory support therapies, escalation of respiratory support, adverse events, and patient comfort. See supplementary material for detailed description of methods of data collection and definitions of escalation of respiratory support.\(^{16}\)

Statistical Analysis

Although we assumed there would be no difference in failure rate in high BMI versus low BMI patients, we stratified for BMI at randomisation to ensure balance between groups for this possible prognostic factor. A pre-trial audit of patients at the study site found the incidence of patients recording a SpO\(_2\)/FiO\(_2\) < 445 on day 3 was 40%.\(^{18}\) Assuming an alpha of 0.05, a sample size of 332 (166 per arm) would give a 90% power to detect a 15% reduction in the proportion of patients with a SpO\(_2\)/FiO\(_2\) < 445 on day 3. We planned to randomise a total of 340 patients (170 per arm) in order to allow for a small (3%) loss to follow-up. All analyses were conducted according to a predefined statistical analysis plan using the intention-to-treat principle, with no imputation for missing values. Proportions were compared with the use of the chi-square test, and continuous variables were analysed using Student’s t-test. Incidence rates, absolute differences and 95% confidence intervals (95%CI) were obtained for binary variables in the first instance with subsequent multiple logistic regression adjusted for stratification factors. Pre-specified subgroup analyses were performed using logistic regression analysis to assess effect of sex, ejection fraction, BMI and usage of internal mammary artery graft (IMAG). Data was entered into Excel spread sheets, and then extracted into STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP), for analysis.
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Results

Patients’ characteristics

Over 14 months, 416 patients were enrolled into the study of which 341 were randomised (Figure 15). One patient in the NHF arm withdrew consent for use of any data; one withdrew on day 2 of the study however did allow use of data collected up to that point and one did not have day 3 outcome data collected. Therefore a total of 338 patients were available for analysis of primary outcome. Of the 340 patients enrolled, 169 were allocated to nasal high flow and 171 to usual care.

Figure 15. Participant flow through study.
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Baseline characteristics of the group are described in Table 8. Mean bypass time across the whole group was 110 minutes (SD 53), 13 patients had surgery performed without cardiopulmonary bypass even though this was scheduled.

Table 8. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Usual Care n=171 (50.3%)</th>
<th>NHF n=169 (49.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender - Male n (%)</td>
<td>129 75.4</td>
<td>129 76.3</td>
</tr>
<tr>
<td>- Female</td>
<td>42 24.6</td>
<td>40 23.5</td>
</tr>
<tr>
<td>Ethnicity - European n (%)</td>
<td>120 70</td>
<td>128 75</td>
</tr>
<tr>
<td>- Maori</td>
<td>16 9.3</td>
<td>22 13</td>
</tr>
<tr>
<td>- Pacific Island</td>
<td>25 14.6</td>
<td>11 6.5</td>
</tr>
<tr>
<td>- Asian</td>
<td>8 4.7</td>
<td>5 2.9</td>
</tr>
<tr>
<td>- Other</td>
<td>2 1.1</td>
<td>4 2.2</td>
</tr>
<tr>
<td>BMI mean(SD)</td>
<td>29.2 5.5</td>
<td>28.4 5.3</td>
</tr>
<tr>
<td>Age years median(range)</td>
<td>66 21-87</td>
<td>65 19-88</td>
</tr>
<tr>
<td>Weight kgs mean(SD)</td>
<td>84.2 16.7</td>
<td>82.3 17.0</td>
</tr>
<tr>
<td>EuroSCORE mean(SD)</td>
<td>5.3 2.8</td>
<td>5.1 2.8</td>
</tr>
<tr>
<td>At enrolment mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- SpO₂ %</td>
<td>97.1 1.6</td>
<td>96.9 1.7</td>
</tr>
<tr>
<td>- Resp rate per min</td>
<td>16.5 1.7</td>
<td>16.6 1.9</td>
</tr>
<tr>
<td>- Heart rate per min</td>
<td>68.5 14.4</td>
<td>67.3 10.7</td>
</tr>
<tr>
<td>- Systolic BP mmHg</td>
<td>127.0 19.6</td>
<td>126.4 17.8</td>
</tr>
<tr>
<td>- Diastolic BP mmHg</td>
<td>69.6 9.7</td>
<td>69.2 10.3</td>
</tr>
<tr>
<td>- FEV₁ L/min</td>
<td>2.3 0.8</td>
<td>2.3 0.8</td>
</tr>
<tr>
<td>- FVC L/min</td>
<td>2.9 0.9</td>
<td>2.9 0.9</td>
</tr>
<tr>
<td>Surgery n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CABG</td>
<td>91 53.5</td>
<td>109 64.5</td>
</tr>
<tr>
<td>- Valve</td>
<td>49 28.8</td>
<td>26 15.4</td>
</tr>
<tr>
<td>- CABG + Valve</td>
<td>19 11.2</td>
<td>20 11.8</td>
</tr>
<tr>
<td>- Other</td>
<td>12 7.1</td>
<td>14 8.3</td>
</tr>
</tbody>
</table>
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Primary Outcome

The number of patients with a \( \text{SpO}_2/\text{FiO}_2 \) ratio \( \geq 445 \) on day 3 was 78 (46.4%) in the NHF group versus 72 (42.4%) in the usual care group (Odds Ratio 1.18 95% CI 0.77 to 1.81, \( p = 0.45 \)).

Secondary Outcomes

Measures of oxygenation are shown in Figure 16. Arterial blood gas measurements did not differ significantly between groups for \( \text{pH} \), and \( \text{PaO}_2 \) measurements, however mean \( \text{PaCO}_2 \) was significantly lower in the NHF group at 4 hours post-extubation (5.3 kPa NHF group vs. 5.5 kPa usual care, \( p = 0.03 \)) and at day 1 (5.1 kPa NHF group and 5.3 kPa usual care group, \( p = 0.03 \)). \( \text{SpO}_2/\text{FiO}_2 \) ratios were higher in the usual care group at 30mins, 4 hours, day and day 2 when compared to the NHF group.

![Figure 16. Measures of oxygenation.](image)

*indicates \( p < 0.05 \)

Cardiovascular parameters and measurements of FVC or FEV\(_1\) did not differ significantly through to discharge. Of note, both FVC and FEV\(_1\) at discharge were considerably lower in both groups than pre-operatively. Chest radiograph scores for atelectasis, total oxygen therapy received, hospital and ICU length of stay, and requirement for antibiotic therapy for chest infection whilst in ICU did not differ between groups. Comfort scores differed at all time points; with NHF oxygen therapy scored lower than standard care (Table 9).
In 20 patients tolerability of NHF caused early removal - 12 complained of excess heat.

Table 9. Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>NHF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atelectasis score on CXR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Baseline</td>
<td>3.2</td>
<td>3.4</td>
<td>0.33</td>
</tr>
<tr>
<td>- Day 1</td>
<td>4.9</td>
<td>4.8</td>
<td>0.63</td>
</tr>
<tr>
<td>- Day 3</td>
<td>4.7</td>
<td>4.8</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Total O₂ therapy received - hours</strong></td>
<td>65.0</td>
<td>59.0</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>ICU length of stay - hours</strong></td>
<td>28.9</td>
<td>33.4</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Hospital length of stay - days</strong></td>
<td>11.4</td>
<td>11.6</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Comfort score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 4 hours after extubation</td>
<td>8.1</td>
<td>7.5</td>
<td>0.03</td>
</tr>
<tr>
<td>- day 1</td>
<td>8.25</td>
<td>7.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- day 2</td>
<td>7.78</td>
<td>6.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC - Baseline (n=339)</td>
<td>2.90</td>
<td>2.93</td>
<td>0.81</td>
</tr>
<tr>
<td>- Day 2 (n=291)</td>
<td>1.19</td>
<td>1.35</td>
<td>0.34</td>
</tr>
<tr>
<td>- Day 3 (n=306)</td>
<td>1.57</td>
<td>1.58</td>
<td>0.93</td>
</tr>
<tr>
<td>- Discharge (n=323)</td>
<td>1.91</td>
<td>1.95</td>
<td>0.48</td>
</tr>
<tr>
<td>FEV₁ - Baseline (n=339)</td>
<td>2.23</td>
<td>2.29</td>
<td>0.48</td>
</tr>
<tr>
<td>- Day 2 (n=291)</td>
<td>0.98</td>
<td>1.00</td>
<td>0.73</td>
</tr>
<tr>
<td>- Day 3 (n=306)</td>
<td>1.18</td>
<td>1.16</td>
<td>0.75</td>
</tr>
<tr>
<td>- Discharge (n=323)</td>
<td>1.42</td>
<td>1.45</td>
<td>0.61</td>
</tr>
</tbody>
</table>

The number of patients requiring an escalation of respiratory support therapy was significantly different (Table 10). The main reason for escalation in respiratory support was impaired oxygenation. In the usual care group 6 patients required therapy with a high flow face mask, 12 required NHF, 5 required NIV (CPAP or BiPAP) and 54 required reintroduction of oxygen therapy after discontinuation of study allocation on day 2. In the NHF group 7 patients required an increase in NHF flow above 45 L min⁻¹ or reintroduction of the therapy after discontinuation of study period, 9 required NIV (CPAP or BiPAP) and 2 required re-intubation and mechanical ventilation. A further 29 required reintroduction of
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oxygen therapy by means of low flow nasal cannulae after discontinuation of study allocation on day 2.

Table 10. Number of patients requiring escalation of respiratory support.

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Usual Care</th>
<th>NHF</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 4 hours after extubation</td>
<td>1 33.3</td>
<td>2   66.7</td>
<td>0.1 – 0.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>On day 1 post-op</td>
<td>35 76.1</td>
<td>11 23.9</td>
<td>0.3</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>On day 2 post-op</td>
<td>35 66.0</td>
<td>18 34.0</td>
<td>0.5</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>On day 3 post-op</td>
<td>6 28.6</td>
<td>15 71.4</td>
<td>2.7</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Day 3 post-op to discharge</td>
<td>0 0.0</td>
<td>1 100.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase anytime on study</td>
<td>77 62.1</td>
<td>47 37.9</td>
<td>0.5</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

At day 28 there was no difference found in patient status. Most patients (98.8%) were alive and discharged from ICU (167 usual care vs. 168 NHF); 2 had died (1 usual care and 1 NHF-giving an overall 28 day mortality of 0.6%) and 2 usual care patients were alive, but still in the study hospital. Twenty eight patients had seen their general practitioner for respiratory complaints since discharge from hospital, of which 23 had had antibiotics prescribed (12 usual care vs. 11 NHF, p = 0.83).

Discussion

The routine use of NHF from extubation to day 2 following cardiac surgery did not significantly increase SpO\textsubscript{2}/FiO\textsubscript{2} ratio on day 3 after surgery. A weak association with a lower PaCO\textsubscript{2} and a lower requirement for escalation of respiratory support were found.

The prospective nature of the study, group enrolled, use of a randomised controlled trial design and the hypothesis differ from most studies so far which have evaluated NHF in a range of patient populations. This study is the first to aim to determine if the use of NHF therapy can reduce the development of respiratory complications following cardiac surgery. Three studies have enrolled cardiac surgical patients, but all have enrolled patients post-operatively once patients were deemed to exhibit signs of respiratory dysfunction or hypoxaemia.\textsuperscript{13-15} Patient baseline characteristics are comparable to these studies and we feel that our findings are generalisable to this patient population.
Previous studies have assessed the efficacy of prophylactic NIV post-extubation in cardiac surgery patients. These studies have shown an improvement in gas exchange; reduction in pulmonary complications and work of breathing; and decrease in ICU and hospital length of stay. However, NIV is not without its difficulties. In many hospitals it can only be used in an ICU/HDU setting and success often depends on tolerability and fit of the interface, which may impede the ability of the patient to eat, drink and communicate. Improved comfort scores have been reported with NHF compared to NIV, but in our study we found that patients comfort scores were significantly lower in the NHF group compared to usual care. We believe that the difference in comfort scores found in this study may be because the trial participants were a reasonably “well” group compared to the other studies, which have enrolled patients suffering acute respiratory failure who seem to benefit more from NHF. In our experience, once “sicker” patients with a higher inspiratory flow demand start to recover, they too start to find NHF less comfortable and request removal of the therapy. Perhaps this is an indicator of who may require and benefit the most from NHF. Comfort and tolerability of therapy remains an important consideration when choosing an appropriate oxygen delivery device for patients.

No significant heterogeneity was found in the primary outcome after subgroup analysis was undertaken for sex, BMI, ejection fraction and usage of the internal mammary artery for bypass grafting in patients undergoing CABG surgery. Previous work has shown a link between gender and amount of airway pressure generated by NHF, but was observational and used healthy volunteers. The evidence surrounding the effect of BMI on NHF results is mixed with weight and BMI having no influence in healthy adults, but being associated with generated airway pressure in neonates. A recent observational study of cardiac surgical patients experiencing post-operative respiratory dysfunction treated with NHF, found that increases in end expiratory lung impedance were influenced by BMI, with larger increases associated with higher BMIs (p < 0.001). However, the mean BMI in that study was 32 kg/m² while the mean BMI in the NHF group of our study was 28.4 kg/m².

A reduction in escalation of therapy is a similar finding to a previous study, which also reported more patients allocated to NHF succeeded on their therapy compared to those allocated to high flow humidified face mask (HFFM). That study also found a difference in NIV rates between patients allocated to NHF and those allocated to HFFM therapy although the study was not powered to detect such a treatment effect. The exact mechanism by which NHF reduces the need for escalation of therapy remains to be elucidated though it is
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hypothesised that the low level airway pressure provided by the system may play a role in this, improving gas exchange and reducing respiratory effort.\textsuperscript{13}

In contrast to previous work,\textsuperscript{14, 23, 26-28} this study found no significant difference in respiratory rate, cardiovascular parameters and measures of oxygenation between the groups.

Study strengths and limitations

Strengths of this study include the pragmatic design employed leading to timely enrolment and completion of the study and generalisability of study results as all patients presenting for cardiac surgery were considered for enrolment as opposed to specific high risk groups. A protocol was developed which was easily instituted in both the ICU and the post-operative ward to guide clinicians on escalation therapies for participants (Figure 14). However, it was not possible to prevent all incidents of cross-over in the usual care group, which would not have truly represented usual care at this institution if NHF had been excluded as an escalation. This approach may have diluted the treatment effect, as more participants had oxygen therapy escalated in the usual group than in the NHF group. However, such an approach is necessary to test routine use of NHF compared to usual care and thus models a real world of evaluation clinical practices.

Finally, this early phase study used a surrogate outcome (SpO\textsubscript{2}/FiO\textsubscript{2} ratio) as a primary outcome rather than a more patient-oriented outcome, which would have required greater numbers of participants. Surrogate outcomes may be more sensitive to the effect of the therapeutic interventions than patient-oriented outcomes, leading to over-estimation of effects.\textsuperscript{29} Such a problem is unlikely to be the case in our trial, with no clear difference in effects.

Conclusion

Routine use of NHF oxygen therapy was not associated with an increase in post-operative oxygenation compared to usual oxygen therapy, although it may have been associated with a reduced requirement for escalation of therapy and a lower PaCO\textsubscript{2}. In the absence of any demonstrable benefit, it would be hard to justify the routine use of NHF following extubation in patients undergoing a normal post-operative trajectory after cardiac surgery.
Chapter 9. An open label, phase II study of routine high flow nasal oxygen therapy in cardiac surgical patients

Funding

This work was supported by: the Health Research Council of New Zealand Clinical Research training fellowship (HRC11/144) (RLP) a PhD scholarship (10/60/4079) (RLP) and a project grant from the Green Lane Research and Education Fund (11/25/4083). Research in the CVICU is supported in part by an unrestricted grant from Fisher and Paykel Healthcare, New Zealand. Fisher and Paykel Healthcare also supplied the consumables used in this study. These sponsors had no input into the study design and no access to trial data. All analyses, reporting and decisions to publish have been made independent of the sponsors.

Acknowledgements

We would like to thank the CVICU research nurses: Jodi Brown, Eileen Gilder, Charlotte Firth, Lianne McCarthy and Anna Whitley; the staff of the CVICU and Ward 42, Auckland City Hospital who provided care to the patients; and Chris Triggs and Kai Xiong, Department of Mathematics, The University of Auckland for statistical advice.

Finally and most importantly we would like to thank the patients who so generously agreed to participate in this study.

References


Chapter 9. An open label, phase II study of routine high flow nasal oxygen therapy in cardiac surgical patients


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Chapter 10. Study 4: Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit: a Point Prevalence Study

Preamble

Oxygen therapy is probably the one intervention most commonly delivered to patients in the ICU. There is little published evidence to describe how it is delivered, what devices are used and what flow rates are commonly prescribed. When planning a study involving “routine” oxygen therapy it was necessary to have contemporary evidence regarding how oxygen therapy is routinely delivered to the population of interest in order to inform design of the study arms. A literature search undertaken to identify studies describing oxygen therapy in non-intubated adult ICU patients failed to find any studies. Seeing this as an opportunity, a point prevalence study was designed and undertaken to answer the question “In non-intubated ICU patients what is the current practice by clinicians with respect to oxygen therapy?”

This study was undertaken utilising the point prevalence programme run and endorsed by the Australia and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG). This programme provides infrastructure to researchers to assist them in conducting basic observational studies to inform future research and trial design. The point prevalence programme utilises a cross-sectional research methodology to collect information on all patients admitted to participating ICUs at 10:00 hours on the study day. It provides the investigator with a snapshot of clinical practice in relationship to one area of interest at one time point. Investigators, who wish to use this programme, present their proposal for peer review by the ANZICS-CTG community at a scientific meeting thus providing feedback and advice on study design and endpoints. Once the study protocol is fully developed, the investigator submits specific questions regarding their topic of interest for inclusion in a standardised case report form (CRF). The CRF is then distributed to and used by trained research coordinators in each ICU. Information collected includes generic patient characteristics, admission details, illness severity, organ dysfunction, mortality and outcome at day 28 as well as the questions of specific interest to each investigator included on that day.

As part of the process, a payment to the point prevalence programme of $5000.00 AUD is required. To provide this, a grant was submitted to the A+ Charitable Trust and was awarded
for $11,285. This covered both the study payment and also costs associated with developing the CRF and undertaking the research at Auckland District Health Board.

Once completed, data analysis was undertaken and the manuscript prepared by the principal investigator in consultation with the co-investigators. Because the point prevalence programme is an endorsed activity of the ANZCIS-CTG, the paper underwent initial review and endorsement by the CTG Executive Committee prior to submission to the target journal (see Appendix D for endorsement letter).

This study presents, for the first time, data on the use of oxygen therapy in non-intubated patients in the ICU. Using an established point prevalence programme utilising experienced research coordinators at participating sites through the ANZICS-CTG network has allowed the prospective collection of multi-centre, bi-national data. By using standardised, established data collection tools and methods and robust outcomes, data has been captured on all eligible patients resident in the ICU on the study day.

These results represent a snapshot of oxygen therapy administered to non-intubated patients in the ICU. This study has several limitations including the lack of longitudinal data which is not possible to collect using this single-day study design. Due to the study design, data was collected over a 24 hour period only and therefore may not be truly representative of the range of therapies delivered to patients while in the ICU. Also, depending on the clinical condition of the patients on the day the data was collected, the group enrolled and reflected in the data may not be representative of the ICU population on another day. Because of the data collected and the short timeframe observed, there is no true ability to establish causality. However this study was devised as an exploratory observational study designed to collect data quickly and easily from a large cohort in order to inform the design of further observational or interventional studies involving the routine use of oxygen therapy devices in non-intubated ICU patients.

See Appendix D for study related materials and approvals.
Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

**Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit: A Point Prevalence Study**

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See Appendix 1 for list of Site Investigators.

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This study has received funding from the A+ Charitable Trust (Auckland). Rachael Parke currently has funding as follows: a PhD scholarship and project grant from the Green Lane Research and Education Fund and a Clinical Research Training Fellowship from the Health Research Council of New Zealand. Research in CVICU is supported in part by an unrestricted grant from Fisher and Paykel Healthcare, NZ, Ltd. These sponsors had no input into the study design and no access to trial data. All analyses, reporting and decisions to publish have been made independent of the sponsors.

**Keywords:** observational; intensive care; oxygen therapy
Abstract

Background

Oxygen is commonly administered to intensive care unit (ICU) patients. Although there is knowledge of how oxygen is administered to mechanically ventilated patients, there is little data about its use in non-intubated patients in ICU.

Objective

This study aimed to describe how oxygen therapy is prescribed, administered and monitored for non-intubated patients in New Zealand and Australian ICUs.

Design

Prospective, observational, bi-national, multicentre, single-day point-prevalence study.

Participants and Setting:

All adult patients in 40 New Zealand and Australian ICUs at 10:00am on the study day.

Main Outcome Measures:

Patient demographic data, day-28 mortality and details of oxygen therapy (oxygen therapy prescription, oxygen delivery device use and oxygen saturation targets) were collected.

Results:

Five hundred and six patients were audited of which 178 (35.2%) were not intubated but receiving oxygen therapy at that time. 59.5 % were male; mean age 57.2 years (SD±18), mean APACHE II score 15.7 (SD±8.2) and 47.2% were admitted following surgery. Most patients (66%) received oxygen via simple nasal cannulae, while fewer patients also received oxygen by other methods such as open facemask, nasal high flow and non-invasive ventilation. Only 24.4% of patients had a documented prescription for oxygen therapy, of which only 7% would be considered complete and comprehensive.

Conclusions:

Oxygen therapy is commonly administered to non-intubated adult patients in New Zealand and Australian ICUs. Most patients received oxygen by simple nasal cannulae and oxygen
therapy prescriptions were often absent or incomplete. Continuing education interventions to ensure that oxygen therapy is prescribed, administered and documented correctly are advised.

**Introduction**

Oxygen is one of the most widely available and prescribed therapeutic drugs in medicine.\(^1\) Intensive care unit (ICU) patients are usually given supplemental oxygen to avoid or treat hypoxaemia or as routine post-operative care. Optimisation of oxygen delivery remains the cornerstone of treatment for common ICU syndromes such as sepsis, multi-organ dysfunction, acute respiratory distress syndrome and acute lung injury.\(^2\) When administered correctly oxygen may be lifesaving, but given without careful management can lead to adverse effects and poor patient outcomes.\(^1\) Furthermore, while the risks associated with hypoxaemia are well recognised, there is growing evidence that prolonged hyperoxia should also be avoided, as high fractions of inspired oxygen may cause damage to the lungs and have other detrimental systemic effects.\(^3\)\(^-\)\(^5\) Further findings from previous intensive care based studies have shown that oxygen is poorly prescribed, monitored and administered in the critical care setting.\(^6\)\(^-\)\(^8\) To optimise the safe and effective administration of oxygen, a prescription detailing the oxygen flow rate, oxygen concentration, oxygen delivery method and a method of assessing treatment should be available.\(^1\)\(^,\)\(^7\)

At the present time there is little published evidence to guide ICU clinician’s selection and use of oxygen delivery devices or the prescription of oxygen therapy for non-intubated patients.\(^9\) In 1999, Mao et al surveyed 52 medical directors of ICUs in 48 institutions via a structured postal questionnaire. All respondents considered oxygen toxicity was a concern yet only 71% reported assessing tissue oxygenation on a routine basis as there was considerable variation in the attitudes, beliefs and self-reported practice of oxygen therapy.\(^10\) Two Australian surveys have been published describing attitudes of both intensive care physicians and intensive care nurses to oxygen therapy.\(^11\)\(^,\)\(^12\) Eastwood et al, in an online survey of intensivists, suggested that variability in oxygen therapy practice is likely to continue until there is evidence from clinical trials to support clinical practice guidelines and concluded that there is a need to further explore factors that influence clinical decisions around oxygen therapy.\(^11\) A large international study providing information on the characteristics and outcomes in 15,757 adult patients in 20 countries receiving mechanical ventilation was performed in 2002 by Esteban et al.\(^13\) Although this prospective cohort study detailed current
practice in intubated patients in the ICU, it does not provide evidence with regards current practice regarding oxygen therapy in non-intubated patients.

There appears however to be minimal literature describing oxygen therapy in non-intubated adult intensive care patients. In response, we sought to describe how oxygen therapy was prescribed, administered and monitored to non-intubated ICU patients.

**Methods**

This observational study was embedded within the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) Point Prevalence Program (PPP). Infrastructure support for the ANZICS-CTG PPP was provided by the George Institute for Global Health. The PPP is a prospective, one day, bi-national research initiative of the ANZICS-CTG used by researchers to support avenues of clinical enquiry.

**Ethics**

Ethics committee approval to conduct the audit and for collection of data related to the study was obtained by all sites. The need for informed patient consent was waived by each committee.

**Data collection**

Data for this study was collected on either the 13th November, 21st November or 6th December 2012. A choice of dates allowed flexibility for sites to participate. Trained research staff collected data on all adult (aged 16 years or older) patients present in their ICU at 10:00 am on the study day. General demographic data (age, gender, admission diagnosis), care and therapeutic intervention data for 24-hours and 28-day mortality data was collected. For all non-intubated patients oxygen therapy related data including prescription (oxygen flow rate or inspired oxygen concentration, device, level of monitoring and target oxygen saturation), method of administration (delivery device use and oxygen flow rate or inspired oxygen concentration) and monitoring of therapy (presence of arterial or cutaneous oxygen saturation monitoring) was collected. Details of the highest and lowest partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2) in the previous 24 hours were recorded in patients who had had routine arterial blood gas sampling performed. Inspired oxygen concentration (FiO2) was measured for high flow devices and estimated for low flow devices according to Table 11.
Table 11. Estimated inspired oxygen concentration.

<table>
<thead>
<tr>
<th>Nasal Cannulae</th>
<th>Estimated FiO₂ %</th>
<th>Face Mask</th>
<th>Flow Rate L/min</th>
<th>Estimated FiO₂ %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 L</td>
<td>24%</td>
<td>5 L</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>2 L</td>
<td>28%</td>
<td>6 L</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>3 L</td>
<td>32%</td>
<td>7 L</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>4 L</td>
<td>36%</td>
<td>8 L</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>5 L</td>
<td>40%</td>
<td>9 L</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>6 L</td>
<td>44%</td>
<td>10 L</td>
<td>55%</td>
<td></td>
</tr>
</tbody>
</table>

L/min, Litre per minute; FiO₂, fraction of inspired oxygen

In addition, a ‘unit level’ survey regarding oxygen therapy protocols and devices available for oxygen therapy within the ICU was sent to each site.

Data analysis

Data was entered by the participating sites into a single electronic database managed by The George Institute for Global Health. Data for this study was extracted into Excel (Microsoft, U.S.A) spread sheets, and then entered into STATA (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP) for analysis. Descriptive statistics were used for all clinical and demographic data.

Results

In total 506 patients were enrolled from 40 New Zealand and Australian ICUs of which 178 (35.2%) were not intubated but were receiving oxygen therapy and have been included in the analysis. Mortality of non-intubated patients who received oxygen therapy at day 28 was 6.2%. Baseline patient characteristics of the non-intubated patients receiving oxygen therapy are shown in Table 12. When compared to the intubated patients, all non-intubated patients on the study day were older [61.2yrs (17.5) vs. 57.3 (18.8) p = 0.02] and had a lower APACHE II score [16.2 (7.3) vs. 21.4 (7.2) p < 0.001].
Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

**Table 12. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 178</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>57.3 ± 18.8</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>110 (59.5%)</td>
</tr>
<tr>
<td>Body weight(^1), kg mean (SD)</td>
<td>81.1 ± 24.3</td>
</tr>
<tr>
<td>APACHE II score(^2), mean (SD)</td>
<td>16.2 ± 7.3</td>
</tr>
<tr>
<td>ICU admission source, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Operating theatre</td>
<td>84 (47.2%)</td>
</tr>
<tr>
<td>Emergency Department</td>
<td>42 (23.6%)</td>
</tr>
<tr>
<td>Hospital floor</td>
<td>33 (18.5%)</td>
</tr>
<tr>
<td>Transfer from other hospital</td>
<td>17 (9.6%)</td>
</tr>
<tr>
<td>Transfer from other ICU</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>APACHE III diagnostic categories, no. (%)</td>
<td>n = 175</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>38 (21.7%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>35 (19.7%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>29 (16.3%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>15 (8.4%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>18 (10.1%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>11 (6.2%)</td>
</tr>
<tr>
<td>Renal/Genitourinary</td>
<td>7 (3.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (12.4%)</td>
</tr>
<tr>
<td>Mortality 28 days after study day, no (%)</td>
<td>11 (6.2%)</td>
</tr>
</tbody>
</table>

\(^1\) Body weight is estimated or measured.

\(^2\) APACHE = Acute Physiological and Chronic Health Evaluation.
Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

Indication for oxygen therapy

The primary indications for oxygen therapy were hypoxaemia on peripheral oxygen saturations [30.5% (n=54/177; n=1 missing)], routine therapy (not protocolised) [29.9% (53/177; n=1 missing)] and hypoxaemia on arterial blood gas analysis [23.7% (42/177; n=1 missing)]. A further 11.9% (n=21/177; n=1 missing) were receiving oxygen as part of protocolised care.

Oxygen delivery device use

Of the 506 eligible participants, 208 patients (41.1%) were not mechanically ventilated. Of these non-ventilated patients 178 (85.6%) were receiving oxygen therapy at the time of the survey. Of these, 94 patients (52.8%) had been mechanically ventilated previously during this ICU admission. Of the 178 patients receiving supplemental oxygen: 117 (65.7%) received it via simple nasal prongs, 10 (5.6%) via face mask, 5 (2.8%) via restricted flow mask, 5 (2.8%) via high flow mask, 33 (18.5%) via nasal high flow, 4 (2.2%) via non-invasive ventilation, and 4 (2.2%) via other devices (Figure 17).

Figure 17. Oxygen delivery device used at time of survey

There were no differences in baseline demographics or indications for current oxygen therapy device used between the group receiving oxygen therapy via simple nasal prongs when compared to all others receiving oxygen therapy. There was a significant difference however
in the FiO₂ when comparing those using simple nasal prongs to all others [mean (SD) 30.5% (7.9) vs. 43.3% (14.9)]. There was also a significant difference in mean ages of those comparison groups (59.8yrs [SD, 19years] versus 53.7yrs [SD, 17.6]).

The primary reason the device in use had been employed is shown in Figure 18.

Figure 18. Reason cited for the chosen oxygen therapy delivery device

Details of oxygen therapy prescription

Patients who were receiving supplemental oxygen had a mean estimated FiO₂ of 34.2% (SD±11.9) range 24 – 100%. Only 45 patients (25.4%) were receiving oxygen therapy which was humidified – all by means of an active humidification device, such as a water bath or heated humidifier. The majority of these patients (73.3%) were receiving nasal high flow oxygen therapy all of whom received humidification. Of the patients not receiving humidified oxygen therapy, two were receiving non-invasive ventilation. The remaining patients were using a restrictive flow mask e.g. Venturi mask, simple facemask or simple nasal cannulae.

Assessment of oxygen therapy prescriptions found that only 43 patients (24.4%, n = 2 missing data) had a current written therapy order with only three (7%) covering all suggested parameters for a complete oxygen therapy prescription. Table 13 shows how oxygen therapy prescriptions had been detailed.
Table 13. Oxygen therapy prescriptions

| Current prescription for oxygen therapy, n (%) | 43  | 24.4 |
| Patient receiving therapy as prescribed, n (%) | 41  | 95.4 |

Prescription details, n (%):

- Oxygen flow rate: 22 51.1
- Inspired oxygen concentration: 16 37.2
- Delivery device to be used: 31 72.1
- Monitoring required: 12 27.9
- Target oxygen saturation parameters: 28 65.1

**Monitoring of oxygen therapy**

Overall, 73 patients (41.2%) had an oxygen saturation target documented. The mean lower oxygen saturation target was 92.5% (SD±2.8; range 80 - 99) while the mean upper oxygen saturation target was 94.4% (SD±3.5; range 90 – 99).

For patients with arterial lines in situ for at least part of the previous 24hrs highest and lowest arterial blood gas measurements of PaO$_2$ and PaCO$_2$ for 108 patients were available for analysis. The mean highest PaO$_2$ was 129mmHg (SD±94 range 58 - 681); mean lowest PaO$_2$ was 88mmHg (SD±52 range 35 - 383); mean highest PaCO$_2$ was 47mmHg (SD±23 range 31 - 192) and the mean lowest PaCO$_2$ was 40mmHg (SD±16 range 24 - 139). Figure 19 shows the mean and standard deviations for the highest and lowest PaO$_2$ and PaCO$_2$ recorded in the 24 hours prior to 10:00 on the study day.
Figure 19. Comparison of highest and lowest arterial oxygen tension and arterial carbon dioxide tension values

Of the patients receiving oxygen therapy, 106 had an arterial line in situ (59.9%; 1 missing); 161 had continuous respiratory rate monitoring available (91%; 1 missing); and 176 (99.4%) had continuous pulse oximetry monitoring in situ and 173 had continuous ECG monitoring in place (98.3%; 1 missing). All patients had at least one or more of the above monitoring devices in situ.
Day-28 patient outcome

Day-28 mortality data was also assessed. One hundred and seventy seven (99.4%) patients had been discharged from the study ICU by day 28, of these 175 (98.9%) were discharged alive; 2 patients (1.1%) remained in the ICU. Eleven (6.2%) had died by day 28 either in the ICU or between ICU discharge and day 28. Day-28 mortality is shown in Figure 20.

Figure 20. Patient status at Day 28 of oxygen therapy study

Unit level data.

Twenty six ICUs (65%) submitted data identifying availability of oxygen therapy protocols and devices available for use within their unit. Only 50% of units (n=13) had a protocol to guide oxygen therapy in the unit. All 26 ICUs used nasal high flow oxygen therapy (NHF) with 61.5% (n=16) having a protocol to guide use of this therapy. The mean starting flow rate for NHF recommended by these protocols was 38 L/min (SD±5; range 30 – 50 L/min) and a mean highest flow rate of 57L/min (SD±12; range 35 – 70 L/min). Units were asked if non-invasive ventilation (NIV) was actively humidified. We found this was humidified 100% of the time in 16 units (61.5%), 9 units (34.6%) humidified 50 – 99% of the time and 1 unit
Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

never humidified NIV. Some hospital wards (including the respiratory, cardiothoracic, neurology, oncology and ear-nose-throat wards and Coronary Care Unit) were identified as being able to receive patients receiving humidified oxygen therapy, NHF or non-invasive oxygen therapy.

Discussion

Statement of key findings

We conducted a point prevalence study to describe how oxygen therapy is prescribed, administered and monitored for non-intubated adult patients admitted to New Zealand and Australia ICUs. There were three key findings. Firstly, we found that on the study day 85.6% of non-intubated adult patients in the ICUs were receiving oxygen therapy and this resulted in supra-physiological arterial oxygenation on occasion. Secondly, the majority of patients (66%) received oxygen via simple nasal cannulae, while fewer patients received oxygen by facemasks, nasal high flow and non-invasive ventilation methods. Finally, oxygen therapy was poorly prescribed and failed to meet recommended standards.

Comparison with previous studies

The patient cohort described in this study is similar to that described in other ICU studies both internationally and across Australasia.\textsuperscript{13-16} To the best of our knowledge, no other study has described how oxygen therapy is administered to non-intubated patients in the ICU. This is the first study to do so therefore comparisons with regards the range of delivery devices employed and the reasons for oxygen therapy cannot be made. Oxygen therapy has been described in patients residing in hospital wards and emergency departments but poorly described in the ICU.\textsuperscript{17-20}

This study confirmed that supplemental oxygen administration is almost universal in non-intubated patients within intensive care. Despite the availability of monitoring of oxygenation parameters, including pulse oximetry and arterial blood gas analysis, there is little apparent attempt to titrate oxygen to physiological levels.

In our study only 24.4% of patients had a prescription for oxygen therapy meaning that 75.6% were receiving oxygen therapy that was not prescribed. Failure to have a documented oxygen therapy prescription may result in inappropriate administration of oxygen and may
contribute to prolongation of therapy that is no longer required. Differing results have been found in other studies - for example, in one only 8% of patients receiving oxygen therapy in a medical ward had an oxygen prescription,\(^7\) while in another study 93.4% had a current prescription.\(^{17}\) The criteria we used to determine if a prescription covered all necessary components is consistent with other studies which have assessed similar points for inclusion.\(^{18}\)

Our findings support previously identified concerns over the safety of oxygen administration in New Zealand and Australian ICUs.\(^7,9,18\) Although receiving high level monitoring, patients still require a current prescription for oxygen therapy in order to ensure high quality care. Further training in oxygen therapy prescription is required and more frequent surveys of practice undertaken with feedback of results to individual sites that could use these results as the basis for future quality assurance projects. A possible reason oxygen therapy may be poorly prescribed is that many of the ‘large format’ bedside charts used in most ICUs. Large format charts may not have a specific area for oxygen therapy or the space that exists may be small or located on the reverse side of the chart. Additionally, oxygen therapy related variables are often termed “ventilation orders” and may be better termed “oxygen therapy” to encompass both intubated and non-intubated patients. Also, many institutions are now moving towards prescribing oxygen therapy on combination drug charts. Two studies have shown that the institution of specific documentation for prescribing oxygen results in improved prescription.\(^{18,21}\) It was pleasing to see though that our findings, like that of a previous audit, found that all patients had some form of oxygen monitoring in place and that essentially all had continuous pulse oximetry in situ.\(^{18}\) However it was unclear how often these devices were being used to wean patients off oxygen.

**Strengths and Limitations**

Our study has several strengths, including a prospective design, standardised data collection methods, robust outcomes and the capture of data from multiple sites from two countries. Furthermore, to the best of our knowledge this is the first study of the use of oxygen in an undifferentiated, non-intubated adult patient population in the ICU.

The actual FiO\(_2\) delivered using low flow systems (and any systems in which the patients peak inspiratory flow exceeds the flow provided by the device) is difficult to estimate accurately and varies according to patient characteristics (including respiratory rate, peak inspiratory flow and mouth open vs. mouth closed breathing).\(^{22,23}\) Despite this, we have used
a widely used conversion chart to convert device and flow data into FiO$_2$. In clinical practice the actual FiO$_2$ delivered in the range possible for low flow devices (0.24-0.55) is less important than the ability to titrate oxygen to a measured end-point, however in this study there is little evidence that down-titration in particular is widely practiced.

Our findings however should be interpreted with caution as they represent a snapshot of oxygen therapy administered to non-intubated patients in the ICU and cannot be compared to other longitudinal data. Also, depending on the clinical condition of the patients on the study day, the study cohort may not be representative of the broader ICU population on another day. However, because oxygen therapy is essentially applied to all intensive care patients, there is a degree of generalisability of our study findings to reflect oxygen therapy practice in other New Zealand and Australian ICUs.

**Conclusion**

In our point prevalence study of oxygen therapy for non-intubated adult patients admitted to New Zealand and Australian ICUs, we found a large proportion of patients were receiving oxygen therapy yet this was rarely titrated to monitored endpoints. The most commonly used oxygen delivery device was the simple nasal cannulae. Furthermore, the oxygen therapy was poorly prescribed and prescriptions did not meet standard recommendations. These findings are important for understanding current oxygen therapy practice in ICU and will inform future interventional clinical trials of oxygen therapy. Continuing education interventions to ensure that oxygen therapy is prescribed, administered and documented correctly are advised.

**References**


Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study


Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study


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Lyell McEwin Hospital, Adelaide, SA, Australia: R Ramadoss, J Wood

Mater Health Services, Brisbane, QLD, Australia: A Schibler, C Stocker, S Mayfield

Middlemore Hospital, Auckland, New Zealand: A Williams, A Tilsley, R Song, L Rust

Nepean Hospital, Sydney, NSW, Australia: I Seppelt, L Weisbrodt

North Shore Hospital, Auckland, New Zealand: J Liang, J Bell

North Shore Private Hospital, Sydney, NSW, Australia: A Delaney, S Ash, D Hogben
Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

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Royal Children's Hospital, Melbourne, VIC, Australia: W Butt, C Delzoppo
Royal Hobart Hospital, Hobart, TAS, Australia: A Turner, D Cooper, R McAllister
Royal Melbourne Hospital, Melbourne, VIC, Australia: C Macisaac, D Barge
Royal North Shore Hospital, Sydney, NSW, Australia: S Bird, A O'Conner
Royal Perth Hospital, Perth, WA, Australia: S Webb, J Chamberlain
Royal Prince Alfred Hospital, Sydney, NSW, Australia: D Gattas, H Buhr, M Keir
Sir Charles Gardiner Hospital Perth, WA, Australia: S Baker, B Roberts
St George Hospital, Sydney, NSW, Australia: J Myburgh, J Miller, R Sidoli, D Inskip
St Vincents Hospital, Melbourne, VIC, Australia: J Santamaria, R Smith, J Holmes
Starship Childrens’ Hospital, Auckland, New Zealand: J Beca, E Segedin, C Sherring, M Rea, T Bushell
Sydney Children's Hospital, Sydney, NSW, Australia: M Morritt, G Williams, J Young
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The Alfred Hospital, Melbourne, VIC, Australia: A Davies, S Vallance, J Board
The Canberra Hospital, Canberra, ACT, Australia: Imogen Mitchell, H Rodgers, E Taylor, E Fulton
The Northern Hospital, Melbourne, VIC, Australia: G Duke, J Green, A Casamento, M Park, O Burgess
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Chapter 10. Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

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Chapter 11. Discussion

11.1. Introduction

This thesis represents a systematic programme of advanced research undertaken to produce an original contribution to the body of evidence surrounding nasal high flow oxygen therapy.

The main aims addressed by this research were:

- To investigate the pressure effect created by nasal high flow
- To evaluate the routine use of nasal high flow oxygen in a patient population following cardiac surgery
- To describe current practice with regards oxygen therapy in non-intubated patients in ICUs in New Zealand and Australia

These aims were met by undertaking an evaluation of two methods for assessing atelectasis on chest x-rays; an observational study to measure airway pressure in patients using NHF; an RCT of routine NHF as compared to usual care in patients following cardiac surgery and finally an observational study of oxygen therapy in non-intubated adult patients in ICUs across New Zealand and Australia. This chapter will consider the new information generated by the completion of the investigations and examine the body of work as follows:

- Consistency of new findings with current evidence
- Strengths and limitations of the work
- Key implications and recommendations for clinical practice
- Implications of this work for future research.

11.2. Findings

11.2.1 Mechanisms of Action - Pressure Effect of NHF

Chapter 6 presents a study undertaken to measure the pressure generated in the nasopharynx when NHF is used by participants and to further describe the airway pressure recorded across the various phases of the respiratory cycle. The key finding of this study was that the airway pressure generated by NHF during expiration was higher than the mean airway pressure
recorded over the whole of the respiratory cycle. Although NHF was unable to provide pressures like those generated by CPAP, this study showed that both the mean and peak expiratory pressures during NHF were in a range that is likely to have a clinical effect.\textsuperscript{250}

Previous studies have shown that NHF provides a low level, flow dependent positive airway pressure which is believed to be one of the main mechanisms of action of this therapy.\textsuperscript{7,8,107} However these studies have used varying methods to calculate and report the pressure generated. One study reported inspiratory and expiratory pharyngeal pressures\textsuperscript{107} while the other studies reported mean nasopharyngeal airway pressure calculated over one minute of breathing.\textsuperscript{7,8} Uncertainty has remained with regards the most significant pressure to report, at which point in the respiratory cycle the highest degree of pressure is generated and around whether or not this pressure varies throughout respiration thus creating the physiological benefits that are seen in clinical practice.

Two other studies support the findings of the current work and both reported positive airway pressures generated by NHF.\textsuperscript{12,180} One study reported a similar end expiratory pressure to that found in the current research (see Table 4) although that study was undertaken in 8 healthy volunteers rather than in a patient population.\textsuperscript{180} The second study used a similar method to record airway pressure, but there was no attempt to report pressure in any particular phase of the respiratory cycle; the authors only reporting mean airway pressure.\textsuperscript{12} Although that study was undertaken in patients following cardiac surgery, the patients enrolled had mild respiratory failure unlike the patients enrolled in the study in chapter 7. There may have been unexplained differences in respiratory pattern such as increased peak inspiratory flow rate, which are not reported or accounted for due to the group enrolled and which may have influenced study results.

Therefore the current study is the only one to have reported pressures throughout the respiratory cycle in a broadly representative clinical population and showed that the pressures vary throughout the cycle. Measuring an average of one breath or at different time points in the cycle is unlikely to determine the full effects of NHF. These pressures have not been reported before and they add to the understanding of the mechanisms of action of NHF and how this therapy may improve respiratory outcomes.
11.2.2 Diagnosis of Atelectasis

Chapter 7 describes a study undertaken to evaluate two scoring systems to be used in the assessment of atelectasis on chest radiographs in the HOT-AS study. This study was undertaken as it was felt that previously published scoring systems did not accurately reflect the degree of atelectasis seen in patients following cardiac surgery. This study was the first to compare these two methods of assessing atelectasis on chest x-ray. The study found the proposed modified atelectasis score (m-RAS) to be more sensitive than a previously published radiological atelectasis scoring system (RAS) and thus was used in the HOT-AS trial.

Comparisons between this and similar work cannot be made as there have been no other studies published assessing the validity of the RAS system employed in the HOT-AS study. There has been one study published which used the original RAS system to report atelectasis in patients following upper abdominal surgery, \(^{251}\) but the authors of that study did not provide commentary on the utility or acceptability of the RAS as a tool for measuring atelectasis. Therefore the current work was the first to explore the ability of the RAS to adequately determine atelectasis and to provide an alternative scoring system that appears better suited to a cardiac patient population.

11.2.3 Routine Use of Nasal High Flow Oxygen Therapy Following Cardiac Surgery

Chapter 8 presents the protocol for a phase II open label randomised controlled trial undertaken to determine if NHF improved oxygenation following cardiac surgery when compared to usual care while Chapter 9 presents the main paper from that study. There was found to be no significant difference in oxygenation ratio on day 3 after surgery but NHF may have resulted in a reduction in requirement for an escalation of therapy and a reduction in PaCO\(_2\).

NHF has previously been shown to be effective in improving oxygenation in patients experiencing respiratory failure.\(^{10-12,174,175,178,186}\) When the HOT-AS RCT was designed there was a lack of evidence regarding the clinical utility of NHF in patient populations. There was no evidence regarding the use of prophylactic NHF, no studies that had enrolled participants prior to the development of hypoxaemia or respiratory failure, no evidence in patients following cardiac surgery and no studies reporting patient centred outcomes. Hence the HOT-AS study was designed to address these gaps in the literature. Since the HOT-AS study
commenced, studies have been published describing the use of NHF in adult populations (see Chapter 4). Nevertheless gaps remain in the literature. There are still no other prospective RCTs of patients enrolled prior to ICU admission or prior to the development of respiratory failure nor data to describe the use of NHF as a routine therapy at extubation.

The HOT-AS RCT is the largest study of NHF undertaken so far and the only one to prospectively enrol patients prior to surgery or entry to the ICU. It is the only trial that has been undertaken that compared NHF to routine care following elective cardiac surgery. Two studies have enrolled cardiac surgical patients,\textsuperscript{12,185} though both were small studies that enrolled patients who had developed postoperative respiratory dysfunction.

In the HOT-AS study the routine use of NHF was not associated with an improvement in oxygenation or a reduction in respiratory rate. This finding is in contradiction to other previous studies which have reported improvements in dyspnoea and oxygenation variables.\textsuperscript{10-12,174,175,178,186} This absence of effect may be due to the relatively “healthy” patient population enrolled and the reduced incidence of primary outcome found in this study compared to the predicted incidence. There were fewer patients found to have an SpO\textsubscript{2}/FiO\textsubscript{2} ratio over 445 in the HOT-AS study than in the x-ray evaluation study. When calculating the sample size for the RCT described in Chapters 8 and 9, it was assumed that 40\% of patients would have an SpO\textsubscript{2}/FiO\textsubscript{2} ratio below 445 on day 3 after surgery as had been found in the chest x-ray study (Chapter 7), whereas in the HOT-AS study 55\% of patients were found to have an SpO\textsubscript{2}/FiO\textsubscript{2} ratio below 445. The data used to calculate the sample size was the best information available to the investigators at the time, but it should be recognised that this is only ever an estimate and may have been influenced by the method of accumulating the sample in the x-ray study.

It was surprising not to find enhanced comfort and compliance with NHF therapy. In comparison to other studies that have reported improved patient comfort and satisfaction with the therapy,\textsuperscript{2,10,175,177,181,185} participants in the HOT-AS study consistently scored NHF as being significantly less comfortable than routine care at all time points it was measured. Four other RCTs have reported comfort levels. One RCT of patients using NHF following extubation found higher levels of comfort with NHF when compared to a Venturi mask,\textsuperscript{175} the other RCTs involving patients with acute hypoxaemic respiratory distress have also reported improved comfort levels with NHF when compared to facemask oxygen therapy.\textsuperscript{2,177,185} These studies differ when compared to the HOT-AS study as they were all
small studies and enrolled a different, “sicker” patient population. The lower levels of comfort found in the HOT-AS trial may be because the participants were relatively “well” and therefore felt able to express their discomfort and intolerance of the therapy. It may also have occurred as these were participants in a study and therefore asked for a subjective assessment of comfort rather than patients requiring the therapy as part of their care. Patients who are hypoxaemic and require the therapy, either in usual clinical practice or in published observational studies, may be more tolerant of NHF.

The HOT-AS study found a significantly reduced PaCO$_2$ in patients randomised to NHF. Few other studies have reported PaCO$_2$ measures. In a study of 40 patients following cardiac surgery, Nicolet and colleagues found no difference in PaCO$_2$ when comparing NHF to facemask oxygen therapy. However, findings of an improvement in PaCO$_2$ measures have also been reported in a study of NHF in patients with acute heart failure. That study reports a series of only 5 patients and was not a randomised controlled trial. Whether or not the reduction in PaCO$_2$ found in the HOT-AS study is clinically relevant is open to debate as such a small reduction in PaO$_2$ may be unlikely to deliver any overt clinical benefit though this finding does provide further evidence to support the view that NHF generates a washout effect in the nasal cavity assisting in the clearance of CO$_2$.

The HOT-AS study also found a reduction in requirement for escalation of therapy in the group allocated to receive NHF a finding previously reported, though important differences between that study and the current study should be noted. Although undertaken in a similar environment, patients enrolled in each study were quite different. The previous study enrolled patients with mild to moderate respiratory distress while the HOT-AS study has enrolled relatively “well” patients. It is possible that the reduced usage of more advanced respiratory support is most likely due to the added pressure effect that is delivered by NHF when compared to standard face mask or nasal cannulae. It must be kept in mind though that comfort, PaCO$_2$ and requirement for escalation of therapy were all secondary outcomes in the HOT-AS study and thus findings should be interpreted with caution to prevent Type I error.

11.2.4 Management of Oxygen Therapy in Non-intubated Patients in ICUs in New Zealand and Australia

Chapter 10 describes a study undertaken to report the current practice in prescribing, administering and monitoring oxygen therapy administered to non-intubated adult patients in
the ICU. A prospective, observational, bi-national, multicentre, single-day point-prevalence study was undertaken in 40 ICUs. This study found that oxygen therapy was commonly administered to non-intubated adult patients predominantly by way of simple nasal cannulae. It was also found that oxygen therapy was poorly prescribed.

Comparisons with previous work cannot be made as this study appears to be the first which reports on oxygen therapy in non-intubated patients in the intensive care. However some facets of oxygen therapy in other populations have been investigated previously. A one day, multi-centre study was undertaken in 24 hospitals in Portugal,\textsuperscript{252} which reported the prescription, administration and monitoring of oxygen therapy to 773 patients in internal medicine wards. It was found in that study that 11.6\% of prescriptions fulfilled all required parameters for accuracy, and the authors suggested that incomplete or inaccurate oxygen prescriptions could compromise safety and efficacy of therapy. This compares to only 7\% of prescriptions in the study presented in Chapter 10.

While previous work provides some information with regards oxygen therapy, there are no reports of ICU patients and no reports of usage of respiratory support therapies such as NHF and NIV. Therefore this point prevalence study has generated previously unavailable data to inform both current practice and future study design for interventional studies involving self-ventilating patients in the ICU. In this study, 20\% of patients were utilising NHF demonstrating that it is frequently used although we still do not know exactly the rationale behind the choice of this device and in which patient groups it is used.

11.3. Strengths and Limitations of this Work

Strengths and limitations of the individual studies that comprise this body of work have been presented in previous chapters reporting each study. The studies reported herein describe robust and verifiable outcomes (such as airway pressure, atelectasis score, $\text{SpO}_2/\text{FiO}_2$, respiratory rate), self-reported data from patients about the comfort of NHF, the use of established methods (for airway pressure measuring, spirometry, atelectasis assessment, blood gas analysis) and important patient outcomes such as requirement for escalation of respiratory support therapies, ICU and hospital length of stay and mortality. These studies form a programme of research that built on previously published work and used sound methodology and methods.\textsuperscript{7,8} The major strength of this body of work is that it represents a


pragmatic programme of research undertaken in the real world of clinical practice designed to address evidence gaps the findings of which are broadly generalisable.

Pragmatic studies measure, test and report what happens in normal clinical practice. Frequently, studies are undertaken in very controlled, experimental settings and are so different to real world practice that they cannot answer the questions they set out to address and from which the results cannot be generalised. For instance, the control arm mandates a practice other than “usual” care for the participants or the intervention arm is so strictly controlled that no departure from the study protocol is allowed unless the patient is removed from the study entirely. Neither of these scenarios mirrors real world clinical practice where interventions may be altered depending on the response to the therapy. The challenge with the HOT-AS study was to retain the features and advantages of an RCT whilst allowing a pragmatic approach to study design and study procedures and permitting clinician preference and decision making. By adopting a pragmatic study design and having few enrolment criteria, we enrolled a broadly representative cohort reflective of the diverse cultural and socioeconomic range of patients presenting for cardiac surgery in New Zealand. This design aids in the generalisability of study results to other ICUs that admit patients following cardiac surgery.

The outcome measure chosen for the RCT also reflects a real world concern for clinicians at the institution where this study was undertaken. Choosing endpoints for phase II studies can be problematic. Outcomes need to be objective, well defined and of relevance to the treatment under investigation, however the primary outcome may not be one that is widely accepted. When designing the HOT-AS study selecting the primary outcome measure was difficult. Initially discussion centred around focusing the primary outcome on reduction of respiratory complications such as atelectasis, hence the study described in Chapter 7. Advice was that the overall incidence of respiratory complications may have been low and thus would require a large sample size beyond the resources available for this project. Therefore an intermediate outcome measure was chosen as being acceptable for a Phase II trial to determine whether or not it was then worthwhile engaging in a larger study which would be required for important patient centred outcomes that may have a low incidence. Day 2 was chosen as the discontinuation point for oxygen therapy as this reflected current practice at the study site. At that time, routine cardiac surgical patients have their central line removed and oxygen therapy discontinued as long as condition allows. Day 3 was chosen for primary outcome measurement based on data obtained from the previous observational study (Chapter
7) which demonstrated that a significant proportion of patients still required either oxygen therapy or had an SpO\textsubscript{2} < 94\% on day 3 thereby having an SpO\textsubscript{2}/FiO\textsubscript{2} ratio < 445. As this study was a phase II trial the use of a surrogate outcome was acceptable. The choice of SpO\textsubscript{2}/FiO\textsubscript{2} ratio ≥ 445 measured on day 3 was considered clinically relevant as an on-going requirement for oxygen therapy in this patient population would limit mobility and rehabilitation plans and therefore any improvement in oxygenation may lead to improved patient outcomes and reduced length of stay.

Two important limitations must be acknowledged and considered when interpreting these study findings. First, apart from the point prevalence study (Chapter 10), all other work in this thesis has been undertaken in an adult patient population undergoing cardiac surgery at one site only. It would have been more desirable to have undertaken a multi-centre study to enhance external validity but this was not feasible given available resources. In view of the limited inclusion criteria used, the pragmatic study design and the broad cohort enrolled it is expected that the results would be generalisable to most adult patients undergoing cardiac surgery. Second, apart from the chest x-ray evaluation study (Chapter 7), none of the studies undertaken were blinded. Blinding of studies involving oxygen therapy devices is problematic and difficult to overcome. A recent systematic review suggested however that it is hard to quantify the impact of observer bias or to what degree potential confounders in a trial create bias.\textsuperscript{254} This review found that effects of interventions in RCTs were overestimated more when a non-blinded assessment was included than when compared with a blinded assessment, possibly an important consideration in regards to the HOT-AS study. If a lack of blinding leads to the over-estimation of treatment effect then in reality the effect may be even less than observed here when used in routine practice.

**11.4. Implications of this Work for Clinical Practice**

Pragmatic clinical research such as that employed in this thesis, provides an important link between new therapies introduced into healthcare and the actual practice of healthcare delivery in the clinical setting. This body of work has provided an alternate method for measuring atelectasis on chest x-ray in patients following cardiac surgery, shown that NHF not only delivers positive airway pressure throughout the respiratory cycle but also increases end expiratory pressure, shown that NHF does not significantly improve oxygenation when used routinely in stable patients following cardiac surgery and provided an overview of delivery of oxygen therapy to non-intubated patients in ICUs.
Chapter 11. Discussion

This work provides valuable new evidence with regards the use of NHF therapy and adds to the evidence surrounding oxygen therapy in general. Based on the evidence provided by the point prevalence oxygen therapy study, there is important work to be done with regards development of protocols and practices regarding oxygen therapy in order to improve documentation and delivery of therapy. Guidelines should be developed to guide clinicians in the objective selection of oxygen therapy devices for patients in the ICU and protocols made available to guide them in identifying patients with worsening oxygenation and help assist them in determining appropriate therapy. Of equal importance is the requirement for further education and auditing around prescription of therapy in order to safeguard administration of oxygen therapies for patients in the ICU.

11.5. Implications of this Work for Future Research

Following on from this work, further areas for research include:

- Use of alternate measuring techniques to describe the pressure effect such as oesophageal balloon pressure measurement. Studies that quantify pressure generated by NHF so far have all used a similar method involving a narrow bore tube inserted into the hypopharynx or nasopharynx. Pharyngeal pressure is relatively easily measured in participants when awake however it is a surrogate measure of presumed pressure generated further down the airways. Oesophageal pressure measurements allow assessment of changes in intrathoracic pressure and together with volume and flow recordings would allow an estimate of respiratory system resistance and compliance and could reflect the actual work of breathing. The pressure effect created by NHF is purported to reduce work of breathing and improve respiratory function.

- Further work to elucidate the exact contribution of each of the proposed mechanisms of action to the overall effects seen by NHF is still required. Is it the flow dependent positive airway pressure, the humidification, the delivery of accurate FiO₂, the washout of nasopharyngeal dead space or a combination of all that enhances patient oxygenation and outcomes in some groups? This may be of particular interest in healthcare systems where a concern exists over the cost of delivering NHF therapy and provide definitive results in specific patient populations thus aiding requests for approval by key stakeholders and funders for purchase of devices and consumables.
Chapter 11. Discussion

- Though the HOT-AS RCT provides evidence that in cardiac surgical patients the routine use of NHF following extubation does not lead to an improvement in oxygenation on day 3 post-operative, future research should concentrate on assessing the utility of NHF in other patient populations which may benefit from delivery of optimal oxygen therapy such as in patients following upper abdominal surgery or those scheduled for surgery who are current smokers. Further research should include patient centred outcomes i.e. how the patient feels, functions and survives. This is of particular importance when assessing NHF in patients with chronic conditions such as COPD or those who are accustomed to using long term respiratory support devices such as patients with OSA who use home CPAP machines overnight.

- For future studies of NHF utilising a lower flow rate may prove more tolerable and acceptable. For example delivering 35 L/min may make it more comfortable for participants and they may comply with therapy for longer. By using a lower flow which may be quieter and less “blowy” participants may tolerate intervention for the entire study period.

Other potential areas for research identified during the development of this work include:

- Investigation into the effects of diameter of the NHF cannula in relation to size of the nares which has been suggested may affect the expiratory pressure generated

- Investigation of the delivery of higher flows e.g. up to 100 L/min and their effect on airway pressure generated, outcomes and patient comfort. Currently, published evidence describes the pressure effect of flows ranging from 0 – 60L/min only

- Determination of the effects of NHF in specific patient populations and effects of particular mechanisms of action in these patient groups e.g. patients with COPD, OSA, cystic fibrosis, congestive heart failure, head and neck oncology patients undergoing radiotherapy

- Investigation of the differing effects of NHF in hypoxaemic vs. hypercapnic respiratory failure which may be of benefit in elucidating further any potential benefit to either group.

This chapter has presented each of the studies undertaken in this thesis in view of the main findings, updated literature, strengths and limitations of each and implications both from a clinical perspective and in terms of future research in each area.
11.6. Conclusion

This thesis presents a programme of research involving a series of studies linked by the theme of nasal high flow oxygen therapy.

The studies are linked by the theme of investigation into NHF; its mechanisms of action and determination of efficacy and by a desire to add to the current body of evidence and knowledge regarding various facets of this novel and increasingly popular therapy. These intentions have been achieved by the execution and publication of the studies described in the chapters of this thesis. Despite this, the exact mechanisms of action of NHF still remain unclear. Further work remains to be undertaken to elucidate the effects of NHF on work of breathing, changes in lung volume, intrathoracic pressure and oxygenation.

In the HOT-AS trial, the routine use of NHF was not associated with an improvement in oxygenation on day 3 post-operative although it was associated with a reduction in requirement for escalation of therapy and a reduction in PaCO$_2$. Given the higher cost associated with NHF and a reduction in measured patient comfort scores and in the absence of any demonstrable benefit, it would be hard to justify the routine use of NHF post extubation in routine cardiac surgery patients.

The purpose of clinical research is to generate evidence to inform and, where able, change clinical practice and policy. The issue for clinicians is now to determine how the new evidence presented in this thesis is best translated into practice. Level II evidence does exist of improved clinical effect in patients experiencing respiratory failure who are treated with NHF however we now have reliable Level II evidence of a null effect when used routinely following extubation after cardiac surgery. Therefore it is not possible to advocate as a routine practice NHF therapy for all cardiac surgery patients from the time of extubation. This is important information to prevent the unintended acceptance into routine practice of a device that appears to be more effective only in sicker patients. There is always a risk with new or novel therapies that they are accepted into practice on minimal evidence perhaps resulting in unintended harm and increased mortality. As clinicians it is all too easy to be swayed by scant evidence that supports our theory or belief that a treatment may work because we have seen the effect in practice. Much harder by far to go out and generate the evidence to truly and unequivocally support or refute our hypothesis or belief. This thesis and the work contained within presents a comprehensive body of work that makes an original contribution to the knowledge regarding nasal high flow oxygen therapy.
The essence of research... is the ability to reflect, question and critically examine our practices, then seek answers in a rigorous and logical way. Seeking these answers will ultimately improve our core business – quality patient care.

(Elliott, 2000, page 2)
Appendices
Appendix A: Pressures Delivered by Nasal High Flow Therapy During All Phases of the Respiratory Cycle

ADHB Approval

Ethics Approval

Study Protocol

Information and Consent Form for Participants

Data Collection Forms
Appendix A.

Clinical Study Protocol

A COMPARATIVE STUDY OF AIRWAY PRESSURES GENERATED BY TWO METHODS OF NON-INVASIVE RESPIRATORY SUPPORT USED IN CARDIAC SURGICAL PATIENTS.

The Airway Pressure Study
Research Protocol

Agreement:
This study will be conducted in full accordance with all applicable regulations and Good Clinical Research Practice Guidelines.

____________________________________
Representative of Fisher & Paykel Healthcare

____________________________________
Signature of Fisher & Paykel Healthcare                         Date

____________________________________
Principal Investigator

____________________________________
Signature of Principal Investigator                         Date

Glossary of Terms
CPAP: Continuous positive airway pressure
NHFT: Nasal High Flow Therapy
CVICU: Cardiothoracic and Vascular Intensive Care Unit
ICU: Intensive Care Unit
PPT: precision pressure transducer
NIV: non-invasive ventilation
Section 1 – Study Characteristics and Objectives

1.1 Study Objectives
To compare the airway pressure generated in cardiac surgical patients receiving high flow humidified nasal oxygen therapy (Fisher and Paykel Healthcare Optiflow™) to that generated in the same patient when receiving non-invasive ventilation via a face mask.

1.2 Background and literature review
Non-invasive ventilation (NIV) and nasal high flow therapy (NHFT) are both used to improve oxygenation in patients in the Cardiothoracic and Vascular Intensive Care Unit at Auckland City Hospital.

Currently there is little published evidence to inform clinicians as to the real pressure generated in the airway, compared with the pressure programmed into the non-invasive ventilation device. Likewise, there is little published evidence to inform clinicians as to the airway pressure generated at different flow rates when using the Optiflow™ system.

Information on airway pressure generated by both devices would be useful to clinicians when deciding which mode of respiratory support would be most beneficial to a patient.

A recent study in cardiac surgical patients demonstrated that a positive pressure (mean airway pressure of 2.7cmH₂O with mouth closed) is delivered with the NHFT system at 35 L/min of gas flow (1). This study also demonstrated a significant reduction in non-invasive ventilation rates in patients who received NHFT, when compared with patients who received standard oxygen therapy (p=0.03).

Another study, in healthy volunteers, has shown that mean airway pressures of approximately 4.6 cmH₂O are delivered with the Optiflow™ system when gas flows of 40 L/min were used (2).

We have also just completed a study measuring and comparing the flow and pressure generated by the Optiflow™ system in one group of patients to that generated by traditional non-invasive ventilation delivered via a facemask in another group of patients. This study showed that the pressure generated by the Optiflow™ system increased as the flow was increased (3).

We now wish to compare the airway pressure generated in patients receiving NHFT to that generated in the same patient when receiving NIV to determine if a relationship exists.

With the Optiflow™ system, humidified oxygen may be delivered at high flow rates nasally, with the inspired gas heated and humidified to 37° C, 44mg H₂O/L. As described above, we now know that low level positive pressure is also generated by this system.

Traditionally, a tightly sealed mask or an intubated airway has been needed to deliver any positive pressure to the lungs. The Optiflow™ system can offer clinicians and patients a mechanism for delivering such pressure, at low levels, without some of the complications and comfort issues associated with these other methods. Some of the reported risks associated
with face mask non-invasive ventilation include mask discomfort, nasal dryness, oral dryness and eye irritation (4), nasal or eye trauma and gastric distension / aspiration (5).

The data gathered from this study will aide clinicians to judge the level of pressure they are delivering, based on the flow of gas being administered when patients are receiving NIV or NHFT.

1.3 Hypothesis

Optiflow™ generates a positive airway pressure similar to that generated by conventional continuous positive airway pressure (CPAP).

1.4 Primary Outcome

To describe the relationship between flow and/or pressure delivered and mean pressure generated in the airway in group of patients following cardiac surgery using:

1. Optiflow™
2. NIV via face mask

1.6 Study Design

This is a prospective, descriptive study.

1.7 Study Intervention

Patients undergoing cardiac surgery will be invited pre-operatively to participate in this study. A total of 15 patients, who give informed consent, will have pressure measurements carried out with both Optiflow™ and facemask NIV.

Following surgery, whilst the participant is sedated and ventilated in the Intensive Care Unit, a 10F catheter will be inserted into the nasopharynx via the nose. Once the patient has been woken and extubated, the position of the tube will be confirmed using end tidal CO₂ monitoring.

Intervention:

A baseline airway pressure measurement will be performed while the patient breathes spontaneously on their routine oxygen therapy device e.g. standard nasal cannulae or facemask.

Pressure measurements will then be carried out following a random sequence generated with the aid of a Latin square design for both the Optiflow™ system and NIV delivered via a facemask. Participants will have 3 measurements performed on the Optiflow™ interface and 3 measurements performed on NIV via a facemask.

The Optiflow™ system comprises the Fisher and Paykel Healthcare MR880 humidifier delivering gas heated and humidified to 37°C, 44mg H₂O/L. The heated circuit will comprise an RT241 circuit, and MR290 autofeed chamber and the RT034 (small) adult nasal interface.
Appendix A.

For measurements of NIV, the Respironics Vision Ventilatory Support machine will be used. Delivery of humidification for this support will be via a Fisher and Paykel Healthcare MR850 heated humidifier set to “mask mode” to deliver ventilator gases at approximately 31°C, 32 mgH₂O /L. The heated humidification system will comprise an RT319 bi-level heated-wire circuit, an MR290 autofeed chamber and an RT040 mask.

Pressure measurement for each flow rate will be recorded over one minute of breathing using precision pressure transducer (PPT). All measurements will be performed with patients breathing with their mouth closed.

This procedure is expected to take around 30 mins in total.

The catheter will be removed at the end of this period.

Nasopharyngeal pressure and mask pressure will be measured using a Honeywell precision pressure transducer (PPT – 0001 DWWW2VA-B, Honeywell International Ltd) with a laptop computer interface. The pressures will be recorded over one minute of breathing. The mean airway pressure will be determined by averaging the pressure from the peak of inspiration of the first to the last breath within the one minute recording. This will allow the entire pressure profile of each breath to be included within the mean airway pressure calculation.

1.8 Trial Description:

The study will be a single centre trial. The trial will begin after ethical approval has been granted and will continue until 15 patients in total have had a complete set of pressure measurements recorded. This is anticipated to take up to 4 months.

Section 2 – Eligibility Criteria, Recruitment and Enrolment

2.1 Inclusion Criteria:

Patients are eligible for inclusion if all of the following criteria are met:

- The patient is 18 years or older
- Consent has been obtained
- The patient is undergoing cardiac surgery requiring sternotomy

2.2 Exclusion Criteria:

Patients will be excluded from the study if one or more of the following criteria are present:

- The patient has significant nasal septum deviation.
- High flow nasal oxygen therapy is contraindicated.
- Non-invasive ventilation is contraindicated
- Following surgery the patient is unable to follow simple commands once awake and extubated
2.3 Recruitment and Consent:

Informed written consent will be obtained from the patient prior to cardiac surgery. Participation in this study may be withdrawn at any time at the discretion of the patient, or the treating physician. If the participant withdraws or is withdrawn from the trial, a “participant withdrawal code” will be allocated and recorded. Participant data will be collected up to this point and retained for analysis at the discretion of the patient once specific consent for this has been obtained.

2.4 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 Nurses 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 Cardiothoracic and Vascular Intensive Care Unit at Auckland City Hospital, accessible only by the Research Nurses.

Section 3 – Study Design

The 15 patients will be allocated to the six treatments they each undergo in an order determined by two Latin squares, as follows, where rows are patients and columns are periods 1 to 6 giving the order over time:

```
1 6 2 5 3 4
2 1 3 6 4 5
3 2 4 1 5 6
4 3 5 2 6 1
5 4 6 3 1 2
6 5 1 4 2 3
```

The two Latin squares were constructed as Williams squares to give balance (6) so that each treatment occurs once per patient, twice per period and there is also balance for any carryover effect (each treatment follows each other treatment exactly twice).

Randomisation will occur separately for each group, with treatment randomly allocated to numbers 1 – 6, and sequences randomly allocated to patients square by square.

In case the 15 treatment sequences per group are not completed by the first 15 patients, the sequence(s) not completed will be randomly allocated to the 16, 17th … patient.
Appendix A.

**Section 4 - Measurements and Outcomes**

The Research Nurses will collect recordings which are routinely documented on the patient charts for the purposes of reporting as follows:

**4.1 Baseline Assessment:**
- Height and weight
- Demographic data including ethnicity
- Clinical diagnosis, surgical procedure and morbid conditions

**4.2 Pressure Measurement Data**

Airway pressures measured will be recorded onto a laptop computer using uniquely coded PPT software. An engineer/Research scientist from Fisher and Paykel Healthcare skilled in the use of this software may assist the Research Nurses in the use of the programme and may initially be present when measurements are performed. Participants will be informed of this when consent is sought.

**4.3 Participant Withdrawal:**

Should withdrawal occur, the reason for the decision will be recorded. Reasons for withdrawal may include, but are not limited to, subject withdrawal of informed consent or a physicians’ decision to withdraw the patient from the study.

**Section 5 - Trial Monitoring**

**5.1 Consent checks:**

100% consent checks will be done.

**5.2 Monitoring of data collection:**

Data collected from the hospital record will be checked by the Research Nurses. If any queries arise, the source data will be verified. The uniquely coded PPT data will be monitored by an engineer skilled in the use of this software.

**5.3 Monitoring of Events:**

*Adverse Events*

There may be a potential risk of minor bleeding in the nose due to the insertion of the 10F catheter. This risk will be minimised by ensuring that the catheter is inserted by an individual skilled in the technique of inserting such tubes. If this occurred more than twice, we would reassess the procedure.
Appendix A.

The catheter may also cause some minor discomfort. Patients will be offered simple analgesia (pain relief) if required and lignocaine gel or spray is available for local application. In a similar study by the same investigators no adverse events were observed and overall, patients tolerated the catheter well with very little discomfort (1).

A patient experiencing an adverse event may result in their withdrawal from the trial. This decision is at the discretion of the Principal Investigator and will be reported to Fisher & Paykel Healthcare and the ethics committee.

5.4 Halting of trial:

In the situation where a participant has suffered an adverse event, the Principal Investigator may halt the trial so that an investigation may be carried out to identify the cause of the adverse event. The trial will be resumed once the cause is identified and can be addressed and prevented from recurrence by research staff.

Section 6 – Data Management and Security

6.1 Data Forms:

Coded Recording Forms will be used.

6.2 Identification of Data:

All data collected will be linked by a unique Patient Study Number.

6.3 Data Accuracy:

All data will be double checked by Research Nurses. Coded Recording Forms will be used to ensure clean and accurate data. The Research Nurses will compare with patient notes if any discrepancy occurs.

6.4 Data Storage:

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

Section 7 - Analysis

Pressure will be recorded over one minute of breathing. Mean airway pressure will be determined by averaging the peak pressure from each breath over one minute. This allows inclusion of the entire pressure profile of each breath in the mean airway pressure calculation.

Mean pressure will then be analysed in the framework of the general linear model and will include terms for patient, period and treatment. The six treatments will have contrasts comparing mouth open to mouth closed and the linear and quadratic effect of gas flow or pressure flow. The treatment effect will also be presented graphically.
In case of incomplete sequences and thus the use of more than 15 patients, a secondary analysis will use all patient data in a mixed model framework treating patient as a random effect.

Section 8 - Publication of Data

8.1 Results

Results will be presented at an international conference and submitted for publication in a peer reviewed journal. The data may also be used as a basis for future research.

Section 9 – References


Information Sheet for Participants

The Airway Pressure Study

A Comparative Study of Airway Pressures Generated by Two Methods of Respiratory Support used in Cardiac Surgical Patients.

Local investigator: Dr. Shay McGuinness Tel. (09) 307 4949 ext. 24471
Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital

Introduction

You are invited to participate in a research study measuring airway pressures in patients using two forms of oxygen delivery available in the Cardiothoracic and Vascular Intensive Care Unit: high-flow nasal oxygen and non-invasive ventilation (breathing support without a tube into the windpipe).

One of the reasons that high-flow nasal oxygen is thought to be effective is due to an increased pressure in the airways generated by the system, which makes it easier for patients to breathe. This increased pressure has been described in two previous studies undertaken on people in the Cardiothoracic and Vascular Intensive Care Unit.

When doctors use non-invasive ventilation to provide respiratory support for patients, they choose the level of pressure that the machine uses to deliver oxygen to the patient, depending on how much pressure they feel the patient requires.

We would now like to measure the amount of airway pressure created by these two therapies at three different levels of delivery in the one patient. We would like to carry out this study in patients following heart surgery, and we would like to invite you to consider taking part in this study.

The study

A small number of patients (approximately 15) are being asked to have pressure measurements recorded in their upper airway. Pressure measurement will involve the insertion of a fine tube (approximately 3mm in size across) through your nose and into the back of your mouth. This tube will be inserted while you are sedated in the intensive care unit after your operation. The tube sits quite high so that when you look in your mouth you would be unable to see its tip in the back of your throat. When you are awake and not needing the breathing machine (ventilator) anymore, this fine tube in your nose will be connected by fine tubing to a computer to measure the pressure in the back of your throat. Measurements will then be carried out while you are receiving high flow nasal oxygen at three different flow rates and also while you are receiving non-invasive ventilation at three different pressure...
levels. The whole process is expected to take around 30 minutes and the tube in your nose will be gently removed at the end of this period. All other treatment will be unaffected by being in this study. You will receive normal intensive care treatment. No extra blood tests or x-rays are taken. No material which could personally identify you will be used in any reports on this study. Some information such as your height and weight will be collected from your medical notes by the research nurses. All the information is kept by the research nurses in a form that will not allow you to be identified.

Fisher and Paykel Healthcare Ltd. Support, in part, research in the ICU and are providing the masks and tubing required for this study but are not sponsoring the study. One of their engineers may be present during the study measurements on some occasions. If the doctors in the ICU or the researchers consider that you should not participate in the study due to your clinical condition, then the tube will be removed and measurements will not be performed. In a previous study, this occurred 15% of the time.

Benefits of being in the study
Information generated may benefit patients in the future. There may be no benefit to individual patients from being in this study.

Risks of being in the study
There may be some minor discomfort in the nose or throat due to the presence of the measuring tube. You should not be aware of the tube being inserted as you will still be asleep after your surgery. Some minor bleeding (like a small nose bleed) may occur. Discomfort and bleeding will be minimised by gentle insertion and ensuring secure fixation of the tube. You will be offered pain killers and/or a local anaesthetic spray or gel if needed. The side effects of the local anaesthetic (Lignocaine) may include allergy, local irritation, bitter taste or tingling in mouth and very occasionally ringing in the ears, seizures, disturbance to heart rhythm or cardiac arrest. If you think you may be allergic to Lignocaine, you should not participate in this study.

Is the study voluntary?
Your participation is entirely voluntary (your choice). You do not have to take part (or continue to take part) in this study. Whether or not you choose to take part you will continue to receive all usual treatment. You are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your future healthcare.

Compensation.
In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

Statement of Approval
Appendix A.

This study has received ethical approval from the Northern X Regional Ethics Committee. This committee is responsible for making sure that research with participants is appropriate and the participants’ rights and welfare are being protected.

Questions:

If you have any questions or concerns about your rights as a participant in a research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone: (NZ wide) 0800 555 050  
Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)  
Email (NZ wide): advocacy@hdc.org.nz

For Maori health support, or to discuss any concerns or issues regarding this study, please contact Mata Forbes RGON, Maori Health Services Co-ordinator / Advisor, 5th Level, GM Suite, Auckland City Hospital. Tel 307 4949 extn. 23939 or Mobile 021 348 432

Please feel free to contact any of the Cardiothoracic and Vascular Intensive Care doctors or the local investigator (Dr Shay McGuinness; tel. (09) 307 4949 ext24471) if you have any questions about this study.

*Thank you in advance for your help in this study*
Appendix A.

CONSENT FORM (Participant)

The Airway Pressure Study

A Comparative Study of Airway Pressures Generated by Two Methods of Respiratory Support used in Cardiac Surgical Patients.

Name of Participant:……………………………………………………………………

<table>
<thead>
<tr>
<th>Language</th>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/ka‘ihwhaka pakeha koreo</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Samoan</td>
<td>Oute mana‘o e iai se fa’amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>‘Oku fiema‘u ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au I tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoega e tagata fakahokohoko vagahau</td>
<td>E</td>
<td>Nakai</td>
</tr>
</tbody>
</table>

I have read and I understand the information sheet dated 25 February 2009 for volunteers taking part in this study designed to measure airway pressure while receiving high flow nasal oxygen therapy and non-invasive ventilation.

I have had an opportunity to discuss this study. I am satisfied with the answers I have been given.

I understand the contents of the information sheet, including but not limited to, the following points:

- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time. This in no way will affect my continuing health care.
- I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
- I understand that the investigation will be stopped if it should appear to be harmful to me.
- I understand the compensation provisions for this study.
- I have had sufficient time to consider whether to take part and the opportunity to discuss with whanau/family/or a friend.
- I know whom to contact if I have any side effects to the study or if my relatives or I have any questions about the study.
Appendix A.

I agree to the access of my patient notes for the sole purpose of this study  

YES/NO

I wish to receive a copy of the published results of the study when it is finished  

YES/NO

Participant

I,__________________________ (full name) hereby consent to my participation in the airway pressure study.

____________________________________ (signature)

________/________/________ (date)

_______:______ (time, 24 hours)

Witness: I believe this opinion was given freely and with understanding

____________________________________ (full name)

____________________________________ (signature)

________/________/________ (date)

Investigator

____________________________________ (full name)

____________________________________ (signature)

____________________________________ (study role)

________/________/________ (date)

Name of Researcher: Dr. Shay McGuinness Tel. (09) 307 4949 ext. 24471

Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital

Copies: Original in study file, 1 copy in clinical records, 1 copy to patient
### PATIENT INFORMATION

| 3.01 | I__I/I__I/2009 (dd/mm/yyyy) ICU admission date |
| 3.02 | I__I:I__I (24hour clock) ICU admission time |
| 3.03 | I__I/I__I/I__I/I__I/I__I (dd/mm/yyyy) Patient date of birth |
| 3.04 | Female □  Male □ |
| 3.05 | Ethnicity code I__I  Other Please specify I________________I |

### CLINICAL STATUS

**3.14** (Primary diagnosis, significant medical history and morbid conditions)

Height ____________cm    Weight _____________kg

Date and Time of airway measures ________________________________

Signed ____________________________
Appendix B.

Appendix B: A study to validate an atelectasis scoring system in patients following cardiac surgery

ADHB Approval

Ethics Approval

Study Protocol
A study to validate an atelectasis scoring system in patients following cardiac surgery
- Study Protocol

Study Centre
Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital (CVICU).

Organisation

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Rachael Parke RN, MHSc (hons)</th>
<th>Research Coordinator PhD candidate Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-investigator</td>
<td>Dr. David Milne</td>
<td>Consultant Radiologist, Auckland City Hospital</td>
</tr>
<tr>
<td>Co-investigator</td>
<td>Dr. Shay McGuinness</td>
<td>Intensive Care Consultant, Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital</td>
</tr>
<tr>
<td>Academic Supervisors</td>
<td>A/Prof Robyn Dixon A/Prof Andrew Jull</td>
<td>School of Nursing, Faculty of Medical and Health Sciences, The University of Auckland</td>
</tr>
</tbody>
</table>

Background
Postoperative complications following cardiac surgery can increase mortality, morbidity and costs due to prolonged ICU and hospital stay. One major cause of postoperative respiratory complications is atelectasis where regions of collapsed, airless alveoli are present. The development of atelectasis following cardiac surgery is almost inevitable. Atelectasis has been described as present in most patients with an incidence of around 90% of cardiac surgical patients. Atelectasis may also be resistant to simple techniques employed to improve lung function such as patient positioning, physiotherapy and incentive spirometry. Ensuring adequate oxygenation and respiratory support is vital in the postoperative period, however there is little published evidence to guide intensive care clinicians in the objective selection and use of oxygen delivery devices. It is the intention of the principal investigator to conduct a large scale randomised controlled trial to assess the effect of prophylactic nasal high flow oxygen therapy on the degree of atelectasis. In order to assess the primary outcome, we require a reliable, validated atelectasis scoring system. Currently there is little available to the clinician in terms of scoring systems to ensure an accurate and reliable standard of reporting of atelectasis for chest x-rays. One published score exists, the Radiological Atelectasis
Appendix B.

Score 1 however we believe this score to be flawed as it does not account for significant subtotal atelectasis in both lower lobes and would not attribute any extra score if both upper lobes were collapsed as well.

Therefore a new scoring system is proposed which would take into account involvement of all lobes, of 0-3 summed for both lungs.

0=Normal
1=Plate or minor infiltrate
2=Moderate atelectasis
3=Total atelectasis

The sums of each lobe would be added giving a maximum score for the lungs of 3x6 Lobes=18.

**Study Aims**

To determine current degrees of atelectasis in patients recovering from cardiac surgery in the Cardiothoracic and Vascular ICU at Auckland City Hospital.

To validate the proposed atelectasis scoring system in a group of patients following cardiac surgery.

The results would then be used to inform study design of a large randomised controlled trial of oxygen therapy aimed at reducing the degree of atelectasis seen post cardiac surgery.

**Methods**

**Basic study design**

Eligible patients will be identified by the principal investigator through the CVICU admission book.

A unique patient identifier will be allocated for use on all x-rays. No personal information will be stored or used in this study.

The principal investigator will retrieve and download the baseline (first x-ray performed on return to the ICU following surgery), post-operative day 1 and post-operative day 3 x-rays of all patients onto disc. All x-rays will be identified by unique patient identifier which will have no identifying features.

A list or corresponding unique patient identifiers will be kept by the principal investigator until study completion and then destroyed.

The x-rays will then be assessed by the radiologist using the proposed scoring system.

No other information will be recorded.
Appendix B.

Study Participants

Patients admitted to the CVICU from 01/01/2010 onwards will be assessed for eligibility as below. A total of 100 patients will have x-rays reviewed.

50 consecutive patients who received standard oxygen therapy will be identified and 50 consecutive patients who received nasal high flow oxygen therapy will be identified from existing CVICU database.

Inclusion criteria

Patients admitted to CVICU following cardiac surgery: coronary artery bypass grafting; valve replacement or coronary artery bypass grafting with concomitant valve replacement.

Age >18 years.

Length of stay in CVICU < 24 hours.

Presentation and Publication

It is intended that the results of this validation will form the basis of sample size calculations for a future randomised controlled trial of oxygen therapy in patients following cardiac surgery.

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

References

Appendix C: A Randomised Controlled Trial of High Flow Nasal Oxygen Therapy Compared to Standard Care in Patients Following Cardiac Surgery - the HOT-AS Study

ADHB Approval

Ethics Approval

Study Protocol

Information and Consent Form for Participants

Data Collection Forms

Data Dictionary

Policy and Procedures Manual

Statistical Analysis Plan
High flow nasal Oxygen Therapy in patients After cardiac Surgery

The HOT-AS study.

Rachael Parke
Research Coordinator
Cardiothoracic & Vascular ICU/HDU
Auckland City Hospital
Auckland
New Zealand
rparke@adhb.govt.nz
Appendix C.

Study Characteristics and Objectives

Background

Following cardiac surgery, patients are admitted routinely to the Cardiothoracic Intensive Care Unit (CVICU). They are intubated and mechanically ventilated until ready for extubation. Oxygen delivery after extubation is critical to maintain adequate oxygenation and avoid reintubation. Postoperative complications can increase mortality, morbidity and costs due to prolonged ICU and hospital stay. One major cause of postoperative respiratory complications such as pneumonia and hypoxaemic respiratory failure is atelectasis where regions of collapsed, airless alveoli are present. The development of atelectasis post general anaesthesia is almost inevitable and can extend into the postoperative period. Atelectasis has been described as present in most patients with reports involving around 90% of cardiac surgical patients. It has been suggested that recruitment manoeuvres may reduce atelectasis formation but this effect may be lost prior to or following removal of mechanical ventilation. Atelectasis may also be resistant to simple techniques employed to improve lung function such as patient positioning and incentive spirometry.

Ensuring adequate oxygenation and respiratory support is vital in the postoperative period, however there is little published evidence to guide intensive care clinicians in the objective selection and use of oxygen delivery devices. Noninvasive respiratory support (NRS) therapies partially compensate for changes in respiratory function by reducing work of breathing, recruiting alveoli and improving gas exchange while also reducing cardiac workload, increasing cardiac output and improving haemodynamics. Postoperative NRS can be applied as either a prophylactic or curative therapy. Preventive NRS can be used in patients following cardiac surgery to avoid atelectasis. Overall, the literature supports NRS as an adjunctive respiratory support therapy for patients following cardiac surgery. NRS is not without its complications, it can only be used in an ICU/HDU setting and success often depends on the fit and tolerability of the interface. Facemasks impede the ability of the patient to eat, drink and communicate. Patients report reduced levels of comfort with a facemask and are often agitated and poorly compliant removing the mask frequently leading to a greater incidence of hypoxaemia and increased nursing workload. Studies have demonstrated increased levels of patient satisfaction when using nasal cannulae when compared to a facemask.

Some centres have devised methods of delivering oxygen and/or positive pressure directly into the nares. Nasal high flow oxygen therapy (NHF) has recently been introduced into the adult intensive care arena following successful use in paediatric populations. One such system (Optiflow™ Fisher and Paykel Healthcare Ltd, New Zealand) delivers high flows of conditioned gas via a unique nasal interface. This allows the delivery of accurate concentrations of inspired oxygen; delivers flow dependent continuous positive airway pressure (CPAP) and provides humidification to enhance the mucociliary transport system and promote secretion clearance. It has been shown to be as effective as and significantly better tolerated than high flow humidified face mask (HFFM) oxygen.

NHF has been used in the CVICU for four years now. During that time a systematic research programme has been undertaken in an attempt to describe how NHF works. It has been shown that NHF reduces use of non-invasive ventilation, and
delivers a positive airway pressure\textsuperscript{18, 20}. Anecdotally, clinicians have reported satisfaction with the system and it appears well tolerated by patients. A recent study described the patient population utilising NHF in the CVICU\textsuperscript{21}. This study concluded that NHF was straightforward to initiate, could be employed for a relatively short period of time and was often discontinued before transfer of the patient to the ward. However, there remains a dearth of literature surrounding the clinical utility of NHF, it’s indications and limitations.

Currently, Ministry of Health projects are being undertaken to increase throughput in the CVICU in order to address concerns raised over lengthy waiting lists in New Zealand for cardiac surgery. One reason surgery is delayed is demand for limited ICU beds. Often patients cannot be discharged from the ICU due to respiratory insufficiency manifesting itself as the need for noninvasive ventilation\textsuperscript{3}. Once on the ward, it has been found that a significant number of patients have reduced pulmonary function out to day 3 postoperatively. A recent audit of post-operative cardiac surgical patients by the principal and co-investigator has found that on day 3 post-op 20\% of patients were still requiring oxygen; 26\% had an oxygen saturation of <94\% and 48\% have a documented SpO2/FiO2 ratio of ≤ 450 . (SpO2/FiO2 is the ratio of peripheral oxygen saturation to fraction of inspired oxygen).

A recent study reported reduced incidence of pulmonary complications in patients following cardiac surgery by employing prophylactic nasal CPAP (nCPAP) for at least 6 hours\textsuperscript{2}. It has been proposed through the neonatal literature that NHF may be a substitute for nCPAP. Indeed anecdotally NHF is gaining a reputation amongst clinicians from adult intensive care units as being increasingly used instead of NRS for the prevention or treatment of hypoxaemia and respiratory complications. It is now time to undertake a randomised controlled trial to determine whether NHF can be used post extubation of cardiac surgical patients to improve pulmonary function and reduce pulmonary complications.

We intend to conduct a phase IIB single centre randomised controlled trial to determine if the prophylactic use of nasal high flow oxygen therapy can improve pulmonary function in patients following cardiac surgery.

If significant physiological improvement in pulmonary function and patient oriented outcome benefits can be demonstrated in this planned Phase IIB study, these findings will influence changes in practice on both a national and international scale. If benefits to patient oriented outcomes are not found to be statistically significant, estimates of potential patient oriented benefits obtained from this Phase IIB trial will be used to investigate sample size requirements for a future definitive Phase III randomised controlled trial.

This study will add substantially to the limited body of knowledge surrounding NHF and provide evidence to inform the use of the therapy for patients in the ICU following cardiac surgery. This study will inform the debate regarding the clinical utility of NHF and in particular its impact on respiratory complications; ICU throughput and length of stay and patient comfort.

**Research Question**
Does the administration of prophylactic nasal high flow oxygen improve pulmonary function in patients following cardiac surgery?

**Hypothesis**
The administration of prophylactic nasal high flow oxygen post-extubation improves pulmonary function in patients following cardiac surgery.
Appendix C.

**Primary Outcome Measure**
Improved pulmonary function demonstrated by SpO2/FiO2 ratio > 445 on post-op day 3.

**Secondary Outcome Measures**
- X-ray score for atelectasis
- Spirometry measurements: FVC; FEV1
- Readmission to ICU for respiratory causes
- ICU length of stay
- Hospital length of stay
- Mortality and incidence of respiratory complications at day 28
- Respiratory Rate
- Oxygenation variables: measured pO2 and pCO2
- Use of adjunctive respiratory support therapies and escalation of respiratory support
- Adverse events such as barotrauma and pneumothorax
- Patient comfort during administration of oxygen therapy

**Study Design and Methodology.**
A prospective, open label, randomised controlled trial will be undertaken.

A total of 340 patients will be randomised into this study. 170 patients each arm.

Following approval from the Northern X regional ethics committee, patients scheduled for elective cardiac surgery and meeting the inclusion/exclusion criteria will be approached and invited to participate in this study. Written informed consent obtained pre-operatively.

**Sample Size and Power**
A recent audit of patients in the CVICU has demonstrated a 40% incidence of patients recording a SpO2/FiO2 <445 on day 3 post-operative. As there is little published evidence to inform sample size calculations for this study, the following has been assumed and is determined to be both feasible and clinically meaningful for this population.

It is assumed that there is no difference in failure rate or treatment effect in high BMI vs low BMI. (The evidence is contradictory on BMI effect with nasal high flow which is why we have stratified for BMI in the randomisation process). Therefore for this study it is assumed that the expected probability of failure in the control group is 0.4 and we would expect to reduce that probability down to 0.25 under the nasal high flow.

Assuming an α = 0.05 a sample size of 332 (166 per arm) would give a 90% power to detect a treatment effect. We plan to randomise a total of 340 patients (170 per arm) in order to allow for a 3% loss to follow-up rate.

**Eligibility Criteria**

**Inclusion criteria**
Patients will be screened and are eligible for inclusion in the study if all of the following criteria are met:

- Over 18 years of age
Appendix C.

- informed consent obtained
- scheduled for cardiac surgery involving full median sternotomy.
- cardiac surgery = CABG; valvular; CABG + valve
- patient not normally on NIV at home
- patient is extubated prior to 1000 hours day after surgery

**Exclusion criteria**
Patients will be excluded if any of the following exist:
- contraindication for NHF use e.g. severe nasal septal defect
- need for timely NIV e.g. CPAP to treat obstructive sleep apnoea
- previous recruitment into this study
- patient is likely to be intubated and mechanically ventilated for >24 hours following operation
- post-operatively patient is still ventilated at 1000 post-op day 1

**Randomisation**
Due to the nature of the intervention it is not possible to blind participants or treating clinicians to allocated therapy. Randomisation will be performed using opaque, sealed envelopes, sequentially numbered. These envelopes will contain the unique patient identifier code and allocated study therapy details. Randomisation to treatment group will be done using a pre-generated random number table. Patients will be randomised in blocks of 12 to ensure even distribution of sample size between the two study arms.

Participants will be stratified according to body mass index (BMI). There will be two groups: BMI < 35 or BMI ≥ 35.
Participants will be randomised to treatment just prior to extubation and allocated therapy will be commenced as soon as participant is extubated. (This will help reduce possible bias and changes in extubation procedure or time, which may arise if the bedside clinician is aware of allocated therapy).

**Study Intervention**
Once patient is deemed clinically “ready for extubation” in accordance with the CVICU protocol for mechanical ventilation, the patient will be screened by research staff, or bedside clinicians after hours to ensure continued participation. Patients will then have an arterial blood gas drawn (as per CVICU protocol). Once this is taken, the randomisation envelope will be opened and patient allocation revealed. The patient will then be extubated and allocated therapy commenced immediately as follows:

**Intervention group:** If patient is randomised to the intervention group then they will receive NHF at a flow rate of 45 L/min– FiO2 (fraction of inspired oxygen) as determined by bedside clinician to maintain SpO2 > 93%.

**Control group:** If the patient is randomised to the control group then they will receive standard care, which may include oxygen therapy at 2 - 4 L/min via either simple facemask or nasal prongs titrated by the bedside clinician to maintain SpO2 > 93%.
Allocated therapy will be continued until 0900 hours day 2 post-operative at which point study therapy will be discontinued in conjunction with the CVICU research nurses and ongoing requirement for oxygen therapy assessed.

**Escalation of therapy**

A protocol will guide clinicians as to what defines the moment when patients could be said to require increasing respiratory support (Appendix 1). If this occurs, the next step would be to provide:

**Intervention Arm:** non-invasive ventilation and/or reintubation and mechanical ventilation as necessary.

**Control Arm:** high flow humidified facemask oxygen therapy and/or non-invasive ventilation, and/or reintubation and mechanical ventilation as necessary.

*Note, the control arm will not be offered nasal high flow as a rescue therapy.*

At all times, the final decision to escalate therapy and what therapy will be deemed most appropriate for the patient will be left to the clinician responsible for the patient.

**NB**

There is expected to be a small number of patients who are consented and enrolled but may not meet extubation criteria by 1000 hours day 1 due to their clinical condition. This group will therefore not meet randomisation criteria. This group will have baseline demographic data collected and reason for continued mechanical ventilation recorded. Research staff will explain to patients why they were not randomised.

**Data Collection, Measurements and Outcomes**

Data will be collected as follows:

**PaO2/FiO2 ratio** - will be recorded from the arterial blood gas taken prior to extubation, at 30 minutes and four hours post commencement of study therapy and again prior to discharge from ICU or at 0900 hours day 2 which ever occurs first. At these time points heart rate, mean arterial pressure, oxygen saturation as measured by finger probe, central venous pressure and respiratory rate will be measured. %FiO2 and gas flow rate will also be recorded.

**SpO2/FiO2 ratio** – amount of oxygen delivered to patients and their SpO2 will be collected at 0900 hours on day 3 and on day of discharge from the hospital and the SaO2/FiO2 ratio calculated.

**CXR** - Routinely following cardiac surgery patients receive a chest x-ray on return to the ICU (baseline), day 1 and day 3. The CXR will be reviewed and scored for atelectasis by a radiologist blinded to treatment allocation. They will also note any abnormalities such as pneumothorax. Scoring will be a lobar scoring of 0-3 summed for both lungs.

0=Normal  
1=Plate or minor infiltrate  
2=Moderate atelectasis  
3=Total atelectasis

The sums of each lobe are added giving a maximum score for the lungs of 18. This scoring system has been tested by the investigators and found to have similar sensitivity but a higher degree of specificity when compared to a previously published scoring system22. The new score also performed better than the old score at predicting day 3 clinical status from the day 1 CXR.
Appendix C.

X-rays will also be scored according to the previously published Richter Larsen score as follows:
The presence of atelectasis will be expressed by a 5-point score:
0 = clear lung fields
1 = plate-like atelectasis or slight infiltration
2 = partial atelectasis
3 = lobar atelectasis
4 = bilateral atelectasis

**Spirometry** - will be performed at study enrolment, at 1000 hours day 2 post-op; 1000 hours day 3 post-op and again as close to day of discharge as possible to assess FVC and FEV1.

**Demographic data** will include patient age, sex, ethnicity, height, weight, co-morbidities, EUROSCORE, surgical procedure, length of ventilation, time of admission and discharge to hospital and ICU, details of readmission to ICU.

**Use of adjunctive respiratory support therapies** e.g. non-invasive ventilation; requirement for reintubation/mechanical ventilation; details of total length of time on oxygen therapy will be recorded. Number of physiotherapy sessions will also be recorded whilst patient is admitted to hospital.

**To assess patient comfort**, patients in either arm of the study will be asked the following question by the bedside nurse at four hours post commencement of study therapy and again at discontinuation:
“On a scale of 0 – 10, how comfortable do you find the oxygen mask/prongs that you are wearing? 0 = not comfortable at all 10 = extremely comfortable”

**Day 28 Mortality and incidence of respiratory complications following discharge** – patients will be phoned one month after enrolment to ascertain mortality and whether they have required treatment for respiratory complications since hospital discharge e.g. antibiotic therapy.

**Statistics**
Data from the trial will be entered into an excel spreadsheet, and then extracted into STATA for analysis. All data analyses will be carried out on an intention-to-treat basis. Incidence rates and absolute differences (with corresponding NNTs) and 95% CIs will be obtained for binary variables in the first instance with subsequent multiple logistic regression adjusted for stratification factors. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow-up or death on the primary outcome. If important balance imbalances exist, these factors will also be entered into the regression analysis. Time to event data will be analysed using Cox regression modelling thereby taking into account known covariates and the varying times since randomisation. The proportionality assumption will be checked using standard graphical techniques. However, prior to undertaking any Cox regression modelling, the effectiveness of the interventions on time to outcome will be analysed using Kaplan-Meier curves to compare the differences between the two groups using the log rank test. Continuous data will be analysed using the appropriate parametric or non-parametric analysis after testing for normality.
Patient Identification and Privacy
Participants will each be allocated a unique study number at the time of randomisation which will be recorded on each of their respective data sets. The Research Nurses in CVICU/HDU will retain a log 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 study personnel.

Resources required
Provision of nasal high flow equipment and consumables – in agreement with Fisher and Paykel Healthcare.
Handheld spirometer to be purchased.
Office space will be provided within CVICU.
Research nurse time – 1.0 FTE for one year.

Funding
A grant has been submitted to the Green Lane Research and Education Fund to support data collection; statistical analysis and support for travel to present findings. Fisher and Paykel Healthcare, NZ, Ltd will provide consumables for the intervention arm.
A PhD scholarship has been awarded to the lead investigator by the Green Lane Research and Education Fund.

Organisation
Lead Investigator: Rachael Parke
Co-investigator: Dr Shay McGuinness, CVICU, Auckland City Hospital
Academic Supervisors: A/Prof Robyn Dixon, The University of Auckland; A/Prof Andrew Jull, The University of Auckland.
Access to raw data will be restricted to the study investigators and research nurses. Approval will be obtained from the Northern X regional ethics committee, the Maori Research Review Committee Auckland District Health Board (ADHB) and the Research Review Committee (ADHB).

References
Appendix C.

Appendix C.

Appendix 1. Escalation of Therapy - up to 1000hrs day 2.

Whilst on the study, a patient will be deemed to have increasing requirements for respiratory support when one or more of the following criteria are met:

1. Increased dyspnoea ±
2. Tachypnoea - Respiratory rate ≥ 35 breaths/minute ±
3. Oxygen saturation (SpO2) ≤ 90% ±
4. Heart rate ≥ 120 per minute (or > 30% increase above baseline) ±
5. Arterial pressure > 30% increase above baseline ±
6. Anxiety, restlessness ±
7. Signs of increased work of breathing as seen by use of accessory muscles and abdominal paradox ±
8. Ratio of PaO2 / FiO2 < 200 mmHg ±

Oxygen therapy should then be escalated as follows:

**Intervention Arm:**

- Nasal High Flow
- Non-invasive ventilation then if required...
- Reintubation and mechanical ventilation

**Control Arm:**

- Standard care
- High flow humidified facemask therapy then if required...
- Non-invasive ventilation then if required...
- Reintubation and mechanical ventilation

**Amendment 1.**

If patient is randomised to NHF and is finding difficulty in complying with study treatment due to increased temperature:

1. **↓ flow rate from 45 L/min to 40 L/min**
   - Reassess comfort and compliance
   - Is patient able to remain on 40 L/min?

   - **Yes**
     - Patient remains on 40 L/min – reassess as necessary - consider ↓ flow rate to 35 L/min for remainder of study period if patient becomes uncomfortable

   - **No**
     - ↓ flow rate to 35 L/min if necessary for comfort for remainder of study period

**Documentation:**
- Please document time of alteration of flow on the patients observation chart and reason for change.
- Please contact Rachael Parke (Principal Investigator) 021893176 or Shay McGuinness (Co-investigator) 021324771 or one of the CVICU research nurses on ext 24489 to discuss if necessary.
Appendix C.

SCHOOL OF NURSING
Faculty of Medical and Health Sciences

28 February 2014

PARTICIPANT INFORMATION SHEET

THE HOT-AS STUDY
The High flow Oxygen Therapy After cardiac Surgery study.

<table>
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<tr>
<th>Principal Investigator Name:</th>
<th>Rachael Parke</th>
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<tbody>
<tr>
<td>Site:</td>
<td>Cardiothoracic &amp; Vascular Intensive Care</td>
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<tr>
<td>Contact No:</td>
<td>(09) 3074949 ext 24489</td>
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Introduction
You are invited to participate in a research study to compare using one of two different methods of delivering oxygen after your cardiac surgery. Your participation is entirely voluntary (your choice). You do not have to take part in this study, and whether or not you choose to take part you will continue to receive all usual treatment.

We would like to include you in this study because you are scheduled to have cardiac (heart) surgery and will require the use of oxygen after your surgery. After cardiac surgery, you require the help of a ventilator (breathing machine) to ensure that adequate oxygen levels are maintained while you wake from your anaesthetic. Usually you are woken from your anaesthetic around 6 hours after arrival in the Intensive Care Unit (ICU). Once you are awake, we remove the breathing tube and deliver oxygen to you by way of a mask or nasal prongs for around two days following surgery.

Nasal oxygen therapy may have several advantages over face mask oxygen such as: improved comfort and the ability to eat and talk. One oxygen delivery device used in our hospital allows higher amounts - flows - of oxygen to be used due to the way the oxygen is heated and humidified (warmed and moistened). High flow nasal oxygen delivered to the nose may mean that oxygen delivery is more efficient than when using a face mask, however this has not been shown in cardiac surgery patients. We are uncertain as to the best method of delivering oxygen therapy to patients and wish to do a study comparing the two methods to see which one is best at preventing breathing complications after cardiac surgery. The study will compare standard oxygen therapy delivered by way of a facemask or nasal prongs with high flow oxygen therapy delivered via the nose in patients after cardiac surgery. Around 340 patients will be included in the study.

The study
If you agree to participate in this study you will receive oxygen therapy by way of either a standard oxygen mask/nasal prong or receive oxygen therapy by way of the high flow nasal oxygen system. This will be until 0900 hours two days after your surgery. After that time, the doctor caring for you will decide which is the best way of giving you oxygen if you still require it.

The group you are in is decided randomly. This is like tossing a coin and you would have an equal (50:50) chance of being in either group. One group of participants will receive oxygen delivered to the nose by way of the high flow system. The other group of participants will receive oxygen therapy using a face mask or standard nasal prongs. This study is not a “blinded” study, which means that you and your relative/friend’s and doctors will know to which treatment group you have been allocated. We will measure your oxygen levels and...
breathing rate and also perform some lung function tests using an electronic flow measuring
device for one minute. These tests will take place in the Intensive care unit and in the ward
after your surgery.
All other treatment will be unaffected by being in this study. You will receive normal intensive
care treatment. No extra blood tests or x-rays are taken and all treatment occurs in the ICU
and ward. The research nurse will take some of the information required for the study from
your medical notes. The information is kept by the study organisers, in a form that will not
allow you to be identified. We will also call you one month after your surgery to ask whether
or not you have had any breathing problems since going home. If you have seen your GP for
breathing problems since going home, we may ask your permission to contact them for
further details if necessary.
No material that could personally identify you will be used in any reports on this study.

Benefits of being in the study.
It is hoped that information generated from this study will benefit patients in the future. There
may be no benefit to individual patients from being in this study.

Risks of being in the study.
It is believed that there are no additional risks of receiving either high flow nasal oxygen or
face mask/nasal prong oxygen. Being in the study does not pose any extra risk to you above
the risks associated with usual treatment in the intensive care unit. Both treatments are used
currently in the intensive care unit and ward, and the staff caring for you are trained in using
both oxygen systems. However, if you feel there is a problem you should immediately alert
the staff caring for you. Even though your treatment is a routine procedure the treatment
used in this study may also involve other risks, which at the time of treatment are unknown.
You will be informed in a timely manner of any significant new information that may affect
your willingness to continue to participate in this study.

Is the study voluntary?
Participation in this study is voluntary. You are free to withdraw from the study at any time,
without having to give a reason and this will in no way affect your future healthcare.
If you decide not to be included, your treatment will not be affected in any way and you will
continue to receive all standard treatment for your condition.

Compensation.
In the unlikely event of a physical injury as a result of your participation in this study, you
may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act
2001. ACC cover is not automatic, and your case will need to be assessed by ACC
according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act
2001. If your claim is accepted by ACC, you still might not get any compensation. This
depends on a number of factors, such as whether you are an earner or non-earner. ACC
usually provides only partial reimbursement of costs and expenses, and there may be no
lump sum compensation payable. There is no cover for mental injury unless it is a result of
physical injury. If you have ACC cover, generally this will affect your right to sue the
investigators. If you have any questions about ACC, contact your nearest ACC office or the
investigator.

Statement of Approval
This study has received ethical approval from the Northern X Regional Ethics Committee.
This committee is responsible for making sure that research with participants is appropriate
and the participant’s rights and welfare are being protected. This means that the Committee
may check at any time that the study is following appropriate ethical procedures.
Questions:
If you have queries or concerns regarding your rights as a participant in this study you may wish to contact an independent health and disability advocate:
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz
For Maori health support, or to discuss any concerns or issues regarding this study, please contact Mata Forbes RGON, Maori Health Services Co-ordinator / Advisor, 5th Level, GM Suite, Auckland City Hospital. Tel 307 4949 extn. 23939 or Mobile 021 348 432
Please feel free to contact any of the Cardiovascular Intensive Care doctors or the local investigator (Rachael Parke; tel. (09) 307 4949 ext. 24470) if you have any questions about this study.

Thank you for taking the time to consider this study. This information sheet is for you to keep.
CONSENT FORM - PARTICIPANT

The HOT-AS STUDY
The High flow Oxygen Therapy After cardiac Surgery study.

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I have read and I understand the information sheet dated 17th December 2010 for patients taking part in the study designed to assess two different oxygen therapy systems after cardiac surgery.

I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.

I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time if I wish. This will in no way affect my continuing future health care.

I have had this project explained to me by ________________________________.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

I understand that the treatment, will be stopped if it should appear harmful.

I understand the compensation provisions for this study.

I have had time to consider whether I would want to take part in the study.

The HOT-AS Study CVICU Version 2 date 17/12/2010. Patient Information Sheet & Consent Form
I know who to contact if I have any side effects from the study or if anything occurs which I would consider a reason to withdraw from the study.

I know who to contact if I have any questions about the oxygen therapy systems used in this study or about the study in general.

I wish to receive a copy of the published results of the study when it is finished.  

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<th>YES</th>
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Participant

I, __________________________ (full name) hereby consent to my participation in this study

____________________________________ (signature)

_______/_______/_______ (date) _____:____ (time, 24 hours)

Investigator

____________________________________(full name)

____________________________________(signature)

____________________________________(study role)

_____/_____/_____(date)

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<thead>
<tr>
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<td>Contact No:</td>
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Copies: Original in study file, 1 copy in clinical records, 1 copy to patient
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## The HOT-AS Study

### Enrolled Patient Log

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**HOT-AS Study Checklist**

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- **Baseline Data Form**

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<th>Date</th>
<th>Initial</th>
<th>Comments</th>
</tr>
</thead>
</table>

- **Daily data collection (initial when done)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Chest Xray**

<table>
<thead>
<tr>
<th>Day</th>
<th>Baseline</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Date due</th>
<th>Performed</th>
<th>Signature</th>
</tr>
</thead>
</table>

- **Spirometry**

<table>
<thead>
<tr>
<th>Day</th>
<th>Baseline</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Discharge/ Day before discharge/ Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date due</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date Performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Day 28 followup Due**

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BD1 | Screening number ____________________________
BD2 | Consent by ___________________________  BD3 | Date __________________

Demographics
BD4 | Height ______________ cm  BD5 | Weight ______________ kg  BD6 | BMI ______________
BD7 | Age ______________ yrs  BD8 | Sex  Male / Female (circle one)
BD9 | Ethnicity (circle)  European  NZ Maori  Pacific Island  Asian  Other __________

Medical History
BD10 | Primary diagnosis ____________________________________________
BD11 | Co-morbid conditions/Resp conditions

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

BD12 | Ejection fraction ______________ %  BD13 | Pre-op serum creatinine ______________
BD14 | Is there documented spirometry?  Yes / No  If so FEV1 __________  FVC __________
BD15 | Smoker?  Current  Ex-smoker  Never  When stopped ______________

BD16 | Insulin dependent diabetes mellitus  Yes / No
BD17 | Non-insulin dependent diabetes mellitus  Yes / No
BD18 | Hypercholesterolaemia (on medication)  Yes / No
BD19 | Arterial hypertension (on medication)  Yes / No
BD20 | Pulmonary hypertension  Yes / No
BD21 | Cerebrovascular disease  Yes / No
BD22 | Peripheral vascular disease  Yes / No
BD23 | Asthma (on medication)  Yes / No  COPD  Yes / No
BD24 | NYHA score  3  4  N/A
### Baseline Data

**BD25** EUROSCORE *(please use scoring worksheet and calculate online)* Total__________

<table>
<thead>
<tr>
<th><strong>Patient Factors</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>Y / N</td>
</tr>
<tr>
<td>Extracardiac arteriopathy</td>
<td>Y / N</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
<td>Y / N</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>Y / N</td>
</tr>
<tr>
<td>Serum creatinine &gt; 200 µmol/ L</td>
<td>Y / N</td>
</tr>
<tr>
<td>Active endocarditis</td>
<td>Y / N</td>
</tr>
<tr>
<td>Critical preoperative state</td>
<td>Y / N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiac Factors</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>Y / N</td>
</tr>
<tr>
<td>LV dysfunction moderate or LVEF 30-50%</td>
<td>Y / N</td>
</tr>
<tr>
<td>LV dysfunction poor or LVEF&lt;30</td>
<td>Y / N</td>
</tr>
<tr>
<td>Recent myocardial infarct</td>
<td>Y / N</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Y / N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Operation Factors</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency</td>
<td>Y / N</td>
</tr>
<tr>
<td>Other than isolated CABG</td>
<td>Y / N</td>
</tr>
<tr>
<td>Surgery on thoracic aorta</td>
<td>Y / N</td>
</tr>
<tr>
<td>Postinfarct septal rupture</td>
<td>Y / N</td>
</tr>
</tbody>
</table>

**BD26** Medications

*Please list the following medications if taken at least 24 hours prior to enrolment)*

<table>
<thead>
<tr>
<th><strong>Diuretics</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Inhalers</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Steroids</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
</tbody>
</table>
Baseline Measurements.

Baseline measurements  date __________  time _________ by ___________________

<table>
<thead>
<tr>
<th>SpO2 %</th>
<th>RR</th>
<th>HR</th>
<th>BP</th>
<th>FEV1</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BD31 Comments:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
### Admission

| DD1 | Date and time of admission to hospital | ___________________________ |
| DD2 | Date and time of discharge from hospital | ___________________________ |
| DD3 | Date and time of admission to ICU | ___________________________ |
| DD4 | Date and time of discharge from ICU | ___________________________ |
| DD5 | Date and time of intubation | ___________________________ |
| DD6 | Date and time of extubation | ___________________________ |

#### Type of surgery:

- [ ] Coronary Artery Bypass graft x _____
- [ ] Valve Surgery
- [ ] CABG + Valve

| DD7 | Date of surgery | ___________________________ |
| DD8 | Length of surgery (hh:min) | ___________ Length of bypass (hh:mm) | ___________ |
| DD9 | APACHE II score (on admission) | ___________________________ |
| DD10 | SOFA score (on admission to ICU) Resp | _________ Cardiovascular | _________ |

#### Study Period

| DD11 | Patient meets all inclusion criteria at randomisation | Yes / No |
| DD12 | Date and time pt ready for extubation | ___________________________ |
| DD13 | SOFA score (prior to extubation) Resp | _________ Cardiovascular | _________ Renal | _________ |
| DD14 | Date/time study therapy commenced | ___________________________ |

#### Allocated to receive

- [ ] NHF
- [ ] Standard Care

#### Ventilation immediately prior to extubation

<table>
<thead>
<tr>
<th>Mode</th>
<th>FiO2%</th>
<th>PEEP (cmH₂O)</th>
<th>PS (cmH₂O)</th>
<th>CPAP (cmH₂O)</th>
</tr>
</thead>
</table>

If found please return to CVICU, Research Nurses
**Table 1. Arterial Blood Gas Measurements and Cardiovascular Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Immediately prior to extubation</th>
<th>30mins post extubation</th>
<th>4 hours post extubation</th>
<th>Day 1 prior to transfer to ward or at 1200 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DD18 pH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD19 pCO₂ (kPa)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD20 pO₂ (kPa)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD21 HR (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD22 RR (breaths/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD23 MAP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD24 SpO₂ %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD25 FiO₂ %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD26 Method of Oxygen delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DD27 Patient Comfort Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD28</td>
<td>Table 2. Daily data</td>
<td>Day 1 post-op Date _ _ / _ _ /_ _ _ _</td>
<td>Day 2 post-op Date _ _ / _ _ /_ _ _ _</td>
<td>Day 3 Post-op Date _ _ / _ _ /_ _ _ _</td>
</tr>
<tr>
<td>------</td>
<td>---------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>DD29</td>
<td>HR (beats/min) @ 09:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD30</td>
<td>RR (breaths/min) @ 09:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD31</td>
<td>SBP/DBP @ 09:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD32</td>
<td>SpO₂ % @ 09:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD33</td>
<td>FiO₂ % @ 09:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD34</td>
<td>Method of O₂ delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD35</td>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD36</td>
<td>No. physio sessions today</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD37</td>
<td>Did patient require ↑ resp support ? (Yes/No) If yes – reason (see data dictionary); mode/FiO₂/time commenced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD38</td>
<td>Diuretics (Yes/No)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD39</td>
<td>Patient Comfort Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 3. Spirometry</td>
<td>Baseline (pre-op)</td>
<td>Day 2 post-op</td>
<td>Day 3 Post-op</td>
<td>Day of discharge (or day before)</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Date _ _ / _ _ / _ _ _ _</td>
<td>Date _ _ / _ _ / _ _ _ _</td>
<td>Date _ _ / _ _ / _ _ _ _</td>
<td>Date _ _ / _ _ / _ _ _ _</td>
</tr>
<tr>
<td></td>
<td>Time _ _ : _ _</td>
<td>Time _ _ : _ _</td>
<td>Time _ _ : _ _</td>
<td>Time _ _ : _ _</td>
</tr>
</tbody>
</table>

**Performed by:**

**Table 4: Chest X-ray**

<table>
<thead>
<tr>
<th>Return to ICU</th>
<th>Score</th>
<th>Day 1</th>
<th>Score</th>
<th>Day 3</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest Xray taken (Yes/No)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old</td>
<td>Old</td>
<td>Old</td>
<td>Old</td>
<td>Old</td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>New</td>
<td>New</td>
<td>New</td>
<td>New</td>
<td></td>
</tr>
</tbody>
</table>

**Downloaded and stored**

<table>
<thead>
<tr>
<th>Date/Signature</th>
<th>Old</th>
<th>Old</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>New</td>
<td>New</td>
<td>New</td>
</tr>
</tbody>
</table>
Other

DD48 Oxygen delivery on discharge from CVICU/HDU

Mode of oxygen delivery ________________

FiO₂ _________%

Flow _______ lpm (where appropriate)

DD49 Date and Time of discontinuation of Oxygen

Date _________________________ Time ____________

DD50 Was study treatment discontinued prior to 0900 hours day 2? Yes No (circle)

DD51 If Yes (to DD50) record reason ____________________________________________________________

DD52 Please record ongoing oxygen therapy __________________________________________

DD53 Prior to discharge from hospital

DD54 Did patient receive/were they prescribed antibiotic therapy for suspected chest infection?

YES NO

Details

____________________________________________________________

____________________________________________________________

DD55 After discontinuation of study intervention did patient require ANY further oxygen therapy?

YES NO

DD56 Date and time patient last received oxygen __________________________
### APACHE II Severity Of Disease Classification

**Subject Number: I__I__I__I__I__I__I**

**Subject Initials: I__I__I__I**

If found please return to CVICU, Research Nurses

#### A. ACUTE PHYSIOLOGY SCORE (APS)

<table>
<thead>
<tr>
<th>PHYSIOLOGIC VARIABLE</th>
<th>High Abnormal Range</th>
<th>Low Abnormal Range</th>
<th>APS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+4</td>
<td>+3</td>
<td>+2</td>
</tr>
<tr>
<td>Temperature – rectal (°C)</td>
<td>≥ 41</td>
<td>39 – 40.9</td>
<td>38.5 – 38.9</td>
</tr>
<tr>
<td>Mean arterial pressure – mmHg</td>
<td>≥ 160</td>
<td>130 - 159</td>
<td>110 – 129</td>
</tr>
<tr>
<td>Heart rate (ventricular response)</td>
<td>≥ 180</td>
<td>140 – 179</td>
<td>110 – 139</td>
</tr>
<tr>
<td>Respiratory rate (non-ventilated or ventilated)</td>
<td>≥ 50</td>
<td>35 – 49</td>
<td>25 - 34</td>
</tr>
<tr>
<td>Oxygenation: A - aDO₂ or PaO₂ (mmHg)</td>
<td>&gt; 500</td>
<td>350 – 499</td>
<td>200 – 349</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>≥ 7.7</td>
<td>7.6 – 7.69</td>
<td>7.5 – 7.59</td>
</tr>
<tr>
<td>Serum sodium (mMol/L)</td>
<td>≥ 180</td>
<td>160 – 179</td>
<td>155 – 159</td>
</tr>
<tr>
<td>Serum potassium (mMol/L)</td>
<td>≥ 7</td>
<td>6 – 6.9</td>
<td>5.5 – 5.9</td>
</tr>
<tr>
<td>Serum creatinine (mMol/L) (double point score for acute renal failure)</td>
<td>≥ 0.300</td>
<td>0.171-0.299</td>
<td>0.121-0.17</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>≥ 60</td>
<td>50 – 59.9</td>
<td>46 – 49.9</td>
</tr>
<tr>
<td>White blood count (total/mm³) (in 1,000s)</td>
<td>≥ 40</td>
<td>20 – 39.9</td>
<td>15 – 19.9</td>
</tr>
<tr>
<td>Glasgow Coma Score (GCS) (Score = 15 minus actual GCS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum HCO₃ (venous – mMol/L) (Only use this if no ABGs available)</td>
<td>≥52</td>
<td>41 – 51.9</td>
<td>32 – 40.9</td>
</tr>
</tbody>
</table>
### APACHE II Severity Of Disease Classification

#### Subject Number: I__I__I__I__I__I__I

#### Subject Initials: I__I__I__I

---

**B. AGE POINTS**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 44</td>
<td>0</td>
</tr>
<tr>
<td>45–54</td>
<td>2</td>
</tr>
<tr>
<td>55–64</td>
<td>3</td>
</tr>
<tr>
<td>65–74</td>
<td>5</td>
</tr>
<tr>
<td>≥ 75</td>
<td>6</td>
</tr>
</tbody>
</table>

**C. CHRONIC HEALTH POINTS**

<table>
<thead>
<tr>
<th>Points</th>
<th>DEFINITIONS: Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LIVER: Biopsy proven cirrhosis &amp; documented portal hypertension (PH); episodes of upper GI bleeding due to PH; or prior episodes of hepatic failure/encephalopathy/coma</td>
</tr>
<tr>
<td></td>
<td>RENAL: Receiving chronic dialysis</td>
</tr>
<tr>
<td></td>
<td>CARDIOVASCULAR: New York Heart Association Class IV</td>
</tr>
<tr>
<td></td>
<td>RESPIRATORY: Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (i.e. unable to climb stairs, perform household duties); or documented chronic hypoxia, hypercapnia, 2° polycythaemia, severe pulmonary hypertension (&gt;40mmHg) or respiratory dependency</td>
</tr>
<tr>
<td></td>
<td>IMMUNOCOMPROMISED: Patient has received therapy that suppresses resistance to infection, eg. immuno-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids, or has a disease sufficiently advanced to suppress resistance to infection (eg leukaemia, lymphoma, AIDS)</td>
</tr>
</tbody>
</table>

**APACHE II SCORE - a sum of:**

<table>
<thead>
<tr>
<th>A. APS points</th>
<th>B. Age points</th>
<th>C. Chronic Health points</th>
<th>Sum of A + B + C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORGAN SYSTEM</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>--------------</td>
<td>---</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mmHg)</td>
<td>&gt;400</td>
<td>301 - 400</td>
<td>201 - 300</td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt; 70 mmHg</td>
<td>Dopamine ≤ 5 ………………………… Or any dose Dobutamine</td>
</tr>
<tr>
<td>Renal Creatinine (μmol/L) OR urine output</td>
<td>&lt; 110</td>
<td>110 - 170</td>
<td>171 - 299</td>
</tr>
</tbody>
</table>
Please complete for all patients NOT extubated prior to 10:00 hours post-op Day 1.

**Admission**

DD1 Date and time of admission to hospital

DD2 Date and time of discharge from hospital

DD3 Date and time of admission to ICU

DD4 Date and time of discharge from ICU

DD5 Date and time of intubation

DD6 Date and time of extubation

DD7 Type of surgery:  □  Coronary Artery Bypass graft x _____

□  Valve Surgery

□  CABG + Valve

DD8 Date of surgery

DD9 Length of surgery (hh:min)_____________ Length of bypass (hh:mm) ____________

DD10 APACHE II score (on admission)

DD11 SOFA score (on admission to ICU)  Resp _________ Cardiovascular _________

DD11a Patient meets all inclusion criteria at randomisation  Yes / No

DD40 Table 1. Spirometry

<table>
<thead>
<tr>
<th></th>
<th>Baseline (pre-op)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date _ _ / _ _ /_ _ _ _</td>
<td></td>
</tr>
<tr>
<td>Time _ _ : _ _</td>
<td></td>
</tr>
</tbody>
</table>

DD41 Performed by:

DD42 FVC

DD43 FEV1

DD44 Comments

DD42 Reason for prolonged intubation _______________________________________________

If found please return to CVICU, Research Nurses. v1#February 2011
Appendix C.

The HOT-AS Study

DAY 28 follow-up

PSN: I__I__I__I__I__I__
Pt Initials: I__I__I__I

DT1 Phone call completed Date ________________________________ Time __________

DT2 Interview completed with: Patient ☐ Proxy ☐

DT3 Status at day 28

a. Patient alive and discharged from hospital ☐ b. Deceased ☐
c. Alive and still in study ICU? ☐ d. Alive and still in study hospital? ☐

DT4 If patient is deceased:

a. Date of death ________________________________
b. Location ________________________________
c. Primary cause of death ________________________________
d. Underlying causes:
   ___________________________________________
   ___________________________________________
   ___________________________________________

DT5 Has the patient seen their GP/attended medical facility for respiratory illness YES / NO

If yes Date ________________________________

Were they prescribed antibiotics? YES / NO

DT6 Intensive Care Discharge Date ________________________________ Time __________

DT7 Hospital Discharge Date ________________________________ Time __________

DT8 Was patient readmitted to ICU with respiratory complications Yes / No

If Yes a. Date ________________________________ Time __________

Reason for readmission _____________________________________

Did patient require any of the following:

i. NHF ☐ ii. NIV ☐ iii. Reintubation ☐ iv. Antibiotics ☐

Completed by ______________________________ Date ________________

If found please return to CVICU, Research Nurses. v1#February 2011
### Appendix C.

#### The HOT-AS Study

<table>
<thead>
<tr>
<th><strong>SERIOUS ADVERSE EVENT REPORT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSN:</strong> I__I__I__I__I__I</td>
</tr>
<tr>
<td><strong>Pt Initials:</strong> I__I__I__I</td>
</tr>
</tbody>
</table>

#### A. ADVERSE EVENT

<table>
<thead>
<tr>
<th><strong>AE1. Event:</strong></th>
<th><strong>AE2 Date of Event Onset:</strong></th>
<th></th>
</tr>
</thead>
</table>

**AE3 □ Is this the initial event?**  **or**  **□ A follow up of a pre-existing AE?**

**AE4 Narrative of Event (please describe the event):**

#### B. AE5 Do you regard the adverse event as serious (see list below)?  **□ Yes**  **□ No**

If YES tick one box, did the Serious Adverse Event:

- □ Resulted in death  **Date of Death:** |__|__| / |__|__| / |__|__|__|__|
- □ Threatened life
- □ Caused persistent or significant disability/incapacity
- □ Prolonged existing hospitalisation
  - □ Resulted in congenital anomaly or birth defect in offspring

#### C. AE6 CAUSALITY: In your opinion was the cause of the Adverse Event related to study follow up procedures?

**□ Possibly**  **□ Probably**  **□ Definitely**

#### D. AE7 ACTION TAKEN:  **□ None**  **□ Intervention, describe below:**

#### E. AE8 OUTCOME OF ADVERSE EVENT

**□ Unknown**  **□ Ongoing**  **□ Resolved**  **Date of resolution:** |__|__| / |__|__| / |__|__|__|__|

#### F. AE9 PLEASE SIGN BELOW

**Name of person completing:** :..........................................................

**Signature person completing:**  **Date:** |__|__| / |__|__| / |__|__|__|__|

**PI Signature:**  **Date:** |__|__| / |__|__| / |__|__|__|__|

---

If found please return to CVICU, Research Nurses.
Appendix C.

The HOT-AS Study

Telephone Contact Log

The telephone contact log is a required part of the HOT-AS study and must be routinely completed when attempting to follow-up patients enrolled into the HOT-AS study at day 28.

Complete ALL details for each attempt to contact a patient (or proxy) for day 28 follow-up.

<table>
<thead>
<tr>
<th>Pt Study Number</th>
<th>Day 28 due (Date)</th>
<th>Follow-up attempt Date/Time</th>
<th>Outcome (completed/not completed)</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
### AIRVO Disinfection Log

<table>
<thead>
<tr>
<th>SetUp I.D.</th>
<th>Date (dd/mm/yyyy)</th>
<th>Time (hh:mm)</th>
<th>Cycle No.</th>
<th>Name</th>
<th>Signature</th>
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<tbody>
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</tbody>
</table>

If found please return to CVICU, Research Nurses.
<table>
<thead>
<tr>
<th></th>
<th>Atelectasis Score (old score 0-5)</th>
<th>Atelectasis score (new score 0-18)</th>
<th>Evidence of barotrauma/pneumothorax/other</th>
<th>Radiologist Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Day 3</td>
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</tbody>
</table>

If found please return to CVICU, Research Nurses.
The HOT-AS Study

High flow nasal Oxygen Therapy in patients After cardiac Surgery

Data Dictionary
HOT-AS study: Data Dictionary January 2011

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Study Committee
Rachael Parke
Shay McGuinness
A/Prof Robyn Dixon, School of Nursing, The University of Auckland
A/Prof Andrew Jull, School of Nursing, The University of Auckland

If you have any questions regarding this project please do not hesitate to contact in the first instance Rachael (021893176) or Shay (021324771). If Rachael or Shay are unavailable please contact Andrew (0212433772) or Robyn (021702330).

For timely response to email queries please ensure email is sent to both Rachael and Shay.
HOT-AS study: Data Dictionary January 2011

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HOT-AS study: Data Dictionary January 2011

General Information
The HOT-AS study will be conducted in the CVICU at Auckland City Hospital and involve recruiting 340 patients.

Data accuracy is very important.

Please ensure the following when collecting data for consistency and accuracy. We would rather ensure we were all doing the same thing from the beginning and aim to reduce the number of data queries generated as the study progresses.

With this in mind, to improve the overall validity of the trial and reduce the amount of time spent following up on data queried, please follow these simple rules:

1. Sometimes 1s can look like Is and 7s can look like 4s or 1s or…… Therefore please use a good quality, dark ink pen and please write as clearly as possible.
2. If a requested variable is not recorded in the patients notes and it is not going to be available at a later date (i.e. not become available ever) please do not leave a field blank. If a variable is truly missing, draw a “cross” through the data collection box. This will let us know that the variable was unavailable and we will not need to follow-up for it.

Part 1. Baseline Data CRF.

Most of the CRFs require you to record patient study number and patient initials. The patient study number will comprise the following: Study code HA followed by the patient number allocated in ascending order i.e. patient 1 will be HA001; patient 2 will be HA002; etc.

For patient initials please record as follows: record three initials if available e.g. Jane Mary Smith will be recorded as JMS. If the patient only has two names please use a hyphen to fill the middle space e.g. Donald Duck will be recorded as D-D.

It is important that you record accurately the allocated patient study number in order that all CRFs belonging to the one patient can be accounted for at the end of the study.

Record baseline data only for the first time the patient is enrolled into the study.

Ideally the baseline data CRF will be completed at the time that the patient is screened, consented and enrolled into the study.

BD1 Screening number
Record corresponding screening number from “screening log”. This will allow us to document the number of patient screened for study inclusion.
HOT-AS study: Data Dictionary January 2011

BD2 Consent
Please record the name of person obtaining informed consent.

BD3 Date
Please record the date consent is obtained. Please record the full date in the following format
c.e.g. 01/01/2011.

BD4 Height
Please record the patient’s height in centimetres.

This height should be obtained by measuring the patient not by patient report as this may be
highly questionable. It is permissible to record the height obtained by the ward staff and
documented in the patient observation chart. Record to the nearest cm.

BD5 Weight
Please record the patient’s current weight in kilograms.

This weight should be obtained by weighing the patient not by patient report as this may be
highly questionable. It is permissible to record the weight obtained by the ward staff and
documented in the patient observation chart. Record to the nearest 0.1kg.

BD6 BMI
Use the following formula to calculate BMI and record

\[ BMI = \frac{\text{weight}(kg)}{\text{height}(m)^2} \]

BD7 Age
Please record the patients age in years

BD8 Sex
Please select the appropriate legal gender for the patient – male or female.

BD9 Ethnicity
Please circle the appropriate ethnicity for the patient.

BD10 Primary Diagnosis
Please record the primary reason that the patient has been admitted for surgery.

e.g. a patient who has been admitted for an aortic valve replacement for aortic stenosis would
be recorded as having primary diagnosis of aortic stenosis

BD11 Co-morbid conditions/respiratory conditions
Please record other co-morbid or respiratory conditions listed in the patient cardiosurgical
summary

BD12 Ejection Fraction
Please record the documented ejection fraction of the patient if available. Record as
percentage where available or “normal” if that is how it is remarked on.
HOT-AS study: Data Dictionary January 2011

**BD13** Pre-op serum creatinine
Please record the most recent documented creatinine recorded for the patient measured prior to surgery.

**BD14** Documented spirometry
If formal spirometry measurements have been undertaken and recorded please document the FVC and FEV₁ recorded in the patient notes.

**BD15** Smoker?
Please document whether the patient is a current smoker, an ex-smoker or has never smoked.
For the purposes of this study a **current smoker** is one who was still **smoking on admission or in the week prior to admission** to hospital; an **ex-smoker** is one who has **stopped smoking at least one week prior to admission**. If the patient is a current or ex-smoker please record when they last smoked.

**BD16** Insulin dependent diabetes mellitus
Record whether the patient is an insulin dependent diabetic or not.

**BD17** Noninsulin dependent diabetes mellitus
Record whether the patient is a noninsulin dependent diabetic or not.

**BD18** Hypercholesterolaemia
Please record whether or not the patient has hypercholesterolaemia. Select “Yes” if the patient is taking lipid lowering medication.

**BD19** Arterial hypertension
Please record whether or not the patient has arterial hypertension. Select “Yes” if the patient is taking medication to lower blood pressure.

**BD20** Pulmonary hypertension
Please record whether or not the patient as a documented history of pulmonary hypertension.

**BD21** Cerebrovascular disease
Please record whether or not the patient has a documented history of cerebrovascular disease.

**BD22** Peripheral vascular disease
Please record whether or not the patient has a documented history of peripheral vascular disease.

**BD23** Asthma/COPD
Please record whether or not the patient has a documented history of asthma or COPD for which they are receiving medication.

**BD24** NYHA score
Please circle the appropriate NYHA score of 3 or 4 if documented in patient notes.
**HOT-AS study: Data Dictionary January 2011**

**BD25 EUROSCORE**
Please record the appropriate information and use on line tool to calculate the patient EUROSCORE.

<table>
<thead>
<tr>
<th>Patient Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (M / F)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
</tr>
<tr>
<td>Extracardiac arteriopathy</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
</tr>
<tr>
<td>Serum creatinine &gt;200 µmol/ L</td>
</tr>
<tr>
<td>Active endocarditis</td>
</tr>
<tr>
<td>Critical preoperative state</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>LV dysfunction moderate or LVEF 30-50%</td>
</tr>
<tr>
<td>LVEF&lt;30</td>
</tr>
<tr>
<td>Recent myocardial infarct</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operation Factors</th>
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</thead>
<tbody>
<tr>
<td>Emergency</td>
</tr>
<tr>
<td>Other than isolated CABG</td>
</tr>
<tr>
<td>Surgery on thoracic aorta</td>
</tr>
<tr>
<td>Postinfarct septal rupture</td>
</tr>
</tbody>
</table>

**BD26 Medications**
List the following medications if taken by the patient for at least 24 hours prior to study enrolment.

**BD27 Diuretics**
Record type and dose of any diuretics the patient may be receiving. These may include Frusemide; etc.

**BD28 Inhalers**
Record type and dose of any inhaled medications the patient may be receiving. These may include Salbutamol (Ventolin); Flixtide;

**BD29 Steroids**
Record type and dose of any oral steroids the patient may be receiving. These may include Prednisone; Methylprednisolone; Hydrocortisone; Dexamethasone.
**BD30 Baseline Measurements**
Please perform and document the following baseline measurements:
- SpO₂ – measure using a pulse oximeter and record as a percentage
- RR – measure and record the patient respiratory rate as breaths per minute
- HR – measure and record the patient heart rate as beats per minute
- BP – measure and record the patient systolic and diastolic blood pressure
- FEV₁ – once baseline spirometry is undertaken record FEV₁
- FVC – once baseline spirometry is undertaken record the FVC

**BD31 Comments**
Document any other concerns; notes of importance; difficulties encountered with spirometry measurements etc.
HOT-AS study: Data Dictionary January 2011

Part 2. Daily Data CRF.

Admission
DD1 Date and time of admission to hospital
Enter the date and time that the patient was admitted to the study hospital.

Please write the date in the format 1/01/2011 to indicate 1st January 2011. Please write the
time using the 24-hour clock as follows: 13:55 for 1:55pm.

Please only record the date of admission to this hospital. For example, if the patient had been
admitted to another hospital two weeks ago and transferred here for surgery yesterday, the
date of admission to hospital would be yesterday’s date.

DD2 Date and time of discharge from hospital
Please record the date and time of discharge from the study hospital following this surgery.

DD3 Date and time of admission to ICU
Please record the date and time that the patient was admitted to the study ICU. Please record
the date and time in the format described above.

DD4 Date and time of discharge from ICU
Please record the date and time that the patient is discharged from the study ICU following
their booked surgery.

DD5 Date and time of intubation
Please record the date and time that the patient is intubated obtained from the intraoperative
anesthetic record. If the time of intubation is not recorded, please record the time that the
patient was first administered muscle relaxants as part of their anesthesia.

DD6 Date and time of extubation
Please record the date and time that the patient is extubated after their surgery. This time will
be recorded on the CVICU bypass chart.

DD7 Type of surgery
Please indicate the type of surgery that the patient had performed. Choose from either:
Coronary Artery Bypass graft (please record number of grafts performed); Valve Surgery
(describe what surgery) or CABG + Valve (record number of grafts and type of valvular
surgery)

DD8 Date of surgery
Record the date that surgery was performed.
HOT-AS study: Data Dictionary January 2011

DD9 Length of surgery

Record the length of surgery in the following format hh:mm. This will be calculated from the printed intra-op record (form CR4046). Use “into OR” as the start time and “surgery end” as the finish time. Length of time on cardiopulmonary bypass will also be collected from the HLM (perfusion) chart and calculated as time off bypass less time on bypass.

DD10 APACHE II score

An APACHE II form has been provided with the CRFs. Please complete and keep with patient CRFs. It may be used data checking purposes. Please ensure you complete the patient study number and patient initials.

The APACHE II score is derived from 3 scoring domains: a) Acute Physiology, b) Age Points and c) Chronic Health Points and represents a patient’s overall “severity of illness”. It is extremely important that APACHE II variables are collected in the same way by all.

When completing the Acute Physiology score, identify and record the value on admission to the ICU post surgery, i.e. the first measurements for each variable taken after admission to the CVICU.

Score by circling the value recorded on admission and writing the corresponding value in the APS column.

E.g. if patient temperature on admission to CVICU post-op is recorded as 33.5°C then circle 32 – 33.9 and record “2” in the APS box.

Mean Arterial Pressure (MAP) is usually recorded on the CVICU bypass chart. If the ICU bypass chart only reports systolic (SBP) and diastolic blood pressure (DBP) then calculate MAP as follows:

\[
MAP = \frac{2}{3} \times DBP + \frac{1}{3} \times SBP.
\]

Please record in mmHg.

Oxygenation:

a. For FiO2 ≥ 0.5, record the A-a gradient
   • If the patient's inspired fractional concentration of oxygen (FiO2) is greater than or equal to 0.5 (or 50%) record the A-a gradient on admission
   • A-a gradient is calculated by subtracting the partial pressure of alveolar oxygen (PAO2) from the partial pressure of arterial oxygen (PaO2) using the following equation:
HOT-AS study: Data Dictionary January 2011

A-a gradient = $\text{PAO}_2 - \text{PaO}_2$

$$= (713 \times \text{FiO}_2) - (1.25 \times \text{PaCO}_2) - \text{PaO}_2$$

*NB FiO\textsubscript{2} should be recorded as a fraction e.g. 0.6: 0.7: etc*

The only variables you need to calculate the A-a gradient are the FiO\textsubscript{2}, PaO\textsubscript{2} and the PaCO\textsubscript{2} which must be obtained from the same blood gas. Please note that these values should be in mmHg NOT kPa. To change kPa to mmHg multiply kPa by 0.13333.

b. For FiO\textsubscript{2} < 0.5 record the PaO\textsubscript{2} in mmHg.

To obtain the GCS (Glasgow coma scale) use the GCS worksheet provided (Appendix 1).
Subtract the GCS score from 15 to obtain score on the APACHE worksheet. If the GCS cannot be estimated because the patient is sedated (most of the HOTAS patients will be sedated on arrival in the CVICU) then record the GCS as 15 and thus the APACHE component score will be 0.

To obtain Part B – assign points to the age range that the patient fits e.g. a 65 year old patient would be assigned 5 points.

To obtain Part C – first decide if the patient meets any of the criteria provided. If there is no history assign 0 points. If there is a history, assign points depending on whether the patient is a non-operative or emergency post-operative admission (5 points) OR an elective post-operative admission (2 points). For the purposes of the HOT-AS study all patients should be elective post-operative admission.

Finally add the points recorded for each of the 3 parts together and enter this total score at question DD10.

DD11 SOFA score

Please record the following components of the Sequential Organ Failure (SOFA) score. For this data point, these values reflect the variables at the time of admission to the CVICU.

Please note that if the variable has not been measured – record “9”.

Use the table below and included as part of the patient CRFs to calculate and record SOFA.

**Respiratory component** - please use the following table to assign a score reflective of the SOFA respiratory score on admission. Use the first arterial blood gas measured on arrival to the CVICU to calculate PaO\textsubscript{2}/FiO\textsubscript{2} ratio and record in DD11.
HOT-AS study: Data Dictionary January 2011

**Cardiovascular component** – please use the table below to assign a score reflective of the SOFA cardiovascular score on admission. Use the first documented obs on admission to CVICU. Record the SOFA score in DD11.

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>9</th>
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<tbody>
<tr>
<td>Respiratory</td>
<td>&gt;400</td>
<td>301 - 400</td>
<td>201 - 300</td>
<td>101 - 200 (with respiratory support)</td>
<td>≤ 100 (with respiratory support)</td>
<td>Variable not measured</td>
</tr>
<tr>
<td>( \text{PaO}_2 / \text{FiO}_2 ) (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt; 70 mmHg</td>
<td>Dopamine ≤ 5</td>
<td>Dopamine &gt; 5</td>
<td>Dopamine &gt; 15</td>
<td>Variable not measured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Or any dose Dobutamine</td>
<td>Or Adrenaline ≤ 0.1</td>
<td>Or Adrenaline &gt; 0.1</td>
<td>Or Noradrenaline &gt; 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Or any Metaraminol</td>
<td>Or any Vasopressin</td>
<td>Or any Metaraminol</td>
<td>Or any Phenylephrine</td>
</tr>
</tbody>
</table>

**Study Period**

**DD12 Date and time pt ready for extubation**

Enter the date and time that the patient has been deemed clinically “ready for extubation”.

Please write the date in the format 1/01/2011 to indicate 1st January 2011. Please write the time using the 24-hour clock as follows: 13:55 for 1:55pm.

**DD13 SOFA score**

Please record the following components of the Sequential Organ Failure (SOFA) score. For this data point, these values reflect the variables obtained immediately prior to extubation.

Please note that if the variable has not been measured – record “9”.

Use the table above and include as part of the patient CRFs to calculate and record SOFA.

**Respiratory component** - please use the table above to assign a score reflective of the SOFA respiratory score on admission. Use the first arterial blood gas measured on arrival to the CVICU to calculate \( \text{PaO}_2 / \text{FiO}_2 \) ratio and record in DD13.
HOT-AS study: Data Dictionary January 2011

Cardiovascular component – please use the table above to assign a score reflective of the SOFA cardiovascular score on admission. Use the first documented observations on admission to CVICU. Record the SOFA score in DD13.

RENAL component - if documented prior to extubation record the creatinine or urine output as follows. Record the SOFA score in DD13. Where creatinine has not been measured, urine output for the time available can be extrapolated to provide a 24 hour total to determine whether urine output is < 500mls (score = 3) or < 200mls (score = 4).

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Creatinine (μmol/L)</td>
<td>&lt; 110</td>
<td>110 - 170</td>
<td>171 - 299</td>
<td>300 - 440</td>
<td>&gt; 440</td>
<td>Variable not measured</td>
</tr>
<tr>
<td>OR urine output</td>
<td>Or &lt; 500 ml/day</td>
<td>Or &lt; 200 ml/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DD14 Date/time study therapy commenced

Please write the date in the format 1/01/2011 to indicate 1st January 2011. Please write the time using the 24 hour clock as follows: 13:55 for 1:55pm.

DD15 Allocated to receive

Please circle which arm of the study the patient was allocated to. Choose “NHF” if patient allocated to intervention arm to receive nasal high flow (AIRVO™ and Optiflow™) or choose “Standard Care” if patient allocated to receive low flow oxygen via nasal prongs or facemask.

DD16 Ventilation immediately prior to extubation

<table>
<thead>
<tr>
<th>Mode</th>
<th>FiO2%</th>
<th>PEEP</th>
<th>PS</th>
<th>CPAP</th>
</tr>
</thead>
</table>

Complete this table with the values measured immediately prior to extubation.

Mode – describe the mode of ventilation delivered by the patient immediately prior to extubation e.g. CPAP; CPAP + PS; MMV; etc.

FiO2 – record the percentage FiO2 delivered to the patient immediately prior to extubation

PEEP – record the positive end expiratory pressure – if used - (PEEP) in cmH2O delivered to the patient immediately prior to extubation.
HOT-AS study: Data Dictionary January 2011

PS – record the pressure support - if used – (PS) in cmH₂O delivered to the patient immediately prior to extubation.

DD17 Table 1. Arterial Blood Gas Measurements and Cardiovascular Parameters
For each of the variables listed please record the value measured at the corresponding time point. These time points are: Immediately prior to extubation; 30mins post extubation; 4hours post extubation and on Day 1 immediately prior to transfer to ward or at 1200 hours if patient remains in CVICU/HDU.

NB. If the variable has not been measured and will never be available please cross through this box. 

DD18 pH
Record the patient’s pH measured at each time point.

DD19 pCO₂ (kPa)
Record the patient’s arterial pCO₂ measured at each time point. Please record in kPa.

DD20 pO₂ (kPa)
Record the patient’s arterial pO₂ measured at each time point. Please record in kPa.

DD21 HR (beats/min)
Record the patient’s heart rate in beats per minute as documented on the CVICU bypass chart. Please document if the patient is in any rhythm other than sinus rhythm at this time.

DD22 RR (breaths/min)
Record the patient’s respiratory rate in breaths per minute as documented on the CVICU bypass chart.

DD23 MAP (mmHg)
Record the patient’s mean arterial pressure (MAP) in mmHg as documented on the CVICU bypass chart. If there is no documented MAP please use the following formula to calculate MAP:

MAP = 2/3 DBP + 1/3 SBP.

DD24 SpO₂ %
Record the patient’s peripheral oxygen saturation as measured by pulse oximetry and documented on the CVICU bypass chart. If there is no recorded measure on the bypass chart please record the SpO₂ on the corresponding arterial blood gas.
**HOT-AS study: Data Dictionary January 2011**

**DD25 FiO₂%**
Record the amount of oxygen documented as being delivered to the patient.

If the patient is currently being administered oxygen via a low flow face mask or nasal cannulae please use the following table to record FiO₂:

<table>
<thead>
<tr>
<th>Nasal Cannulae</th>
<th>Flow Rate L/min</th>
<th>Estimated FiO₂ %</th>
<th>Face Mask</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flow Rate L/min</td>
<td>Estimated FiO₂ %</td>
<td></td>
</tr>
<tr>
<td>1 L</td>
<td>5 L</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>2 L</td>
<td>6 L</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>3 L</td>
<td>7 L</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>4 L</td>
<td>8 L</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>5 L</td>
<td>9 L</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>6 L</td>
<td>10 L</td>
<td>55%</td>
<td></td>
</tr>
</tbody>
</table>

**DD26 Method of Oxygen delivery**
Please record the current method of oxygen delivery e.g. NHF; FM (low flow/Hudson facemask); NP (low flow nasal prongs); HFFM (high flow humidified face mask); if another device is used please describe.

**DD27 Patient Comfort Score**
At the stated time points, the patients will be asked the following question:

"On a scale of 0 – 10, how comfortable do you find the oxygen mask/prongs that you are wearing? 0 = not comfortable at all  10 = extremely comfortable"

Please record the value stated by the patient and recorded on the bedside form.

**DD28 Table 2. Daily data.**
For each of the variables listed please record the value measured at 0900 hours. These measurements should be made on: Day 1 post-op; Day 2 post-op; Day 3 Post-op and Day of discharge (-1 day). Some of these measures will be performed by the research nurse when attending the patient. Others will be recorded from the Ward/ICU observation/bypass chart as appropriate. For each of the time points please record the date.

**DD29 HR**
Record the patient’s heart rate in beats per minute @ 09:00 hours.
HOT-AS study: Data Dictionary January 2011

**DD30 RR**
Record the patient’s respiratory rate in breaths per minute @ 09:00 hours.

**DD31 SBP/DBP**
Record the patient’s systolic and diastolic blood pressure @ 09:00 hours. This will then be used to calculate MAP.

**DD32 SpO₂ %**
Using a pulse oximeter record the patient’s SpO₂ % @ 09:00 hours.

**DD33 FiO₂ %**
Record the delivered FiO₂ @ 09:00 hours. If the patient is not receiving ANY supplementary oxygen and is breathing on room air please record 21%.

**DD34 Method of O₂ delivery**
Please record the current method of oxygen delivery e.g. NHF; FM (low flow/Hudson facemask); NP (low flow nasal prongs); HFFM (high flow humidified face mask); if another device is used please describe.

**DD35 Weight**
Please record the patient weight measured that day in kilograms. Round to the nearest 0.1kg.

**DD36 Number of physiotherapy sessions today**
Please record the number of physiotherapy sessions received today by the patient and documented in their medical record. These sessions will have been conducted by a registered physiotherapist or student physiotherapist and does not include informal physiotherapy delivered by nursing staff.

**DD37 Did patient require an escalation in respiratory support?**
Please circle “Yes” or “No” to describe whether the patient required an escalation in respiratory support today. If yes is selected please identify the reason the escalation was required by selecting one or more of the following options:

1. Increased dyspnoea ±
2. Tachypnoea - Respiratory rate ≥ 35 breaths/minute ±
3. Oxygen saturation (SpO₂) ≤ 90% ±
4. Heart rate ≥ 120 per minute (or > 30% increase above baseline) ±
5. Arterial pressure > 30 % increase above baseline ±
6. Anxiety, restlessness ±
7. Signs of increased work of breathing as seen by use of accessory muscles and abdominal paradox ±
HOT-AS study: Data Dictionary January 2011

8. Ratio of PaO₂ / FiO₂ <200 mmHg ±

Please also record the new mode of oxygen delivery; the new FiO₂% and the time the new therapy was commenced. This information will be found in the bedside data collection form; on the CVICU/HDU bypass chart; in the ward observation chart or in the patient medical notes.

DD38 Diuretics
Please record whether or not the patient received diuretic therapy today by selecting either “Yes” or “No”.

If yes is selected please describe which diuretic and the total daily dose administered for that post-operative day i.e. 07:01 – 07:00 hours

DD39 Patient Comfort Score
At 09:00 hours on day 2 post-op, please ask the patient the following question prior to removing the oxygen delivery device:

“On a scale of 0 – 10, how comfortable do you find the oxygen mask/prongs that you are wearing? 0 = not comfortable at all 10 = extremely comfortable”

Please record the value stated by the patient.

DD40 Table 3 Spirometry
Spirometry measurements will be undertaken in all patients randomised to the study at the following time points: baseline measurements at study consent and enrolment; day 2 and 3 post-op and as close to day of discharge as possible.

Please record date and time measurements were undertaken.

DD41 Performed by:
Please write name of person performing Spirometry

DD42 FVC
Record the calculated FVC for this patient for each measurement.

DD43 FEV₁
Please record the calculated FEV₁ for this patient for each measurement.

DD44 Comments
Please record any details of Spirometry measurements which may be of value. E.g. poor patient effort; pain issues; positioning; etc.

DD45 Table 4. Chest X-Ray
For the purposes of assessing atelectasis in study patients the routine post-operative chest x-rays will be used. These chest x-rays are routinely taken at baseline (return to the CVICU post-op); on day 1 and on day 3 post-op.
HOT-AS study: Data Dictionary January 2011

DD46 Chest x-ray taken
Please record “Yes” or “No” to ensure that the chest x-ray for the patient has been taken today. If chest x-ray NOT taken please record reason why.

DD47 Downloaded and Stored
Please record date and sign to ensure that chest x-rays for study have patients have been downloaded, de-identified and stored appropriately.

DD48 Oxygen delivery on discharge from CVICU/HDU
Please record the following details of oxygen therapy immediately prior to discharge from CVICU/HDU.

Mode of oxygen delivery
FiO2 _____

Flow ______ lpm where patient is receiving nasal high flow oxygen.

DD49 Date and Time of discontinuation of Oxygen
Please enter the date and time oxygen therapy is discontinued. This should in most cases be 0900hours of the second postoperative day however we need to allow for the fact that some patients may have therapy discontinued earlier for other reasons e.g. poor compliance; escalation of therapy; etc.

DD50 Was study treatment discontinued prior to 0900hours?
Circle yes or no as appropriate

DD51 Reason
If study treatment was discontinued prematurely please record the reason e.g. patient non-compliant; complained of heat; did not like; required escalation etc.

Use free text.

DD52 Ongoing oxygen therapy
If discontinued early please record what therapy the patient then received. E.g. flow decreased to 40 L/min; standard oxygen therapy nasal cannulae; air...

DD53 Prior to discharge from hospital
Please record the following details as close to hospital discharge as possible.

DD54 Antibiotic therapy for suspected chest infection
Please review patient medical notes and medication charts and record if the patient was prescribed antibiotics for a suspected or confirmed chest infection prior to discharge from the ward. Please record details including any of the following information if available:

Date and time first suspected; date and time antibiotics first taken; name and dose of antibiotics; organism cultured if available. Also record if this resulted in further oxygen therapy; readmission to CVICU/HDU or escalation in oxygen therapy
DD55 Oxygen Therapy after discontinuation of study intervention

Please indicate whether the patient received any further oxygen therapy after discontinuation of study intervention at 09:00 hours on day 2 post-op.

DD56 Date and time patient last received oxygen

Please record date and time patient last received any oxygen therapy.
HOT-AS study: Data Dictionary January 2011

Day 28 Outcome Interview
Patients should be followed up 28 days after study randomisation. If you are unable to make contact on day 28 then you are required to call them back on subsequent days until contact is made.

Please complete the Telephone Contact Log each time a call is attempted.

Because follow-up should routinely occur as close to day 28 as possible please consider the following:

1. Please do not routinely attempt to follow-up prior to day 28.
2. If you can only contact a patient after day 28 e.g. day 30, then ask the questions such that you obtain an answer that indicates the person’s status on the day of contact i.e. day 30. For example, if you contact the patient on day 30 and they have just been prescribed antibiotics for a chest infection by their G.P but they were not on antibiotics at day 28 then please record “Yes” at DT5 for “Has the patient seen their GP/attended medical facility for respiratory illness”
3. Please ensure that others are aware that a follow-up call is due if you are to be away.
   One handy way of ensuring this is to utilise Microsoft Outlook to schedule an appointment in peoples calendars that way they are aware that a phone call is due.
   Schedule using the patient’s name and “Day 28 follow-up call HOT-AS” in the subject line.

Please complete the Day 28 follow-up form at time of phone call and place in patient study folder.

DT1 Phone call completed
Please record date and time successful contact was made for day 28 follow-up phone call.

DT2 Interview completed with
Please record whether the interview was conducted with the patient or a proxy e.g. caregiver; spouse; relative; friend or whanau member.

DT3 Status at day 28
Please select the option that best describes the location and vital status of the patient on the actual date that contact is made.

a. Patient alive and discharged from hospital
b. Deceased
c. Alive and still in study ICU - patients alive and still inpatients in CVICU/HDU will require follow-up until hospital discharge.
d. Alive and still in study hospital – patients alive and still inpatients at Auckland City Hospital will require follow-up until hospital discharge.
HOT-AS study: Data Dictionary January 2011

DT4 If patient is deceased
a. Date of death – please record date of death
b. Location – please record where patient died e.g. home; hospital; ICU
c. Primary cause of death – please record primary reason of death
d. Underlying causes – please record any underlying conditions that may have contributed to mortality

DT5 Has the patient seen their GP/attended medical facility for respiratory illness
Ask patient/proxy whether or not they have attended their GP or other medical facility e.g. A&E; after hours clinic etc. For signs and symptoms of a respiratory like illness.

If they have please record “Yes” and answer the following:
   Date: please record the date that the patient visited the GP or other facility
   Please record whether or not they were prescribed antibiotics for this episode.

DT6 Intensive Care Discharge
Please record date and time patient was discharged from the CVICU/HDU after their initial surgery.

DT7 Hospital Discharge
Please record date and time patient was discharged from the study hospital following this surgery.

DT8 Was patient readmitted to ICU with respiratory complications
Please record whether or not the patient was readmitted to the CVICU/HDU with a primary diagnosis of respiratory complication following their initial discharge from CVICU/HDU.

If “Yes” is selected please record the following:
   a. Date and Time of readmission to CVICU/HDU
   b. Reason for readmission
   c. Whether the patient required
      i. nasal high flow (NHF)
      ii. noninvasive ventilation (NIV = facemask CPAP or BiPAP)
      iii. reintubation and mechanical ventilation
      iv. antibiotic therapy prescribed for presumed or proven chest infection

Please sign and date when completed.
HOT-AS study: Data Dictionary January 2011

Serious Adverse Event Report
The serious adverse event (SAE) report is an essential study instrument which will allow complete and accurate reporting of any adverse events by the principal investigator to the ethics committee in a timely fashion.

As per the ICH-GCP standards an SAE is defined as: “any untoward medical occurrence that, at any dose: results in death, is life-threatening (i.e. the patient was at risk of death at the time of the event. It does not refer to an event that might hypothetically have caused death had it been more severe than it was), requires prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or results in congenital anomaly or birth defect”.

Any and all SAEs should be reported to Rachael or Shay immediately. They may also require to be reported to the Northern X regional ethics committee. It will be the responsibility of the principal investigator to ensure that all appropriate reporting requirements are met.

AE1 Event.
Briefly describe the event.

AE2 Date of Onset of Event
Please record the date that the event first become evident.

AE3 Initial event or follow-up
Please indicate whether this is a report of the initial event or a follow-up on a previous event.

AE4 Narrative of Event
Describe the SAE as accurately and concisely as possible. Use standard medical terminology where appropriate. Be specific.

AE5 Type of serious adverse event.
As per ICH-GCP the event should result in one of the five following consequences. If the untoward event you are reporting did not result in one of these five consequences then it may not be an SAE. Please discuss with Rachael or Shay.

Select one of the following:

a. Resulted in death Please also record date of death: ______/_____/_____
b. Life threatening in the opinion of the investigator or clinician responsible (i.e. the patient was at risk of death at the time of the event. It does not refer to an event that might hypothetically have caused death had it been more severe than it was).

c. Caused persistent or significant disability/incapacity
d. Prolonged existing hospitalisation
e. Resulted in congenital anomaly or birth defect in offspring

AE6 Causality
Please record whether, in your opinion, the SAE was related to study procedures. You may chose whether you think it may have possibly, probably or definitely be related.
AE7 Action Taken
Describe whether or not intervention was required.
If intervention was required please describe in detail what was done and by whom.

AE8 Outcome of Adverse Event
Please describe whether the outcome is unknown; ongoing or resolved. If you select resolved please record the date of resolution.

AE9 Signature
Please ensure that this form is signed by the person completing. Please ensure that the name of person completing and signature are legible.

It must also be signed by the principal investigator reporting the SAE.
Telephone Contact Log
The telephone contact log is a required part of the HOT-AS study and must be routinely completed when attempting to follow-up patients enrolled into the HOT-AS study at day 28.

Complete ALL details for each attempt to contact a patient (or proxy) for day 28 follow-up.

Pt Study Number
Enter the patient study number allocated to this patient on study enrolment

Day 28 due (Date)
Enter the date that the day 28 follow-up phone call is due. This is calculated as 28 days after study randomisation.

Follow-up attempt Date/Time
Please record the date and time that this phone call was attempted

Outcome
Please record the result of this phone call as follows:

Completed = patient or proxy contacted and day 28 form completed
Not completed = phone call unanswered/ not completed

If not completed, you should continue to attempt to contact the patient and record all further attempts until day 28 has been successfully completed.
HOT-AS study: Data Dictionary January 2011

AIRVO™ Disinfection Log

Set-Up

Record the Set-Up being disinfected.

Date

Record the date that disinfection is completed.

Time

Record the time that disinfection is completed hh:mm

Cycle No.

Record the cycle number displayed on the AIRVO™ humidifier.

Please complete form by writing your name and signing the form.
Appendix 1. Glasgow Coma Scale (GCS) worksheet.

To obtain GCS, add together the best verbal response score, the best motor response score and the best eye opening score. For intubated patients use the last recorded verbal score prior to intubation. For sedated patients use the last recorded score prior to administration of sedation.

<table>
<thead>
<tr>
<th>Motor Response</th>
<th>Verbal Response</th>
<th>Eye Opening</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Obey</td>
<td>5 Oriented</td>
<td>4 Spontaneous</td>
</tr>
<tr>
<td>5 Localises</td>
<td>4 Confused</td>
<td>3 To command</td>
</tr>
<tr>
<td>4 Normal flexion (withdraws)</td>
<td>3 Inappropriate</td>
<td>2 To pain</td>
</tr>
<tr>
<td>3 Abnormal flexion (decerebrate)</td>
<td>2 Incomprehensible</td>
<td>1 No response</td>
</tr>
<tr>
<td>2 Extension (decerebrate)</td>
<td>1 No response</td>
<td></td>
</tr>
<tr>
<td>1 No response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The HOT-AS Study

High flow nasal Oxygen Therapy in patients After cardiac Surgery

Policy and Procedures Manual
Appendix C.


Contact Information:

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Study Committee
Rachael Parke
Shay McGuinness
A/Prof Robyn Dixon, School of Nursing, The University of Auckland
A/Prof Andrew Jull, School of Nursing, The University of Auckland

If you have any questions regarding this project please do not hesitate to contact in the first instance Rachael (021893176) or Shay (021324771). If Rachael or Shay are unavailable please contact Andrew (0212433772) or Robyn (021702330).

For timely response to email queries please ensure email is sent to both Rachael and Shay.
Appendix C.


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Case Report Forms

All study case report forms (CRFs) are available on the N: drive as follows:

N:/Groups/ICUResearch/Common/HOTAS/StudyDocs

Please use these originals to download and copy further copies as needed.

When complete please store in the filing cabinet in the research office in the dedicated study drawer.

Study Run-in Phase

A run-in phase comprising 10 complete patients will be conducted to:

- assist site investigators and research coordinators in identifying eligible patients
- allow site investigators and research coordinators to educate the participating centre on study protocols and procedures
- familiarise the team with data collection tools and key study procedures

At the end of the run-in phase the management committee will meet to discuss any changes to study procedures. Once this is complete then the formal study will be undertaken.

Timing of screening, study entry, protocol start, study end and other key events.

Timing of screening

- Patient can be screened for eligibility when waitlisted for surgery; when they attend preadmission clinic or on the ward prior to surgery. This may include Ward 42, Ward 31 or CCU.
- For detailed inclusion and exclusion criteria please see Appendix 1.

Study entry

Patients are considered enrolled into the trial once informed consent is obtained.
Appendix C.


Protocol Commencement
Patients will be deemed to be eligible for continued participation and randomisation into this study as long as the following criteria are met:

- Patient is ready for extubation prior to 1000 hours day after surgery

At the point in time where the patient is deemed "ready for extubation" the trial protocol must be commenced immediately.

1. Patient to be rescreened to ensure continued eligibility
2. Randomisation envelope opened
3. Study intervention prepared
4. Blood gas analysis performed prior to extubation if not already taken in the previous 45 minutes

It is anticipated that the above should take no longer than 20 minutes to complete.

Study End points
All patients will be followed up at:

- 0900 hours Day 2 post-op for discontinuation of study intervention
- 0900 hours Day 3 post-op for study procedures
- Day of discharge from hospital (± 1 day) for study procedures
- Day 28 phone-call (can occur up to 5 days after day 28 days)

Readmission to the ICU/HDU
At point of readmission to the ICU/HDU, the treating clinician should determine the appropriate method of oxygen delivery for the patient.
Please record readmission to the ICU/HDU in the CRF.
Please record any escalation in oxygen therapy in the CRF.

If the patient is readmitted to the ICU prior to day 3 please ensure that all study procedures are completed as appropriate e.g. chest x-ray; cardiorespiratory variables.

If the patient remains in the ICU/HDU by day 28 post enrolment then please complete day 28 follow-up form.

IMPORTANT STUDY INTERVENTION AND RELATED TOOLS AND PROCEDURES

Study Intervention; Discontinuation if Study Therapy; Escalation of Therapy and Related Tools and Procedures

Study Intervention
If randomised to the intervention arm, the patient will receive NHF via the AIRVO™ system and Optiflow™ interface at a flow rate of 45 L/min – FiO₂ (fraction of inspired oxygen) as determined by bedside clinician to maintain SpO₂ > 93%.

Control group
If the patient is randomised to the control group then they will receive standard care, which may include oxygen therapy at 2 - 4 L/min via either simple facemask or nasal prongs titrated by the bedside clinician to maintain SpO₂ > 93%.

Discontinuation of Study Therapy
Allocated therapy will be continued until 0900 hours day 2 post-operative at which point study therapy will be discontinued – in Ward 42 or in CVICU/HDU - in conjunction with the CVICU research nurses and ongoing requirement for oxygen therapy assessed.

Escalation of Therapy up to 1000hrs day 2 post-operative
A protocol will guide clinicians as to what defines the moment when patients could be said to require increasing respiratory support (Appendix 2).
If this occurs, the next step would be to provide:

Intervention Arm: non-invasive ventilation and/or reintubation and mechanical ventilation as necessary.

Control Arm: high flow humidified facemask oxygen therapy and/or non-invasive ventilation, and/or reintubation and mechanical ventilation as necessary.

Note, the control arm will not be offered nasal high flow as a rescue therapy.

At all times, the final decision to escalate therapy and what therapy will be deemed most appropriate for the patient will be left to the clinician responsible for the patient.

AIRVO™ System

At all times a clean and disinfected AIRVO™ system (comprising the AIRVO flow generator, power supply and oxygen cylinder mounted on a transportable pole) will be available in the CVICU ready for patients who may be randomised to the intervention arm of the study.
All study personnel will be trained in the following set-up; cleaning; disinfection and storage procedures.
Study personnel will be responsible for ensuring that all Ward and ICU/HDU staff caring for patients enrolled in the HOT-AS study are trained in proper use of the AIRVO™ system.
A log will be maintained recording training given.

Set-up

Equipment required:
1. AIRVO™ system
2. AIRVO™ circuit kit including humidifier chamber; chamber adapter; breathing tube
3. Optiflow™ patient interface
4. Sterile water

Set-up involves 8 steps:
1. Install the autofil water chamber
   a. Fit the chamber adapter
   b. Slot the water chamber into the AIRVO™
2. Connect the sterile water and open vent cap
3. Check water level is below the mark
4. Connect heated breathing tube
   a. Connect blue limb to the top of AIRVO™
      i. Slide blue sleeve up
      ii. Attach to AIRVO™
      iii. Ensure blue sleeve is slid down and locked into place
5. Plug the UPS power supply into Electricity and turn AIRVO™ on
6. Check disinfection symbol (do not use if disinfection symbol does not appear)
7. Confirm ready to use symbol is displayed
   a. When AIRVO™ reaches 30°C it is ready to be applied to patient and will complete warming to 37°C when in use.
8. Connect to Optiflow™ patient interface.
   a. Ensure AIRVO™ is below level of patient interface to reduce risk of water entrainment

Supplementary Oxygen
Oxygen may be delivered via the AIRVO™ at up to 60% FiO₂. In order to ensure that oxygen therapy is delivered appropriately, oxygen must be attached to the AIRVO™ system using an oxygen inlet extension kit. Attach one end of extension kit to pendent/wall oxygen flow meter. The oxygen cylinder attached to the pole stand is only to be used when transferring the patient between bedspaces or when mobilising the patient away from a piped oxygen supply. Other end attaches to AIRVO™ at the filter holder - ensure a firm fit. Use the oxygen chart (on side of AIRVO™) to ensure correct oxygen flow selection and therefore oxygen delivery. Check and record oxygen saturation of patient. At discontinuation of therapy please ensure that oxygen is turned off at flow meter to ensure it does not build up within the humidifier.

Cleaning, Disinfection and Storage
Correct cleaning, disinfection and storage ensures prevention of cross contamination and infection. It is vital that this is done as soon as the AIRVO™ is removed from a patient. Once disconnected, return the unit to CVICU and commence the following procedure. The procedure will take approximately one hour and at completion the process must be recorded in the “AIRVO™ Disinfection log”.

Cleaning
Equipment required: cleaning sponges; cleaning wipes; lint-free cloth; cleaning solution

Procedure:
1. Ensure system is disconnected from electricity.
2. Remove interface; humidifier; breathing tubing and water bag and discard according to local policy.
3. Soak sponge in cleaning solution and use to thoroughly clean right hand elbow both from top port and from bottom of port. Ensure any dirt/debris is removed.
4. Rinse sponge in clean water (tap water is fine) and remove any residue from cleaning solution.
5. Clean outside of AIRVO™ unit with cleaning wipes and wipe dry with lint free cloth.
6. Immediately after completion of cleaning process commence disinfection.

Disinfection

Procedure:
1. Connect the red disinfection tubing to the AIRVO™ as follows
   a. Blue end to top port
   b. Opposite end to LEFT port
   c. Attach blue cap to RIGHT port
2. Connect to electricity
3. Press disinfection button
   The disinfection cycle will take 55 minutes and is complete when the countdown timer reaches “0”.
   When complete, hold down power button to turn off and disconnect from power supply.
4. Complete the “AIRVO™ disinfection log” detailing which setup has been disinfected; date, time, cycle number and person completing.

Storage
Either cover with clean dust cover or store with red disinfection tube in situ.
Store in a clean, dust free environment as per local policy.

Ordering AIRVO™ systems or Optiflow™ interfaces

Further consumables will be obtained from Fisher and Paykel Healthcare as follows:
contact Dawson Ward, Nurse Technician, CVICU. dward@adhb.govt.nz

Order once there are only 20 units remaining.

Please ensure Rachael and Shay and research coordinators are copied into the email.

If stock does not arrive in a timely fashion please ask Rachael or Shay for assistance.

Excess stock will be kept in the inside store room CVICU/HDU and only enough product for each of the available AIRVO™ setups will be kept on the floor to reduce risk of wastage/misplacement of stock.

Assessment of Patient Comfort

Patients in either arm of the study will be asked the following question by the bedside nurse at four hours post commencement of study therapy and again at discontinuation:
“On a scale of 0 – 10, how comfortable do you find the oxygen mask/prongs that you are wearing? 0 = not comfortable at all 10 = extremely comfortable”
This will be recorded in the CRF.
Appendix C.


Day 28 follow-up - Mortality and incidence of respiratory complications following discharge

Patients will be phoned 28 days (+ maximum 5 days) after enrolment to ascertain mortality and whether they have required treatment for respiratory complications since hospital discharge e.g. antibiotic therapy.

Prior to undertaking phone calls the research nurse will attempt to ascertain mortality through other means such as scanning electronic databases e.g. CONCERTO, CHIPS, etc for information to determine whether the patient is alive or dead. These systems may also give clues as to use of antibiotics.

At the time of the phone call the research nurse will introduce themselves and explain the purpose of their call reminding the patient of their participation in the HOT-AS study. Patients (or if necessary their relative/friend/whanau) will be asked about requirement for treatment for any chest infection/respiratory complications since discharge including the need for antibiotic therapy since discharge from hospital. Following completion of the phone call the nurse will complete the “Day 28 follow-up” CRF and place in patient study folder.

If patient is still in the study ICU or hospital at day 28 follow-up may be conducted at that location.
If the patient has died prior to day 28 the reason for death will be recorded in the CRF.

Chest X-ray

Routinely following cardiac surgery patients receive a Chest X-Ray on return to the ICU (baseline), day 1 and day 3. The CXR will subsequently be reviewed and scored for atelectasis by a radiologist blinded to treatment allocation. They will also note any abnormalities such as pneumothorax.

Scoring will be a lobar scoring of 0-3 summed for both lungs.
0=Normal
1=Plate or minor infiltrate
2=Moderate atelectasis
3=Total atelectasis

The sums of each lobe are added giving a maximum score for the lungs of 18.

This scoring system has been tested by the investigators and found to have similar sensitivity but a higher degree of specificity when compared to a previously published scoring system. The new score also performed better than the old score at predicting day 3 clinical status from the day 1 CXR.
**HOT-AS study: Policy and Procedures Manual January 2011**

X-rays will also be scored according to the previously published Richter Larsen score\textsuperscript{22} as follows:

The presence of atelectasis will be expressed by a 5-point score:

0 = clear lung fields
1 = plate-like atelectasis or slight infiltration
2 = partial atelectasis
3 = lobar atelectasis
4 = bilateral atelectasis

It will be the responsibility of the research nurse to ensure that patients enrolled in the HOT-AS study have chest x-rays undertaken as per the adult cardiac surgical pathway and as required by the study protocol. This will be recorded on the daily data log.

The research nurse will also download the three x-rays per patient, de-identify them by storing them with their allocated patient study number and then store them in the allocated folder on the N drive as follows:

N:/Groups/ICUResearch/Common/HOTAS/Xrays

It will be the responsibility of the principal investigator to ensure that the x-rays are stored securely and then forwarded to the radiologist in a timely fashion for interpretation.

The radiologist will use the x-ray report form to record atelectasis score and incidence of adverse event such as barotraumas or pneumothorax.

**Spirometry**

Will be performed at study enrolment, at 1000 hours day 2 post-op; 1000 hours day 3 post-op and again as close to day of discharge as possible to assess FVC and FEV\textsubscript{1}. Spirometry will be undertaken by the principal investigator or research nurse trained in the technique.

**Equipment required**

- Laptop
- Ultrasonic flow meter
- Spirette
- Mediwipes

**Procedure**

1. Attach Flow meter to USB port
2. Start laptop
3. Password = puppies
4. Click “Out of The Office” & enter
5. Control + Alt + Delete
6. User name = probesensor  Password = probesensor
7. On desktop select “Shortcut to WBreath” - double click
Appendix C.


8. Select “Sampling” - then “Duration
9. Change to 180 - OK
10. Ready for use
11. Ensure patient sitting upright
12. Instruct patient in Spirometry breathing technique
13. Start WBreath programme running by clicking on red/yellow arrow
14. Get patient to take biggest breath in then blow out hard and fast for as long as they can!
15. Have a breather then repeat...
16. Have a breather then repeat! You should have three big breaths.

To Save Waveforms...........
1. File - Save As - Open pt folder and save with file name e.g. HA001baseline; HA002 baseline etc.

To Save Data...........
1. F5 - breath analysis - OK
2. F6 - breath table - OK
3. Click “File” - “Export Breath Table”
4. Save in HOTAS study under patient study number (save as brt file)

To convert to Excel spreadsheet ...........
5. Open pt folder - Open excel spreadsheet - select appropriate visit
6. Data - Import external data - import data
7. Desktop - HOTAS study - pt study number - Under files of type click on Show All files dropdown box - double click on pt name
8. Select “delimited” - next - select space and tab - next - finish.
9. Existing worksheet - OK
10. File - Save

Download data to N:/Groups/ICUresearch/Common/HOTAS/Spirometry
Record results in baseline and daily data CRFs as appropriate.

Cleaning
Ensure that following procedure all equipment is wiped down with Mediwipes and stored cleanly.
Individual patient spirettes and nose clips to be stored in sealed plastic bag and labelled with patient ID label til next use.

Quality Control
Once per week a QC measurement will be performed by the principal investigator and stored. Data will be checked for consistency.
Appendix C.


Data
Download data to N:/Groups/ICUResearch/Common/HOTAS/Spirometry
Record results in baseline and daily data CRFs as appropriate.

Discontinuation of study intervention at 0900 hours Day 2 post-op
Note: this may occur either in Ward 42 or in CVICU/HDU depending on patient progress.

Either study intervention or control is to be discontinued at 0900 hours day 2 post-operatively as follows:
1. Locate nurse caring for study patient.
2. Discuss progress to date.
3. In conjunction with nurse or clinician caring for patient, discontinue study therapy.
4. Need for ongoing oxygen therapy should be assessed and discussed with treating clinician by measuring and recording respiratory rate and oxygen saturation.
Appendix C.


Appendix 1 – detailed inclusion and exclusion criteria.

**Inclusion criteria**
Patients will be screened and are eligible for inclusion in the study if all of the following criteria are met:
- over 18 years of age
- informed consent obtained
- scheduled for cardiac surgery involving full median sternotomy.
- cardiac surgery = CABG; valvular; CABG + valve
- patient not normally on NIV or oxygen therapy at home
- patient is extubated prior to 1000 hours day after surgery

**Exclusion criteria**
Patients will be excluded if any of the following exist:
- contraindication for NHF use e.g. severe nasal septal defect
- need for timely NIV e.g. CPAP to treat obstructive sleep apnoea
- previous recruitment into this study
- patient is likely to be intubated and mechanically ventilated for >24 hours following operation
- post-operatively patient is still ventilated at 1000 post-op day 1
Appendix C.


Appendix 2. Escalation of Therapy - up to 1000hrs day 2.

NB At all times the decision to escalate therapy and which respiratory therapy is most appropriate for the patient is at the discretion of the treating clinician. Patient safety takes priority.

Whilst on the study, a patient will be deemed to have increasing requirements for respiratory support when one or more of the following criteria are met:

1. Increased dyspnoea ±
2. Tachypnoea - Respiratory rate ≥ 35 breaths/minute ±
3. Oxygen saturation (SpO₂) ≤ 90% ±
4. Heart rate ≥ 120 per minute (or > 30% increase above baseline) ±
5. Arterial pressure > 30% increase above baseline ±
6. Anxiety, restlessness ±
7. Signs of increased work of breathing as seen by use of accessory muscles and abdominal paradox ±
8. Ratio of PaO₂ / FiO₂ < 200 mmHg ±


Oxygen therapy should then be escalated as follows:

Intervention Arm:

Nasal High Flow

Non-invasive ventilation then if required ...

Reintubation and mechanical ventilation

Control Arm:

Standard care

High flow humidified facemask therapy then if required....

Non-invasive ventilation then if required ...

Reintubation and mechanical ventilation
Statistical Analysis Plan

The HOT-AS Study

High flow nasal Oxygen Therapy in patients After cardiac Surgery

Rachael Parke, Shay McGuinness, Andrew Jull, Robyn Dixon
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1 Introduction
The purpose of the statistical analysis plan is to provide an in-depth description of the statistical analysis that will be undertaken in the HOT-AS study. In line with other randomised controlled trials undertaken recently, the statistical analysis plan (SAP) has been completed and made public prior to completion of participant recruitment and data collection. As recommended, this SAP will be adhered to for final data analysis of this study in order to avoid or minimise bias arising from study findings. The SAP has been designed by the principal investigator and approved by the co-investigators and statistician.

The HOT-AS study is a single-centre randomised controlled trial comparing standard care to prophylactic nasal high flow oxygen therapy from the time of extubation through until 0900 hours on day 2 postoperative in patients undergoing cardiac surgery. This study is part of a programme of research partly funded by the Health Research Council of New Zealand and the Green Lane Research and Education Fund. Research in the CVICU is partially funded by an unrestricted grant from Fisher and Paykel Healthcare, New Zealand.

The trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000973011) and the trial protocol has been published in the International Journal of Nursing Studies.

2 Study overview

2.1 Objectives
The primary aim of the study is to determine whether the administration of prophylactic nasal high flow oxygen post-extubation improves pulmonary function in patients following cardiac surgery.

2.2 Study Design and Methodology.
A prospective, single centre, open label, randomised controlled trial will be undertaken.

A total of 340 patients will be randomised into this study. 170 patients each arm.

2.3 Randomisation
Randomisation will be performed using opaque, sealed envelopes, sequentially numbered. These envelopes will contain the unique patient identifier code and allocated study therapy details. Randomisation to treatment group will be done using a computer-generated random number table. Patients will be randomised in blocks of 12 to ensure even distribution of sample size between the two study arms.

Participants will be stratified according to body mass index (BMI). There will be two groups: BMI < 35 or BMI ≥ 35.

Participants will be randomised to treatment just prior to extubation and allocated therapy will be commenced as soon as participant is extubated.

2.4 Sample Size and Power
A recent audit of patients in the CVICU has demonstrated a 40% incidence of patients recording a $\text{SpO}_2$/FiO$_2$<44.5 on day 3 post-operative. As there is little published evidence to inform sample size calculations for this study, the following has been assumed and is determined to be both feasible and clinically meaningful for this population.

Therefore for this study it is assumed that the expected probability of failure in the control group is 0.4 and we would expect to reduce that probability down to 0.25 under the nasal high flow.
Assuming \( \alpha = 0.05 \) a sample size of 332 (166 per arm) would give a 90\% power to detect a treatment effect. We plan to randomise a total of 340 patients (170 per arm) in order to allow for a 3\% loss to follow-up rate.

2.5 Inclusion Criteria
Patients will be screened and are eligible for inclusion in the study if all of the following criteria are met:

- Over 18 years of age
- Informed consent obtained
- Scheduled for cardiac surgery involving full median sternotomy.
- Cardiac surgery = CABG; valvular; CABG + valve
- Patient not normally on NIV at home
- Patient is extubated prior to 1000 hours day on the morning after surgery

2.6 Exclusion criteria
Patients will be excluded if any of the following exist:

- Contraindication for NHF use e.g. severe nasal septal defect
- Need for timely NIV e.g. CPAP to treat obstructive sleep apnoea
- Previous recruitment into this study
- Patient is likely to be intubated and mechanically ventilated for >24 hours following operation
- Post-operatively patient is still ventilated at 1000 post-op day 1

3 Study Outcomes

3.1 Primary Outcome Measure
Improved pulmonary function demonstrated by \( \text{SpO}_2/\text{FiO}_2 \) ratio > 445 on post-op day 3.

3.2 Secondary Outcome Measures
- X-ray score for atelectasis
- Spirometry measurements – FVC; FEV\(_1\)
- Readmission to ICU for respiratory causes
- ICU length of stay
- Hospital length of stay
- Mortality and incidence of respiratory complications at day 28
- Respiratory Rate
- Oxygenation variables - measured p\(_{O_2}\) and p\(_{CO_2}\)
- Use of adjunctive respiratory support therapies and escalation of respiratory support
• Adverse events such as barotrauma and pneumothorax
• Patient comfort during administration of oxygen therapy

3.3 Definition of Variables

3.3.1 $\text{PaO}_2/\text{FiO}_2$ ratio
The ratio of partial pressure of arterial $O_2$ to the fraction of inspired $O_2$ will be determined from the arterial blood gas taken prior to extubation, at 30 minutes and four hours post commencement of study therapy and again prior to discharge from ICU or at 0900 hours day 2 whichever occurs first.

3.3.2 Cardiovascular Parameters
Heart rate, mean arterial pressure, oxygen saturation, central venous pressure and respiratory rate will be measured. $\%\text{FiO}_2$ and gas flow rate will also be recorded.

3.3.3 $\text{SpO}_2/\text{FiO}_2$ ratio
The ratio of oxygen saturation as measured by pulse oximetry to the fraction of inspired $O_2$ will be determined at 0900 hours on day 3 and on day of discharge from the hospital.

3.3.4 Chest X-Ray score for atelectasis
Routinely following cardiac surgery patients receive a Chest X-Ray (CXR) on return to the ICU (baseline), day 1 and day 3 postoperative. These CXRs will be reviewed and scored for atelectasis by a radiologist blinded to treatment allocation. They will also note any abnormalities such as pneumothorax. In order to minimise observer bias, 10% of CXRs will be scored by a second radiologist. The scoring system is as follows:

Scoring will be a lobar scoring of 0-3 summed for both lungs.

0=Normal
1=Plate or minor infiltrate
2=Moderate atelectasis
3=Total atelectasis

The sums of each lobe are added giving a maximum score for the lungs of 18.

X-rays will also be scored according to the previously published Richter Larsen score[6] as follows:

The presence of atelectasis will be expressed by a 5-point score:

0 = clear lung fields
1 = plate-like atelectasis or slight infiltration
2 = partial atelectasis
3 = lobar atelectasis
4 = bilateral atelectasis
3.3.5 Spirometry
Spirometry will be performed at study enrolment, at 1000 hours days 2 and 3 post-op; and again on day of discharge or day 7 if remaining in hospital, to record FVC and FEV1.

3.3.6 Patient comfort
Patients in both arms of the study will be asked the following question by the bedside nurse or research nurse at four hours post commencement of allocated therapy, on day 1 and day 2:

"On a scale of 0 – 10, how comfortable do you find the oxygen mask/prongs that you are wearing? 0 = not comfortable at all 10 = extremely comfortable"

3.3.7 Day 28 mortality and incidence of respiratory complications.
Patients will be phoned one month after enrolment to ascertain mortality and whether they have required treatment for respiratory complications since hospital discharge e.g. antibiotic therapy.

3.3.8 Use of adjunctive respiratory support therapy
Use of adjunctive respiratory support therapies e.g. non-invasive ventilation; requirement for reintubation/mechanical ventilation; details of total length of time on oxygen therapy will be recorded. Number of physiotherapy sessions will also be recorded whilst patient is admitted to hospital.

3.3.9 Incidence of respiratory complications
Use of antibiotic therapy for presumed or confirmed chest infection will be collected whilst patient is in the hospital.

3.3.10 Adverse Events
Any signs of barotrauma and/or pneumothorax will be reported on by the radiologist assessing the chest x-rays.

Any signs or symptoms of pressure area formation will be documented.

3.4 Analysis principles
1. All analyses will be conducted on an intention-to-treat basis. The only exception will be patients where consent to use their data in the analysis is withheld or withdrawn.
2. All tests are two sided with alpha of 5%.
3. All statistical analyses will be unadjusted except where indicated. Reports will carry both crude and adjusted data – each clearly indicated. Conclusions drawn will be based on the primary outcome analysis.
4. Subgroup analyses will be carried out irrespective of whether there is a significant effect of treatment on the primary outcome. These analyses will be considered exploratory in nature.
5. Missing values will not be imputed unless specified otherwise. We will report the number of observations used in the analysis.
3.5 Data collection Follow-up

The different stages of data collection and follow-up can be summarized in the table below:

<table>
<thead>
<tr>
<th>Form</th>
<th>Period of study</th>
<th>Data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline Data</td>
<td>Height; weight; BMI; age; sex; ethnicity; medical history including</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ejection fraction, creatinine, previous measured spirometry; smoking status;</td>
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<tr>
<td></td>
<td></td>
<td>presence of diabetes, hypercholesterolaemia, hypertension, cerebrovascular</td>
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<tr>
<td></td>
<td></td>
<td>or peripheral vascular disease, asthma or COPD; NYHA score; EUROSCORE;</td>
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<tr>
<td></td>
<td></td>
<td>medications including diuretics, inhalers and steroids; baseline measurements</td>
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<tr>
<td></td>
<td></td>
<td>of SpO₂(%), respiratory rate, heart rate, blood pressure, FEV₁ and FVC.</td>
</tr>
<tr>
<td>2</td>
<td>Daily Data</td>
<td>The following will be recorded on admission:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Date and time of admission to hospital and ICU</td>
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<tr>
<td></td>
<td></td>
<td>• Date and time of intubation and extubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• operative procedure</td>
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<tr>
<td></td>
<td></td>
<td>• length of surgery and time on bypass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• APACHE II score and SOFA score (respiratory and cardiovascular) on admission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The following will be recorded during the study period:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SOFA score (respiratory, cardiovascular and renal) prior to extubation</td>
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<td></td>
<td>• Ventilation details (mode, oxygen, pressure) prior to extubation</td>
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<tr>
<td></td>
<td></td>
<td>• Arterial blood gas measurements and cardiovascular parameters immediately</td>
</tr>
<tr>
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<td></td>
<td>prior to extubation, 30mins and 4 hours post extubation and on day 1 prior to</td>
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<td></td>
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<td>transfer to ward or at midday if still in ICU</td>
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<td></td>
<td></td>
<td>• Weight, physiotherapy interventions; requirement for escalation of</td>
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<tr>
<td></td>
<td></td>
<td>respiratory support therapy and use of diuretics on days 1, 2 and 3</td>
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<td></td>
<td></td>
<td>postoperative and on day of discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient comfort score at 4 hours post extubation, on day 1 and day 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>post-operative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Heart rate, respiratory rate, blood pressure, SpO₂, FiO₂ and method of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oxygen delivery on days 2 and 3 postoperative and on day of discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FEV₁ and FVC on days 2 and 3 postoperative and on day of discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chest x-ray score for atelectasis on x-rays taken on return to ICU and days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 and 3 postoperative</td>
</tr>
</tbody>
</table>
Appendix C. HOT-AS study Statistical Analysis Plan March 2012

<table>
<thead>
<tr>
<th></th>
<th>Oxygen therapy on transfer to ward and date and time of discontinuation of oxygen therapy will be recorded. At hospital discharge requirement for antibiotic therapy for suspected chest infection will be recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><strong>28 Day Follow-up</strong></td>
</tr>
<tr>
<td></td>
<td>Vital status (alive or dead) at day 28. Place, date and cause of death; whether patient has attended their GP for a respiratory illness and whether or not they received antibiotics; readmission to the ICU for respiratory complications; requirement for NIV and/or reintubation.</td>
</tr>
</tbody>
</table>

Due to the inclusion criteria of the patient only being randomised if they are extubated prior to 1000 hours day 1 postoperative there are potentially two data sets for baseline data: the non-randomized patients and the randomized patients. Baseline data for both groups will be presented separately.

4 Statistical Analysis

4.1 CONSORT statement

The flow of patients through the study will be described in a CONSORT diagram (Figure 1).[7] All participants who were screened for inclusion in the study and/or invited to consider participation in the study will be accounted for in the CONSORT diagram and reasons for non-participation will be documented. The total number of patients enrolled will be presented as well the number who were randomised and the reasons for non-randomisation shown. Reasons for non-inclusion in data analysis will also be summarised e.g. lost to follow-up, withdrawal of data. Patients who withdraw from therapy will still be included in the analysis in the group which they were allocated to at the time of randomisation.
Figure 1. Flow of patients through study

4.2 Characteristics of patients and baseline comparisons
Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in either the body or a footnote in the corresponding summary table. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated in the list below. Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation or quantile points at 0.25, 0.5 and 0.75 where appropriate.
4.2.1 Baseline characteristics of patients
All patients enrolled in the study will have the following reported:

- Sex
- Age
- Ethnicity
- Height
- Weight
- BMI
- Primary diagnosis
- Co-morbidities
- EUROSCORE

4.2.2 Characteristics of patients on admission to ICU
- Operative admission diagnosis (number and % in categories a-d)
  a. Coronary artery bypass only (CABG)
  b. Valve replacement only
  c. Concomitant CABG and valve replacement
  d. Other
- Length of time on cardiopulmonary bypass
- APACHE II score
- SOFA score
  a. Cardiovascular domain
  b. Respiratory domain
  (SOFA score domains will be analysed as continuous variables and as categorical variables divided into normal function (SOFA score 0) dysfunction (SOFA score 1-2) and failure: SOFA score 3-4).
- Length of ventilation

4.3 Process measures and concomitant therapies

4.3.1 Process measures

4.3.1.1 Day 1 – discharge
- Cardiovascular measurements including heart rate, mean arterial blood pressure
- Respiratory variables including pH, pCO₂, pO₂, respiratory rate, SpO₂, FiO₂, method of oxygen delivery
- Weight
- Number of physiotherapy sessions
- Use of diuretics
- Requirement for escalation of respiratory support
- Readmission to ICU for respiratory complications

4.3.1.2 Day 28 follow-up
- Status at day 28 – alive or deceased
- Incidence of respiratory complications

4.3.1.3 Other
- Hospital length of stay
  - Intensive care unit length of stay
- Comfort scores
- Presence of respiratory complications
- Oxygen free days
- Chest x-ray score
- Spirometry values of FEV₁ and FVC

4.4 Analysis
Data from the trial will be entered into an excel spreadsheet, and then extracted into STATA for analysis. All data analyses will be carried out on an intention-to-treat basis. Incidence rates and absolute differences (with corresponding NNTs) and 95% CIs will be obtained for binary variables in the first instance with subsequent multiple logistic regression adjusted for stratification factors. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow-up or death on the primary outcome. If important balance imbalances exist, these factors will also be entered into the regression analysis. Time to event data will be analysed using Cox regression modelling thereby taking into account known covariates and the varying times since randomisation. The proportionality assumption will be checked using standard graphical techniques. However, prior to undertaking any Cox regression modelling, the effectiveness of the interventions on time to outcome will be analysed using Kaplan-Meier curves to compare the differences between the two groups using the log rank test. Continuous data will be analysed using the appropriate parametric or non-parametric analysis after testing for normality.

The principal investigator and a statistician will conduct the analyses. The principal investigator will remain blind to study allocation until the final statistical report is complete.

4.4.1 Escalation of therapy
Patients for whom an escalation of respiratory support therapy was required will be presented (n and % in each category below)

- Required CPAP
- Required B/PAP
- Required intubation and mechanical ventilation

Reasons for escalation of therapy will also be summarised.
4.4.2 Discontinuation of study treatment
Patients for whom study treatment was permanently discontinued will be presented (n and % in each category below)

- Patient requested discontinuation
- Treatment discontinued by treating clinician
- Treatment discontinued due to serious adverse event
- Treatment discontinued for other reason

4.5 Primary Outcome
We will compare the mean SpO₂/FI O₂ ratio obtained on day 3 postoperative in each group by using standard Chi square test and a 95% confidence interval. Subsequent multiple logistic regression adjusted for stratification factors i.e. BMI. Sensitivity analysis will also be carried out to determine the effect of missing data from patients that are lost to follow-up or death on the primary outcome. If important imbalances exist, these factors will also be entered into the regression analysis.

4.6 Secondary outcomes
A standard Chi-square test and 95% CI testing the difference in proportion between two treatment groups will be used to assess the effect of treatment on binary or categorical outcomes, i.e. day 28 outcome, incidence of respiratory infection and use of antibiotics.

4.7 Safety Outcomes
Safety outcomes will be analysed via frequencies and percentages per treatment group. The difference in proportion of patients experiencing a particular event will be tested across treatment arm by means of a Chi-square test.

4.8 Subgroup analyses
It is planned that the following subgroup analyses will be conducted on the main outcome:

1. Sex (Male vs Female)
2. Ejection fraction (Ejection fraction ≤35% vs Ejection fraction >35%)
3. BMI >35 (BMI <35 vs BMI ≥35)
4. Coronary artery bypass surgery utilising left internal mammary artery

5 Tables and Figures

5.5 Planned tables will be included as follows:
1. Baseline characteristics of all enrolled study participants
2. Baseline characteristics of randomised participants vs non-randomised participants
3. Primary and secondary outcomes
4. Respiratory and cardiovascular parameters of randomised participants over the study period
5. Subgroup analyses
5.6 Figures will be included as follows:
   1. A CONSORT diagram describing patient flow through the study
   2. Kaplan Meier curve for oxygen free days.
6 References


Appendix D.

Appendix D: Oxygen Therapy in Non-intubated Patients in the Intensive Care Unit – a Point Prevalence Study

ADHB Approval

Ethics Approval

Data Collection Forms

Data Dictionary

Letter of Manuscript Endorsement ANZICS - CTG
### GENERAL PATIENT INFORMATION

1.01 ☐ ☐ Patient’s gender
1.02 ☐ ☐ Patient’s age (years)
1.03 ☐ ☐ 01/01/2001 ICU admission date (dd/mm/yyyy)
1.04 ☐ ☐ 12:12 ICU admission time (use 24 hour clock)

1.05 From where was the patient admitted to the ICU?

- ☐ Emergency Department
- ☐ Hospital Floor (Ward)
- ☐ Transfer from another ICU
- ☐ Transfer from another hospital (except from another ICU)
- ☐ Admitted from Operating Theatre following EMERGENCY surgery
- ☐ Admitted from Operating Theatre following ELECTIVE surgery

Tick one box only

1.06 ☐ ☐ Has this patient previously been in ICU in THIS hospital during THIS hospital admission?

1.07 ☐ ☐ Was this a POST-OPERATIVE admission to ICU? (Answer yes if patient admitted DIRECTLY from the operating theatre or the recovery room)

1.08 [APACHE III Code] [See list of codes in Data Dictionary, Appendix 1]

- ☐ ☐ ☐ ☐ If Yes, What is the APACHE III postoperative diagnostic code?
- ☐ ☐ ☐ ☐ If No, What is the APACHE III non-operative diagnostic code?

1.09 ☐ ☐ Patients weight (kg)
1.10 Was the above weight estimated or measured?

- ☐ Estimated
- ☐ Measured
## Appendix D.

### CTG POINT PREVALENCE

**ICU ADMISSION DATA – ALL PATIENTS (Age 16 and above)**

**Form 1**

| Hospital ID: | I __ I I | Patient ID: | I __ I |

### Patient Sub Category

#### Trauma

1.11 [ ] [ ]

- Was trauma the patient’s primary reason for hospital admission (include burns or any type of trauma including falls in the elderly)?
  - If no, go to question 1.19
  - If yes, go to question 1.12

Which of the following criteria for TRAUMA did the patient meet? (refer to manual for definitions)

1.12 [ ] [ ]

- An injury to the body produced by mechanical forces

1.13 [ ] [ ]

- A primary admission diagnosis of burns
  - If no, go to question 1.15
  - If yes, answer question 1.14

1.14 [ ] [ ]

- What was the percentage of body area of burns?

1.15 [ ] [ ]

- What was the last GCS prior to sedation?

1.16 [ ] [ ]

- Was the GCS recorded in the patient record or estimated from a description of the patient’s neurological state?
  - Recorded
  - Estimated

1.17 [ ] [ ]

- Was a cranial CT scan performed prior to ICU admission?
  - If no, go to question 1.19
  - If yes, answer question 1.18

1.18 [ ] [ ]

- Was there an abnormality on cranial CT consistent with acute traumatic brain injury?

### Sepsis on Study Day

1.19 [ ] [ ]

- Does the patient meet BOTH of the following criteria for sepsis today (refer to data dictionary for definitions)
  - a defined focus of infection (positive cultures not required)
  - 2 or more of the Systemic Inflammatory Response Syndrome criteria
    - Core temperature >38°C or <36°C.
    - WCC >12 x 10⁹/L or < 4 x 10⁹/L or > 10% immature neutrophils (Band forms)
    - Tachycardia - Heart rate >90 beats/minute
    - Tachypnoea - >20 breaths per minute or a PaCO₂ <32 mmHg or mechanical ventilation

### Acute Respiratory Distress Syndrome (ARDS) or Acute Lung Injury (ALI) on Study Day

1.20 [ ] [ ]

- Does the patient meet ALL of the following criteria for ARDS today (refer to data dictionary for definitions)
  - Bilateral diffuse alveolar infiltrates
  - A recognised risk factor for ARDS
  - PAOP (wedge pressure) < 18 mmHg or NO evidence of left atrial hypertension on echo or clinical grounds
  - $PaO_2/FiO_2 < 200$
  - If yes go to question 1.22. If no go to question 1.21

1.21 [ ] [ ]

- Does the patient meet ALL of the criteria for ALI but not ARDS today (refer to data dictionary for definitions)
  - As for ARDS except $PaO_2/FiO_2 < 300$
Appendix D.

**ICU ADMISSION DATA – ALL PATIENTS (Age 16 and above)**

**CTG POINT PREVALENCE**

<table>
<thead>
<tr>
<th>APACHE &amp; SOFA SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
</tr>
<tr>
<td>1.22</td>
</tr>
<tr>
<td>L</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>R</td>
</tr>
<tr>
<td>I</td>
</tr>
</tbody>
</table>

What was the total APACHE II score for the first 24 hours of the ICU admission? (Record the APACHE II from your ICU database, or if necessary derive the score using an APACHE II worksheet. See Data Dictionary, Appendix 3)

What was the chronic health points score (part C). If the patient had chronic health points, indicate all that apply below:

- Biopsy proven cirrhosis & documented portal hypertension (PH); episodes of upper GI bleeding due to PH; or prior episodes of hepatic failure/encephalopathy/coma
- Receiving chronic dialysis
- New York Heart Association Class IV – symptoms at rest
- Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (i.e. unable to climb stairs, perform household duties); or documented chronic hypoxia, hypercapnia, 2° polycythemia, severe pulmonary hypertension (>40mmHg) or respiratory dependency
- Patient has received therapy that suppresses resistance to infection, eg. immuno-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids, or has a disease sufficiently advanced to suppress resistance to infection (e.g. leukaemia, lymphoma, AIDS)

**SOFA Domains**

Please document each of the SOFA domains using data for the most deranged score within the 24 hr study period today (see Data Dictionary, Appendix 4).

- 1.24 | __ | SOFA Respiratory
- 1.25 | __ | SOFA Coagulation
- 1.26 | __ | SOFA Liver (Hepatic)
- 1.27 | __ | SOFA Cardiovascular
- 1.28 | __ | SOFA Renal

**ICU RESEARCH CAPACITY**

- 1.29 | __ | Is this patient enrolled in one (or more) interventional clinical trial?

  - If yes, go to question 1.30
  - If no, form is complete – go to form 2

- 1.30 | If this patient is enrolled in an interventional clinical trial is it: *(Can tick more than one)*

  - A fully sponsored commercial trial?
  - A CTG endorsed multicentre trial?
  - Another investigator initiated trial?

*This form is complete*
Appendix D.

Octogen Therapy — All Patients Form 2

Hospital ID: __________
Patient ID: __________

Important Information

Complete Form 2 for EVERY patient present in the ICU on the study day who is NOT mechanically ventilated/breathing through an endotracheal or tracheostomy tube. The aim of this study is to describe the oxygen therapy used on patients who are breathing through normal airways.

In addition to individual patient data, please also complete the unit level survey, once only per ICU.

Some questions need to be answered ‘now’ [the word ‘currently’ or ‘now’ appears in the question], which is whatever applies at whatever time you get to this patient’s bedside after the 10 am census. Other questions can be answered retrospectively at the end of the study day.

Answers to each question can be sourced from
1. Referring to the patient’s bedside monitor, flow chart or observation sheet
2. Asking the bedside nurse for information, if unknown then
3. Referring to patient’s medical record, if not documented or unclear then
4. Asking the attending medical staff

Oxygen Therapy

2.1 [ ] [ ] Is the patient currently intubated (orotracheal, nasotracheal or tracheostomy tube) or being ventilated invasively using a mechanical ventilator?

If yes, no further questions. Please go to Form 3, otherwise continue

2.2 [ ] [ ] Has this patient had open abdominal (not cardiac or thoracic) surgery with incision extending above the umbilicus during this hospital admission?

If no, go to question 2.6, otherwise continue

2.3 What was date of surgery? (dd/mm/yyyy) ________________

2.4 How urgent was the surgery? (choose one):

[ ] Elective [planned procedure with elective hospital admission or booked more than 48 hours preoperatively]

[ ] Acute [urgent or emergency procedure, which was unplanned at time of hospital admission]

2.5 What was the nature of the surgery? (choose one only)

[ ] Aortic or other major vascular surgery

[ ] GI perforation or rupture

[ ] GI bleeding

[ ] GI obstruction/neoplasm/bowel resection

[ ] GI perforation or rupture

[ ] Gastrectomy or oesophagectomy

[ ] Gallbladder or other biliary surgery

[ ] Liver surgery

[ ] Pancreatic surgery

[ ] Drainage of collection or abscess

[ ] Other procedure Specify ___________________________
2.6 [ ] [ ] Is this patient currently self ventilating but not receiving supplementary oxygen therapy by any means?

If yes, patient is breathing room air spontaneously. No further questions. Please go to Form 3. If no please continue.

2.7 [ ] [ ] Was the patient mechanically ventilated at any time during this admission to ICU?

If yes, what was the time and date of extubation (or decannulation of trachy)?

Time (24hr clock) 1_1_1_1_1_1_1

Date 1_1_1_1_1_1_1

2.8 When extubated (or decannulated), what was the first oxygen delivery device used? (choose one)

[ ] Simple nasul cannula
[ ] Simple facemask (Hudson or similar)
[ ] Restricted flow mask (Venturi or similar)
[ ] High Flow Face Mask (partial non-rebreather or similar)
[ ] Nasal high flow therapy
[ ] Noninvasive therapy (includes facemask or nasal mask CPAP or BiPAP)
[ ] Other Specify _______________________________

2.9 Currently (now), what is the indication for oxygen therapy? (choose the one most appropriate)

[ ] Documented hypoxaemia (blood gas)
[ ] Documented hypoxaemia (pulse oximetry)
[ ] Protocol driven
[ ] Routine but not protocolised
[ ] Other Specify _______________________________

2.10 Currently (now), what oxygen delivery device is being used? (choose one)

[ ] Simple nasal cannula
[ ] Simple facemask (Hudson or similar)
[ ] Restricted flow mask (Venturi or similar)
[ ] High Flow Face Mask (partial non-rebreather or similar)
[ ] Nasal high flow therapy
[ ] Noninvasive therapy (includes facemask or nasal mask CPAP or BiPAP)
[ ] Other Specify _______________________________
Appendix D.

OXYGEN THERAPY – ALL PATIENTS FORM 2

2.11 Why is the current oxygen delivery device being employed? (reasons may differ from question 2.7 - choose the one most appropriate)

☐ Unit protocol
☐ Unit practice (but no written protocol)
☐ Clinician decision (nurse initiated)
☐ Clinician decision (medical request)
☐ Patient requires positive airway pressure
☐ Patient requires humidification
☐ Other Specify __________________________

2.12 Has the patient used any of the following oxygen delivery in the previous 24 hours? [can have multiple answers]

☐ Simple nasal cannula
☐ Simple facemask (Hudson or similar)
☐ Restricted flow mask (Venturi or similar)
☐ High Flow Face Mask (partial non-rebreather or similar)
☐ Nasal high flow therapy
☐ Noninvasive therapy (includes facemask or nasal mask CPAP or BiPAP)
☐ Other Specify __________________________

Answer EITHER question 2.13 or question 2.14

2.13 What is the current oxygen flow rate ________ litres / min (round up to whole number)

2.14 What is the current inspired oxygen concentration ________ % [21 – 100%]

2.15 ☐ ☐ Is the oxygen humidified before delivery to the patient?
If no, go to question 2.17, otherwise continue

2.16 How is the oxygen being humidified?

☐ HME [Heat and Moisture Exchanger, includes HME filters, ‘Swedish nose’ etc]
☐ Active humidification [heated waterbath, Fisher and Paykel or equivalent]
☐ Other Specify __________________________

2.17 ☐ ☐ Is there a current medical order for oxygen therapy for this patient? [written order or written protocol]
If no, go to question 2.20, otherwise continue

2.18 ☐ ☐ Is the patient receiving what is ordered / in written protocol?
## CTG POINT PREVALENCE

### OXYGEN THERAPY – ALL PATIENTS FORM 2

<table>
<thead>
<tr>
<th>Hospital ID:</th>
<th>Patient ID:</th>
</tr>
</thead>
</table>

#### 2.19
Does the written order identify each of the following? [tick all that apply]
- [ ] Oxygen flow rate
- [ ] Inspired oxygen concentration [percentage 21-100% or FiO₂ 0.21 – 1.0]
- [ ] Name of delivery device
- [ ] How treatment is to be monitored?
- [ ] Target oxygenation parameters?

#### 2.20
- [ ] [ ] Is there an oxygen saturation target for this patient? [SpO₂ or SaO₂] [may be prescribed or unit policy]
  - [ ] If no, go to question 2.22, otherwise continue

#### 2.21
- [ ] What is the lower oxygen saturation target? SpO₂ [ ] %
- [ ] What is the upper oxygen saturation target? SpO₂ [ ] % [leave blank if no target]

#### Monitoring

| 2.22 | [ ] [ ] Does the patient currently have an arterial line? |
| 2.23 | [ ] [ ] Does the patient currently have continuous ECG monitoring? |
| 2.24 | [ ] [ ] Does the patient currently have continuous (automatic) respiratory rate monitoring? |
| 2.25 | [ ] [ ] Does the patient currently continuous pulse oximetry (SpO₂) monitoring? |

#### BLOOD GASES and PHYSIOLOGICAL PARAMETERS

Please check blood gas results from the study day [best checked the next day]

For each, record the highest and lowest results available and note the time. If only one measurement please record the same number twice. If not done or not available, please leave boxes blank and tick ‘not done’.

- Please record the highest and lowest PaO₂ (partial pressure of oxygen) on the study day
- Please record the highest and lowest PaCO₂ (partial pressure of carbon dioxide) on the study day

| 2.26 | Not done |
| 2.27 | Not done |

Highest PaO₂ [ ] mmHg
Time (24hr clock) [ ]

Lowest PaO₂ [ ] mmHg
Time (24hr clock) [ ]

Highest PaO₂ [ ] mmHg
Time (24hr clock) [ ]

Lowest PaO₂ [ ] mmHg
Appendix D.

CTG POINT PREVALENCE

OXYGEN THERAPY – ALL PATIENTS
FORM 2

Hospital ID: __ __ __
Patient ID: __ ___

Please check the following physiological parameters at the end of the study day [best checked next day] and record the observations which correspond to the time of the highest and lowest PaO₂. [If no observations at the exact time, record the first observations after the time of the blood gas] If blood gas only done once, then please record the same number twice. If no blood gas done, please document the first observations after 10am on the study day.

At the time of the highest PaO₂ (partial pressure of oxygen) on the study day please document:

| SpO₂ | __ __ __ % |
| Heart rate | __ __ lpm |

2.28
Respiratory rate | __ __ lpm
Oxygen delivery | __ __ __ % or flow | __ __ __ lpm

2.29 At the time of the highest PaO₂ (partial pressure of oxygen) what oxygen delivery device was being used? (choose one)

☐ Simple nasal cannula
☐ Simple facemask (Hudson or similar)
☐ Restricted flow mask (Venturi or similar)
☐ High Flow Face Mask (partial non-rebreather or similar)
☐ Nasal high flow therapy
☐ Noninvasive therapy (includes facemask or nasal mask CPAP or BiPAP)
☐ Other

Specify ____________________________________________________________________________

At the time of the lowest PaO₂ (partial pressure of oxygen) on the study day please document:

| SpO₂ | __ __ __ % |
| Heart rate | __ __ lpm |

2.30
Respiratory rate | __ __ lpm
Oxygen delivery | __ __ __ % or flow | __ __ __ lpm

2.31 At the time of the lowest PaO₂ (partial pressure of oxygen) what oxygen delivery device was being used? (choose one)

☐ Simple nasal cannula
☐ Simple facemask (Hudson or similar)
☐ Restricted flow mask (Venturi or similar)
☐ High Flow Face Mask (partial non-rebreather or similar)
☐ Nasal high flow therapy
☐ Noninvasive therapy (includes facemask or nasal mask CPAP or BiPAP)
☐ Other

Specify ____________________________________________________________________________

THANK YOU – Please go to Form 3

PP_FORM_2, 1.11.2012

Page 5 of 5
Appendix D.

### CTG POINT PREVALENCE

#### PATIENT OUTCOME – ALL PATIENTS

| FORM 6 | Hospital ID: 1,1,1,1 |
| Patient ID: 1,1,1 |

#### IMPORTANT INFORMATION

Please collect the following information from your hospital database on day 28 [counting the Point Prevalence Day as Day 1] so collect data on Mon Dec 10th or Tues Dec 18th, or Tues Jan 8th, depending on Point Prevalence Day chosen.

### PATIENT OUTCOME

6.1 [ ] [ ] At the end of day 28 has the patient been discharged (alive or dead) from your ICU?
   - If yes, go to 6.2
   - If no, form is complete

6.2 [ ] [ ] [ ] [ ] [ ] [ ] [ ] What was the date of ICU discharge? (dd/mm/yyyy)

6.3 [ ] [ ] Was the patient alive at ICU discharge?
   - If yes, go to 6.4
   - If no, form is complete

6.4 [ ] [ ] At the end of day 28 has the patient been discharged (alive or dead) from your hospital? [This includes transfer to a different hospital]
   - If yes, go to 6.5
   - If no, form is complete

6.5 [ ] [ ] [ ] [ ] [ ] [ ] [ ] What was the date of hospital discharge? (dd/mm/yyyy)

6.6 [ ] [ ] Was the patient alive at hospital discharge?

**THANK YOU – Data Collection for this patient is complete**
Appendix D.

**CTG POINT PREVALENCE**

### IMPORTANT INFORMATION

Please complete the unit level questions **only once**.

This form cannot be entered in RedCap and should be faxed or mailed attn to: Lynsey Willenberg, Critical Care and Trauma Division, The George Institute for Global Health, PO Box M201 Missenden Rd, Camperdown NSW 2050 Australia

### OXYGEN THERAPY – UNIT LEVEL QUESTIONS

9.1 Is there an oxygen therapy protocol available in your ICU?

9.2 Is nasal high flow oxygen therapy available in your ICU?
   - If no, go to question 9.6 otherwise continue

9.3 Does the ICU have a nasal high flow protocol to guide therapy?
   - If no, go to question 9.6 otherwise continue

9.4 What starting flow is recommended? __________ litres per minute

9.5 What is the highest flow to be used? __________ litres per minute

9.6 Is noninvasive ventilation [NIV, CPAP, BiPAP etc] humidified in your ICU?
   - If no, go to question 9.6 otherwise continue
   - If yes, do NIV patients have humidified oxygen [tick one]
     - 100% of the time [always]
     - 50 – 99% of the time [usually / almost always]
     - 1 – 49% of the time [sometimes]
     - Never

Oxygen therapy on discharge from ICU

9.7 When patients are discharged from the ICU [including ICU managed HDU], can they be discharged on any of the following therapies [tick all that apply]
   - Humidified oxygen All wards □ Specific wards □ No ward □
   - Nasal high flow oxygen All wards □ Specific wards □ No ward □
   - Noninvasive ventilation All wards □ Specific wards □ No ward □

9.8 If you indicated ‘specific wards’ to any of these, please explain which wards (free text):

9.9 Are there any other methods you use to deliver oxygen to nonintubated patients that are not covered in this Point Prevalence Study? (free text):

PP_UNIT_FORM. 1.11.2012
The ANZICS Clinical Trials Group
Point Prevalence Program – Age 16 and over
Study day 6, Nov 13th or 21st, 2012
[backup date Dec 13th, 2012]

DATA DICTIONARY
General information

The aim of the CTG Point Prevalence Program is to provide the structure for individual researchers to conduct basic observational Point Prevalence Studies to inform future research, while minimising the workload on participating ICUs by combining studies using a common and standardised Case Report Form, on predictable dates. After the first four successful Point Prevalence Days in 2009, 2010 and 2011, this fifth Point Prevalence Day will include two studies:

1. A point prevalence study of patients in atrial fibrillation (AF)
2. an evaluation of fluid resuscitation practices [as part of a longitudinal research program]

Explanations for the completion of each question are provided. Each number in the left hand column refers to the question number on the data form.

If you have any questions, please contact your site principal investigator or Lynsey Willenberg lwillenberg@georgeinstitute.org.au or Dr lan Seppelt seppelt@med.usyd.edu.au

Study day

The study day is the 24 hour period corresponding to the chart day at your institution which includes 10am Wednesday May 16th, 2012. June 13th, 2012 is a reserve date if your site is unable to collect data on May 16th. For example:

• If your unit keeps charts from 2400 hours to 2400 hours (midnight to midnight) then your study day is from 2400 hrs on May 15th to 2359 hrs on May 16th.
• If your charts are from 1200 hours to 1200 hours (midday to midday) then your study day is from 1200 hrs on May 15th to 1159 hrs on May 16th.
• If your charts are from 0800 hours to 0800 hours then your study day is from 0800 hrs May 16th to 0759 hrs May 17th.

Inclusion criteria

All adult patients (aged 16 or over) who are in the ICU at 10am on the study day are included. If an adult or mixed ICU has patients under age 16 on the study day please use the Paediatric CRF.

Please fill in the patient log (Appendix 5) at 10am to assign patient study numbers. Keep this log confidential and do NOT send it to the George Institute with the Case Report Forms.
Appendix D.

**Forms and Documents**

1. Case Report Form - Adult
2. Study protocol
3. Data dictionary (this document)
4. Patient log – please print from Appendix 5 of this document and record all patients who are in the ICU at 10am

THE PATIENT LOG IS TO BE FILLED IN FOR ALL PATIENTS IN THE ICU AT 10am ON THE STUDY DAY. 'ICU' includes all HDU patients in a co-located HDU managed by the intensive care service, but does NOT include HDU patients in a separate HDU NOT managed by the intensive care service.

The patient log is to be kept securely at the participating hospital. The log contains identifiable information and must not be sent to The George Institute. However, should data checks be requested the log will allow you to match patient study numbers to hospital records.

If possible, please transcribe the data once collected to the Electronic CRF [you will be sent details of URL and password]. For this study day a new eCRF (Redcap) will be used, rather than the SurveyMonkey platform used previously, which was problematic. Keep the original paper documentation as your record.

If it is not possible for you to use the eCRF then, once complete, all the case report forms (including the 28-day follow-up, CRF 4) need to be photocopied.

The originals are to be sent by mail to:

Attn: Lynsey Willenberg, Critical Care and Trauma Division
The George Institute for International Health
PO Box M201 Missenden Rd, Camperdown NSW 2050 Australia

The photocopies should be kept securely in your hospital. We will notify you once the originals are received at The George Institute.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>Acute Lung Injury</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute physiology and chronic health evaluation</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CCU</td>
<td>Coronary care unit</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Score</td>
</tr>
<tr>
<td>HDU</td>
<td>High dependency unit</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Non-invasive Positive Pressure Ventilation</td>
</tr>
<tr>
<td>PCWP</td>
<td>Pulmonary capillary wedge pressure</td>
</tr>
<tr>
<td>PAOP</td>
<td>Pulmonary artery occlusion Pressure</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td>URL</td>
<td>Universal Resource Locator (Internet ‘address’)</td>
</tr>
</tbody>
</table>
## GENERAL COMMENTS

All Patients: **Forms 1 and 2**

All Patients having a Fluid Bolus for Resuscitation: **Form 3**

All Patients: **Form 4**

**Hospital ID:**

**Patient ID:**

- Complete Forms 1, 2, and 4 for **EVERY** patient who is in the ICU at 10am on the study day.

- Complete Form 3 for every patient who has a **FLUID BOLUS FOR RESUSCITATION** at any time on the study day.

- Your hospital has been allocated a 3-digit number by the Coordinating Centre. Contact your site principal investigator or email Lynsey Willenberg (willenberg@georgeinstitute.org.au) if you do not know your hospital ID.

- Each patient at your site is to be allocated a 2 digit patient number by you. The first patient enrolled at your hospital will be 01, the second will be 02 and so on [starting again from 01 if you participated in PP day no 1]. Please keep a record at your site which identifies each patient by their patient number - use the **patient log** form for this (Appendix 5). This record MUST NOT be sent to The George Institute. The George Institute will identify data by the hospital and patient ID only.
Appendix D.

CTG PPP  
Explanatory notes for data collection and entry

FORM 1 – ICU ADMISSION DATA: THIS FORM SHOULD BE COMPLETED FOR ALL PATIENTS

General tips

- Complete Form 1 for EVERY patient who is in the ICU at 10am on the study day.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Definition or explanation of question</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital ID</td>
<td>Your hospital has been allocated a 3-digit number by the Coordinating Centre. This number will be the same for every form you complete at your hospital</td>
<td>This is the unique study number that identifies which hospital the form is from</td>
</tr>
<tr>
<td></td>
<td>Patient’s Study ID</td>
<td>The individual patient number will be 01 for the first patient enrolled at your hospital, 02 for the second patient enrolled, 03 for the third patient etc.</td>
<td>This is the unique study number that, together with the hospital number, identifies the patient</td>
</tr>
<tr>
<td>1.01</td>
<td>Patient’s gender</td>
<td>Select the patient’s legal gender (sex) as M (male) or F (female)</td>
<td></td>
</tr>
<tr>
<td>1.02</td>
<td>Age</td>
<td>Enter the patient’s age on the study day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If the patient’s age is not known enter 999.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A query will be generated and the correct age may be added if it is later determined.</td>
<td></td>
</tr>
<tr>
<td>1.03</td>
<td>ICU admission date</td>
<td>Enter the date the patient was admitted to your ICU using the following date format e.g. 01/04/2009 for 1st April 2009. This date must be before the end of your study day (e.g. on or before 18th Nov 2009)</td>
<td>All patients in your ICU at 10am on the study day will be included</td>
</tr>
<tr>
<td>1.04</td>
<td>ICU admission time</td>
<td>Enter time in hours and minutes of the patient’s admission to your ICU using 24 hour clock e.g. 15:20 for 3:20pm</td>
<td>If the exact time of admission is not recorded than enter the start of the first hour for which data appears on the ICU observation chart.</td>
</tr>
<tr>
<td>No.</td>
<td>Question</td>
<td>Definition or explanation of question</td>
<td>Comments</td>
</tr>
<tr>
<td>-----</td>
<td>----------</td>
<td>--------------------------------------</td>
<td>----------</td>
</tr>
</tbody>
</table>
| 1.05 | Source of admission to ICU | Select the response that corresponds with the source of admission to your ICU. Only one box should be selected.  
- ‘Emergency Department’ = the ED (A&E) at your hospital  
- ‘Hospital Floor’ = any WARD in your hospital, including day care facilities but not including an ICU. A separate HDU not managed by the Intensive Care service is included as a ‘ward’  
- ‘Transfer from other ICU’ = any other ICU from within your hospital or an ICU from another hospital. This includes transfer from a separate HDU which is managed by the Intensive Care Service but which is not otherwise being included in this study.  
- ‘Transfer from another hospital’ = transfer from any area in another hospital except an ICU  
- ‘Operating theatre following emergency surgery’. Emergency surgery is defined as surgery that the patient needed immediately due to physiological instability that was potentially life threatening.  
- ‘Operating theatre following elective surgery’ = from operating theatre or recovery ward following any surgery that is NOT defined as ‘emergency’. | The definition of emergency surgery is taken from the original APACHE II study data dictionary.  
For the purposes of the Point Prevalence Program High Dependency Units (or HDU patients) are counted as follows:  
- a co-located HDU managed by the Intensive Care service is part of your ICU and all patients are included in this study  
- a separate HDU which is run as a different area (and different nursing unit) but which is managed by the Intensive Care service counts as a different ICU in your hospital  
- a separate HDU which is not managed by the Intensive Care service counts as a ward. |
| 1.06 | Previous ICU admission to YOUR ICU | Select ‘Y’ if the patient has had a previous admission episode in your ICU during THIS hospital admission  
Select ‘N’ if the patient has not previously been in your ICU during this hospital admission. | This guides selection of APACHE-III operative or non-operative admission codes |
| 1.07 | Post-operative admission to ICU | Select ‘Y’ if patient was admitted DIRECTLY from the operating theatre or the recovery room.  
Select ‘N’ if the patient was not admitted directly from the operating theatre or recovery room. | The type of admission together with a primary diagnosis as listed in questions 1.08 can be used to calculate prognosis with the APACHE II score.  
The diagnosis code can be recorded from your ICU database (eg AORTIC) if available. Ignore descriptors after decimal point. Please add a leading ‘0’ [zero] to 3 digit non operative codes [there are a few 4 digit non operative codes]. |
| 1.08 | Primary diagnosis | Choose the single most important reason for ICU treatment from the list of POST-OPERATIVE and NON-OPERATIVE diagnoses in Appendix 1. Only ONE primary diagnosis can be selected. The diagnosis leading to this ICU admission does not necessarily have to be the same diagnosis that led to the hospital admission: eg. A patient admitted to hospital for investigation of chronic anaemia who has an emergency bowel resection for a bleeding colonic neoplasm leading to ICU admission would be classed as: POSTOPERATIVE / Gastrointestinal / Neoplasm (1405). ‘Neoplasm’ should be selected in this case rather than ‘Bleeding’ as it is a more specific diagnosis that led to the ICU admission. |  |
## Appendix D.

### Explanatory notes for data collection and entry

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.09</td>
<td>Patient's weight</td>
<td>Enter patient’s weight in kilograms. Use leading zero if needed e.g. 60 kg is 060. Weight may be measured, documented in medical records, obtained from patient or relative questioning or visually estimated. If there are multiple weights, record the most recent. The patient’s weight will be used to calculate tidal volumes and drug doses. A useful source for patients’ weight may include dietitian notes.</td>
</tr>
<tr>
<td>1.10</td>
<td>Weight estimated or measured</td>
<td>Select ‘ESTIMATED’ if the patient’s weight was obtained by asking relatives or the patient or visually estimated. Select ‘MEASURED’ if the patient’s weight was measured and documented in the medical record.</td>
</tr>
<tr>
<td>1.11</td>
<td>Hospital admission due to trauma</td>
<td>Select ‘Y’ if the primary hospital admission diagnosis is trauma of any kind, including burns. Go to question 1.12. Select ‘N’ if the patient was not admitted to hospital due to trauma. Go to question 1.19. These data are requested so that patients admitted to hospital because of trauma with or without traumatic brain injury can be prospectively defined for subgroup analysis.</td>
</tr>
<tr>
<td>1.12</td>
<td>Trauma criteria – injury by mechanical forces</td>
<td>Select ‘Y’ if there is a history of blunt or penetrating bodily injury caused by mechanical physical forces or ‘N’ if there is no trauma OR no mechanical injury.</td>
</tr>
<tr>
<td>1.13</td>
<td>Trauma criteria – primary admission diagnosis of burns</td>
<td>Select ‘Y’ if the primary ICU admission diagnosis is burns and go to question 1.14. or ‘N’ if the patient does not have burns OR burns are not the primary ICU admission diagnosis and go to question 1.15.</td>
</tr>
<tr>
<td>1.14</td>
<td>Percentage body area of burns</td>
<td>Enter percentage as proportion out of 100 to nearest whole number. Use leading zero if necessary e.g. burns to 10% of the body surface area should be coded as 010</td>
</tr>
<tr>
<td>1.15</td>
<td>Last GCS prior to sedation</td>
<td>Enter the last GCS score prior to the patient receiving sedation, including sedation given pre-hospital. Use leading zero where necessary e.g. a GCS score of 3 is coded as 03. For information on how to calculate the GCS, see appendix 2.</td>
</tr>
<tr>
<td>1.16</td>
<td>GCS recorded or estimated</td>
<td>Select ‘RECORDED’ if the GCS was documented in the patient record or ‘ESTIMATED’ if the GCS was obtained from a description of the patient’s neurological state.</td>
</tr>
<tr>
<td>1.17</td>
<td>Cranial CT</td>
<td>Select ‘Y’ if a cranial CT scan was not performed and go to question 1.19. Select ‘N’ if CT scan was performed.</td>
</tr>
</tbody>
</table>
### Appendix D.

**Explanatory notes for data collection and entry**

<table>
<thead>
<tr>
<th>No.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.18</td>
<td>Trauma criteria - Abnormality on cranial CT</td>
<td>Select 'Y' if there was any abnormality on a cranial CT scan that was deemed consistent with an acute traumatic brain injury [this can be documented in the notes or on a radiology report]. Select 'N' if the CT results were not consistent with acute brain injury.</td>
<td>These data are requested so that patients admitted to hospital because of trauma with or without traumatic brain injury can be prospectively defined for sub group analysis.</td>
</tr>
</tbody>
</table>

1.19 Sepsis on study day

Select 'Y' only if the patient has a defined focus of infection AND TWO (2) systemic inflammatory response syndrome [SIRS] criteria on the study day. Select 'N' if these criteria are absent.

A **defined focus of infection** is indicated by either:

(i) An organism grown in blood or sterile site | OR |

(ii) An abscess or volume of infected tissue (e.g. pneumonia, peritonitis, vascular line infection, soft tissue, etc).

The 4 SIRS criteria are:

1. Core temperature >38°C or <36°C. (Core temperature isrectal, central line, or tympanic). If oral or axillary temp is used, add 0.5°C to the measured value. Hypothermia <36°C must be confirmed by core temperature only. Use the most deranged value recorded on the study day.

2. Heart rate >90 beats/minute. If patients have a known medical condition or are receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they must meet two of the remaining three SIRS criteria. Use the most deranged value recorded on the study day.

3. Respiratory rate > 20 breaths per minute or a PaCO₂ < 32 mmHg or mechanical ventilation for an acute process. Use the most deranged respiratory rate or PaCO₂ recorded on the study day. White blood cell (WBC) count of >12 x 10⁹/L or < 4 x 10⁹/L or > 10% immature neutrophils (band forms). Use the most deranged value recorded on the study day.

Positive cultures are NOT required. A defined focus of infection may be indicated by chest x-ray changes and a clinical picture consistent with infection or by peritonitis reported on a surgical operation record or other clinical indicators of a defined focus of infection.

These data are requested so that we can prospectively identify patients with sepsis. For question 1.19 select 'Y' only if the patient has a defined focus of infection AND two SIRS criteria.
### Appendix D.

#### Explanatory notes for data collection and entry

<table>
<thead>
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</tr>
</thead>
</table>
| 1.20 | ARDS on study day | Select ‘Y’ if the patient has met all 4 criteria for ARDS on the study day. Select ‘N’ if ANY of the 4 criteria are NOT met. The 4 ARDS criteria are:  
1. **Alveolar infiltrates**  
   Bilateral and diffuse alveolar infiltrates should be visible on a chest X-ray. If no Xray was taken on the study day but infiltrates were present on the **most recent** Xray that is sufficient. If these infiltrates are present in only ONE of two lungs this criterion is **NOT** met.  
   If the patient has had one lung removed and the infiltrates are present in the remaining lung, this criterion **IS** met.  
2. **ARDS & risk factors**  
   Risk factors for ARDS are: aspiration, massive transfusion, systemic non-pulmonary sepsis, pulmonary sepsis, pulmonary and non-pulmonary trauma or pancreatitis. If none of these risk factors are present, this criterion is **NOT** met.  
3. **ARDS & pulmonary pressures or left atrial hypertension**  
   If the PAOP (wedge) pressure is <18mmHg, this criterion is met. If there is no pulmonary artery catheter in situ or a PAOP (wedge) pressure cannot be obtained but there is NO clinical or echocardiographic evidence of left atrial hypertension (e.g. upper lobe blood diversion on UPRIGHT chest X-Ray, left ventricular failure, raised central venous pressure or paroxysmal nocturnal dyspnoea), this criterion is met. If the PAOP (wedge) pressure is ≥18mmHg or there is clinical or echocardiographic evidence of left atrial hypertension, this criterion is **NOT** met.  
4. **ARDS & oxygenation**  
   If the PaO₂/FiO₂ ratio (arterial oxygen pressure / fractional concentration of inhaled oxygen) is less than or equal to 200 mmHg (or ≤26.7 if in kPa), the criterion is met. If no blood gas is available or the ratio is greater than 200 mmHg (or >26.7 if in kPa), the criterion has **NOT** been met. | ALL 4 criteria in questions 1.20 and 1.21 MUST be present for the full definition of ARDS (or ALI) on the study day to be met. |
Appendix D.

### Explanatory notes for data collection and entry

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</tr>
</thead>
</table>
| 1.21 | ALI on study day | Same as question 1.20 except for criterion 4: 
4. **ALI & oxygenation**
If the $\text{PaO}_2/\text{FiO}_2$ ratio (arterial oxygen pressure / fractional concentration of inhaled oxygen) is less than or equal to 300 mmHg (or $\leq$40.0 kPa), the criterion is met.
If no blood gas is available or the ratio is greater than 300 mmHg (or $>40.0$ kPa), the criterion has **NOT** been met. | If patient meets criteria for ARDS (question 1.20) then tick ‘N’ for ALI. |

1.22 APACHE II Score

Enter the **ICU admission APACHE II score** using leading zero where necessary eg a score of 5 would be 05. **APACHE II** from the **AORTIC database or other source is acceptable.**

An APACHE form has been provided with the Case Report Forms (CRFs), and a sample APACHE form is in **Appendix 2** and can be printed and copied, if needed.

The following instructions apply if you need to derive the APACHE-II yourself (PART A of the APACHE form):

1. If mean arterial pressure (MAP) is not recorded, MAP can be calculated from systolic (SBP) and diastolic blood pressure (DBP) using this equation:

   \[
   \text{MAP} = \left[\frac{\text{DBP} \times 2}{3}\right] + \text{SBP}
   \]

2. $A - a\text{DO}_2$ is the difference between the calculated alveolar oxygen tension and the arterial oxygen tension (partial pressure). The alveolar oxygen tension is calculated by this equation: $\text{PaO}_2 = 713 \times \text{FiO}_2 - \text{PaCO}_2 \times 1.25$. The PaO$_2$ is then subtracted to give the $A - a\text{DO}_2$.

   \[
   A - a\text{DO}_2 = [713 \times \text{FiO}_2 - \text{PaCO}_2 \times 1.25] - \text{PaO}_2
   \]

   The $\text{FiO}_2$ here is expressed as a fraction of a unit, eg $\text{FiO}_2 = 1.0$ if on 100% oxygen and $\text{FiO}_2 = 0.5$ if on 60% oxygen. If the $\text{FiO}_2$ (inhaled oxygen concentration) is greater than 0.5 record the most deranged value for the $A - a\text{DO}_2$. If the $\text{FiO}_2$ is less than 0.5 record only the $\text{PaO}_2$ (arterial oxygen pressure). All measurements are in mmHg.

3. A simple $A-a\text{DO}_2$ calculator can be sent to you on request.

   To obtain a score for the Glasgow Coma Scale (GCS) use the GCS worksheet provided (Appendix 2) and subtract the GCS score from 15 to arrive at a score on the APACHE worksheet. If the GCS can not be estimated because the patient is sedated, record the GCS as 15.

   To derive the APACHE II score, complete the worksheet provided and follow these instructions for completion:

   - **The APACHE II score is derived from 3 scoring systems:** Part A – Acute Physiology Score, Part B – Age Points, Part C – Chronic Health Points
   - To complete **Part A** - Acute Physiology Score, for each of the 12 physiological variables, select the most deranged value over the first 24 hours of the ICU admission. The most deranged value is the value that is associated with the highest point score assigned by APACHE II. Select the score that relates to the most deranged value and enter this in the left hand column. If the patient has not been in ICU for 24 hours then use the most deranged scores from the data available.

   For example, if the temperature in the first 24 hours was been as high as 40°C and as low as 33°C, tick the box in the column that assigns 3 points in the ‘high abnormal range’ column because 40°C attracts 3 points but 33°C, whilst still abnormal, only attracts 2 points.

   For exact non-integer data that is not found in any of the given ranges, round the figure up or down to the nearest whole number. E.g., 44 years and 3 months is rounded down to ≤ 44 years and assigned 6 points; a calculated MAP of 129.7 is rounded up to 130 and assigned 3 points. For integers of xx.5 and above always round upwards. This must be followed for every patient to ensure consistency.
### Explanatory notes for data collection and entry

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<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Whenever possible, make an attempt to obtain a score for each physiological variable. If one of the 12 variables is not available, assign 0 points and make a note of this absence on the APACHE II worksheet. The assumption is made that a test or measurement was not ordered because the status of the patient did not warrant investigation, rather than that the data were missing. To complete PART B – assign points to the age range that the patient fits into, e.g., a 48 year old patient would be assigned 2 points. To complete PART C – first decide if the patient meets any of the criteria provided on the worksheet for a history of severe organ insufficiency or immunocompromised. If there is no history, assign 0 points. If there is a history, assign points depending on whether the patient is a non-operative emergency admission or an emergency post-operative admission (5 points) OR a post-operative admission following elective/planned surgery (2 points). Finally, add the points recorded for each of the 3 parts and enter this total score at question 2.13. The minimum score is 0 and the maximum score is 71. Keep the completed APACHE II worksheet in the documentation folder for this patient. It may be used for quality assurance measures. You will therefore need to print your Patient's Study Number on the APACHE worksheet. [Not required if you get the APACHE II from your ICU database]</td>
<td></td>
</tr>
<tr>
<td>1.23</td>
<td>Chronic health points score</td>
<td>Enter the score (0, 2 or 5 points) the patient received for Part C of the APACHE II worksheet. If the patient had a history of organ insufficiency or immunocompromised state, select “Y” or “N” for each category of chronic health conditions the patient met (liver, renal, cardiovascular, respiratory and immunocompromised). You can select more than one category.</td>
<td></td>
</tr>
<tr>
<td>1.24</td>
<td>SOFA score domains</td>
<td>Please document each of the five SOFA domains for the <strong>most deranged</strong> score in the 24 hour study period (see Appendix 4). Record “9” if information not measured/not available. Note APACHE II is the ICU admission score, but the SOFA score relates to today.</td>
<td></td>
</tr>
<tr>
<td>1.28</td>
<td>Research capacity</td>
<td>Record “Y” if the patient has been enrolled into an <strong>interventional</strong> clinical trial (where the patient receives a treatment specified by the trial protocol). Do not include observational or physiological studies where the patient’s treatment has not changed.</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix D.

**Explanatory notes for data collection and entry**

<table>
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</tr>
</thead>
</table>
| 1.30 | Type of clinical trial | Select all that apply.  
- A fully sponsored commercial trial is a trial designed and funded by a commercial entity, where that entity will 'own' and analyse the data and present the results.  
- A CTG endorsed trial is an investigator initiated trial that has been through the endorsement process of the ANZICS CTG  
- An investigator initiated trial is a trial which has been designed by a clinician or collaborative group outside industry, where that group has full control of the data, analysis and publication. An investigator initiated trial can still receive financial support from industry but is not primarily run by industry. | As of Nov 2009 the following actively recruiting interventional trials have been endorsed by the CTG:  
- ARISE  
- DECRA  
- Early PN  
- PROTECT  
- STATinS  
- CHEST |
### General tips
Complete Form 2 for **EVERY** patient present in the ICU on the study day who is **NOT** mechanically ventilated / breathing through an endotracheal or tracheostomy tube. The aim of this study is to describe the oxygen therapy used on patients who are breathing through normal airways.

In addition to individual patient data, please also complete the **unit level survey**, once only per ICU.

Some questions need to be answered ‘now’ [the word ‘currently’ or ‘now’ appears in the question], which is whatever applies at whatever time you get to this patient’s bedside after the 10am census. Other questions can be answered retrospectively at the end of the study day.

Answers to each question can be sourced from:
1. Referring to the patient’s bedside monitor, flow chart or observation sheet
2. Asking the bedside nurse for information, if unknown then
3. Referring to patient’s medical record, if not documented or unclear then
4. Asking the attending medical staff

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Definition or explanation of question</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Patient intubated?</td>
<td>We are NOT interested in intubated patients, or those with tracheostomy. These questions relate to extubated patients or trache decannulated.</td>
<td>If intubated or trache, please go to form 3</td>
</tr>
<tr>
<td>2.2 - 2.5</td>
<td>Upper abdominal incision</td>
<td>These questions related specifically to patients with an abdominal incision, with at least a components above the umbilicus [regardless of whether midline, transverse, subcostal etc]</td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>Room air</td>
<td>If extubated and on no supplemental oxygen, no further questions</td>
<td>If on air, Go to Form 3</td>
</tr>
<tr>
<td>2.7</td>
<td>Time of extubation or trachy</td>
<td>24 hr clock, date DD/MM/YYYY</td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td>First oxygen therapy mask</td>
<td>This may or may not be easy to identify from the nursing notes. If unsure and not documented, please give best guess but write it in ‘other’ adding the words ‘best guess’</td>
<td></td>
</tr>
<tr>
<td>2.9</td>
<td>Indication for oxygen therapy</td>
<td>If in doubt, ask medical staff</td>
<td></td>
</tr>
<tr>
<td>2.10</td>
<td>Oxygen device</td>
<td>May be multiple answers</td>
<td></td>
</tr>
<tr>
<td>2.11</td>
<td>Indication for oxygen therapy</td>
<td>If in doubt, ask medical staff</td>
<td></td>
</tr>
<tr>
<td>2.12</td>
<td>Oxygen device last 24hr</td>
<td>May be multiple answers</td>
<td></td>
</tr>
<tr>
<td>2.13</td>
<td>Current flow rate</td>
<td>Oxygen litres per min (if less than 1 lpm please indicate ‘1’)</td>
<td></td>
</tr>
<tr>
<td>2.14</td>
<td>Inspired oxygen</td>
<td>Only answer if accurate oxygen mixer used eg gas blender, ‘oxygen therapy’ through ventilator, or other. For simple masks the inspired oxygen is unknown (and depends on minute ventilation and other patient characteristics)</td>
<td></td>
</tr>
<tr>
<td>2.15 – 2.16</td>
<td>Humidification</td>
<td>Humidifiers include varieties of passive ‘heat and moisture exchanger’ (HME) and HME filters including ‘swedish nose’ [‘dry circuits’] and active humidifiers [water bath humidifiers or ‘wet circuits’, as well as ultrasonic and other fancy humidifiers]. A simple ‘T piece’ is only humidified if attached to an active humidifier wet circuit.</td>
<td></td>
</tr>
<tr>
<td>2.17 – 2.19</td>
<td>Medical order for oxygen</td>
<td>Documented order or standing order [written protocol]</td>
<td></td>
</tr>
<tr>
<td>2.20 – 2.21</td>
<td>SaO₂ or SpO₂ targets</td>
<td>Documented order or standing order [written protocol]</td>
<td></td>
</tr>
<tr>
<td>2.22 – 2.25</td>
<td>Monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.26 – 2.27</td>
<td>Blood Gas</td>
<td>Please check blood gas results from the study day [best checked the next day]. For each, record the highest and lowest results available and note the time. If only one measurement please record the same number twice. If not done or not available, please leave boxes blank and tick ‘not done’.</td>
<td></td>
</tr>
<tr>
<td>2.29 – 2.30</td>
<td>Oxygen therapy at time of highest and lowest PaO₂</td>
<td>Please check the following physiological parameters at the end of the study day [best checked next day] and record the observations which correspond to the time of the highest and lowest PaO₂. [If no observations at the exact time, record the first observations after the time of the blood gas] If blood gas only done once, then please record the same number twice. If no blood gas done, please document the first observations after 10am on the study day.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix D.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Definition or explanation of question</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Admitted from ward</td>
<td>If not admitted from ward [i.e. admitted from ED, theatre, or another ICU or another hospital] then no further questions – go to Form 4. Tick ‘No’ if a ward patient required emergency surgery then ICU admission (these were admitted to ICU from theatre, not from the ward).</td>
<td></td>
</tr>
<tr>
<td>3.2 – 3.6</td>
<td>Cardiac Arrest, MET, Treatment Limitation</td>
<td>These five questions examine different aspects of the MET call / Rapid Response call / Emergency Response Team call. ‘Cardiac arrest’ requires either chest compressions (CPR) or defibrillation in order to tick ‘Yes’. ‘Admitted to ICU directly as result of MET’ requires a formal Emergency Call [not an informal ‘patient review’ or other phone call] with the decision for ICU admission made at the time of the Emergency Response. ‘Admitted within 24hr of MET’ requires at least one Emergency Response where the decision was made to not admit to ICU. ‘Preexisting treatment limitation’ is any written document stating any one or more of ‘not for escalation of therapy’ ‘not for CPR’, ‘not for intubation’.</td>
<td></td>
</tr>
<tr>
<td>3.7 – 3.9</td>
<td>Ward &gt; 24hr?</td>
<td>This information will help interpretation of question 3.10 when applied to less than a 24 hour time period.</td>
<td></td>
</tr>
<tr>
<td>3.10</td>
<td>Observations in the 24 hr prior to admission</td>
<td>If the patient was admitted unexpectedly from the ward, please go through the ward observation charts for the 24 hours prior to ICU admission, and document all clinical observations, and all instances of medical review in that time period. If times are not documented please make a reasonable estimate [ICU medical staff may help adjudicate timing of medical review]. If less than 24 hours in the ward please include the last observations (only) taken prior to transfer to the ward (from ED, recovery, etc.). <strong>Fulfilled MET criteria but no MET call (“Afferent Limb Failure”)</strong> – You will need to check your own hospital’s calling criteria. Please tick the box if at this time the patient fulfilled your hospital’s calling criteria / triggers for a Medical Emergency Response / Rapid Response / ALS Team / Clinical Emergency Response, but no call was made [regardless of reason].</td>
<td></td>
</tr>
</tbody>
</table>
### FORM 4 – FLUID RESUSCITATION

This form is to be completed for **ALL** patients who received an intravenous fluid for **volume expansion** (as opposed to maintenance or nutrition), on the study day.

Please include any or all of the following:
1. A bolus of crystalloid
2. A crystalloid infusion of 5 ml/kg/hr [400 ml/hr] or more for one or more hours [includes 0.9% saline, Hartmann’s, Plasmalyte R]
3. A colloid bolus
4. Any colloid by infusion
5. Any transfusion of blood or blood products

Only count fluid given in the ICU (not ED, wards or operating theatre)
- This form is best completed at the end of the study day.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Definition or explanation of question</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Fluid Resuscitation</td>
<td>Please tick any fluid types used, and give the total volume administered in the ICU on the study day</td>
<td>There is no need to given a volume if the Y box has not been ticked</td>
</tr>
</tbody>
</table>
## FORM 5 – NO FORM

<table>
<thead>
<tr>
<th>General Tips</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no adult form 5.</td>
<td></td>
</tr>
<tr>
<td><strong>There is a paediatric Form 5</strong></td>
<td></td>
</tr>
<tr>
<td>This is included to keep the Form 6 numbering consistent</td>
<td></td>
</tr>
</tbody>
</table>
Appendix D.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Definition or explanation of question</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Discharged from ICU</td>
<td>Has the patient been discharged (alive or dead) from ICU by the end of day 28? If the patient has been discharged and subsequently readmitted to ICU and remains in ICU at day 28, select ‘N’. If the patient has been discharged, readmitted and discharged again during the 28 day period, select ‘Y’. If you have selected ‘Y’, go to question 6.2 If you have selected ‘N’, the patient remains alive in ICU at the end of day 28. Form 6 is complete (do not answer any further questions).</td>
<td>Select ‘Y’ if the patient has been transferred to a different hospital (ICU or ward).</td>
</tr>
<tr>
<td>6.2</td>
<td>Date of ICU discharge</td>
<td>Enter date of ICU discharge using the format dd/mm/yyyy. Eg 19/04/2009 for 19th April 2009. If a patient has been discharged from ICU on more than one occasion during the 28 day period, record the latest discharge date.</td>
<td></td>
</tr>
<tr>
<td>6.3</td>
<td>Alive at ICU discharge</td>
<td>Select ‘Y’ if the patient was alive at latest discharge from ICU and go to question 6.4. Select ‘N’ if the patient was dead at discharge and do not complete any further questions on this form.</td>
<td></td>
</tr>
<tr>
<td>6.4</td>
<td>Discharge from hospital</td>
<td>Has the patient been discharged (alive or dead) from hospital by the end of day 28? If the patient has been discharged and subsequently readmitted to hospital and remains in hospital at day 28, select ‘N’. If the patient has been discharged, readmitted and discharged again during the 28 day period, select ‘Y’.</td>
<td>Select ‘Y’ if the patient has been transferred to a different hospital.</td>
</tr>
<tr>
<td>6.5</td>
<td>Date of hospital discharge</td>
<td>Enter date of hospital discharge using the format dd/mm/yyyy. Eg 19/04/2007 for 19th April 2007. If a patient has been discharged from hospital on more than one occasion during the 28 day period, record the latest discharge date.</td>
<td></td>
</tr>
<tr>
<td>6.6</td>
<td>Alive at hospital discharge</td>
<td>Select ‘Y’ if the patient was alive at his or her latest discharge from hospital. Select ‘N’ if the patient was dead at discharge from hospital.</td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX 1  APACHE III Diagnosis Codes

### Non Operative Diagnoses

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Neurological</th>
<th>Sepsis</th>
<th>Trauma</th>
<th>Renal / Genitourinary</th>
</tr>
</thead>
<tbody>
<tr>
<td>101 Cardiogenic Shock</td>
<td>308 GI Perforation</td>
<td>501 Sepsis other than urinary</td>
<td>601 Head Trauma +/- multi trauma</td>
<td>301 Hepatic Failure</td>
</tr>
<tr>
<td>102 Cardiac Arrest</td>
<td>309 GI Obstruction</td>
<td>502 Sepsis of Urinary Tract Origin</td>
<td>602 Multiple trauma excluding head</td>
<td>303 GI Bleeding - varices</td>
</tr>
<tr>
<td>103 Aortic Aneurysm</td>
<td>310 GI Vascular Insufficiency</td>
<td>503 Sepsis with shock other than urinary tract</td>
<td>603 Burns (ANZICS addition)</td>
<td>305 GI Bleeding – ulcer/laceration</td>
</tr>
<tr>
<td>104 Congestive Heart Failure</td>
<td>311 Pancreatitis</td>
<td>504 Sepsis with shock of urinary tract origin</td>
<td>604 Multi-Trauma with spinal injury</td>
<td>306 GI Bleeding - diverticulosis</td>
</tr>
<tr>
<td>105 Peripheral Vascular Disease</td>
<td>312 GI Cancer</td>
<td></td>
<td>605 Isolated cervical spine injury</td>
<td>307 Other GI Disease</td>
</tr>
<tr>
<td>106 Rhythm Disturbance</td>
<td>313 Other GI Inflammatory Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix D.

### CTG PPP

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>901</th>
<th>Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>701 Metabolic coma</td>
<td>902</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>702 Diabetic ketoacidosis</td>
<td>903</td>
<td>Haemorrhage postpartum</td>
</tr>
<tr>
<td>703 Drug overdose</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>704 Other metabolic disease</td>
<td>1002</td>
<td>Other medical disorder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological</th>
<th>Musculoskeletal / skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>801 Coagulopathy/ Neutropenia / Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>802 Other haematologic disease</td>
<td>1101</td>
</tr>
<tr>
<td></td>
<td>1102</td>
</tr>
</tbody>
</table>

### Operative Diagnoses

**Cardiovascular**

| 1202 Peripheral Vascular Disease - No Graft | 1401 GI Perforation / Rupture |
| 1203 Peripheral Artery Bypass Graft        | 1403 GI Bleeding             |
| 1204 Elective AA                            | 1404 GI Obstruction          |
| 1205 Carotid Endarterectomy                 | 1405 GI Neoplasm             |
| 1206 Valvular Heart Surgery                | 1406 Cholecystitis / Cholangitis |
| 1207 CABG                                  | 1407 Liver Transplant        |
| 1208 Other Cardiovascular Diseases         | 1408 Other GI Disease        |
| 1209 Dissecting Aortic Aneurysm             | 1409 Fistula / Abscess surgery |
| 1210 Ruptured Aortic Aneurysm               | 1410 GI Vascular ischemia resection surgery |
| 1211 Aorto-femoral bypass graft             | 1411 Pancreatitis            |
| 1212 CABG with valve repair/replacement incl redo | 1412 Peritonitis    |
| 1213 Endoluminal Aortic Repair              | 1413 Other GI Inflammatory Disease surgery |

**Respiratory**

| 1301 Surgery for Respiratory Infection       | 1501 Intracerebral Haemorrhage |
| 1302 Respiratory Neoplasm - Lung            | 1502 Subdural / epidural Haematoma |
| 1303 Respiratory Neoplasm – Mouth / Larynx / Sinus / trach | 1503 Subarachnoid Haemorrhage |
| 1304 Other Respiratory Diseases             | 1504 Laminectomy / Spinal cord surgery |
|                                               | 1505 Craniotomy for Neoplasm |
|                                               | 1506 Other Neurological Disease |

**Gastrointestinal**

| 1401 GI Perforation / Rupture                 | 1501 Intracerebral Haemorrhage |
| 1403 GI Bleeding                              | 1502 Subdural / epidural Haematoma |
| 1404 GI Obstruction                           | 1503 Subarachnoid Haemorrhage  |
| 1405 GI Neoplasm                              | 1504 Laminectomy / Spinal cord surgery |
| 1406 Cholecystitis / Cholangitis              | 1505 Craniotomy for Neoplasm   |
| 1407 Liver Transplant                         | 1506 Other Neurological Disease |
| 1408 Other GI Disease                         | 1410 GI Vascular ischemia resection surgery |
| 1409 Fistula / Abscess surgery                | 1411 Pancreatitis             |
| 1410 GI Vascular ischemia resection surgery   | 1412 Peritonitis              |
| 1411 Pancreatitis                             | 1413 Other GI Inflammatory Disease surgery |

**Neurological**

| 1501 Intracerebral Haemorrhage                |                        |
| 1502 Subdural / epidural Haematoma            |                        |
| 1503 Subarachnoid Haemorrhage                 |                        |
| 1504 Laminectomy / Spinal cord surgery        |                        |
| 1505 Craniotomy for Neoplasm                  |                        |
| 1506 Other Neurological Disease               |                        |

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## CTG PPP

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1601</td>
<td>Head Trauma +/- multi trauma</td>
</tr>
<tr>
<td>1602</td>
<td>Multiple Trauma excluding head</td>
</tr>
<tr>
<td>1603</td>
<td>Burns</td>
</tr>
<tr>
<td>1604</td>
<td>Multi trauma with spinal injury</td>
</tr>
<tr>
<td>1605</td>
<td>Isolated cervical spinal injury</td>
</tr>
</tbody>
</table>

### Renal / Genitourinary

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1701</td>
<td>Renal Neoplasm</td>
</tr>
<tr>
<td>1703</td>
<td>Other Renal Disease</td>
</tr>
<tr>
<td>1704</td>
<td>Kidney Transplant</td>
</tr>
<tr>
<td>1705</td>
<td>Genitourinary surgery / procedure</td>
</tr>
</tbody>
</table>

### Gynaecological

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1801</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>1802</td>
<td>Pregnancy related disorder</td>
</tr>
<tr>
<td>1803</td>
<td>Other Gynaecological Disease</td>
</tr>
</tbody>
</table>

### Musculoskeletal / Skin

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Orthopaedic Surgery</td>
</tr>
<tr>
<td>1903</td>
<td>Skin Surgery</td>
</tr>
<tr>
<td>1904</td>
<td>Cellulitis / soft tissue infection</td>
</tr>
</tbody>
</table>

### Haematological

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2101</td>
<td>Surgery for Haematological Disease (including staging)</td>
</tr>
</tbody>
</table>

### Metabolic

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2201</td>
<td>Endocrine surgery</td>
</tr>
</tbody>
</table>
APPENDIX 2  

GCS Calculation

To obtain a GCS, add together the best verbal response score, the best motor response score and the best eye opening score. For intubated patients, use the last recorded verbal score prior to intubation. The minimum score is 3 and the maximum score is 15.

<table>
<thead>
<tr>
<th>Best Motor Response</th>
<th>Best Verbal Response</th>
<th>Best Eye Opening</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Obeys</td>
<td>5 Oriented</td>
<td>4 Spontaneous</td>
</tr>
<tr>
<td>5 Localises</td>
<td>4 Confused</td>
<td>3 To command</td>
</tr>
<tr>
<td>4 Normal flexion (withdrawal)</td>
<td>3 Inappropriate</td>
<td>2 To pain</td>
</tr>
<tr>
<td>3 Abnormal flexion (decorticate)</td>
<td>2 Incomprehensible</td>
<td>1 No response</td>
</tr>
<tr>
<td>2 Extension (decerebrate)</td>
<td>1 No response</td>
<td></td>
</tr>
<tr>
<td>1 No response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX 3

**APACHE II Severity Of Disease Classification**

<table>
<thead>
<tr>
<th>PHYSIOLOGIC VARIABLE</th>
<th>High Abnormal Range</th>
<th>Low Abnormal Range</th>
<th>APS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ 4</td>
<td>+ 3</td>
<td>+ 2</td>
</tr>
<tr>
<td>Temperature – rectal (°C)</td>
<td>≥ 41</td>
<td>39 – 40.9</td>
<td>38.5 – 38.9</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg) (kPa)</td>
<td>≥ 160</td>
<td>130 – 159</td>
<td>110 – 129</td>
</tr>
<tr>
<td>Heart rate (ventricular response)</td>
<td>≥ 180</td>
<td>140 – 179</td>
<td>110 – 139</td>
</tr>
<tr>
<td>Respiratory rate (non-ventilated)</td>
<td>≥ 50</td>
<td>35 – 49</td>
<td>25 – 34</td>
</tr>
<tr>
<td>Oxygenation: A - aDO₂ or PaO₂</td>
<td>≥ 500</td>
<td>350 – 499</td>
<td>200 – 349</td>
</tr>
<tr>
<td>a. if FIO₂ ≥ 0.5 record A - aDO₂ (mmHg) (kPa)</td>
<td>&gt; 500</td>
<td>350 – 499</td>
<td>200 – 349</td>
</tr>
<tr>
<td>b. if FIO₂ &lt; 0.5 record only PaO₂ (mmHg) (kPa)</td>
<td>≥ 500</td>
<td>350 – 499</td>
<td>200 – 349</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>≥ 7.7</td>
<td>7.6 – 7.69</td>
<td>7.5 – 7.59</td>
</tr>
<tr>
<td>Serum sodium (mmol/L or mEq/L)</td>
<td>≥ 180</td>
<td>160 – 179</td>
<td>155 – 159</td>
</tr>
<tr>
<td>Serum potassium (mmol/L or mEq/L)</td>
<td>≥ 7</td>
<td>6 – 6.9</td>
<td>5.5 – 5.9</td>
</tr>
<tr>
<td>Serum creatinine (double point score for acute renal failure)</td>
<td>≥ 300</td>
<td>171-299</td>
<td>121-170</td>
</tr>
<tr>
<td>(μmol/L) (mg/dL)</td>
<td>≥ 300</td>
<td>171-299</td>
<td>121-170</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>≥ 60</td>
<td>50 – 59.9</td>
<td>46 – 49.9</td>
</tr>
<tr>
<td>White blood count (total/mm³) (in 1,000s)</td>
<td>≥ 40</td>
<td>20 – 39.9</td>
<td>15 – 19.9</td>
</tr>
<tr>
<td>Glasgow Coma Score (GCS) (Score = 15 minus actual GCS) – see Appendix 2 for GCS calculation</td>
<td>≥52</td>
<td>41 – 51.9</td>
<td>32 – 40.9</td>
</tr>
</tbody>
</table>

**A. ACUTE PHYSIOLOGY SCORE (APS)**

*Acute renal failure: "If abnormal serum creatinine values reflect acute renal failure as opposed to chronic renal failure then the points assigned to the creatinine values should be doubled. Acute renal failure is defined as any creatinine value that is not within the normal range designated by the APACHE II system."

Thus for the purposes of this study if your patient has any points for an increased creatinine and they are not documented to have chronic renal failure then the creatinine points should be doubled.

---

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### Appendix D.

#### B. AGE POINTS

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 44</td>
<td>0</td>
</tr>
<tr>
<td>45–54</td>
<td>2</td>
</tr>
<tr>
<td>55–64</td>
<td>3</td>
</tr>
<tr>
<td>65–74</td>
<td>5</td>
</tr>
<tr>
<td>≥ 75</td>
<td>6</td>
</tr>
</tbody>
</table>

Assign points to age as follows:

- a. for non-operative or emergency post-operative patients
- b. for elective post-operative patients

#### C. CHRONIC HEALTH POINTS

<table>
<thead>
<tr>
<th>Definitions: Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER</td>
</tr>
<tr>
<td>RENAL</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
</tr>
<tr>
<td>RESPIRATORY</td>
</tr>
<tr>
<td>IMMUNOCOMPROMISED</td>
</tr>
</tbody>
</table>

#### APACHE II SCORE - a sum of:

- A. APS points = 
- B. Age points = 
- C. Chronic Health points = 
- Sum of A + B + C = ________ (0 to 71)
### APPENDIX 4

#### SOFA Score Worksheet

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>9</th>
<th>Organ scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ / FiO₂ (in mmHg)</td>
<td>400</td>
<td>301 - 400</td>
<td>201 - 300 (with respiratory support*)</td>
<td>&lt;301 (without respiratory support*)</td>
<td>101 - 200 (with respiratory support*)</td>
<td>≤ 100 (with respiratory support*)</td>
<td>Variable not measured</td>
</tr>
<tr>
<td>(in kPa)</td>
<td>&gt;53.2</td>
<td>40.0 – 53.1</td>
<td>26.7 – 39.9 (with respiratory support*)</td>
<td>&lt;40.0 (without respiratory support*)</td>
<td>13.4 – 26.6 (with respiratory support*)</td>
<td>≤ 13.3 (with respiratory support*)</td>
<td>Variable not measured</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (x 10⁹ / L)</td>
<td>&gt;150</td>
<td>101 - 150</td>
<td>51 - 100</td>
<td>21 - 50</td>
<td>≤ 20</td>
<td>Variable not measured</td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg / dl)</td>
<td>&lt; 1.2</td>
<td>1.2 – 1.9</td>
<td>2.0 – 5.9</td>
<td>6.0 – 11.9</td>
<td>≥ 12.0</td>
<td>Variable not measured</td>
<td></td>
</tr>
<tr>
<td>(μmol / L)</td>
<td>&lt;20</td>
<td>20 - 32</td>
<td>33 - 101</td>
<td>102 - 204</td>
<td>&gt;204</td>
<td>Variable not measured</td>
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<tr>
<td><strong>Cardiovascular Hypotension</strong></td>
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<tr>
<td>MAP ≥ 70 mmHg</td>
<td>MAP &lt; 70 mmHg</td>
<td>dopamine ≤ 5.0 (doses are given in μg / kg / minute)</td>
<td>dopamine 5.1 – 15.0 (doses are given in μg / kg / minute)</td>
<td>dopamine &gt; 15.0 (doses are given in μg / kg / minute)</td>
<td>Variable not measured</td>
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<tr>
<td>or any dose dobutamine</td>
<td>or epinephrine ≤ 0.1 (adrenaline)</td>
<td>or epinephrine &gt; 0.1</td>
<td>Variable not measured</td>
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<td></td>
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<tr>
<td>or any dose mivibnone or any dose levosimendan</td>
<td>or norepinephrine ≤ 0.1 or any dose vasopressin</td>
<td>or any dose metaraminol or any dose phenylephrine</td>
<td>Variable not measured</td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td>Creatinine (mg / dl)</td>
<td>&lt; 1.2</td>
<td>1.2 – 1.9</td>
<td>2.0 – 3.4</td>
<td>3.5 – 4.9</td>
<td>≥ 5.0</td>
<td>Variable not measured</td>
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<tr>
<td>(μmol/l)</td>
<td>&lt; 110</td>
<td>110 – 170</td>
<td>171 – 299</td>
<td>300 – 440</td>
<td>&gt; 440</td>
<td>Variable not measured</td>
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<tr>
<td>OR Urine output</td>
<td>or &lt; 500 ml / day</td>
<td>or &lt; 500 ml / day</td>
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</table>

*Respiratory support is defined as any form of invasive or non-invasive ventilation including mask CPAP or CPAP delivered through a tracheostomy / tracheotomy or endotracheal tube.

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Appendix D.

APPENDIX 5

Master Screening Log

Keep this form confidential and do NOT send to the George Institute.

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<tr>
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References


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152. de Klerk A. Humidified high-flow nasal cannula: is it the new and improved CPAP? Advances in Neonatal Care 2008;8:98 - 106.
References

References


204. McAuley D, O’Kane C, Griffiths M. A stepwise approach to justify phase III randomized clinical trials and enhance the likelihood of a positive result. Critical Care Medicine 2010;38:S523 - 7.
211. Guyatt G, Sackett D, Cook DJ, et al. Users guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? JAMA 1994;271:59 - 63.
References