Oxygen therapy in respiratory disorders

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Oxygen Therapy in Respiratory Disorders

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The work presented in this thesis is my own

Dr Meme Wijesinghe March 2012

This thesis is dedicated to my late father

Oscar Brain Anthony Wijesinghe PhD

Abstract

Background

Oxygen therapy remains a cornerstone of medical practice and is generally regarded as being safe. However, there is a lack of clinical evidence to support the routine use of oxygen therapy, and in certain conditions, injudicious oxygen may cause harm. In this thesis, I will present two audits and three randomised controlled trials of oxygen therapy.

Methods

- A prospective audit of the prescription and use of oxygen therapy before and after the introduction of an oxygen prescription section on a drug chart
- A retrospective audit of ambulance oxygen administration, in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD)
- Two randomised controlled trials of high flow versus titrated oxygen in 150 patients with community acquired pneumonia and 106 patients with acute severe asthma
- A randomised controlled trial of 24 subjects with obesity hypoventilation syndrome (OHS) comparing 100% oxygen with air

Results

- Oxygen prescription is suboptimal in hospital inpatients. Whilst an oxygen prescription section improved prescription, this intervention did not improve clinical practice
- Over 70% of patients presenting with AECOPD received high flow oxygen prior to presentation to the emergency department. The risk of adverse outcomes increased progressively with increased PaO_2
- High concentration oxygen leads to a rise in $PaCO_2$ compared to titrated oxygen, when administered to patients presenting with asthma or pneumonia
- Breathing 100% oxygen leads to a rise in $PaCO_2$ in patients with OHS

Conclusion

This series of studies has shown that further measures are warranted to ensure the safe practice of oxygen therapy in the pre-hospital and hospital setting. In addition, the findings suggest that the potential for high concentration oxygen therapy to increase $PaCO_2$ is not limited to COPD but may occur in other respiratory conditions in which abnormal gas exchange or respiratory drive are present.

Oxygen Therapy in Respiratory Disorders

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List of Abbreviations

A-a	alveolar to arterial gradient
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
ABG	arterial blood gas
ALI	acute lung injury
BP	blood pressure
BTS	British Thoracic Society
CAP	community- acquired pneumonia
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CXR	chest radiograph
DO_2	delivery of oxygen
ED	emergency department
FEV_1	forced expiratory volume in 1 second
FiO_2	fraction of inspired oxygen concentration
FVC	forced vital capacity
HDU	high dependency unit
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
ICU	intensive care unit
IPPV	invasive positive pressure ventilation

L/min	litres per minute
log SD Q	Dispersion of pulmonary blood flow
log SD V	Dispersion of alveolar ventilation
LTOT	long term oxygen therapy
MIGET	multiple inert gas elimination technique
MV	minute ventilation
MVa	alveolar minute ventilation
NIPPV	non-invasive positive pressure ventilation
OSA	obstructive sleep apnoea
OHS	obesity hypoventilation syndrome
$PaCO_2$	arterial carbon dioxide tension
PaO_2	arterial oxygen tension
$PACO_2$	alveolar carbon dioxide tension
PAO_2	alveolar oxygen tension
PE	mixed expired gas tension
$PvCO_2$	carbon dioxide tension mixed venous blood
PvO_2	oxygen tension mixed venous blood
PIO_2	inspired oxygen tension
$PICO_2$	inspired carbon dioxide tension
R	respiratory exchange ratio
RCT	randomised controlled trial
RR	respiratory rate
SaO_2	arterial oxygen saturation

SpO_2	oxygen saturation measured by pulse oximetry
TLC	total lung capacity
Va	alveolar ventilation
Vd	physiological dead space
Vd/Vt	ratio of physiological dead space to tidal volume (Bohr dead space)
Vt	tidal volume
V/Q	ventilation-perfusion ratio

List of Publications and Abstracts

The following publications and abstracts have arisen from the research work presented in this thesis and from studies not formally included in this thesis.

PUBLICATIONS

- **Meme Wijesinghe**, Kyle Perrin, Bridget Healy, Kirsten Wadsworth, Richard Bowditch, Susan Bibby, Tanya Baker, Mark Weatherall, Richard Beasley Randomised controlled trial of high concentration versus titrated oxygen therapy in community-acquired pneumonia. *J Roy Soc Med* 2011 (In press)

- **Meme Wijesinghe**, Mathew Williams, Kyle Perrin, Mark Weatherall, Richard Beasley. The effect of supplemental oxygen on hypercapnia in obesity associated hypoventilation: A randomised crossover clinical study. *Chest* 2011 May;139(5):1018-24.

- **Meme Wijesinghe**, Kyle Perrin, Bridget Healy, Kelli Hart, Jennifer Clay, Mark Weatherall, Richard Beasley. Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. *Internal Medical Journal* 2011; 41(8):618-622

- **Meme Wijesinghe**, Philippa Shirtcliffe, Kyle Perrin, Bridget Healy, Kate James, Mark Weatherall, Richard Beasley. An audit of the effect of oxygen prescription charts on clinical practice. *PostGraduate Medical Journal* 2010; 86:89-93

- **Meme Wijesinghe**, Kyle Perrin, Anil Ranchord, Mark Simmonds, Mark Weatherall, Richard Beasley The Routine use of Oxygen in the Treatment of Myocardial Infarction: Systematic Review. *Heart* 2009; 95: 198-202

- Kyle Perrin, **Meme Wijesinghe**, Bridget Healy, Kirsten Wadsworth, Richard Bowditch, Susan Bibby, Tanya Baker, Mark Weatherall, Richard Beasley
  A randomised controlled trial of high concentration versus titrated oxygen therapy in acute severe asthma. *Thorax* 2011 Nov;66(11):937-41

- Kyle Perrin, **Meme Wijesinghe**, Mark Weatherall, Richard Beasley
  Assessing $PaCO_2$ in the Emergency Department: Accuracy of a transcutaneous carbon dioxide device in acute respiratory disease. *Internal medicine Journal* 2011 Aug 41(8):630-3

- Hamish Farquhar, Mark Weatherall, **Meme Wijesinghe**, Kyle Perrin, Anil Ranchord, Richard Beasley. Systematic Review of Studies of the Effect of Hyperoxia on Coronary Blood Flow. *American Heart Journal* 2009; 158:371-7

ABSTRACTS

American Thoracic Society International Conference 2010, New Orleans

Assessing $PaCO_2$ in the emergency department: Accuracy of a transcutaneous carbon dioxide device in acute respiratory disease**.**

K Perrin, **M Wijesinghe**, M Weatherall, R Beasley

British Thoracic Society Winter Meeting 2009, London

Randomised Controlled Trial of High flow versus titrated oxygen therapy in community acquired pneumonia.

Meme Wijesinghe, Kyle Perrin, Mark Weatherall, Richard Beasley

British Thoracic Society Winter Meeting 2009, London

High flow oxygen causes carbon dioxide retention in severe asthma: a randomised controlled trial.

Kyle Perrin, **Meme Wijesinghe**, Mark Weatherall, Richard Beasley

British Thoracic Society Winter Meeting 2009, London

The Effects of Hyperoxia in Obesity Hypoventilation Syndrome.

Meme Wijesinghe, Kyle Perrin, Richard Beasley

British Thoracic Society Winter Meeting 2009, London

An audit of the effect of oxygen prescription charts on clinical practice.

Meme Wijesinghe, Kyle Perrin, Richard Beasley

British Thoracic Society Winter Meeting 2009, London

Oxygen therapy in acute exacerbations of COPD.

Kyle Perrin, **Meme Wijesinghe,** Bridget Healy, Mark Weatherall, Richard Beasley

Thoracic Society of Australia and New Zealand Conference 2009, Darwin Australia

A Randomised Controlled Trial of High flow versus titrated oxygen therapy in community acquired pneumonia.

Meme Wijesinghe, Kyle Perrin, Mark Weatherall, Richard Beasley

Thoracic Society of Australia and New Zealand Conference 2009, Darwin Australia

High flow oxygen causes carbon dioxide retention in severe asthma: a randomised controlled trial.

Kyle Perrin, **Meme Wijesinghe**, Richard Beasley

SECTION 1 INTRODUCTION

Chapter 1.1 Historical Perspective

Oxygen was first discovered as an element in the late 18th century. The history, however, surrounding its discovery remains a contentious issue. In 1774, the English clergyman, Joseph Priestly liberated a gas from sunlight and mercury oxide which he described as "dephlogisticated air". He published his findings "Experiments and Observations on Different Kind of Air" the following year in which he postulated a medical use for it. As he was the first to publish his findings, he is usually given priority for the discovery of oxygen[1] . However, Carl Wilhelm Scheele, a Swedish apothecary, unaware of Priestly's work, may have generated the gas as early as 1771[2] but erroneously, Scheele's observations were not published until 1777 and thus he has not gained credit for its discovery.

Whether or not it was Priestly whom made the discovery of oxygen, he was amongst the first to suggest that there may be adverse effects of 'pure air', when in 1775, he observed a candle to burn out faster in oxygen than in air, and wondered if "the animal powers be too soon exhausted in this pure kind of air"[1].

Shortly after its discovery, Antoine Laurent Lavoisier a French chemist in 1778, conducted the first experiments on oxidation and named the gas 'oxygène' meaning "acid generator".

Following its discovery as an element, oxygen was used as a therapy particularly in the treatment of tuberculosis. By the 1800s, it was widely touted as a panacea and was delivered by wafting buckets of oxygen towards the face of the patient. Further, unconventional routes of administration were developed including intra-abdominal, intravenous, rectal and subcutaneous routes which were claimed to provide the cells of the body with a direct source of oxygen [3 4]. The first use of continuous oxygen therapy was described by Dr Albert Blodgett[5] in a 37 year old woman with severe pneumonia to whom he administered two hundred gallons in twenty-four hours. He noted "the patient not only obtained the relief desired, but was enabled to continue the function of respiration".

Oxygen therapy was revolutionized during the early part of the 20th century. This was in part due to better understanding of basic oxygen physiology brought to light by Adolph Fick and Paul Bert who described oxygen tension in terms of units of partial pressure. These units were used to describe the difference in oxygenation between arterial and venous blood relating the difference to tissue oxygen consumption and cardiac output; they also described central nervous system toxicity at high oxygen tensions, named the 'Bert effect'[6]. J Lorrain Smith in 1899, in trying to reproduce the 'Bert effect', was one of the first to demonstrate local pulmonary toxicity of oxygen at ambient pressure, the so called 'Smith effect'.[7]

It was John Scott Haldane, the eminent Scottish respiratory Physiologist who brought oxygen therapy to a rational and scientific basis and is often heralded the "father of oxygen therapy". His ardent interest on the effect of various gases on the respiratory system, lead him to use his own son in his investigations. At the age of 9, the younger Haldane was sent down a coal mine shaft to test the state of the air and at 12, his father put him in a leaking diving suit to descend 40 feet in the waters of a freezing lake[8]. In 1917, Haldane published "The Therapeutic administration of Oxygen"[9] which is considered to mark the beginning of modern oxygen therapy. In this publication Haldane describes the concepts of anoxaemia, the regulation of respiratory drive and the concepts of ventilation- perfusion matching.

Haldane went onto publish "Respiration" [10] in which he discusses oxygen and carbon-dioxide transport, the nervous control of breathing and the effects of low and high atmospheric pressures. Following Haldane's work and the experience of the benefits of oxygen in the First World War, oxygen as a therapeutic agent became widely accepted.

However, even in these early days of oxygen therapy, Haldane recognized the benefits of keeping inspired oxygen percentage as low as possible "and to know roughly what percentage is being breathed". He also warns of the potential dangers[9]

> "The probable risks of prolonged administration of pure oxygen must be borne in mind, and if necessary balanced against the risks of allowing the oxygen want to continue. No fixed rule can be given. The proper course to pursue must be determined by the physician after careful observation of the patient"

Since its discovery and the work of Haldane it has been used in a wide range of settings and conditions, and remains one of the most effective therapeutic agents available.

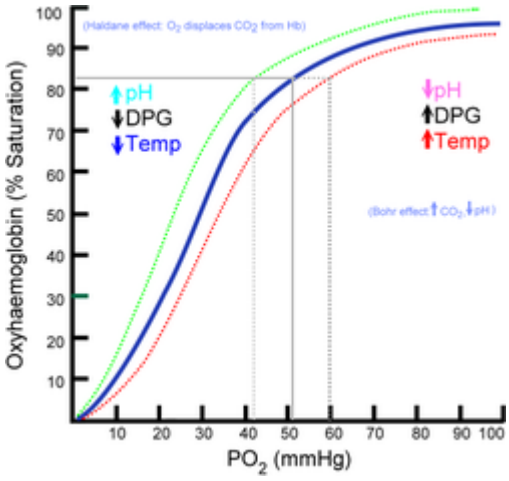
Chapter 1.2 Physiology of Oxygen

The transport of oxygen from the air to the tissues involves complex physiological processes which include pulmonary gas exchange, transport of oxygen in the blood and delivery of oxygen to the mitochondria. In this section I will describe in detail the physiology of oxygen, paying attention to the pathophysiology of hypoxia.

Oxygen transport

Oxygen is transported in the blood in two forms: the majority is carried in the blood bound to the haemoglobin molecule and a small amount is carried dissolved in the plasma. The latter is usually very small and negligible. Haemoglobin is a molecule in red blood cells that consists of an iron-containing porphyrin compound and a protein with four polypeptide chains. The avidity which oxygen binds to haemoglobin is modulated by its molecular structure and the changes it undergoes as oxygen is bound or released. When oxygen binds to haemoglobin, oxyhaemoglobin is formed and is easily reversible. The molecular weight of haemoglobin is nearly 68,000 Daltons and each molecule can potentially bind to four oxygen atoms. The number of molecules bound to haemoglobin is a function of the PaO_2 in the blood known as the oxygen dissociation curve.

Figure 1. Oxygen-Haemoglobin dissociation curve



This illustrates the PaO_2 in blood and the percentage of the oxygen binding sites that are occupied by haemoglobin molecules (saturation). The curvilinear shape of the curve has

two particular features that serve to protect from tissue hypoxia. The upper flat portion of the curve means that a marked fall in PaO_2 is still compatible with a nearly complete oxygen saturation. Secondly the steep portion of the curve means that despite rapidly falling oxyhaemoglobin saturation, the oxygen tension remains relatively well preserved. This property facilitates the continued delivery of oxygen to the tissues despite progressively lower levels of saturation.

Various factors influence the position of the oxygen dissociation curve. The curve is shifted to the right because of an increase in temperature, $PaCO_2$ and hydrogen ion concentration (low pH) or an increase in 2,3-diphosphoglycerate (DPG). This shift to the right enhances release of oxygen to the tissues and improves oxygen availability, named the Bohr Effect.

Ventilation

Effective ventilation is controlled by three elements: respiratory centres in the brainstem, chemoreceptors and the respiratory muscles[11]. The respiratory centres in the brainstem comprise of different groups of neurons in the medulla and pons which are responsible for the automatic control of breathing. The cortex can override these centres if voluntary control is desired.

The chemoreceptors are divided into central and peripheral. The central chemoreceptors are near the ventral surface of the medulla. They are surrounded by brain extracellular fluid and respond to changes in its hydrogen ion (H+) concentration- an increase in H+ stimulates ventilation whereas a decrease inhibits it. Peripheral chemoreceptors are located in the carotid bodies at the bifurcation of the common carotid arteries, and in the aortic bodies above and below the aortic arch. The peripheral chemoreceptors respond to decreases in arterial PaO_2 and pH, and increases in arterial PCO_2. Further receptors are found in the respiratory tract and respond to stretch and irritants.

The volume of gas inspired and expired with each breath is the tidal volume (Vt). The total lung capacity (TLC) is defined as the volume of gas contained in the lungs at maximum inspiration; the residual volume is the gas remaining in the lungs after maximal expiration. The functional residual capacity is the volume of gas remaining in the lungs at

the end-tidal expiration. At functional residual capacity, most of the gas volume, approx 30 mls/kg in healthy adults, is contained in the alveoli. About 150ml is contained in the conducting airways and does not take part in gas exchange. During inspiration, the alveolar volume increases by an amount equal to tidal volume Vt, 7mls/kg, as the volume in the conducting airways remains essentially unchanged during quiet breathing. Yet the amount of fresh gas entering the alveoli during quiet breathing is only two-thirds of Vt, approximately 350mls or 12% of total alveolar volume, since the first gas to enter the alveoli is the gas located in the anatomical dead space. The product of Vt and respiratory frequency is known as minute ventilation (MV). Alveolar ventilation (Va) is the component of total ventilation that goes to ventilate alveoli. Dead space (Vd) is the remainder portion of MV that does not take part in gas exchange. It is divided into anatomical dead space (mouth, nose, pharynx and large airways not lined with respiratory epithelium) and alveolar dead space (ventilated lung that normally contributes to gas exchange, but does not because of impaired perfusion). Physiological dead space equals the anatomical plus alveolar dead spaces.

The Bohr Equation is used to derive physiological dead space (see Appendix 5). In normal subjects the anatomical and physiological dead space volumes are nearly the same as the alveolar dead space is negligible. However, in patients with lung disease the alveolar dead space may be considerably larger because of inequality of blood flow and ventilation within the lung. This is discussed in detail below.

Efficient gas exchange requires matching of alveolar ventilation and perfusion. Historically, the three compartmental model of Riley and Cournand in the 1940s[12] divided the lungs into (1) ideal lung where ventilation and pulmonary blood flow are equal; (2) shunt fraction in which the compartment remains perfused but not ventilated and (3) dead space in which lung units are ventilated but not perfused. Inequalities of ventilation or perfusion are termed ventilation-perfusion (V/Q) mismatch. V/Q mismatch occurs to an extent in the normal, healthy lung due to unevenness of ventilation and blood flow topographically from apex to base. However in lung disease where the inequality is more marked, it can lead to hypoxaemia, hypercapnia or both.

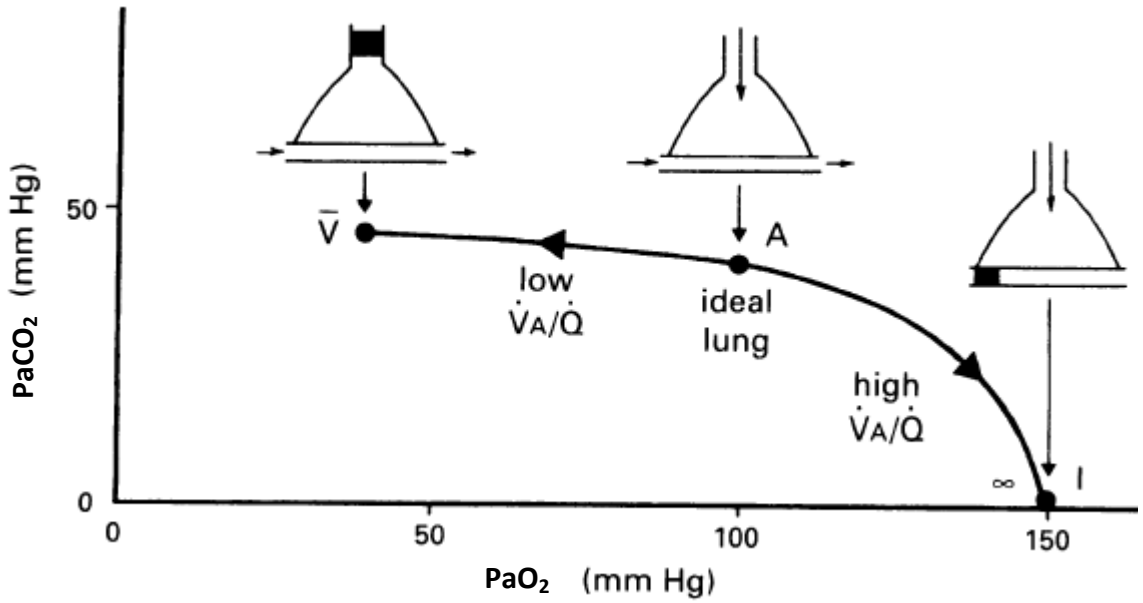


Figure 2. Three Compartment Lung

The lung is represented by three units on the basis of the arterial and the expired partial pressure of oxygen and carbon dioxide. One type of unit (dead space) is unperfused so its V/Q ratio is infinity. A second type of unit (V) is unventilated so its V/Q ratio is zero. Finally, a third type of unit (ideal, A) presents balanced ventilation and perfusion ratios (V/Q ratio =1). Adapted from West, Respiratory Physiology[11]

Oxygen delivery

Oxygen is transported from the atmosphere to each cell in the body. In general, gases move from an area of high concentration to an area of low concentration. The oxygen cascade describes the process of declining oxygen tension from the atmosphere to the mitochondria. Oxygen, being a gas, exerts a partial pressure which is determined by the prevailing environmental pressure. At sea level, the atmospheric pressure is 760mmHg. As oxygen makes up 21% of air, the partial pressure of oxygen in ambient air is 760 X 0.21= 159mmHg.

When oxygen is inspired, water vapour humidifies air and dilutes oxygen thus reducing the inspired partial pressure of oxygen (PIO_2) to 149mmHg.

On reaching the alveoli, a third gas, carbon dioxide, is present. The partial pressure of oxygen in the alveolus (PAO_2) can be calculated by the alveolar gas exchange equation for oxygen. It relates to three variables: R, the respiratory exchange ratio (oxygen uptake/carbon dioxide elimination); PIO_2, inspired partial pressure of oxygen; and the partial pressure of carbon dioxide in the alveolus.

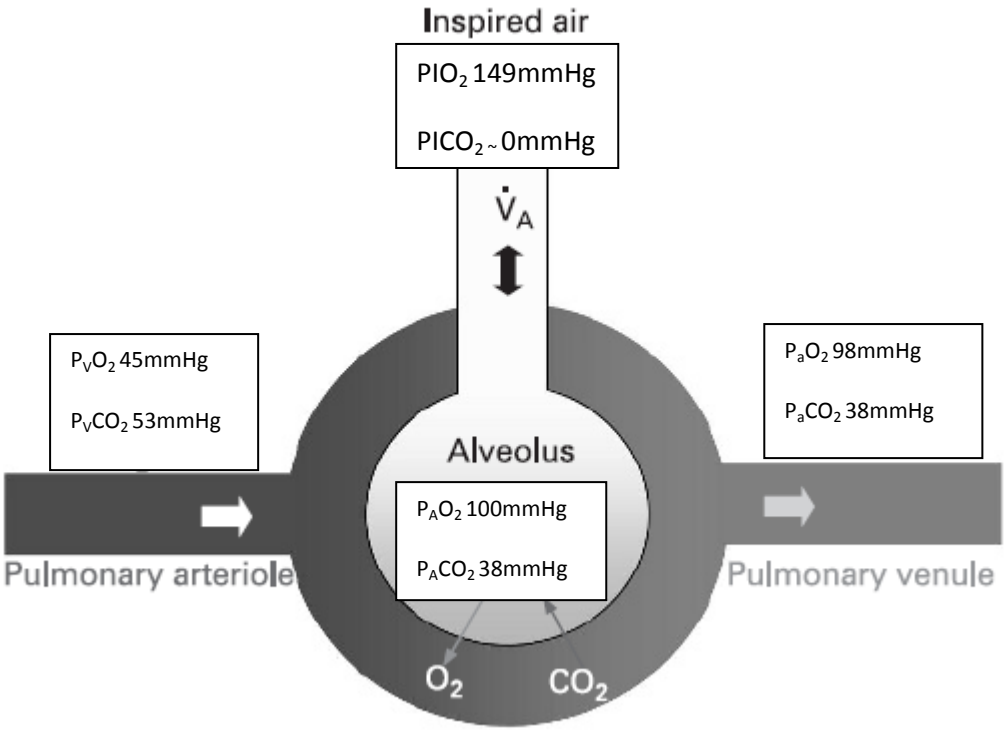
$$PAO_2 = PIO2 - PACO_2/R$$

In normal conditions, the PAO_2 is around 100mmHg.

From the alveolar air, oxygen diffuses into the pulmonary capillaries. The partial pressure of oxygen in the pulmonary arterioles is around 40mmHg which allows for the passive diffusion of oxygen from a zone of high partial pressure to one of low pressure. In accordance with Fick's principle of diffusion the wide surface area and thin alveoli membrane of the blood-gas interface are well suited for the purposes of gas exchange.

Figure 3. Alveolar-Capillary Unit

Adapted from BTS Emergency Oxygen Guidelines 2008[13]



The alveolar-arterial PO_2 gradient is a measure of the difference between the alveolar partial pressure of oxygen and the arterial partial pressure of oxygen

$A\text{-}aPO_2 = (PIO_2 - P_aCO_2/R) - PaO_2$

Under air-breathing conditions, this equation is useful for estimating the degree of alveolar hypoventilation. Normally there is a small A-aPO_2 gradient in the range of 4-8mmHg due to the bronchial circulation. Any differences greater than this between the calculated PAO_2 and the directly measure PaO_2 becomes a rough estimate of V/Q mismatch, increased intrapulmonary shunt and/or diffusion limitation, alone or in combination.

Oxygen delivery (DO_2) is dependent on the arterial content of the blood i.e. the sum of the oxygen dissolved in the blood and the amount of oxygen carried by haemoglobin (CaO_2) and the cardiac output and can be illustrated by the following equation:

$$DO_2 = CaO_2 \times \text{cardiac output}$$

As the amount of dissolved oxygen in the blood is very low, CaO_2 is largely determined by the total amount of haemoglobin and the proportion which is bound by oxygen.

Oxygen is then delivered to the tissues and organs by a process of diffusion across the extracellular matrix between the tissues and capillaries and individual cells to the mitochondria. The amount of diffusive oxygen movement depends on the oxygen tension gradient and the diffusion distance[14].

Hypoxia

Hypoxia occurs when oxygen stores are insufficient to meet oxygen demand in a particular compartment. Hypoxia can be classified as hypoxaemic due to a fall in the oxygen saturation of arterial blood, anaemic due to a reduction of haemoglobin concentration, ischaemic due to inadequate blood flow or histiotoxic due to an inability of the tissues to use oxygen due to interruption of normal cellular mechanisms such as in severe sepsis. Oxygen therapy is used to treat hypoxaemic hypoxia and the mechanisms leading to arterial hypoxaemia are discussed in further detail below.

Reduction in the Inspired Oxygen Partial Pressure

The percentage of oxygen in inspired air is constant at 21% and does not change with altitude. However the fall in atmospheric pressure at higher altitude decreases the partial pressure of inspired oxygen and hence the driving pressure for gas exchange in the lung. Adaptive mechanisms allow people living at such altitudes to tolerate chronic hypoxaemia which is not associated with increased morbidity[15]. In a recent study performed on healthy subjects climbing Mount Everest, the mean PaO_2 when breathing ambient air was 24.6 mmHg[16].

Intrapulmonary Shunts

Shunts occur when alveoli are perfused but not ventilated. Normal subjects have a right-to-left shunt of 2-3% of their cardiac output, this can be greatly increased by lung or

cardiac disease. Shunt is the main mechanism of hypoxaemia in congenital heart disease and pulmonary arteriovenous malformations.

Ventilation-Perfusion Mismatching

V/Q mismatching is the commonest cause of arterial hypoxaemia in lung disease. The assessment of V/Q inequality is discussed in detail below which will identify the physiological processes involved. Changes in the bronchi, parenchyma and pulmonary vessels can lead to severe imbalance of V/Q. The pulmonary circulation, however, is unique in that it responds to hypoxia by vasoconstriction, thus diverting the flow of blood away from poorly ventilated areas of the lung and reducing V/Q mismatch. This mechanism is known as hypoxic pulmonary vasoconstriction (HPV). Because of the relevance to this thesis, HPV is discussed in detail below.

Alveolar Hypoventilation

Hypoventilation may be caused by an overall reduction in ventilation due to muscle weakness or from decreased alveolar ventilation due to respiratory disease such as COPD. Hypoventilation results in hypoxaemia and hypercapnia.

Diffusion Impairment

Impairment of oxygen diffusion across the alveolar-arterial membrane can occur in diseases such as pulmonary fibrosis. This is due to thickening of the alveolar capillary membrane.

Hypoxic Pulmonary Vasoconstriction

Hypoxic pulmonary vasoconstriction is an adaptive mechanism that diverts blood flow away from hypoxic alveoli and thus shifts in blood flow from poorly ventilated areas to better ventilated areas. This reduces ventilation-perfusion mismatch which minimizes arterial hypoxaemia.

This response differs to the systemic circulation which dilates in response to hypoxia. The threshold for vasoconstriction is a PAO_2 60mmHg[17]. The response begins in seconds, reaches a maximum within minutes and can be sustained for hours. It is seen in the

normal as well as the abnormal lung which has been demonstrated by the administration of vasodilator drugs.

The mechanism is modified by a number of factors including changes in pH, age and gender. In addition in severe hypoxia, PAO_2 below 25mmHg, HPV is lost and there is a vasodilator response.

The mechanism of HPV remains largely unknown. There are 2 postulated mechanisms: the first is thought to be due to the release of a vasoactive mediator, and the second is due to a direct effect on the vasculature from hypoxia.

Chapter 1.3 Physiology of Oxygen Therapy

Oxygen is used as an acute therapy and for long term use as discussed below.

Acute Oxygen Therapy

The rationale for oxygen therapy in the acute setting is to increase PAO_2 and therefore should be used to treat or prevent hypoxaemia in order to resolve or avoid tissue hypoxia. Oxygen therapy is only effective when alveolar capillary units have some functional ventilation. If units are poorly ventilated i.e. low V/Q ratio, increasing the fraction of inspired oxygen FiO_2 will increase the PAO_2 and hence, PaO_2. If hypoxaemia is caused by impaired diffusion due to thickening of the alveolar-capillary membrane, increasing the PAO_2 will augment diffusion by increasing the gradient. Oxygen therapy will not resolve hypoxaemia caused by a pure shunt where mixed venous blood does not pass through an alveolar-capillary unit.

The level of PaO_2 at which oxygen therapy should be commenced is debatable. A level of 60mmHg or above is physiologically defensible given that haemoglobin saturation is 90% complete at this PaO_2. However, patients with chronic respiratory disease have been shown to tolerate much lower levels of PaO_2[18-21] and the threshold for administering oxygen to these patients may not be different from normal if tolerating hypoxaemia. Conversely, certain disorders of oxyhaemoglobin saturation, such as carbon monoxide poisoning require treatment with high levels of oxygen to detach carbon monoxide from haemoglobin molecules and speed elimination of carbon monoxide.

Administering oxygen to patients with normal saturations will not increase the delivery of oxygen to tissues and may impact adversely on other physiological parameters which will be discussed in the next section on hyperoxia. The British Thoracic Society Guidelines [13] therefore advocate the prescription and administration of oxygen to a target saturation range rather than for presumed need.

Long-Term Oxygen Therapy (LTOT)

Long term oxygen therapy is used to treat COPD patients with severe hypoxemia. Two randomized controlled trials[22] [23] published in the early 1980s showed a reduction in mortality when oxygen was used for at least 15 hours per day. On the basis of these studies, LTOT is recommended in patients with a PaO_2 of less than 55 mmHg (7.3 kPa) or a PaO_2 of less than 60 mmHg (8 kPa) if there is evidence of pulmonary hypertension, secondary polycythaemia, nocturnal desaturation or peripheral oedema[24]

The mechanism for the increased survival in these patients with LTOT is not precisely understood. Reduction in pulmonary artery pressure may play a part, but these changes were only modest in one of the studies. It is thought that survival may be related to a reduction in arrhythmias related to hypoxia. The effects of LTOT in COPD have been extended to the treatment of other respiratory conditions, although there is no evidence to support this.

Methods of oxygen delivery

Face Masks

Oxygen masks are designed to fit over the mouth and nose and deliver increased concentrations of oxygen in the inspired gas.

- High concentration reservoir masks can increase the inspired concentration to between 60% and 90% when used at a flow rate of 10-15 l/min. However the concentration is variable depending on oxygen flow and the patient's minute ventilation and pattern.

- Simple face masks can deliver concentrations between 40-60%. As the patient may have an inspiratory flow rate greater these masks should not be used with a flow rate <5l/min[25]. However, like the high concentration masks, they are a variable performance device and do not deliver a known, fixed oxygen concentration.

- Venturi masks are a fixed performance device and deliver a constant predetermined oxygen concentration to the patient's mouth unaffected by tidal

volume or pattern of breathing. They work on the Bernouilli effect whereby air is entrained through the side port of the venturi valve and the amount entrained is related to the flow of oxygen. Different concentrations of oxygen can be administered and are available in the following concentrations 24%, 28%, 35%, 40% and 60%.

Nasal Cannulae

Nasal cannulae overcome the difficulties of face masks allowing the patient to eat, talk and expectorate without discontinuing therapy. They are also cheaper than face masks. They can be used to deliver flows of 1-8l/min[26]. However, being a variable performance device, the concentration of oxygen delivered will vary and high flows may cause nasal irritation.

Monitoring oxygen therapy

Oximetry

Pulse oximetry is non-invasive technique used to continuously monitor the oxygen saturation level (SpO_2). An oximeter is a spectrophometric device that measures the different absorption of light by oxy- and deoxyhaemoglobin. Most instruments use only two transmitted wavelengths and therefore include in the measurement other forms of haemoglobin such as carboxyhaemoglobin and methaemoglobin. They do not provide information on pH or $PaCO_2$ and are unreliable when SpO_2 falls below 80%. Oximeters may not be able to achieve a satisfactory reading in clinical situations where there is a poor signal such as shock, skin pigmentation and nail varnish. In addition movement artefacts may produce a false fall in saturations.

Invasive Monitoring

Arterial punctures can be taken from the radial, brachial and femoral arteries. If repeated blood gas measurements are required, an arterial line can be inserted. Causes of error in blood gas measurements include excessive heparin, failure to keep the sample

iced if analysis is not done within 30 minutes, air contamination and a high white blood cell count. Technical errors in measurement are also an important source of error.

Chapter 1.4 Hyperoxia

Hyperoxia is defined as an excess of oxygen in body tissues as a result of breathing elevated concentrations of oxygen. In this chapter I will discuss the effects of hyperoxia at normobaric pressures, that is, at a level equal to atmospheric pressure. The effects and therapeutic use of hyperbaric oxygen are outside the realms of this thesis, and will not be included.

Whilst it cannot be argued that administering oxygen to the hypoxaemic patient leads to an increase in PaO_2 which leads to favourable physiological effects and ultimately the prevention of cell death, administering oxygen to the non-hypoxaemic patient has a number of untoward functional and toxic effects which are not widely appreciated. These effects will be broadly discussed in this chapter.

Oxygen-Induced Hypercapnia

There are a number of mechanisms which are believed to cause oxygen induced hypercapnia in a group of vulnerable individuals. In this chapter I will briefly describe each proposed mechanism but will give a more extensive review of the literature with reference to COPD and asthma in the subsequent two chapters.

Haldane Effect

The Haldane effect was first described in 1914 by Haldane and colleagues[27]. It characterises the haemoglobin molecule's affinity for carbon dioxide at different oxygen concentrations. Low oxygen concentrations promote loading of carbon dioxide onto haemoglobin. Conversely, high oxygen concentrations enhance the unloading of carbon dioxide. Thus if a hypoxaemic patient is administered oxygen, the rise in arterial oxygen saturation will cause carbon dioxide to be released and the $PaCO_2$ will rise. Although studies have been conducted to estimate the degree of oxygen-induced hypercapnia[28 29], the magnitude attributable to the Haldane effect has not been quantified. Additionally, it

has been argued that although the Haldane effect does increase the $PaCO_2$, it does so only transiently[30].

Ventilatory Drive

The peripheral chemoreceptors in the carotid and aortic bodies sense both hypoxia and hypercapnia. The ventilatory response curve to hypoxia is shown in figure 4.

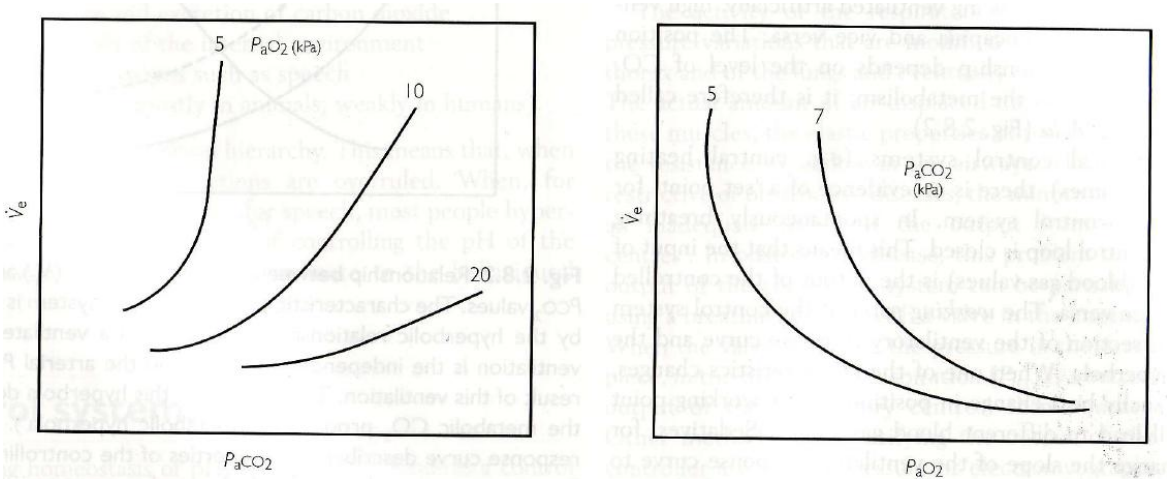


Figure 4. Ventilatory response curve to hypoxia and hypercapnia

Both responses are shown at different values of PaO_2 and $PaCO_2$ respectively, demonstrating the interaction between both stimuli. Hypoxaemia increases the slope of the ventilatory response curve.

Because of interaction between hypoxia and hypercapnia, the sensitivity of the peripheral chemoreceptors for CO_2 is substantially reduced at high levels of arterial PaO_2. Hyperoxia thus removes some of the ventilatory drive in patients with chronic hypoxia and normal subjects. The contribution of “loss of hypoxic drive” to oxygen-induced hypercapnia is debatable and will be discussed in detail in the subsequent chapter.

V/Q Mismatch

Ventilation perfusion mismatch occurs when alveolar capillary units are perfused but not ventilated. As discussed in the preceding chapter the lungs have an adaptive mechanism named hypoxic pulmonary vasoconstriction which diverts blood away from poorly ventilated areas of the lung in order to reduce V/Q mismatch. When supplementary oxygen is administered, PAO_2 will rise, causing release of hypoxic pulmonary vasoconstriction and ultimately a rise in $PaCO_2$.

Absorption Atelectasis

Absorption atelectasis is the tendency of an airway to collapse if proximally obstructed. In normal lungs, nitrogen is poorly soluble in plasma and therefore remains in a high concentration in alveolar gas. If high concentrations of oxygen are administered, it 'washes out' nitrogen and the process of absorption atelectasis is accelerated, increasing V/Q mismatch.

Pulmonary Toxicity

As described in the opening chapter of this thesis the pulmonary toxic effects of oxygen, the 'Smith effect' have been known for some centuries[6]. Gerschman and colleagues[31] in 1954 first suggested oxygen derived free radicals as being the probable aetiological factor in the development of these effects. Pathological changes including oedema, alveolar haemorrhage, inflammation, fibrin deposition, and thickening and hyalinization of alveolar membranes have been described[32] . Specific cell damage is caused by free radicals present in the form of superoxide and hydrogen peroxide. Normally, various antioxidant enzymes such as glutathione peroxidise, catalase, and superoxide dismutase protect the body from these free radicals, but in hyperoxic conditions, there is increased free radical production leading to saturation of the enzyme systems and as a result free radicals escape deactivation[32 33]

The precise concentration of oxygen which is toxic to human lungs is unestablished. Animal studies have shown a clear correlation between progressive increments of oxygen concentration and morphological damage in pulmonary cells[34]. As well as being dose dependent, oxygen toxicity has also been shown to be a function of duration of oxygen administered in human cells[35]. From a synthesis of published data on pulmonary oxygen toxicity in humans, Jackson[36] provides the following time course: decreased tracheal mucus velocity is detectable after six hours of 100% oxygen breathing, and signs of tracheobronchitis appear after 12 hours. Oedema, documented in some studies by bronchoalveolar lavage, occurs at 72-96 hours, and fibrosis follows. Although some of these changes may be reversible, even a short duration of hyperoxia can lead to significant alveolar-capillary 'leak' and induce processes that culminate in fibrosis in the alveolar wall[37].

Cardiovascular Effects

Hyperoxia has a number of well documented effects on the cardiovascular system. In healthy subjects it has been shown to reduce cardiac output, reduce stroke volume and increase systemic vascular resistance[38-41]. These effects have also been shown to occur in myocardial ischaemia[42-45]. More recently we undertook a systematic review [46] to investigate the effect of oxygen on coronary blood flow which found that hyperoxia caused a significant mean reduction in coronary blood flow of 8-29% due to a mean 22-41% increase in coronary vascular resistance. The other major finding of this systematic review was the reduction in myocardial oxygen consumption due to both a reduction in myocardial oxygen delivery as well as a reduction in myocardial oxygen demand resulting in reduced myocardial contractility. The proposed mechanisms which coronary vasoconstriction occurs in the presence of hyperoxia includes the secretion of angiotensin II by myocytes, the production of reactive oxygen species and the sequestration of nitric oxide by the haemoglobin molecule. The clinical implications of these cardiovascular effects are discussed in section 1.7

Central Nervous System Toxicity

Bert originally described that CNS toxicity occurred at oxygen pressures of >3 atmospheres, however even at lower pressures, hyperoxia has been shown to increase the formation of oxygen free radicals in the brain [47 48] inducing cerebral vasoconstriction, which may reduce cerebral blood flow [49 50]. The clinical implications of this are discussed in section 1.7

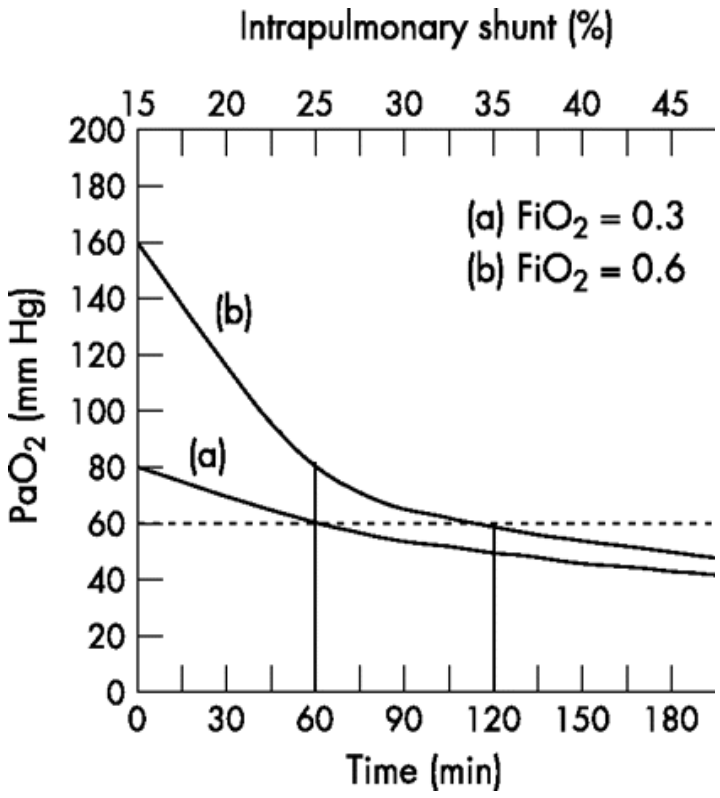
Although the focus of this thesis is on the use of oxygen in adults, it's well recognised causative role in retinopathy of prematurity in children, warrants consideration. Oxygen therapy to reduce apnoea in the 1940s led to an increased incidence of retinopathy of prematurity, known then as retrolental fibroplasia. It was first linked to oxygen therapy in the 1950s[51 52]. It is caused by the disorganised growth of premature retinal vessels which is accelerated by supplemental oxygen exposure, although this is not the single causative

agent. However, a recent Cochrane review[53], has shown a trend for supplemental oxygen to reduce the progression to threshold retinopathy of prematurity but this was not statistically significant. Perhaps of greater concern is the increased adverse pulmonary sequelae with higher oxygen targeting in this group of preterm infants.

Delay in recognition of physiological deterioration

Another less well recognised adverse effect of hyperoxia is the potential to delay the recognition of physiological deterioration[54-56]. By measuring venous admixture and fraction of inspired oxygen Downs and colleagues[54] have shown that worsening intrapulmonary right-to-left shunting of blood occurs as a result of progressive worsening of disease. Despite the shunt increasing, there is only a minimal reduction in oxygen saturation. It is only when the shunt has achieved a certain level that this will be reflected by a low oxygen saturation. This may delay the detection and treatment of an unstable patient. In contrast, if a low concentration of oxygen is used to achieve normoxia, rather than hyperoxia, a subsequent clinical deterioration is likely to be recognised sooner through pulse oximetry. A clinical example to demonstrate this is shown in figure 5.

Figure 5. Intrapulmonary shunt and arterial PaO_2



Arterial oxygen tension (PaO_2) plotted as a function of intrapulmonary shunt increasing at a rate of 1% per 6 min with fractional inspired oxygen (FiO_2) of (a) 0.3 and (b) 0.6. In example (a) with FiO_2 0.3, the time required for the PaO_2 to decrease from 80 mm Hg (95% saturation) to <60 mm Hg (<90% saturation) is around 60 min. At this stage, with the same rate of increasing intrapulmonary shunt, an increase in FiO_2 from 0.3 to 0.6 will maintain the PaO_2 above 60 mm Hg for about a further 60 min. In example (b), if the patient receives an FiO_2 of 0.6, it would take around 120 min for the PaO_2 to decrease to <60 mm Hg (<90% saturation). At this stage, with the same rate of increasing intrapulmonary shunt, there will be a further deterioration in PaO_2 despite maintenance of the FiO_2 at 0.6. Adapted from Beasley, Thorax 2007[56]

Chapter 1.5 Oxygen Therapy in Chronic Obstructive Pulmonary Disease

In this chapter I will focus on the studies which have demonstrated the adverse effects of oxygen in COPD. As these have been known for over 60 years I will first give a summary of the early studies, move onto to discuss some of the findings of the more recent studies particularly those pertaining to the mechanism of oxygen induced hypercapnia and then finally present some of the clinically based studies. I will close this section by presenting the BTS guideline recommendations on ways to reduce oxygen induced hypercapnia in AECOPD.

Early Studies of Oxygen induced Carbon Dioxide Retention in COPD patients

The first reports of oxygen induced carbon dioxide retention date back over sixty years. In 1937, Barach[57] observed that "oxygen treated patients developed a state of stupor, with irrationality when aroused" and in 1941[58] went onto record "A profound disturbance of mental function may take place in patients suffering from longstanding anoxaemia after inhalation of 50% oxygen". Barach originally ascribed these neurological effects to a sudden change in cerebral oxygen tension. It was in 1949 that Donald[59] first described a case of oxygen induced carbon dioxide retention. Following 12 hours of oxygen therapy, the $PaCO_2$ of a patient with severe emphysema rose to 120 mmHg. The patient lapsed into a coma, but following withdrawal of oxygen, he recovered rapidly and had an abrupt fall in his $PaCO_2$ to 60 mmHg. Donald postulated that this neurological effect was a result of hypoventilation due to removal of the anoxic stimulus to breathe. He suggested that administering oxygen intermittently would prevent carbon dioxide retention.

Following this case report, further studies in the 1950s [60-62] described a number of cases in which hypercapnia developed in COPD patients after oxygen therapy. The cases describe the development of profound neurological effects ranging from headache, muscle-twitching, coma and in some cases, death[60]. It soon became widely accepted that

patients with COPD were at risk of developing carbon dioxide retention from oxygen therapy and the mechanism for this was believed to be hypoventilation.

One of the main contributors of our understanding of oxygen therapy and respiratory failure in COPD is from Dr Moran Campbell during the 1960s. Campbell disputed the use of intermittent oxygen therapy, arguing that this could potentially lead to more severe arterial hypoxaemia. He also argued that because of the shape of the oxygen dissociation curve, even a small increase in inspired oxygen would produce a useful increase in oxygen content and tissue supply[63]. Campbell recommended that patients presenting with respiratory failure secondary to acute exacerbations of COPD should be treated with continuous, controlled oxygen to prevent carbon- dioxide retention.

In a subsequent paper[64] in 1960, Campbell was the first to describe the Venturi mask and the concept of controlled oxygen delivery. He demonstrated how this specialised mask used air at a high flow-rate and with controlled oxygen enrichment, provided accuracy of delivery and minimised rebreathing. The prototype and early production models had a fixed Venturi orifice through which oxygen flowed at 2 l/min, entraining a much larger flow of air via holes in the loose fitting mask; a second inlet was supplied with oxygen at varying flow in order to adjust the concentration. This apparatus was modified to a single nozzle with different concentrations (24%, 28% and 35%) by modifying the size of the venturi orifice. Further studies [20 65-67] during this period confirmed the effectiveness of relieving hypoxaemia without causing CO_2 retention using the Venturi mask. The Venturi mask is now universally accepted as the most accurate and safest way to administer oxygen to patients at risk of carbon dioxide retention.

The effect of differing oxygen concentrations and magnitude of hypercapnia was studied in 1962 by Massaro and colleagues[68]. They administered 100% oxygen by face mask for 10 minutes, 1-2 l/min by nasal cannula for 10 minutes and 1-2 l/min by nasal cannula for over 2 hours to patients with stable COPD and hypercapnia. They found that higher concentrations of oxygen would give greater rises in $PaCO_2$ and they also showed that low flow oxygen could also cause CO_2 retention which occurred over varied periods of time.

The Mechanism of Oxygen Induced Carbon Dioxide Retention

Over the past 60 years, a number of studies have been conducted investigating the interesting and important mechanism of oxygen induced hypercapnia in COPD patients. These have been done on a variety of patients- stable and acutely unwell, spontaneously breathing and ventilated- using differing methods. These studies and changes in perception of the mechanism are discussed below.

Following the early case reports and studies of carbon dioxide retention induced by oxygen in patients with emphysema, it was generally accepted that the most likely mechanism for this was due to a fall in ventilation due to relief of anoxia[59 61]. Previous work[69] had demonstrated that these patients have a diminished response to carbon dioxide and low levels of oxygen took on a more important role in driving ventilation. It was postulated that on removal of this stimulus to breathe, a fall in ventilation would lead to a rise in $PACO_2$, a corresponding rise in arterial PCO_2 and fall in pH. If the fall in ventilation was sufficiently large, carbon dioxide narcosis would ensue.

In 1954, Prime and Westlake[70] investigated the respiratory response to carbon dioxide in 35 stable emphysematous patients. In support of earlier work, they found that on administering pure oxygen there was a fall in ventilation in 26 out of 35 of the emphysematous patients, compared to an average increase in ventilation observed in the control group. No patients with a normal initial $PaCO_2$ showed increases in $PaCO_2$. However, not all hypoxic patients had a fall in ventilation.

The first study to suggest that other factors may be responsible for oxygen induced carbon-dioxide retention other than loss of hypoxic drive to breathe, was published in 1965[71]. Pain, Read and Read studied 54 patients with stable chronic lung disease. They made measurements of arterial blood gases and ventilation in a steady state and whilst breathing oxygen. They observed that there was not a close relationship between $PaCO_2$ and changes in ventilation, in particular, increases in $PaCO_2$ occurred in the absence of comparable decreases of ventilation. They went on to propose that increases in the ratio of physiological dead space to tidal volume (Vd/Vt), also known as Bohr dead space, caused by reversal of hypoxic pulmonary vasoconstriction, may also be involved in increasing $PaCO_2$.

In 1967, Lee and Read [72] provided scientific evidence to support the theory of release of hypoxic pulmonary vasoconstriction. They studied 58 patients with stable COPD. They measured arterial blood gases and mixed expired carbon dioxide using the Douglas bag method on air and after breathing oxygen. Using the Bohr equation (see Appendix 5), physiological dead space /tidal volume (Vd/Vt) ratio was derived from the simultaneous measurements of arterial and mixed expired carbon dioxide tension. Whilst breathing air the Vd/Vt did not increase significantly from baseline and at 15 minutes, but during oxygen breathing, there was an increase of more than 0.05 in the Vd/Vt in 39 out of 58 subjects, and by less than this amount in the other 19 subjects. The authors agreed with the observations of Pain and colleagues, that the increase in Vd/Vt ratio due to increased blood flow to poorly ventilated regions of the lung is due to reversal of pre-existing regional pulmonary vasoconstriction and is at least partly responsible for CO_2 retention during oxygen inhalation.

It was in 1967 that Campbell delivered the J Burns Amberson Lecture: The Management of Acute Respiratory Failure in Chronic Bronchitis and Emphysema.[73]In this lecture he focused on exacerbations of COPD, emphasizing particularly on careful initial management with oxygen therapy. The assertion of the "loss of hypoxic drive" theory is usually attributed to his lecture. However, he is widely misquoted, and his exact words were "It is usual to attribute the rise in $PaCO_2$ in these patients to removal of the hypoxic drive to ventilation, but I share the doubts of Pain [71] and co-workers that this is the whole story; changes in the pulmonary circulation may also be important".

The next landmark study in determining the mechanism of oxygen induced carbon dioxide retention came in 1980 from Aubier and colleagues[74]. This was also the first study on COPD patients in acute respiratory failure. They recruited 22 patients who were all severely hypoxaemic and hypercapnic at entry with mean values of PaO_2 38mmHg ±2 and $PaCO_2$ 65 mmHg ±3 mmHg respectively. 100% oxygen was administered for 15 minutes and measurements of arterial blood gases and mixed expired CO_2 were taken. These values were used to measure the Vd/Vt using the Bohr equation.

Following the administration of oxygen, there was a transient decrease in minute ventilation, the nadir occurring at a mean of 71 seconds from the start of inhalation. The decrease in ventilation amounted to 18 ±2% of the control values. However, minute ventilation increased and plateaued at about 12 minutes. The final ventilation

represented 93 ±6% of the control value. The initial decrease in ventilation was due to both a decrease in tidal volume and respiratory rate, but after 15 minutes of breathing oxygen, these were not significantly different from the corresponding room air values. $PaCO_2$ was found to increase significantly in all subjects, average 23 ±5mmHg. However they did not find a correlation between the rise in $PaCO_2$ and minute ventilation.

Aubier and colleagues concluded that an initial reduction in minute ventilation in response to hyperoxia was observed in patients with COPD and respiratory failure. When compared to patients in a stable state, the rise in $PaCO_2$ was of a greater magnitude and they proposed that the increase in $PaCO_2$ may provide an excitatory influence on ventilation in this group of patients.

They went onto argue that following prolonged administration of oxygen, the ventilatory response increases to essentially the same observed whilst breathing room air. This contradicts the common hypothesis that patients with COPD have a lower than normal respiratory sensitivity to changes in CO_2 and rely on a strong hypoxic drive from peripheral chemoreceptors as their main chemical stimulus to breathe which is removed following the administration of oxygen.

In addition, they argued that the observed rise in $PaCO_2$ could not be explained by the "Haldane effect", which may account for some of the increase, but not to the magnitude of a mean value of 23mmHg which was observed in these patients. An explanation for their findings of a rise in Vd/Vt from 77% ±2 to 82% ±2 following the administration of oxygen represents shifts in pulmonary blood flow due to release of hypoxic pulmonary vasoconstriction.

The findings of Aubier were supported by Sassoon and Colleagues in 1986[75]. In this study, the hypoxic and hypercapnic drive of 17 stable COPD patients was examined. They hypothesised that if oxygen induced-hypercapnia was a consequence of diminished total minute ventilation, then patients who were susceptible would have a blunted hypercapnic drive, and an intact hypoxic drive; and patients who did not develop oxygen induced-hypercapnia should have an intact hypercapnic drive. In their study they also examined the contributions of carbon dioxide production, minute ventilation and physiological dead space to tidal volume ratio on oxygen induced hypercapnia. The Vd/Vt was calculated using the Bohr equation.

Sassoon found that on oxygen administration, the Vd/Vt and $PaCO_2$ increased significantly. There was, however, no significant correlation between changes in the $PaCO_2$ whilst breathing oxygen and hypercapnic or hypoxic drive which they measured by ventilatory and mouth occlusion pressures. Based on these observations, they concluded that oxygen induced hypercapnia was therefore not related to the control of ventilation.

In 1991, Dunn[76] and colleagues studied the effects of hyperoxia on 13 ventilator dependent patients with a history of COPD. They concurred with Aubier and Sassoon's work that increases in Vd/Vt contribute to changes in $PaCO_2$. However, by performing recruitment threshold measurements at normoxia and hyperoxia , they demonstrated that oxygen supplementation increased the level of inspired CO_2 which induced spontaneous respiration over mechanical ventilation, indicating a suppression of hypoxic respiratory drive.

In 1993, Berry and co-workers[77] sought to determine the relationship between oxygen-induced decreases in ventilation and mouth occlusion pressures (P0.1, an index of respiratory drive) in patients with COPD and the ventilatory responses to hypoxia. Fourteen patients with severe airflow obstruction FEV1 0.95 ± 0.41L with starting SpO_2 of 90.8 ±0.99 % on room air were administered supplemental oxygen (1-2L/min) or room air in a single blind fashion. Minute ventilation and mouth occlusion pressures were measured on air and oxygen. The tests were also repeated in hypoxic conditions (a reduction in O_2 sats to 75%). On oxygen supplementation both ventilation and mouth occlusion pressures were reduced significantly, but there was no change in these measurements during hypoxic conditions. These findings concurred with Dunn's, that respiratory drive plays a role in the mechanism of oxygen-induced hypercapnia. Although unlike other studies, only low flow oxygen was administered increasing saturations to 95.2% ± 0.46, which may not have been sufficient to abolish vasoconstriction in the pulmonary circulation.

Dick and co-workers[78] recruited 11 patients with stable COPD who were oxygen dependent. At entry, the patients were hypoxaemic and hypercapnic: mean PaO_2 62.3mmHg and PCO_2 58.7 mmHg with severe airflow limitation: mean FEV1 1.00 l/min. In order to clarify the relationship between the O_2 induced change in ventilation and the ventilatory drive they measured the hypercapnic and hypoxic ventilatory response slopes (the expected change in ventilation as a function of ventilatory drive).

Following administration of 100% oxygen for 15 minutes, PaO_2 and SaO_2 increased significantly. The mean increase in PCO_2 was 6.6 ± 3.3 mmHg, but the carbon dioxide production (VCO_2) did not change significantly. 7 of 11 subjects decreased their minute ventilation at 15 minutes, but this did not achieve statistical significance. However there was substantial variation in minute ventilation in individual subjects.

In addition the observed change in ventilation and the predicted change in ventilation were not significantly different which the authors conclude suggests that the O_2-induced change in ventilation is directly determined by the ventilatory response slopes to hypoxia and hypercapnia and the changes in SaO_2 and $PaCO_2$.

In summary the authors concluded that the development of O_2-induced hypercarbia is associated with only a small change in ventilation. The oxygen-induced decrease in ventilation due to suppression of hypoxic drive was almost equal to the expected increase in ventilation caused by the oxygen induced hypercarbia.

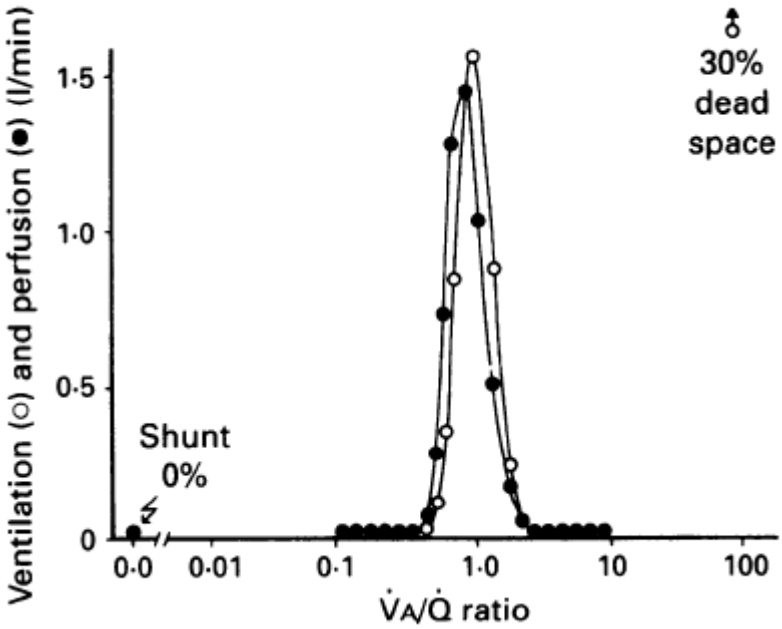
The multiple inert gas elimination technique (MIGET) is a technique developed in the mid-1970s which has enhanced the understanding of the mechanism of the pathophysiology of pulmonary gas exchange in lung diseases. Because of its importance in determining V/Q inequalities and abnormal gas exchange, it will be discussed in some detail here.

Multiple Inert Gas Elimination Technique

As discussed in section 1.2 the three compartmental model of Riley and Cournand divided the lungs into (1) ideal lung where ventilation and pulmonary blood flow are equal; (2) shunt fraction in which the compartment remains perfused but not ventilated and (3) dead space in which lung units are ventilated but not perfused. These measurements were based on the arterial and expired pressures of O_2 and CO_2. Although this model defined the relationship between ventilation/perfusion ratios it did not provide information on extrapulmonary influences or changes that occur in the presence of gas exchange abnormalities. By using inert gases, the MIGET has two principle advantages: (1) it estimates the patterns of alveolar ventilation and pulmonary blood flow without disturbing either vascular or bronchomotor tone; and (2) it facilitates the unravelling of the extrapulmonary determinants (overall ventilation, cardiac output, and oxygen consumption) of abnormal gas exchange[79].

The MIGET uses the simultaneous infusion of six inert gases. Inert gas measurements are then taken from three different sites: mixed venous (Pv), arterial blood(Pa) and mixed expired gas (Pe). For each inert gas , the retentions are calculated as the ratio between arterial partial pressure and mixed venous partial pressure (R=Pa/Pv) and the excretions as the ratio between mixed expired partial pressure and mixed venous partial pressure (E=Pe/Pv). By using a multicompartmental approach with reinforced smoothing, the retentions of the six inert gases allow the estimations of continuous distribution of the pulmonary blood flow against V/Q ratios on the logarithmic scale. Similarly, the excretions of the six inert gases provide an estimation of the distribution of alveolar ventilation against V/Q[80].

Figure 6. Ventilation-perfusion distributions in a healthy subject

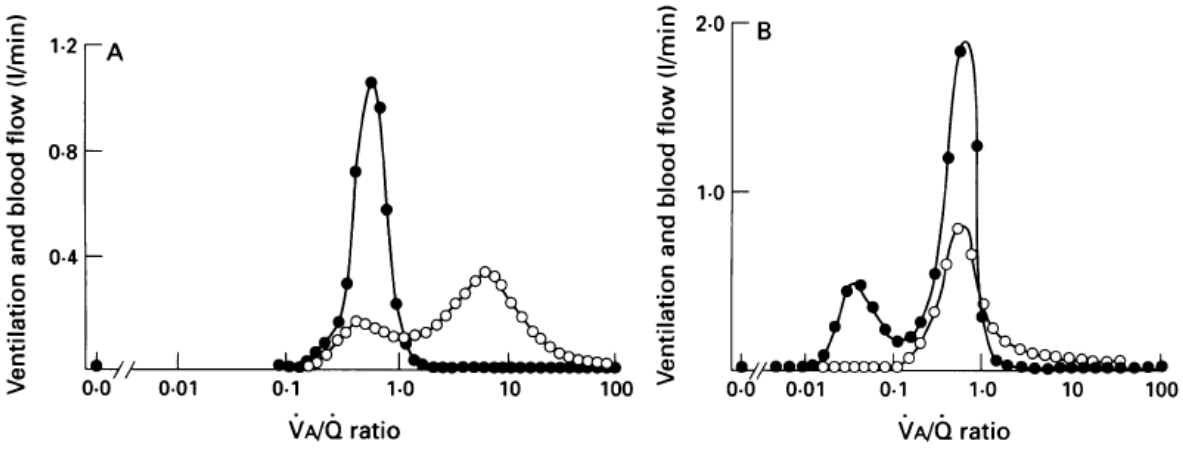


Ventilation (o) and perfusion (•) are plotted against ventilation-perfusion (VA/Q) ratio on a logarithmic scale in a resting young, healthy adult breathing room air. Both ventilation and blood flow curves are centred (first moment) around a VA/Q ratio of 1 and they are narrow (second moment). No perfusion to low VA/Q units (VA/Q<0.1) nor ventilation to high VA/Q areas (VA/Q>0.10) are observed. Note also the absence of shunt. Each individual data point represents a particular amount of blood flow (•) or alveolar ventilation (o) to the corresponding pulmonary compartment (VA/Q ratio). Total cardiac

output corresponds to the sum of the 50 blood flow points and total alveolar ventilation is the sum of the 50 ventilation points. From Roca, Thorax 1993[80]

The dispersion of pulmonary blood flow (log SD Q) and dispersion of alveolar ventilation (log SD V) are widely used overall descriptors of the amount of mismatch. These variables will provide a quantitative estimate of mismatching only when the V/Q distribution is unimodal and showing a logarithmically normal distribution. With other distributions it should be regarded as an index of abnormality only. In many patients with lung disease the most striking finding is the widening of the dispersion with or without the appearance of a true shunt (zero V/Q); in other disease states, however, bimodal or even trimodal V/Q distributions have been recovered. The example below shows ventilation-perfusion distributions in two patients with COPD.

Figure 7. Ventilation-perfusion mismatch in COPD



(A)Ventilation-perfusion ratio distribution in a patient with emphysema-type COPD. Note the bimodal pattern of ventilation distribution (o) with areas of high VA/Q ratio. (B) Ventilation-perfusion ratio distribution ratio in a patient with bronchitis-type COPD. The blood flow distribution (•) is bimodally shaped due to the presence of alveolar units with low VA/Q ratio. From Agusti Thorax 1993[81]

Robinson and colleagues[82] were the first group to use the MIGET to investigate the mechanism of oxygen induced hypercapnia in acute exacerbations of COPD. In this study, 22 patients with AECOPD were recruited within 72 hours of admission. Baseline

measurements of FEV_1 and FVC, and PaO_2 and $PaCO_2$ on room air were taken. Other measurements taken were cardiac output and minute ventilation. Ventilation-perfusion distribution was measured using MIGET. Specific measurements used were log SD Q , log SD V and Disp R-E a measurement of retention and excretion of the 6 gases reflecting V/Q inequality. Patients were then given 100% oxygen via a sealed nasal mask for at least 20 minutes.

Following the administration of oxygen, patients were classified as being retainers (Group R) if there was a rise in CO_2 of ≥ 3mmHg or non-retainers (Group NR) if there was less than a 3mmHg rise in CO_2. Of the 22 patients recruited, 12 patients were retainers and 10 patients were non-retainers. The degree of airflow obstruction was similar in both groups with a mean FEV_1 of 0.71 l/min and 0.80 l/min in Group R and Group NR respectively. The baseline PaO_2 on room air, however, was significantly lower in Group R, 54.5mmHg ±9.4 (mean ± SD) compared with 62.7 mmHg ±10 in the NR group. Baseline $PaCO_2$ was higher in Group R 56.3 ±13.6 mmHg compared with Group NR 49.7 mmHg ±8.3, but this difference was not significant.

Following the administration of oxygen, $PaCO_2$ in group NR decreased by -1.3 mmHg ± 2.2mmHg and in increased in Group R by +8.3mmHg ± 5.6 mmHg.

Minute ventilation fell in Group R from 9.0 L/min ± 2.0 to 7.2 ±1.6, a 20% reduction, following oxygen administration. This was not demonstrated in Group NR, where there was a slight increase from 9.8 ±2.3 to 9.9 ±2.5.

In terms of the ventilation and perfusion distributions, the log SD Q increased in both groups. However the log SD V increased only in Group R, but not Group NR. Bohr dead space (Vd/Vt) calculated by MIGET increased in R group, but not in NR group.

The authors conclude that the significant reduction in minute ventilation seen in Group R, but not in Group NR makes this the likely mechanism of oxygen induced hypercapnia. In addition the increase in dispersion of pulmonary blood flow seen in both groups of patients, is due to release of hypoxic pulmonary vasoconstriction and does not discriminate between retainers and non-retainers.

The increase in dispersion of alveolar ventilation seen in Group R is only likely to represent an increase in true alveolar dead space. The authors have proposed an

additional mechanism in that hypercapnia may lead to bronchodilatation increasing ventilation to some parts of the lung resulting in increasing alveolar dead space and worsening hypercapnia.

Criticisms of this study[83] argue that a rise in pCO_2 of 3mmHg to divide the 2 groups of patients is not clinically significant. In addition the patients, in contrast to the Aubier[74] study, were not adequately hypoxaemic to allow the mechanism of hypoxic pulmonary vasoconstriction to play a physiological role.

Santos and colleagues [84] have also used MIGET, but in mechanically ventilated patients. Of the patients that were studied, 8 patients had acute lung injury (ALI) and 4 patients had COPD as their predominant pathology.

All patients had baseline measurements whilst breathing maintenance FiO_2, then at 30 and 60 minutes whilst breathing FiO_2 100%, and then again at 20 minutes whilst on maintenance FiO_2.

They found that in patients with ALI, $PaCO_2$ increased by 4mmHg at 30 and 60 minutes, and intrapulmonary shunt increased from 16% at baseline to 22% and 23% at 30 and 60 minutes respectively. In patients with COPD the $PaCO_2$ increased by 4 and 5 mmHg and the dispersion of pulmonary blood flow increased significantly.

The authors conclude that in patients with ALI, hyperoxia deteriorates intrapulmonary shunting to collapse of unstable alveolar units with very low ventilation-perfusion ratios, as opposed to patients with COPD, in whom the dispersion of pulmonary blood flow is disturbed, suggesting release of hypoxic pulmonary vasoconstriction.

In summary, there have been a number of well designed trials investigating the mechanisms of oxygen-induced hypercapnia in COPD. Initially this was believed to be due to suppression of hypoxic drive to breath but then through the 1960s and 1970s the mechanism of hypoxic pulmonary vasoconstriction has taken favour. More recently however, these data have been challenged using more powerful investigative techniques showing that both mechanisms play a part.

Clinical Studies and Audits of Oxygen in COPD

The mechanism by which oxygen therapy and hyperoxia leads to hypercapnia in COPD has been discussed in detail. The next section brings together the clinical relevance of this in which I will present studies and audits over the years which have described outcomes and adverse events.

An important study in determining the prevalence of respiratory acidosis in patients with AECOPD was published by Plant and co-workers[85] in 2000. They undertook a one year prospective study identifying patients admitted to 3 large hospitals in the United Kingdom with AECOPD to determine the prevalence of respiratory acidosis and the relationship with oxygenation. Of the 983 patients studied, 11 required immediate intubation and 22 patients were admitted to intensive care. ABGs were performed in 94.6% of patients on admission, nearly half were found to have hypercapnia and 20% had a respiratory acidosis (pH <7.35). Patients with acidosis had between a 6- and 8-fold increased risk of ICU admission depending on their pH, when compared with non-acidotic patients.

The pH was inversely correlated with arterial oxygen tension in the patients who were hypercapnic, with more than 50% of patients with a PaO_2 of >10kPa being acidotic indicating an association between acidosis and oxygen therapy.

Subsequent audits have supported the association of oxygen therapy and acidosis. In 2002 Denniston and colleagues[86] undertook a prospective audit of 101 admissions of AECOPD. They found that over 50% received a FiO_2 of 0.28 in their pre-hospital and hospital emergency management. The mortality in this group was 14% compared with 2% in patients that received ≤ 28% oxygen. Similarly a quarter of the patients in the high flow group had evidence of a severe acidosis, compared with 3% in the low flow group.

A retrospective audit carried out in Melbourne, Australia[87] showed similar findings. Of the 65 AECOPD studied, 66% had ABGs of which nearly half showed hypercapnia. Patients who received >4 l/min were more acidotic, had higher PaO2 and PCO2 readings and a longer length of hospital stay. There was also a greater need for NIPPV and HDU or ICU.

In another UK study, Durrington et al[88] performed an interventional audit. The first involved 108 admissions which again showed an association with high flow oxygen and lower pH and higher $PaCO_2$. Following the first audit, the paramedics were educated and advised that patients with COPD should receive oxygen via a 28% venturi mask to keep oxygen saturations between 88-92%. The second audit showed that the proportion of patients receiving high flow oxygen was reduced to <1%, but complication rates remained unchanged. In addition, they showed that longer ambulance journeys and administration of high flow oxygen was clearly associated with a worse outcome (death, ventilation or IV aminophylline) 19.4% of ambulance journeys were under 30 minutes and 60% if ambulance journeys were greater than 30 minutes.

Conversely, to other reported data, Gomersall et al[89] found the patients with a higher PaO_2 did not have worse outcomes compared to those with a lower PaO_2. In their study 17 patients with AECOPD were randomised to oxygen therapy to keep their PaO_2 above 50mmHg whilst the other group with 17 patients were randomised to oxygen therapy to keep their PaO_2 above 70mmHg. The latter group had no poor outcomes whilst 2 patients in the low oxygen tension group died and another required mechanical ventilation.

Moloney and colleagues performed[90] a study in 24 patients with AECOPD presenting to the Emergency Department with hypercapnic respiratory failure. Each patient was administered controlled oxygen via a venturi mask to maintain SpO_2 of 91-92%, for a period of 2 hours. Three patients developed CO_2 increases of >1kPa, and of these one patient developed a respiratory acidosis with a pH <7.25. They also observed that the patients who were more hypercapnic at baseline were more at risk of developing worsening hypercapnia. Whilst the authors concluded the risk of CO_2 retention is low, there was no control arm in the study. Furthermore, the oxygen was only titrated at intervals of 20 minutes during which time the subjects $PaCO_2$ may have risen significantly.

The Royal College of Physicians National COPD Audit 2008[91] reported on nearly 10,000 admissions of AECOPD nationwide. Of these, 20% were acidotic on admission and 30% had received high-flow oxygen before ABGs were taken. 12% required ventilator support. Reassuringly, however, the proportion of patients receiving high-flow oxygen prior to ABGs has improved from 42% in the 2003 Audit.

The first randomised controlled trial investigating the effect of high flow compared with titrated oxygen in AECOPD was recently published in the British Medical Journal[92]. In this Tasmanian study, paramedics were randomised to administer titrated oxygen (to maintain SpO_2 between 88 to 92%) or high flow oxygen to patients with an AECOPD in the pre-hospital setting. 405 patients were recruited during the trial period, with 214 of these having a confirmed diagnosis of COPD on pulmonary function testing. Their primary outcome variable was pre-hospital or in-hospital mortality. Protocol violations occurred in 37% of the study population (56% in the titrated arm and 21% in the high flow arm). In the intention to treat analysis, the authors found a significantly lower risk of death in the titrated group 7/179 (4%) compared with 21/226 (9%) in the high flow group (relative risk 0.42, 95% confidence interval 0.20 to 0.89). In the subgroup of patients with confirmed COPD (n=214) mortality was reduced even further (0.22, 0.05 to 0.91). In the intention to treat analysis for secondary outcomes, there were no significant differences between treatment arms for length of hospital stay, requirement for ventilation, or arterial blood gas measurements. In the per protocol analysis, death rates were similar for the intention to treat analysis for all patients and the subgroup confirmed with COPD, although the differences did not reach statistical significance. The per protocol analysis, did however, show patients who received titrated oxygen were less likely to have respiratory acidosis (p=0.01) due to acute hypercapnia (p=0.02).

The authors recognise the main limitation of their study namely the lower than expected rate of adherence to study protocols, in both prehopsital oxygen treatment and the measurement of arterial blood gases on arrival at hospital. Paramedics violated the protocol by administering high flow oxygen to over half the patients in the titrated arm. Feedback indicated that some paramedics were concerned about insufficient delivery of oxygen in distressed patients despite adequate saturations.

This randomised controlled trial of oxygen therapy in AECOPD, provides robust evidence to support the British Thoracic Society's guideline[13] to administer oxygen only at concentrations sufficient to maintain adequate oxygen saturations.

Minimising oxygen induced carbon-dioxide retention COPD

The BTS Guideline for Emergency Oxygen use in Adult Patients[13] describes a number of ways harm can be minimised from oxygen use in COPD. Two of these are discussed below

Oxygen Prescription

Medical oxygen is a drug. Like all drugs and other treatments, oxygen has potential risks as well as benefits and there is a need to prescribe it for defined indications, with specification of the dose and method of delivery, the target saturation range and for the patient's response to be monitored. Numerous audits[93-99] have demonstrated the suboptimal prescription of oxygen therapy by medical staff. An interventional audit of patients on a respiratory unit reported that the introduction of an oxygen prescription chart significantly improved oxygen prescription from 55% to 91%, and accurate prescription from 7% to 77% of patients[96].

It recommended that all healthcare facilities have a standard oxygen prescription chart or designated section and oxygen should be prescribed by a doctor with a target saturation range. Nurses should sign the drug chart at every drug round and check that the patient is receiving oxygen therapy correctly and is achieving the required target saturation. The aims of the charts are to improve standards of prescribing and ensure correct administration particularly in those who are at risk.

Further on in this thesis, I will present an interventional audit of oxygen prescription and its effects on clinical practice.

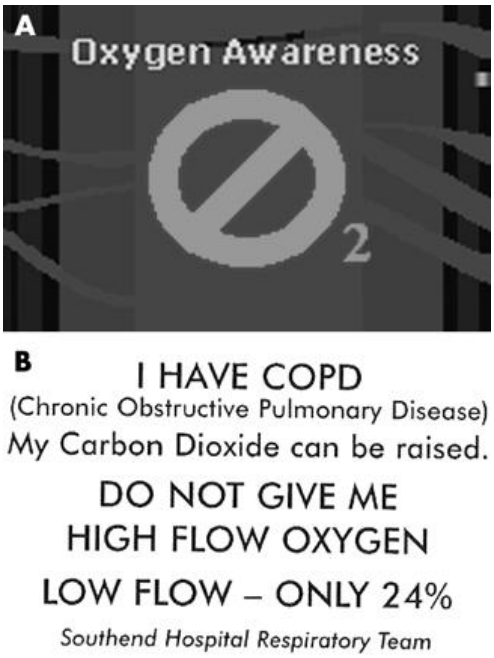
Oxygen Alert Cards and Venturi Masks

Oxygen alert cards and venturi masks have been shown to reduce the potential risks of respiratory acidosis in the pre-hospital and emergency setting in patients with COPD[100]. A study of 18 patients were administered with an "O2 Alert" card (see figure 8) and 24% venturi mask. The patients were instructed to show these to ambulance and A&E staff who will then use the mask to avoid excessive oxygenation. Of the 18 patients, 14 were readmitted on 69 occasions. Of these audited admissions, 63% were managed in the

ambulance, in line with card-holder protocol. This figure rose to 94% in the accident and emergency department.

Figure 8. Example of oxygen alert card

From Gooptu, Emergency Medicine Journal 2006[100]



The BTS recommend patients with COPD who have had an episode of hypercapnic respiratory failure should be issued with an oxygen alert card and with a 24% or 28% Venturimask.

Chapter 1.6 Oxygen Therapy in Asthma

Until recently, high flow oxygen has been universally recommended in the treatment of acute severe asthma. It has been perceived as a safe therapy, without the risks of hypercapnia which are associated with oxygen use in AECOPD. However, the recently published BTS Emergency Oxygen Guidelines[13] and Asthma guidelines update[101] now recommend oxygen only for the treatment of hypoxaemia to aim for a target oxygen saturation of 94-98%. In this section I will review the evidence for oxygen therapy in acute severe asthma.

Hypoxaemia is a common sequelae in acute asthma[102 103]. The treatment for hypoxaemia is to administer oxygen but there are very few studies investigating the physiological and clinical effects of oxygen in asthma. Most of the studies are laboratory based study with only one published randomised controlled trial. I have broadly divided these studies into the effects of oxygen on ventilation-perfusion and the effects of oxygen on arterial carbon dioxide pressures.

Effects of Oxygen on ventilation-perfusion

One of the earliest studies published on the effects of oxygen in acute severe asthma was published in 1967[104]. In addition to oxygen, Field investigated the effects of posture, isoproterenol and atropine on ventilation-perfusion relationships. Only the former will be discussed here. Twenty-six asthmatics were studied during an acute exacerbation. Following baseline measurements on air, 100% oxygen was administered for 20 minutes and the Vd/Vt calculated from the Bohr equation using expired CO_2. There was a highly statistically significant increase in Vd/Vt on breathing oxygen and also an increase in mean $PaCO_2$ which occurred despite an increase in minute ventilation. Furthermore the results in the sitting and supine positions demonstrated the same trends suggesting that changes in pulmonary artery pressure were unlikely to contribute to Vd/Vt increases. Field concluded that these changes were brought about from release in hypoxic pulmonary vasoconstriction.

Similar observations were made by Valabhji[105] in 1968. As well as changes in physiological dead space-tidal volume ratio, he also investigated the effects of oxygen on the A-a gradient. In a single-blind fashion twelve asthmatics breathed air then 100% oxygen for 20 minutes during the acute phase of the illness and again at least a week later when asymptomatic. He found that in the acute phase the A-a gradient and Vd/Vt ratio was raised in all patients and clinical recovery was associated with return of these parameters to normal. Furthermore changing from air to oxygen breathing resulted in a significant increase in mean Vd/Vt in both phases. The $PaCO_2$ was low or normal through all phases of the study. The author concluded that the mechanism for these changes in Vd/Vt are secondary to redistribution of pulmonary blood flow due to either a reduction in cardiac output and pulmonary artery pressure or to reversal of pulmonary vasoconstriction. As these changes were also demonstrated in the asymptomatic phase Valabhji proposes that abnormalities in ventilation-perfusion still persist in the lung following clinical recovery.

Wagner [106] was the first to use the MIGET to demonstrate V/Q mismatch in asthmatic subjects, although these were asymptomatic patients. His study showed a bimodal distribution of Va/Q ratios, and essentially no shunt. However, further studies [107] [108] have not found such an extent of Va/Q inequality despite similar airway obstruction.

A series of later studies confirmed changes in V/Q distributions following the administration of oxygen in asthmatics using the MIGET. These studies include a spectrum of severity: exercise-induced[108], moderately severe[109]and acute severe [110] asthma. Of note Corte et al's study[109] of 10 moderately severe symptomatic asthmatics showed four whom had marked V/Q inequality and the remaining six had minimal V/Q inequality. Following the administration of 100% oxygen both groups developed widening of their V/Q distributions but this was more marked in the six with minimal V/Q inequality. The authors suggest that a greater degree of compensatory pulmonary vasoconstriction is necessary in this latter group which is abolished to a greater extent on the administration of oxygen.

Rodriguez-Roisin[111] and colleagues were the first group to study V/Q abnormalities in life-threatening attacks of asthma using MIGET. All eight patients studied in the first 48 hours of admission required assisted ventilation. Following the administration of 100% oxygen V/Q mismatching substantially worsened such that the index of blood flow

dispersion (log SDQ) rose significantly. There were no significant changes on pulmonary artery pressure or cardiac output, but there was a significant increase in shunt. This study also demonstrated an increase in $PaCO_2$ on maintenance oxygen (mean FiO_2 0.37) to 100% oxygen from a mean of 39.8 mmHg (±SD 9.0) to a mean of 44.7 (± SD 8.7).

Effects of oxygen on carbon dioxide levels

Whilst the effects of oxygen on the pulmonary circulation provide important information on gas exchange abnormalities in acute severe asthma, there have been very few studies looking primarily at the effects on $PaCO_2$.

In 1979 Rudolf and colleagues[19] compared the response to oxygen in ten patient with COPD and eight patients with asthma. The subjects breathed oxygen 4 l/min via a medium concentration mask for 60 minutes. Arterial blood gases were taken during oxygen inspiration and at 15 minute intervals following the cessation of oxygen. In both groups the $PaCO_2$ rose but this rise was not significant in the asthmatic group. Following cessation of oxygen it took up to 10 minutes for the $PaCO_2$ to return to baseline values. In addition the PaO_2 fell to values lower than had been obtained before oxygen was given.

Chien and colleagues[112]have provided useful data on the effects of uncontrolled oxygen on $PaCO_2$ and FEV_1. Following admission to the emergency department, 37 asthmatic subjects (FEV_1 49 ± 3.6% predicted) were administered high-flow uncontrolled oxygen via a non-rebreathing face mask. Arterial blood gases were taken at baseline and during oxygen administration. Twenty-five patients had a rise in $PaCO_2$ during oxygen breathing ranging from 1 to 10 mmHg (mean 4.1 ± 0.6 mmHg). In seven of the patients hypercapnic respiratory failure developed and in six patients it worsened. A fall in FEV_1 was also demonstrated from 49.1 ± 3.6 % predicted to 47.0 ± 3.5 %. The authors do not comment on the mechanism for the rise in $PaCO_2$ but state that rises >2mmHg cannot be attributed to the Haldane effect.

The only randomised control trial of oxygen therapy was published in 2003 by Rodrigo and colleagues [113]. This study was undertaken in two Emergency Departments in Uruguay. Seventy-four patients with acute asthma were randomly assigned to receive 28% oxygen via a standard face mask or 100% via a non-rebreathe facemask for 20 minutes. Measurements of PEFR, respiratory rate, heart rate and arterial blood gases were taken at baseline and at the end of oxygen administration. The primary outcome

variable was $PaCO_2$ at the end of oxygen administration. The patients received bronchodilators after 20 minutes of oxygen therapy.

The patients in this study had severe airways obstruction (mean PEFR, 41.0 ± 12.1% of predicted), moderate hypoxaemia (mean PaO_2, 77.8 ±12.9mmHg), hypocapnia (mean $PaCO_2$ 36.4 ±4.4mmHg) and normal pH (7.39 ± 0.02). Patients in the 28% O_2 group experienced a slight fall in their $PaCO_2$ (-1.3 ±4.0 mmHg) in contrast to the 100% O_2 group who showed an increase in $PaCO_2$ (+1.8 ±3.9 mmHg). This magnitude of the increase was seen particularly in those patients with raised $PaCO_2$ before treatment. A *post hoc* analysis was performed to look at the proportions of patients who had a rise in $PaCO_2$ >2mmHg which showed a greater proportion in the 100% O_2 group (42.1%) compared to the 28% O_2 group (16.6%), p value 0.02.

The authors conclude that this rise in $PaCO_2$ seen in the 100% O_2 group is likely to be explained by release of hypoxic pulmonary vasoconstriction rather than the Haldane effect or changes in minute ventilation and that this rise is greatest in the patients with the most abnormal baseline condition. They advise against the use of uncontrolled high-flow oxygen and oxygen dose in severe asthma should be variable and based on achieving target SpO_2.

Chapter 1.7 Oxygen Therapy in Other Disorders

In the two preceding chapters I have presented studies of the use of oxygen in COPD and asthma of which in the former there is a reasonably substantial body of evidence. There are very few studies investigating the use of oxygen in other respiratory disorders.

In this next section, I will give an overview of the use of oxygen in non-respiratory disorders and the evidence base to support its use in myocardial infarction, stroke and other medical emergencies.

Myocardial Infarction

Oxygen has been used in the treatment of myocardial infarction (MI) and acute coronary syndromes for over 100 years[114]. The rationale for its longstanding use is that it increases oxygen delivery to the ischaemic myocardium, thereby reducing the size of the MI and improving clinical outcomes. Up until recently current international guidelines[115] [116] have recommended the use of supplemental oxygen in the treatment of MI, even in the absence of hypoxaemia. As a result, emergency calls to ambulance services because of chest pain have been treated with high concentration oxygen.

The haemodynamic effects of hyperoxia in MI have been well documented. Studies in man have shown that oxygen reduces cardiac output and stroke volume and increases the mean arterial pressure and systemic vascular resistance[42-45] [117] [118]. There is also substantial evidence that arterial oxygen tension is a major determinant of coronary artery regulatory tone,[119] [120] and that high concentration oxygen therapy resulting in hyperoxia reduced coronary artery blood flow[121-126]. The magnitude of the reduction in coronary artery blood flow with hyperoxia may be substantial in patients with coronary artery disease. This has been shown with the measurement of intracoronary Doppler flow to be in the order of 20-30% with an associated 23-40% increase in coronary resistance[122] [123].

To identify the clinical significance of the above haemodynamic effects, we recently performed a systematic review [127]to identify randomised placebo-controlled trials of

oxygen therapy in the treatment of acute MI. Our search revealed only two RCTs of high flow oxygen therapy in the first 24 hours after an uncomplicated MI. The first, undertaken by Rawles and Kenmure[128] in 1976, pre-thrombolysis, randomised 200 patients to receive either 6 l/min of oxygen or compressed air for 24 hours in a double-blind controlled fashion. There were 9/80 (11.3%) deaths in the oxygen group and 3/77 (3.9%) in the air group, relative risk of death 2.9 (95% CI 0.8 to 10.3, p=0.08). The maximum serum aspartate aminotransferase level which was used as a surrogate for infarct size was higher in the oxygen group compared to the air group. The authors concluded that there was "suggestive evidence of a deleterious effect of oxygen."

The only other RCT of oxygen therapy in MI[129] was a non-blinded study randomising 50 patients to 4 l/min oxygen or room air for 24 hours. However, this study was not designed to investigate infarct size or mortality, and so did not report which group the one death occurred in.

In March 2010, the National Institute for Clinical Excellence published a guideline "Chest pain of recent onset"[130] which now recommends oxygen should not routinely be administered to patients with chest pain and only offered if patients SpO_2 is <94% aiming for SpO_2 94-98%.

In summary, there is little evidence to support the routine use of high-flow oxygen in the treatment of uncomplicated MI. The balance of the limited evidence that does exist, suggests that the routine use of oxygen in this situation may increase infarct size and possibly increase the risk of mortality.

Stroke

There has been only one randomised trial of oxygen therapy in stroke[131]. This study randomised nearly 300 patients with stroke, within 24 hours of presentation, to 100% oxygen or no additional oxygen for 24 hours. Overall, there was no difference in mortality in the two groups, but for patients with minor or moderate strokes, one year survival was 82% in the oxygen group and 91% in the control group (OR 0.45; 95% CI 0.23 to 0.90; P=0.023). The authors propose the mechanism for this to be secondary to a reduction in cerebral blood flow due to the formation of oxygen free radicals. Based on

this sole study, guidelines, recommend that patients with stroke should receive supplemental oxygen only if this treatment is required to achieve an oxygen saturation of 94-98%.

Resuscitation

The Resuscitation Council UK, in their Advanced Life Support guidelines [132] recommend that high concentration oxygen is administered to all adult patients requiring cardiopulmonary resuscitation. This recommendation is based on Grade D evidence. Until recently there has been no clinical data to investigate the effects of hyperoxia following return of spontaneous circulation from cardiac arrest. There are numerous laboratory investigations which have demonstrated that reperfusion after an ischaemic insult is associated with a surge of reactive oxygen species which possibly trigger cellular injury and apoptosis, and this may be accelerated by hyperoxia which worsens the severity of oxidative stress. As such, the administration of high concentrations of supplemental oxygen to patients after cardiac arrest has come into controversy[133]. The only clinical data available is from a study published recently in JAMA in 2010[134]. Using data from the project IMPACT critical care database of intensive care units, 6326 patients were included in this observational study. All patients were aged over 17 years, had suffered a nontraumatic cardiac arrest and received cardiopulmonary resuscitation within 24 hours prior to ICU arrival. Patients were divided into three groups based on PaO_2 on their first ABG performed within 24 hours of arrival to ICU. Hyperoxia was defined as PaO_2 ≥300mmHg, hypoxia PaO_2 <60mmHg and normoxia not classified as either hyperoxia or hypoxia. Of 6,326 patients, 1156 had hyperoxia (18%), 3999 had hypoxia (63%) and 1171 had normoxia (19%). The primary outcome variable of in-hospital mortality was highest in the hyperoxia group (732/1156; 63% [95% CI, 60%-66%]) compared with the hypoxia group (2297/39999; 57% [95% CI, 56%-59%]) and the normoxia group (532/1171; 45% [95% CI 43%-48%]). The hyperoxia group had significantly higher in-hospital mortality compared with the normoxia group (proportion difference , 18% [95% CI, 14%-22%]; P<0.001) and also compared with the hypoxia group (proportion difference, 6%[95% CI, 3%-9%]; P<0.001). In addition, amongst hospital survivors, patients with hyperoxia had a lower proportion of discharges from the hospital as functionally independent compared with patients who were normoxic (29% vs 38%,

respectively proportion difference, 9% [95% CI, 3-15%]; P=0.002). Hyperoxia was found to be a significant predictor of in-hospital death (OR, 1.8 [95% CI, 1.5-2.2]) which is an independent effect that persists after adjusting for all other significant risk factors including age, preadmission functional status and significant physiological factors. In the secondary analysis using a PaO_2 of ≥ 400mmHg to define hyperoxia, mortality was even greater in the hyperoxia group.

Whilst this present study is only an observational study suggesting an association between arterial hyperoxia and poor outcomes after cardiac arrest, it provides clinical evidence which is contrary to current international guidelines. There is a clear need for clinical trials of controlled reoxygenation in adults resuscitated from cardiac arrest.

In neonates there is a large body of evidence that hyperoxia may be harmful in resuscitation due to slowing of blood flow in newborn preterm infants[135] and the generation of oxygen free radicals, which have a role in reperfusion injury after asphyxia[136] . A meta-analysis of five trials[137]reported a significant benefit on mortality for infants resuscitated on air (relative risk 0.71 (95% CI 0.54 to 0.94), risk difference -0.05 (-0.08 to -0.01)).

Obstetrics

Oxygen is routinely given for difficult labour or foetal distress with the rationale that this may improve oxygen supply to the foetus. In 2003, a Cochrane systematic review failed to identify any randomised-controlled trials of oxygen use in foetal distress[138]. Two trials which looked at routine oxygen use in the second stage of normal labour showed a significant lowering of pH in the cord blood of the women given oxygen. Lowering of the pH in this setting is highly suggestive of lower blood flow resulting in less overall oxygen delivery. A study[139] not included in this review, however, did not show any change on foetal and maternal blood vessels flow following maternal oxygen administration.

Chapter 1.8 Aims of this Thesis

Oxygen therapy remains a cornerstone of modern medical practice. In this introduction I have highlighted that there is very little in the way of well conducted clinical trials to support its routine use. Furthermore the potential detrimental effects of hyperoxia, in other conditions aside from AECOPD, need to be elucidated. In this thesis I will focus on the prescription of oxygen therapy, add to what is known on oxygen therapy in AECOPD and investigate its use in the treatment of other acute and chronic respiratory disorders where currently little evidence exists. The body of work is made up of two audits and three randomised controlled trials.

AUDITS

Audit 1: An Audit of the effect of oxygen prescription charts on clinical practice

Aims: To obtain a "snapshot" of the use of oxygen in Wellington Hospital, a tertiary referral centre in New Zealand, and investigate whether the introduction of a new drug chart with an oxygen prescription section would improve hospital-wide prescription, administration and monitoring of oxygen therapy.

Audit 2: An Audit of pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease

Aims : The three main aims of this study are to determine whether the management of AECOPD by the Ambulance Service is consistent with local and international guidelines, whether it is possible to identify particularly high risk patients based on the severity of their underlying disease or their status at presentation, and whether the amount of oxygen administered in the ambulance is associated with poor outcomes.

RANDOMISED CONTROLLED TRIALS

RCT 1: Randomised controlled trial of high concentration versus titrated oxygen therapy in community-acquired pneumonia

Aims: To investigate the effects of high concentration oxygen therapy on $PaCO_2$ in patients presenting to the Emergency Department with suspected community-acquired pneumonia.

RCT 2: Randomised controlled trial of high concentration versus titrated oxygen therapy in acute severe asthma

Aims: to investigate the effects of high concentration oxygen therapy on $PaCO_2$ in patients presenting to the Emergency Department with acute severe asthma

RCT 3: Randomised double-blind cross-over study of the effects of hyperoxia in obesity hypoventilation syndrome

Aims: To investigate whether breathing 100% oxygen results in worsening hypercapnia in subjects with OHS and to investigate the underlying mechanisms of any effect by the measurement of minute ventilation and physiological dead space.

SECTION 2 AUDITS OF OXYGEN THERAPY

Chapter 2.1 An audit of the effect of oxygen prescription charts on clinical practice

2.1.1 Introduction

Like all drugs and other treatments, oxygen has potential risks as well as benefits. The National Patient Safety Agency have recently produced a rapid response report[140] detailing nearly 300 serious incidents which were related to inappropriate administration and monitoring of oxygen between December 2004 and June 2009. Of these incidents, poor oxygen management appears to have caused nine deaths and may have contributed to a further 35 deaths. Clearly, there is a need to prescribe it for defined indications, with specification of the dose and method of delivery, the target saturation range and for the patient's response to be monitored. To facilitate this approach, the British Thoracic Society guideline recommends that every hospital should have a designated oxygen section on the drug chart on which oxygen should be prescribed and a target oxygen saturation range stated[13].

In support of this recommendation, an audit of patients on a respiratory unit reported that the introduction of an oxygen prescription chart significantly improved oxygen prescription from 55% to 91%, and accurate prescription from 7% to 77% of patients[96] This audit, however, did not report whether the improved prescription changed clinical practice in terms of assessment prior to commencing oxygen therapy, monitoring or titration which is the ultimate objective in improving prescribing standards. Certainly there is a well documented need to improve current practice, as numerous audits have demonstrated the suboptimal prescription of oxygen therapy by medical staff, mostly among medical and respiratory patients[93-99].

2.1.2 Objectives

1. To obtain a "snapshot" of the use of oxygen in Wellington Hospital, a tertiary referral centre in New Zealand
2. To investigate whether the introduction of a new drug chart with an oxygen prescription section would improve hospital-wide prescription, administration and monitoring of oxygen therapy.

2.1.3 Methods

Prior to commencing the audit, a pilot audit was performed to ensure the data collection sheets fulfilled the purpose of the audit. An example of the final data collection sheet is shown in Appendix 1. Written consent was obtained from the hospital's audit department. The first audit was performed between April 2007 and May 2007 in Wellington Hospital, Capital & Coast District Health Board, Wellington, New Zealand. All hospital inpatient areas were included except for the neo-natal unit, paediatric ward, psychiatric ward, emergency department (ED) and intensive care unit. The first audit, prior to introduction of a new drug prescription chart, occurred on three separate days, at least two weeks apart. I, co-ordinated the auditing, with four other co-workers. All patients were included unless they were off the ward at the time of the audit or they had been included in the preceding audit. Every patient was viewed to see if they were receiving oxygen at the time of the audit. Each patient's hospital records and observation charts were reviewed and information on monitoring prior to starting therapy, prescription, and monitoring and titration whilst receiving oxygen was recorded. It was also noted if the patient was brought in by ambulance, received oxygen therapy in transfer, and whether the patient was admitted via the ED. Criteria were set to assess whether prescription, assessment, monitoring and titration of oxygen were adequate (Table 1).

Table 1. Criteria set to assess whether prescription, monitoring and titration of oxygen were adequate

Category	Criteria
Prescription	• Device • Flow rate or FiO_2 • Target oxygen saturations
Assessment	• Oxygen saturations measured on room air and oxygen commenced only if saturations ≤92%
Monitoring	• Oxygen saturations recorded ≥2 occasions within a 24 hour period
Titration	• Oxygen increased if saturations ≤92% on ≥2 occasions

For prescription, all criteria had to be met for this feature of oxygen therapy to be considered adequate.

In November 2007 a new drug chart with a specific oxygen prescription section on the front of the chart (see Figure 9), was introduced into the hospital.

Figure 9. Front page of drug chart showing oxygen prescription box

Capital & Coast District Health Board
ŌPOKO KI TE URU HAUORA

Chart ☐ of ☐

MEDICATION CHART

PATIENT ALERTS
☐ Pregnant
☐ Breast Feeding
☐ Impaired Renal Function
☐ Impaired Liver Function
☐ Other _____
Please reconcile with electronic health record alert

Affix patient identification label here

1st Prescriber to write Patient's name and check label correct: _____

Date	Allergies	Reaction	Signature

ONCE ONLY / VERBAL ORDERS
Verbal orders must be countersigned by doctor within 24 hours

DATE	MEDICINE (BLOCK LETTERS) (USE GENERIC NAME)	DOSE	ROUTE	TIME TO BE GIVEN	VERBAL ORDER WITNESSED BY SECOND CHECKER	PRESCRIBER'S SIGNATURE	TIME GIVEN	NURSE'S SIGNATURE(S)

OXYGEN THERAPY & MEDICAL GASES

DATE	DEVICE/FLOW RATE	TARGET 0_2 SATS	PRESCRIBER'S SIGNATURE	STOPPED

INSTRUCTIONS – Sample signature register to be completed

Prescriber Instructions
1 Indelible pen only. **Print** clearly.
2 Use approved or **generic** name where practical and include dose forms.
3 Full signature – one bracketed signature is permitted.
4 To **stop** a medication, enter a stop date and initial. Rule a single line through the medicine to be stopped.
5 To **alter** therapy, cancel original order and represcribe on a new line.

Administrator Instructions
1 Indelible pen only.
2 Record time of administration using 24-hour clock, dose given and initials.
3 For variable dose, record **actual** dose.
4 For variable route, record **actual** route.
5 If dose not given, record appropriate code.
6 For items requiring dispensing send or fax to pharmacy (ensure all charts are sent).

SAMPLE SIGNATURES

NAME & DESIGNATION	SIGNATURE	REG NUMBER	NAME & DESIGNATION	SIGNATURE	REG NUMBER

PRONTO A580(NEW)01NOV07

This section prompts the prescriber to state the flow rate, device and target oxygen saturations range. During the first few months following implementation of the new drug chart, the investigators presented the findings of the first audit and provided education about appropriate oxygen use at various medical meetings including the weekly internal medicine meeting, junior house surgeon teaching, and Grand Round.

A second audit, using identical methodology, was conducted between April 2008 and May 2008, a year after the first audit and six months following the introduction of the new drug chart.

Statistical Analysis

Statistical analysis was performed by Professor Mark Weatherall. The proportions of audited patients with characteristics related to oxygen use were compared using relative risks for 2008 versus 2007. Data was provided for clinical practice in both the wards and the ED settings, and comparisons made between the first and second audit. SAS version 9.1 (SAS Institute, Cary, NC, 2003) was used for the analysis.

2.1.4 Results

There were 610 and 566 patients audited over the 3 separate days in 2007 and 2008 respectively. Approximately one-third of patients were brought in to hospital by ambulance. Of these, 99/188 (52.7%) and 70/177 (39.5%) were administered oxygen at any time during the ambulance journey, in 2007 and 2008 respectively.

Just over half of the patients were admitted via the ED. Of these 82/353 (23.2%) and 66/287 (23.0%) were receiving oxygen at presentation to ED. Of the patients who did not arrive on oxygen, it was commenced in 66/353(18.7%) and 41/287 (14.3%) at any time during their stay in the ED.

The first audit identified 85/610 (13.9%) ward-based hospital inpatients who were receiving oxygen, and 98/566 (17.3%) during the second audit.

Prescription

No patients admitted through the ED who received oxygen therapy had it prescribed. The prescription of oxygen on the drug chart in ward-based hospital inpatients is shown in Table 2

Table 2. Prescription of oxygen therapy in patients receiving oxygen on ward

	2007	**2008**	**Fold change (95% CI)**	**P value**
Oxygen prescribed	15/85 (17.6%)	39/98 (39.8%)	2.3 (1.3 to 3.9)	0.001
Oxygen prescribed adequately				
• Device	10/85 (11.8%)	38/98 (38.8%)	3.3 (1.8 to 6.2)	<0.001
• Flow rate or FiO_2	10/85 (11.8%)	37/98 (37.8%)	3.2 (1.7 to 6.1)	<0.001
• Target SpO_2	11/85 (12.9%)	38/98 (38.8%)	3.0 (1.6 to 5.5)	<0.001
• All three criteria	5/85 (5.9%)	36/98 (36.7%)	6.2 (2.5 to 15.0)	<0.001

In the first audit, 15/85 (17.6%) patients receiving oxygen had an oxygen prescription. In the first audit only 5/85 (5.9%) prescriptions were adequate, i.e. delivery device, flow rate or fraction of inspired oxygen, and target oxygen saturations were clearly stated on the chart. In the second audit, following introduction of the new drug chart with a specific oxygen prescription section, 39/98 (39.8%) patients receiving oxygen had an oxygen prescription, fold change compared to 2007, 2.3 (95% CI 1.3 to 3.9), P=0.001. In

the second audit in 36/98 (36.7%) oxygen prescriptions were adequate, fold change compared to 2007 6.2 (95% CI 2.5 to 15.0), P<0.001.

Assessment prior to commencing oxygen therapy

The proportion of patients who had assessment of oxygen saturations on room air and commenced on oxygen therapy if saturations were <92% in the ambulance, ED and on the ward are shown in Table 3.

Table 3. Assessment of oxygen saturations on room air and commencement of oxygen if oxygen saturation ≤92%

	2007	**2008**	**Relative Risk (95% CI)**	**P value**
Ambulance	22/99 (22.2%)	9/70 (12.9%)	0.6 (0.3 to 1.2)	0.10
Emergency Department	25/66 (37.9%)	18/41(43.9%)	1.2 (0.7 to 1.8)	0.54
Ward	9/38 (23.7%)	10/26 (38.5%)	1.6 (0.8 to 3.4)	0.20

This practice was generally better in the ED than in the ambulance or on the wards, although was still undertaken in a minority of patients. There were no significant differences in the proportion meeting this criterion between the two audits, in the three sites studied.

Monitoring

The proportion of patients who had adequate monitoring of oxygen saturations whilst receiving oxygen was over 90% in both the ward and ED in both audits and there was no significant change between the audits, Table 4.

Table 4. Monitoring of oxygen saturations in patients receiving oxygen

	2007	**2008**	**Relative Risk (95% CI)**	**P value**
Emergency	137/148 (92.6%)	104/107 (97.2%)	1.1 (1.0 to 1.1)	0.11
Ward	83/85 (97.6%)	96/98 (98.0%)	1.0 (1.0 to 1.1)	0.89

† Oxygen saturations recorded ≥2 occasions within a 24 hour period

Titration

The proportion of patients who had their oxygen treatment up-titrated in response to oxygen saturations ≤92% on at least two occasions is shown in Table 5.

Table 5. Titration of oxygen saturations in patients receiving oxygen

	2007	**2008**	**Relative Risk (95% CI)**	**P value**
Emergency Department	14/16 (87.5%)	9/12(75%)	0.9 (0.6 to 1.3)	0.39
Ward	8/12 (66.7%)	4/9 (44.4%)	0.7 (0.3 to 1.5)	0.31

† Oxygen up-titrated in response to oxygen saturations ≤92% on ≥2 occasions

2.1.5 Discussion

This "snapshot" of oxygen therapy shows oxygen is a commonly used drug. Outside critical care areas of the hospital, the initial audit identified that less than 20% of patients receiving oxygen had an oxygen prescription, and in only 6% was the prescription adequate. The institution of an oxygen prescription section on the drug chart led to an improvement in the prescription of oxygen therapy, including documentation of the delivery device, flow rate and target oxygen saturations. However, it did not lead to improved clinical practice in terms of the initial assessment of the requirement for oxygen therapy, or the titration of oxygen therapy in response to low oxygen saturations. This suggests that a prescription box alone is not sufficient to achieve good clinical practice and that other measures are required.

These findings of an improvement in oxygen prescription using a specific section on the drug chart have also been shown by Dodd et al[96]. Although the provision of an oxygen prescription section improved the frequency and quality of oxygen prescription, in this study the quality of the prescription was poor in two thirds of patients receiving oxygen in the wards. Failure to document hypoxemia before oxygen prescription, also reported by Brougher et al[141] suggests that oxygen is commonly administered for presumed rather than documented need.

A positive feature of the audit was that almost all patients receiving oxygen therapy had regular monitoring, defined as oxygen saturations recorded twice a day. It could be argued that stricter criteria would have been preferable, such as those proposed by the BTS guidelines[13], which recommend monitoring four-times-a day in stable patients and continuous monitoring in unstable patients. Nevertheless, the findings do indicate that this component of oxygen therapy is generally well undertaken. However, the response to the documentation of repeatedly low oxygen saturations was disappointing, particularly in the ward situation. Furthermore, the introduction of the new oxygen

prescription section which specifically included a target oxygen saturation range, did not improve this practice.

Clinical practice but not prescription, was better in the ED when compared with the wards. This may reflect the more frequent use of oxygen within this area of the hospital and the closer medical and nursing supervision provided. This feature also illustrates the potential disconnect between prescription and clinical practice.

In summary, this audit has demonstrated a statistically significant and clinically relevant improvement in the frequency and quality of the prescription of oxygen following the introduction of a new drug chart with a specific oxygen prescription section. However, this improvement did not translate to improved clinical practice in the administration of oxygen therapy suggesting that strategies other than an oxygen prescription need to be developed to improve clinical practice. On the basis of these findings it can be recommended that strategies and protocols are developed which facilitate the assessment of oxygen saturation prior to oxygen use and the change in oxygen therapy in response to low or high oxygen saturations. It is likely that there are similar requirements for the delivery of oxygen in the community by doctors, nurses and paramedical staff.

Chapter 2.2. An audit of pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease

2.2.1 Introduction

The British Thoracic Society Guidelines "Emergency oxygen use in adult patients" recommend that oxygen should only be administered to patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) if oxygen saturations are <88% and that oxygen therapy should be adjusted to maintain saturations between 88-92%[13]. This recommendation is based on the well established risk of hypercapnia and respiratory failure in patients with AECOPD when high concentration oxygen is administered[20 66 67 74 85 92 142-147]. The clinical practice guidelines of the Wellington Free Ambulance Service state that patients with COPD should have their oxygen delivery adjusted to maintain saturations of 88 – 92%[148]. These recommendations are important as the ambulance service is often the first medical contact for patients with AECOPD and is responsible for their management during transfer to hospital. Such transfers may take considerable time, particularly in rural areas, and the administration of inappropriately high concentrations of oxygen have the potential to lead to hypercapnia and worse clinical outcomes.

2.2.2 Objectives

To determine

1. whether the use of oxygen in AECOPD by the Ambulance Service is consistent with local and international guidelines
2. whether high flow oxygen administered in the ambulance is associated with poor outcomes

3. whether it is possible to identify high risk patients based on the severity of their underlying disease or their clinical status at presentation.

2.2.3 Methods

The data collection sheet (Appendix 1) was piloted prior to the start of the audit to ensure all the necessary data was recorded. Written permission was given by the hospital's audit department. The audit was retrospective in nature, co-ordinated by myself and three co-workers. 250 presentations of AECOPD admitted to Wellington Hospital (Capital & Coast District Health Board) between June 2006 and June 2007 were audited. Only patients who were brought by ambulance to the Emergency Department were included. Patients were identified by the medical records department and a list of all discharges with a primary diagnosis of COPD (ICD Code J440 or J441) was provided. This included readmissions, patients who were dead on arrival and those who died in hospital following presentation. Markers of the chronic background severity of COPD, severity markers of the acute exacerbation, and clinical outcomes following presentation to the Emergency Department were reviewed. Sources of information included the ambulance case records for details of pre-hospital oxygen administration, and the hospital case records for documentation of management in the Emergency Department and subsequent medical admission.

Particular attention was paid to identifying and documenting the oxygen therapy administered by the ambulance service. Difficulties in identifying oxygen use from some of the ambulance records led to the categorisation of oxygen administration in two ways. First, where the exact flow rate was clearly documented, oxygen therapy was treated as a continuous variable based on the flow rate in L/min. Second, we categorised oxygen therapy as a dichotomous variable, either "high flow" or "low flow". Patients were categorised as "high flow" if they had a documented flow rate of ≥3 L/min, or received oxygen via a medium concentration mask or a non re-breather mask. Patients were categorised as "low flow" if either "room air" or a flow rate <3 L/min was documented, or if there was no mention of oxygen therapy. This categorisation was based on data

which indicates that 2-3 L/min of oxygen through nasal prongs delivers a FiO_2 of approximately 26 – 30%.[149] If oxygen was noted as given but no flow rate or device was recorded, the patient was excluded. All vehicles in the Wellington Free Ambulance fleet carry pulse oximeters but not transcutaneous or end tidal CO_2 monitors. Venturi masks are not used, low flow oxygen is delivered with nasal cannuale, moderate flows with a medium concentration mask, and non re-breather masks are used with a flow rate of 15L/min.

Statistical Analysis

Statistical analysis was performed by Dr Mark Weatherall. Logistic regression was used to describe associations between oxygen use, the main outcome measure, and the chronic and acute severity markers. For multivariate logistic regression a backwards selection process was used with a P value for retaining a variable of 0.1. Oxygen delivery was kept in logistic regression models regardless of the variable retention criterion to adjust for the independent predictors of poor outcome. For univariate odds ratios where there were zero cell counts, Fisher's exact test was used to generate a P value and Peto's method used to calculate a univariate odds ratio.

The main clinical outcome was a composite of death, requirement for invasive or non-invasive positive pressure ventilation, or respiratory failure (defined as a $PaCO_2 \geq 45$ mmHg (6.0 kPa) and a pH <7.35 documented on an arterial blood gas within four hours of presentation.) It was not possible to use death alone in multivariate models because no deaths occurred in subjects receiving low flow oxygen.

2.2.4 Results

There were 406 admissions with AECOPD identified from the Wellington Hospital database. Of these, 113 were not brought in by ambulance, 16 were inpatient hospital transfers and in 27 the medical records were missing, resulting in 250 cases being

included in the audit. The characteristics of the patients, including chronic and acute severity markers and clinical outcomes are shown in Table 6.

Table 6. Characteristics of patients including severity markers and adverse outcomes

Variable	
Mean Age in years: Mean (SD)	72.4 (9.3)
Male Sex: N (%)	120 (48%)
Ambulance time in minutes: Mean (Range)	49.8 (3 to 205)
Chronic Severity Markers: n/N (%)	
• Long term oral steroid use	40/250 (16.0%)
• Tiotropium use	67/250 (26.8%)
• Home nebuliser	87/249 (24.8%)
• Home long term oxygen therapy	62/250 (24.8%)
• Previous respiratory failure†	132/250 (52.8%)
• Previous assisted ventilation (NIPPV or IPPV)	59/247 (23.9%)
Acute Severity Markers: Mean (SD)	
• Glasgow Coma Score (score out of 15)	14.8 (1.1)
• Respiratory rate (per minute)	31.0 (9.7)
• Heart rate (per minute)	103.0 (22.2)
• Systolic blood pressure (mmHg)	155.2 (34.3)
• Oxygen saturation (when clearly documented on air) (%)	86.9 (11.8)
Outcomes: n/N (%)	
• Respiratory failure†	
- Arterial blood gas within 1 hour	45/108 (41.7%)
- Arterial blood gas between 1 and 4 hours	11/61 (18.0%)
• Non-invasive Positive Pressure Ventilation	49/250 (19.6%)
• Invasive Positive Pressure Ventilation	2/250 (0.8%)
• Death	10/250 (4.0%)
• Death or assisted ventilation or respiratory failure within 4 hours	77/250 (30.8%)

† $PaCO_2$ ≥45mmHg and pH <7.35

NIPPV: Non-invasive positive pressure ventilation

IPPV: Invasive positive pressure ventilation

The patients had severe chronic disease with about half having previous respiratory failure documented, a quarter having previous assisted ventilation, and a quarter receiving long term oxygen therapy. Glasgow coma score, respiratory rate, heart rate and systolic blood pressure were documented by the paramedics in most (85% to 98%) patients. However, clear documentation of room air oxygen saturation only occurred in 92/250 (36.8%) of ambulance attendances.

Oxygen flow rate was clearly documented in the ambulance case notes in 182/250 (73%) of patients. Of these patients, 168 (92%) received oxygen at flow rates ≥3 L/min and 90 (49%) received oxygen at ≥8 L/min. Using the dichotomous criteria, 181/250 (72%) received "high flow" and 52 (21%) received "low flow" oxygen.

At presentation to the Emergency Department, 181/242 (75%) patients had an oxygen saturation >92%, and in 70/242 (29%) the oxygen saturation was ≥98%. Of the 107 (43%) patients who had an arterial blood gas within 1 hour of presentation to Emergency Department, the median $PaCO_2$ was 54 mmHg (range 29 mmHg to 133 mmHg), the median pH was 7.36 (range 7.07 to 7.56), and the median PaO_2 was 66.0 mmHg (range 17 mmHg to 300 mmHg).

Ten patients (4%) died, all of whom received high flow oxygen therapy. Overall 31% of patients met the main outcome criteria (either died, required assisted ventilation, or were in respiratory failure). When oxygen delivery was analysed as a continuous variable according to documented flow rate, increased oxygen flow was associated with an increased risk of death, assisted ventilation, or respiratory failure with an odds ratio of 1.2 (95% CI 1.0 to 1.4) per 1 litre per minute in oxygen flow (table 7).

For the dichotomous categories of "high flow" vs "low flow" oxygen the point estimate for risk in the multivariate analysis was consistent with an association between high

concentration oxygen and the main outcome variable however the associations were not statistically significant (Table 7).

Table 7. The association between oxygen administration and clinical outcome: composite of death, positive pressure ventilation or respiratory failure

	Univariate association with poor outcome	Multivariate association with poor outcome[2]
Oxygen flow rate (continuous)[1]	1.1 (1.0 to 1.3)	1.2 (1.0 to 1.4)
High flow vs. low flow	1.0 (0.5 to 1.9)	1.4 (0.6 to 2.9)

[1] Odds ratio for association per l/min oxygen flow

[2] Multivariate analyses adjusted for all chronic severity markers, Glasgow Coma Scale, and heart rate

Increasing arterial oxygen partial pressure was associated with a greater risk of death, requirement for assisted ventilation, or respiratory failure with an odds ratio of 1.1 (95% CI 1.0 to 1.3) per 10mmHg rise in PaO_2.

Patients were at significantly greater risk of death, assisted ventilation or respiratory failure if they were on long term oxygen therapy, had a past history of respiratory failure, had previously required assisted ventilation, or had a home nebuliser (Table 8). The only chronic severity markers not associated with a statistically significant increase in the likelihood of a poor outcome were long term steroid use and tiotropium use.

Table 8. The association between adverse clinical outcome (death, positive pressure ventilation or respiratory failure) and markers of chronic and acute severity

a) Chronic severity markers

	Odds ratio (95% CI)
Long term oral steroids	1.1 (0.5 to 2.3)
Tiotropium	1.4 (0.8 to 2.5)
Home nebuliser	2.4 (1.4 to 4.3)
Long term oxygen therapy	2.8 (1.5 to 5.1)
Previous respiratory failure †	2.6 (1.5 to 4.6)
Previous assisted ventilation ‡	3.3 (1.7 to 5.9)

b) Acute severity markers

	Odds ratio (95% CI)
Glasgow Coma Score (per unit higher)	0.7 (0.5 to 0.9)
Respiratory rate (per 10 breaths/min higher)	1.3 (0.9 to 1.6)
Heart rate (per 10 breaths/min higher)	1.1 (1.0 to 1.3)
Systolic blood pressure (per 10mmHg higher)	1.1 (1.0 to 1.2)
Oxygen saturations on air (per percentage point higher)	0.9 (0.9 to 1.0)

† Previous respiratory failure: $PaCO_2 \geq 45$ mmHg or pH <7.35

‡ NIPPV (non-invasive positive pressure ventilation) or IPPV (invasive positive pressure ventilation)

An increased heart rate and lower Glasgow Coma Score were weakly associated with the risk of death, assisted ventilation or respiratory failure, but an increased respiratory rate

and systolic blood pressure were not. Higher room air oxygen saturations were associated with a lower risk (Table 8b).

2.2.5 Discussion

This study has shown that in patients with AECOPD the administration of high flow oxygen in the ambulance is associated with an increased risk of death, assisted ventilation or respiratory failure, and that the risk of a poor outcome progressively rises as the flow rate of oxygen increases. The impact of pre-hospital oxygen treatment on adverse clinical outcomes was also demonstrated by the progressive increase in risk with increasing PaO_2 following oxygen therapy. In addition, there were a number of easily identified markers of chronic disease severity which were associated with a markedly increased risk of a poor clinical outcome.

At least 70% of patients with AECOPD were administered high flow oxygen therapy on ambulance transfer to the Emergency Department, contrary to local and international guidelines[13 148 150]. Furthermore, of the patients in whom there was definite documentation of oxygen flow rates, about half received ≥8L/min. This occurred despite most patients being at risk of serious adverse outcomes, with 53% having previous respiratory failure documented, 24% having previous invasive or non-invasive ventilation, and 25% receiving long term oxygen therapy. This approach to oxygen delivery resulted in 75% of patients having oxygen saturations in excess of the target range of 88 to 92% at presentation to the Emergency Department, and nearly a third having oxygen saturations ≥98%. Although pulse oximetry is a critical part of the initial patient assessment, oxygen therapy in this study was not based on the routine assessment of oxygen saturations, with only 37% of patients having saturations documented on room air at baseline.

The retrospective nature of the AECOPD audit meant there were a number of limitations in the methodology. Firstly, the use of discharge diagnosis as an identifier created a selection bias against those patients coded incorrectly.

Secondly, the charting of oxygen delivery from ambulance records was variable which relied on making assumption. For example patients were assumed to be on room air if oxygen was not mentioned on the ambulance sheet. Additionally, it was not possible to quantify the amount of oxygen delivered through nebulisers which in cases with long ambulance journey times would have been significant and possibly continuous.

When oxygen was analysed as a continuous variable according to flow rate, there was a statistically significant association between increased flow rates and poor clinical outcomes, consistent with previous studies.[85-88] Importantly, the strength of this association increased in the multivariate analysis, which adjusted for independent predictors of poor outcome. This indicates that there was no major confounding by severity, and that the association was not due to more unwell patients receiving higher concentrations of oxygen therapy. In addition, the observation that the risk of death, assisted ventilation or respiratory failure progressively increased with higher PaO_2 levels suggests that inappropriate high flow oxygen therapy was an important contributor to poor clinical outcomes. The statistical power to detect an association between high flow oxygen therapy, when treated as a dichotomous variable, and poor clinical outcomes was limited because of the small number of patients in the "low flow" group. However, in multivariate analysis adjusted for acute and chronic severity markers, the point estimates were consistent with an association between high flow oxygen and poor outcomes.

These findings complement other studies investigating the relationship between high flow oxygen therapy and poor outcomes in AECOPD discussed in the introduction of this thesis. The Plant study[85] demonstrated an inverse correlation between pH and PaO_2 and more than 50% of patients with a PaO_2 of >10 kPa were acidotic. Their data suggested that a significant number of patients had been made acidotic by injudicious oxygen therapy and that it may be possible to rapidly correct the pH once the inspired oxygen concentration was reduced. Joosten and colleagues reported that the use of high flow oxygen therapy in patients with high $PaCO_2$ levels contributed to an increased length of stay, more frequent admission to a high dependency unit and greater use of NIPPV[87]. Inappropriate oxygen therapy was often initiated at the time of ambulance transfer, as 92% of patients admitted via ambulance received oxygen at a flow rate >2 L/min despite one third having previously documented hypercapnia. Similar findings were reported in

the study by Durrington et al[88] in which initial high concentration oxygen therapy caused significant acidosis and hypercapnia compared with low concentration oxygen. There was a significantly increased complication rate during admission in those COPD patients receiving high concentration oxygen, particularly when ambulance journeys exceeded 30 minutes. This latter finding is relevant to our study in which the average ambulance transit time was 49 minutes. A prospective audit by Denniston et al showed that oxygen therapy >28% was associated with acute hypercapnic respiratory failure and a higher mortality.[86] More recently, the first randomised controlled trial of oxygen therapy in AECOPD[92] has shown that mortality was significantly lower in patients receiving titrated rather than high concentration oxygen (relative risk, 0.42, 95%confidence interval 0.20 to 0.89) and this risk was reduced further in a sub-group of patients with confirmed COPD on pulmonary function testing (0.22, 0.05 to 0.91).

In this present study, there were strong associations between indicators of severe chronic COPD and poor outcomes during an acute exacerbation. For example, a previous episode of respiratory failure or assisted ventilation was associated with a two to three fold risk of death, assisted ventilation or respiratory failure in a subsequent exacerbation, albeit in the setting of initial high flow oxygen therapy by the ambulance service. In contrast to the chronic severity markers there were only weak associations with some of the acute severity markers. The CURB-65 score, has recently been shown to predict risk of inpatient mortality in AECOPD[151], similar to its use in community acquired pneumonia.

One potential limitation when interpreting the results of this study is that less than half the patients (108/250) received arterial blood gas sampling within one hour of arrival to the emergency department. There are a number of potential reasons for this including patient refusal, reluctance of the doctor to perform the test, a perception by the doctor that the test is not indicated, or limited time and staff resources. Current guidelines on the management of AECOPD recommend all patients have arterial blood gas sampling[152]. Our observation that about one-third of patients who had a blood gas measurement had respiratory failure, defined as a $PaCO_2$ $\geq$45 mmHg and a pH <7.35 illustrates the importance of this recommendation. Similarly, Plant et al[85] reported that of nearly 1,000

patients admitted with AECOPD, almost half were hypercapnic and 20% had a respiratory acidosis on admission.

In conclusion, this study has confirmed that the ambulance administration of high flow oxygen to patients with AECOPD is associated with poor clinical outcomes. This practice of ambulance staff administering oxygen at high flow rates to patients with AECOPD seems entrenched despite the demonstration over 60 years ago of the risks[59]. This study emphasises the importance in pre-hospital care of measuring oxygen saturation prior to starting oxygen therapy and identifying patients with severe chronic COPD who are at higher risk of respiratory failure, assisted ventilation and death. Another strategy that has been recommended is to issue all patients with a previous episode of hypercapnic respiratory failure a 24% or 28% venturi mask and an oxygen alert card, an approach which has been shown to improve outcomes and reduce the risk of respiratory failure.[100] However, the institution of an alert card system must be supported by assessment of oxygen saturation and a robust oxygen delivery policy.

SECTION 3 RANDOMISED CONTROLLED TRIALS OF OXYGEN THERAPY

Chapter 3.1 Materials and Methods

In this section I will present three randomised controlled trials of oxygen therapy in respiratory disorders. As the methodology in the three studies varies each will be discussed in detail under the study heading. In this chapter, I will describe the non-invasive equipment used. The repeatability and validity of the data provided by the equipment will be discussed in Chapter 3.2.

3.1.1 Spirometry

Spirometry was measured using a Micro Spirometer, Cardinal Health UK electronic spirometer. Data on subject's height and age were entered into the spirometer in order to calculate their predicted values. All investigators received training on how to perform spirometry by Mathew Williams, respiratory technician. Subjects were given instructions on how to perform spiromtery, and if required, a number of attempts were made until a satisfactory technique was achieved. The following measurements were made:

- Forced vital capacity (FVC) is the maximum volume of air that can be forcibly blown out after full inspiration, measure in litres
- Forced expiratory volume in 1 second (FEV_1) is the maximum volume of air that can be forcibly blown out in the first second during the FVC manoeuvre, measured in litres. FEV_1 of 33-50% predicted is associated with acute severe asthma and FEV_1 of <33% predicted is associated with life threatening asthma[101].
- FEV_1/FVC ratio is the ratio of FEV_1 to FVC. Airflow obstruction is defined as a FEV_1/FVC <0.7[101].

3.1.2 Transcutaneous Carbon Dioxide Monitor

The "gold standard" measurement of $PaCO_2$ requires an arterial blood gas. The original protocols for the pneumonia and acute asthma studies used arterial blood gases. However,

patients were reluctant to have two blood gases taken and therefore the majority who met the inclusion criteria declined to take part in the study. This led us to change the protocol and use an alternative method of CO_2 monitoring.

Portable devices to measure transcutaneous partial pressure of carbon dioxide ($PtCO_2$) provide an alternative to an ABG. Transcutaneous CO_2 devices have been studied in a variety of clinical scenarios including acute exacerbations of COPD, invasive and non-invasive ventilation in intensive care units and overnight studies of sleep disordered breathing.[153-157] Limits of agreement and bias have been reported in most studies, with a variation in results depending on the device used and the clinical setting.

They function on the principle that CO_2 diffuses extremely well through tissues. A probe is attached to an area of skin and warms to 42°C which "arterializes" the underlying capillaries. Warming the skin also softens the keratin layer, thereby making the physical barrier to diffusion more permeable. CO_2 diffuses from the skin through the sensor membrane. It reacts with water to form H_2CO_3, which in turn dissociates into H^+ and HCO_3^-; the former modifies the pH in the electrolyte solution in the probe and the resulting signal is converted to an estimate of the $PaCO_2$.

For our studies, myself and my co-worker Dr Perrin chose the "TOSCA" (Radiometer, Basel, Switzerland) as this analyser has the advantage of a dual sensor which measures $PtCO_2$ and SpO_2. In addition it also had a "quick calibration" mode allowing the machine to calibrate within 5 minutes of being attached to the patient, as compared to some of the older analysers which can take as long as 20 minutes. We received training on how to use the "TOSCA" from the manufacturers.

After consent was obtained from each patient, the patient's ear lobe was cleansed with an alcohol swab and allowed to dry. Where patients had excess hair on their ear lobes, this was

removed with the patient's permission. A low-pressure, adhesive clip was attached to the ear lobe, two drops of contact gel were placed onto the skin and the probe was attached to the clip. After "quick calibration" was complete, the machine signalled that it was ready to use.

At the end of the study protocol, the sensor was removed, cleaned and placed back in the analyser. The clip was removed from the patient's ear lobe. The analyser was calibrated after each use.

This device has a Stow-Severinghaus electrode and a probe membrane which was replaced every 14 days as per manufacturer guidelines. It has integrated automatic calibration which uses a carbon dioxide canister to calibrate the sensor every 4 hours while the machine is switched on.

Three identical "TOSCA" analysers were used for the three randomized-controlled trials.

3.1.3 Titrated Oxygen

In the randomised controlled trials of oxygen and community acquired pneumonia and oxygen and acute severe asthma presented in chapters 3.3 and 3.4 respectively, patients were randomised to either receive high flow oxygen (8l/min via a face mask) or titrated oxygen to keep their SpO_2 between 93-95%. Oxygen saturations were measured every 5 minutes and oxygen was titrated according to the protocol set out below. Less than 4 l/min of oxygen was delivered via nasal cannulae and higher flow rates were delivered by a face mask.

Table 9. Oxygen dose adjustment for the titrated oxygen group

Oxygen Saturation	Dose Adjustment L/min	Next Saturation Check
> 98%	Reduce by 2 L	In 5 minutes
96% - 98%	Reduce by 1L	In 5 minutes
93% - 95%	No change	In 5 minutes
91% - 92%	Increase by 1L	In 5 minutes
89% - 90%	Increase by 2L	In 5 minutes
86% - 88%	Increase by 4L	In 5 minutes
<86% withdraw		

3.1.4 Measurements of minute ventilation and deadspace to tidal volume ratio

As discussed earlier in this thesis, continuous distributions of ventilation-perfusion ratios are best measured by the multiple inert gas elimination technique (MIGET). However this requires invasive measurements, which potentially posed an unacceptable risk to our patients. We, therefore, chose a commercially available, compact monitor which in addition to measuring volumetric capnograms, can also measure multiple respiratory parameters,

including tidal volume (Vt), mixed-expired CO_2 ($PeCO_2$), and airway dead-space volume. (CO_2SMO Plus! Respiratory Profile Monitor, Respironics, Murrysville, Pennsylvania, USA). The minute ventilation was used as a measure of ventilatory drive and the Vd/Vt as a measure of physiological dead space. By using this simple, non-invasive apparatus we were able to obtain validated information on respiratory drive and physiological dead space.

Minute ventilation is defined as the quantity of gas exhaled expressed as volume per minute. It is calculated by measuring the tidal volume and multiplying it by the respiratory rate. The CO_2SMO Plus! calculates the eight-breath moving average of expiratory volume in terms of volume per minute and updates every breath.

To measure Vd/Vt, the CO_2SMO Plus! uses volumetric capnography. Flow is measured with a fixed orifice differential flow sensor. CO_2 is measured by a mainstream infrared absorption technique with a solid state sensor.

Mixed expired CO_2 ($PeCO_2$) is calculated from the volumetric capnogram as a volume weighted average of CO_2. The $PaCO_2$ (we used the $PtCO_2$ as an estimate) is user entered into the CO_2SMO Plus! Using the Enghoff modification of the Bohr equation, dead space to tidal volume ratio was calculated by the analyser:

$$Vd/Vt=(PaCO_2-PeCO_2)/PaCO_2$$

where $PaCO_2$ and $PeCO_2$ are the arterial and mixed expired PCO_2 respectively.
See Appendix for further detail.

The methods section of the OHS study describes in detail how the CO_2SMO Plus! was used for the purposes of the study.

Chapter 3.2 Repeatability and Validation

Non-invasive methods of measurement should be reliable and repeatable. Repeatability concerns the extent to which a measurement yields the same result on repeated testing. While repeated measurements will never precisely duplicate each other, their tendency toward being consistent is a measure of repeatability. Repeatability of a measurement however, does not imply validity, and a method that is not repeatable has no validity. A measurement is valid only if it measures what it is intended to measure. While repeatability focuses on consistency across repeated measurements, validity concerns the relationship between the measurement itself and the variable it is meant to be measuring.

In all three studies we used a transcutaneous portable device "TOSCA" to estimate arterial carbon dioxide levels ($PtCO_2$). In the OHS study we used volumetric capnography "The CO_2SMO Plus!" to measure Vd/Vt and minute ventilation.

To ascertain the repeatability and validity of the methods used in this thesis, the following analyses were undertaken:

- The validity and precision of TOSCA to measure $PaCO_2$
- The repeatability of the TOSCA to measure $PaCO_2$
- The repeatability of the CO_2SMO Plus! to measure Vd/Vt and minute ventilation

3.2.1 Validity and precision of transcutaneous CO_2 monitoring to measure $PaCO_2$

Methods

As part of the two randomized controlled trials, 25 paired $PaCO_2$ and $PtCO_2$ recordings in patients attending the ED with either severe asthma or suspected community-acquired pneumonia. Patients were assessed by one of the study investigators on arrival and if the

enrollment criteria were met written informed consent was obtained. The $PtCO_2$ sensor was attached to the patient's earlobe as described in Chapter 3.1. The $PtCO_2$ was monitored continuously and subjects had an ABG taken during the course of their routine assessment and treatment if the investigator felt it was clinically indicated. The ABG samples were obtained by radial puncture with a 22 gauge needle into a heparinized syringe. Samples were analyzed immediately with an arterial blood gas analyzer (Radiometer ABL800 FLEX, Copenhagen, Denmark) and a simultaneous $PtCO_2$ reading was recorded.

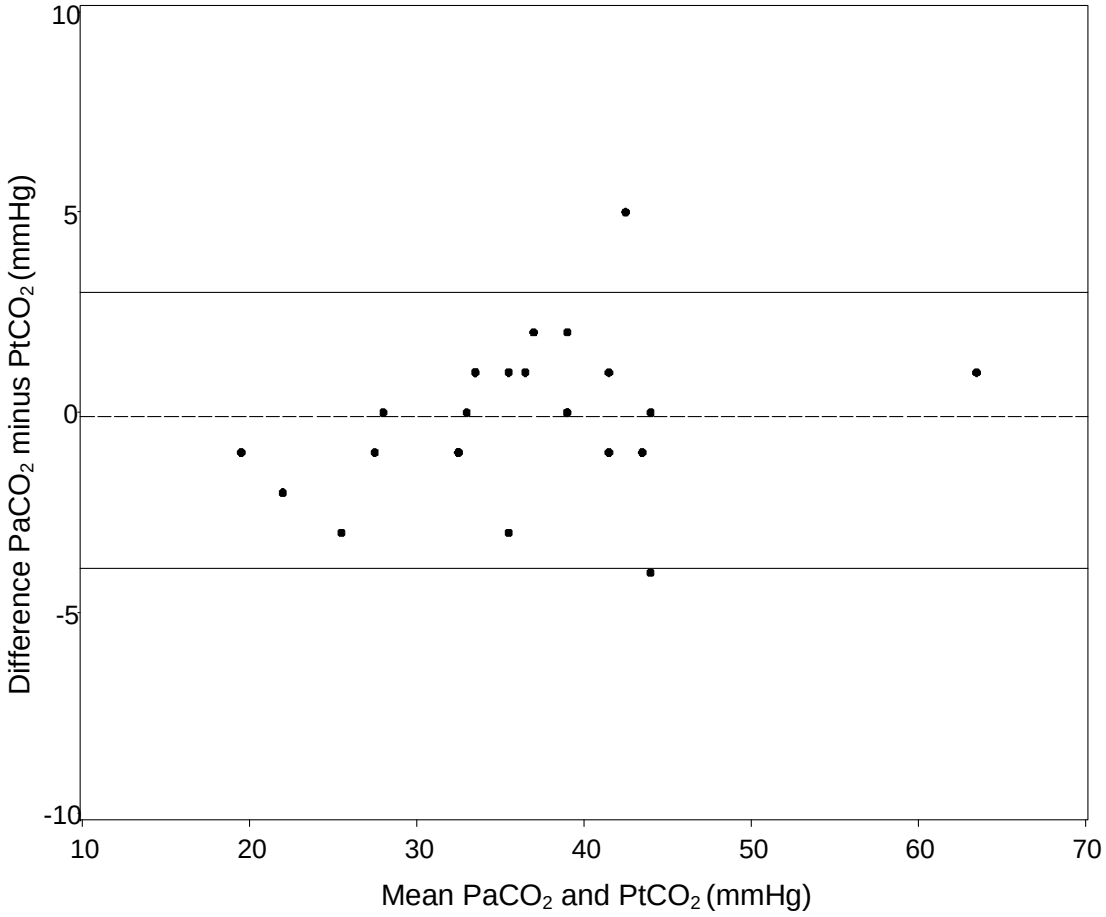
Data are presented as a Bland-Altman plot of $PaCO_2 – PtCO_2$ versus the mean of $PaCO_2$ and $PtCO_2$ together with limits of agreement

Results

Subjects were recruited between June 2007 and December 2008. There were 25 pairs of data in total but one patient was excluded because of difficulty attaching the probe resulting in poor signal quality and unstable $PtCO_2$ readings. This left 24 paired samples for analysis. No patients were in shock or hypothermic and none required vasopressor or inotropic support. The 24 patients (10 men and 14 women) had a mean age of 44 years and included 12 with asthma and 12 with pneumonia. The $PaCO_2$ range for the group was 19 to 64mmHg with a mean of 34.9mmHg. The mean time ABG samples were taken was 39.5 minutes after starting the randomized oxygen treatment regime with a range of 5 to 110 minutes.

The Bland-Altman plot is shown in figure 11. The mean (SD) $PaCO_2 – PtCO_2$ difference was -0.13 (1.9) mmHg with limits of agreement of plus or minus 3.8mmHg (-3.9 to +3.7).

Figure 10. Bland-Altman plot of the difference between the $PaCO_2$ and the $PtCO_2$, against the mean $PaCO_2$ and the $PtCO_2$



Conclusion

This portable $PtCO_2$ device accurately assesses $PaCO_2$ without significant bias and with clinically acceptable limits of agreement when compared to the gold standard measurement of ABG.

3.2.2 Repeatability of Transcutaneous CO_2 Measurements

Methods

Twenty four patients enrolled for the Oxygen and OHS RCT were asked to attend the laboratory on two separate occasions within 7 days. The transcutaneous CO_2 monitor was attached to the patient's earlobe and a reading of $PtCO_2$ using the methodology above, was taken whilst the patient was breathing room air. When the patient returned for visit two, a second $PtCO_2$measurement was taken. All measurements were carried out by the same study investigator. Subjects were tested at approximately the same time of day (± two hours) on both occasions.

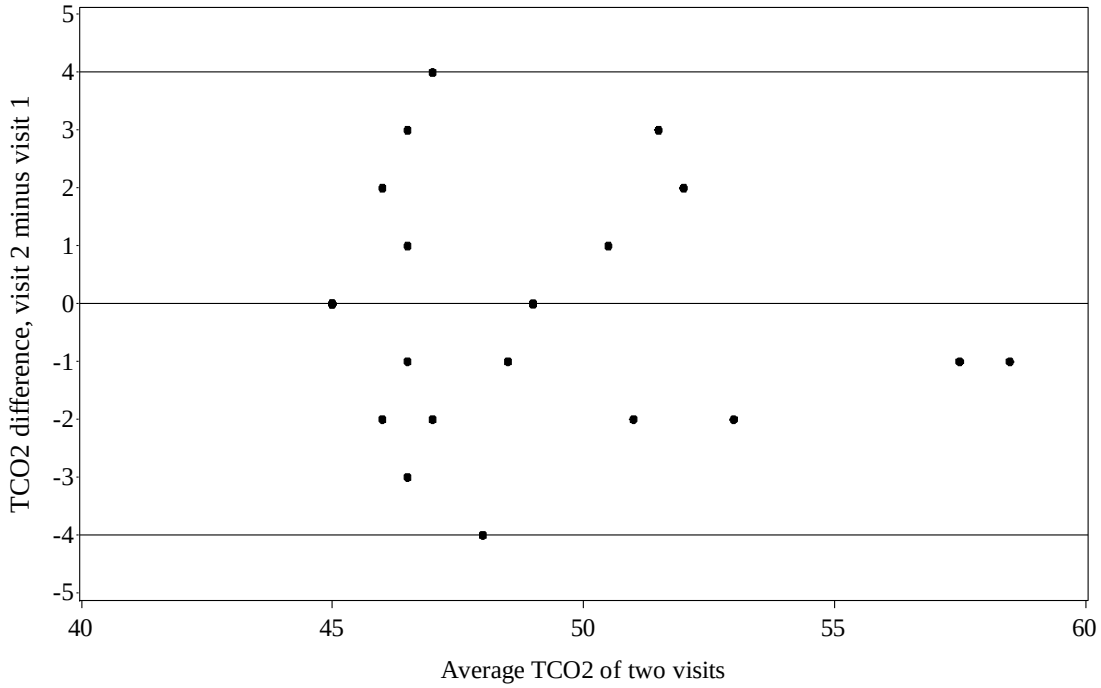
Bland Altman analysis and Intra-class coefficients were used to analyse data

Results

Bland Altman analysis:

The mean (SD) Visit 2 $PtCO_2$ – Visit 1 $PtCO_2$ difference was -0.13 (2.0) mmHg with limits of agreement of plus or minus 4mmHg (-4 to 4).

Figure 11. Bland-Altman plot of the difference between PtCO2 at Visit 1 and PtCO2 at Visit 2



Intra-class correlation coefficients:

The intra-class coefficient with 95% confidence intervals is 0.87 (0.73 to 0.94)

Conclusion

Using both the Bland-Altman analysis and the intra-class correlation coefficient, $PtCO_2$ was very reliable between measurements

3.2.2. Repeatability of Minute Ventilation and Vd/Vt Measurements

Methods

Twenty four patients enrolled for the Oxygen and OHS RCT were asked to attend the laboratory on two separate occasions within 7 days. Measurements of minute ventilation and Vd/Vt were taken using the CO_2SMO Plus! as described in chapter 3.1 whilst the patient

was breathing room air. When the patient returned for visit two, a second set of measurements was taken. All measurements were carried out by the same study investigator. Subjects were tested at approximately the same time of day (± two hours) on both occasions.

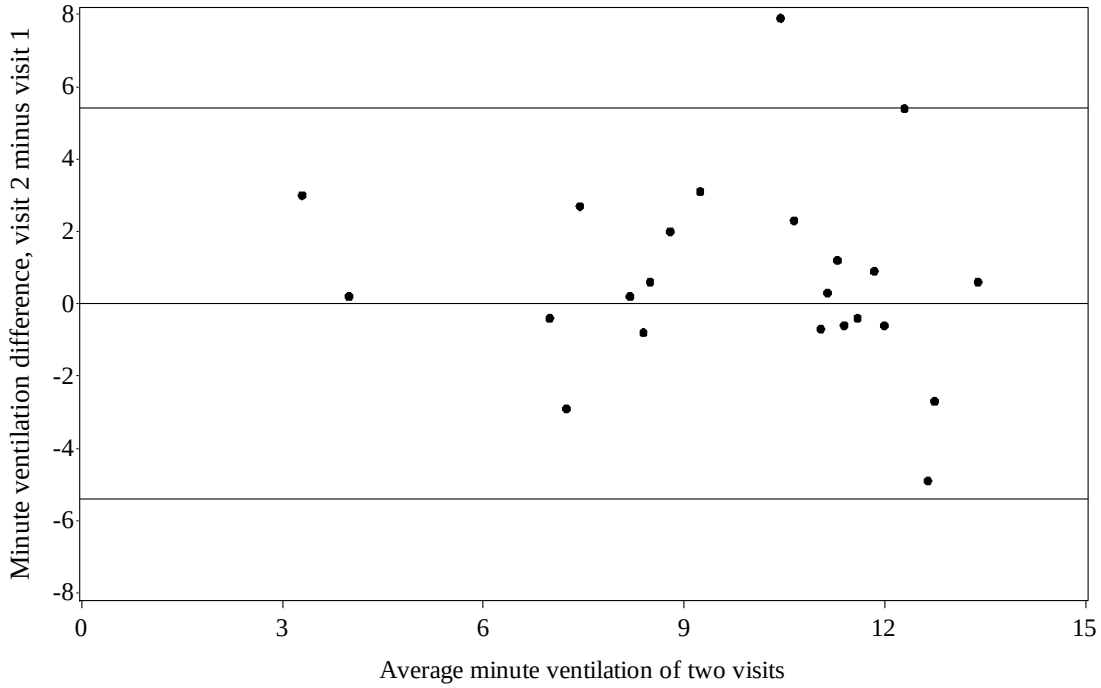
Results

Minute ventilation

Bland-Altman Analysis

The mean (SD) Visit 2 MV – Visit 1 MV difference was 0.71 (2.70) L/min with limits of agreement of plus or minus 5.4 L/min (-4.9 to 7.9).

Figure 12. The Bland-Altman plot of the difference between MV at Visit 1 and MV at Visit 2



Intra-class correlation coefficient

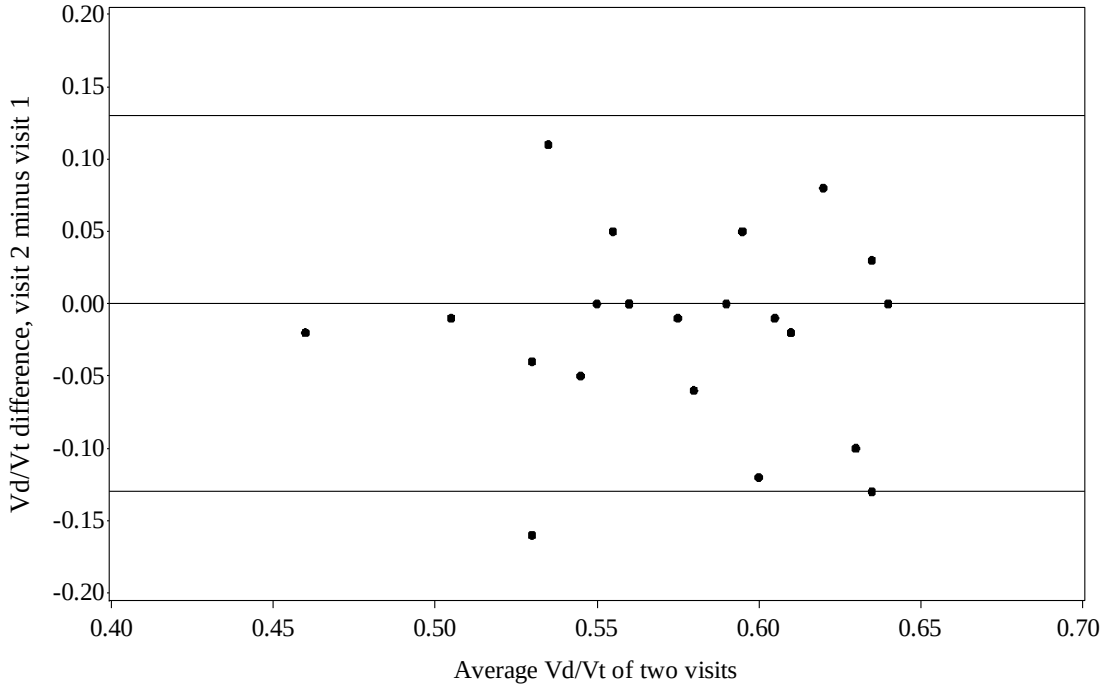
The intra-class correlation coefficient with 95% confidence intervals is 0.59 (0.25 to 0.80)

Vd/Vt

Bland-Altman analysis

The mean (SD) Visit 2 Vd/Vt – Visit 1 Vd/Vt difference was -0.019 (0.065) with limits of agreement of plus or minus 0.13 (-0.16 to 0.11).

Figure 13. Bland-Altman plot of the difference between Vd/Vt at Visit 1 and Vd/Vt at Visit 2



Intra-class correlation coefficient

The intra-class correlation coefficient with 95% confidence intervals is 0.33 (-0.084 to 0.64).

Conclusion

Using both the Bland-Altman analysis and the intra-class correlation coefficient, MV measurements were moderately reliable, but Vd/Vt was not particularly reliable.

Chapter 3.3. Randomised controlled trial of high concentration oxygen therapy in community-acquired pneumonia

3.3.1 Introduction

Community-acquired pneumonia is a common respiratory condition associated with significant morbidity and risk of mortality[158]. Patients presenting with suspected community-acquired pneumonia routinely receive oxygen therapy irrespective of the presence of arterial hypoxemia. This therapeutic approach is likely to be due to many reasons, including the standard clinical practice of administering oxygen to breathless patients and the widely held perception that oxygen therapy is safe. However, there are no randomised controlled trials comparing high concentration oxygen therapy with titrated oxygen administered only to hypoxaemic patients, to relieve hypoxaemia but avoiding hyperoxia, as recommended in recent British community-acquired pneumonia[159] and oxygen guidelines.[13]

3.3.2 Objectives

- To investigate the effects of high concentration oxygen therapy on $PaCO_2$ in patients presenting to the Emergency Department (ED) with suspected community-acquired pneumonia.

3.3.3 Methods

Subjects

Patients presenting to the Wellington (tertiary referral public), Kenepuru and Hutt (secondary referral public) Hospital EDs with suspected community-acquired pneumonia were enrolled in the study.

Inclusion criteria

- Aged 18 to 75 years
- Cough
- Respiratory rate >18 breaths per minute
- At least one systemic feature of sweating, rigors or fever >37.8°C

Exclusion criteria

- COPD
- Disorders associated with hypercapnic respiratory failure (neuromuscular disease, chest wall disease, or obesity hypoventilation syndrome)
- Patients presenting with respiratory failure requiring mechanical ventilation,
- Acute ECG changes suggesting ischaemia or
- Suspected neutropenic sepsis

The study was approved by the Wellington Regional Ethics Committee (Appendix 4), patients were provided with a patient information leaflet (Appendix 2) and informed consent was obtained from each patient. The study was registered on the Australia New Zealand Clinical Trials Registry, ACTRN12607000196448.

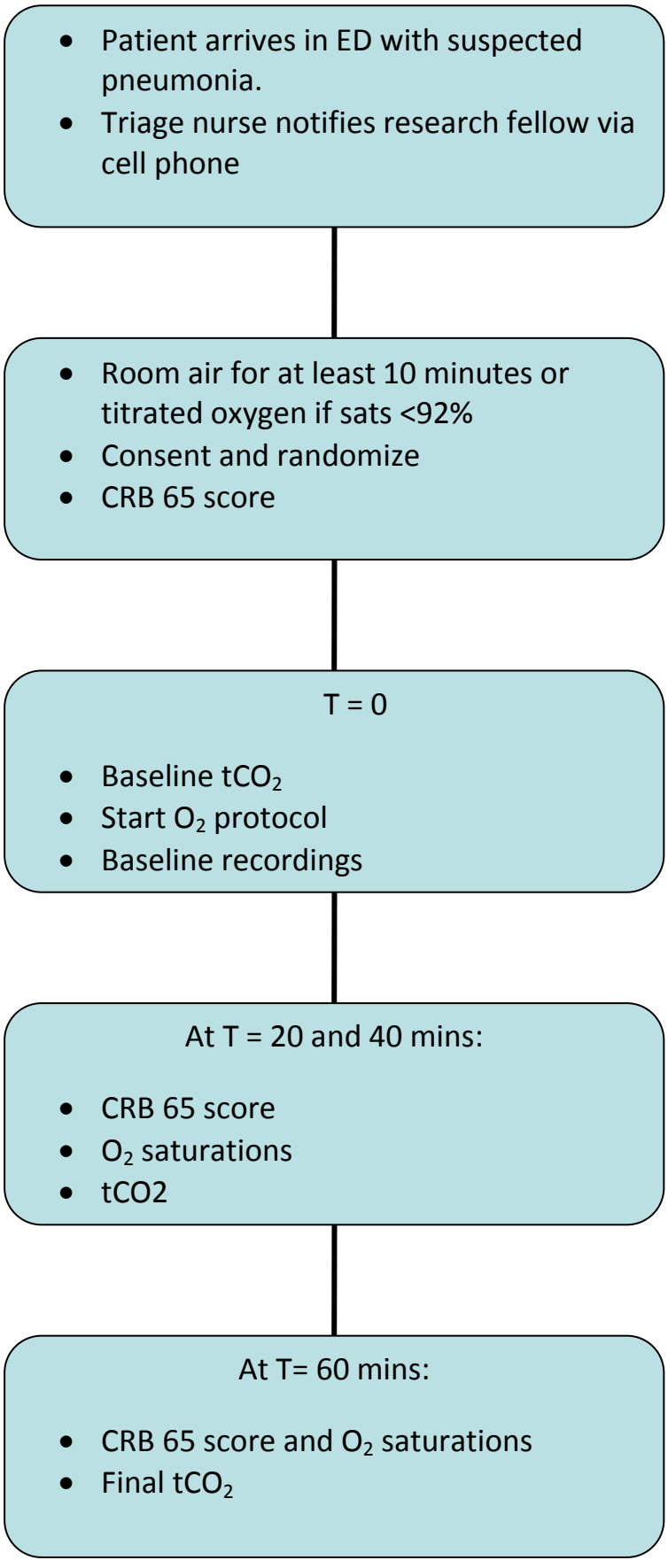
Study Protocol

A copy of the detailed study protocol is shown in Appendix 3. Patients were randomly assigned using a computer-generated method, to one of two oxygen regimes for one hour. All patients in the high concentration oxygen group received 8 L/min via a medium concentration mask. Patients in the titrated group received oxygen only if their saturation was $\leq$92% on room air, with oxygen titrated as required at 5 minute intervals, to achieve an oxygen saturation of 93 to 95% according to the protocol outlined in Chapter 3.1, Table 9. A computerized randomisation sequence was generated by the biostatistician, Professor Mark Weatherall, and the patients were enrolled and assigned to their treatment group by the clinical research fellows. Allocation concealment was achieved by using a secure database

which contained the randomisation sequence. Allocation was revealed to the researchers only, when the subjects name was entered. The clinical research fellows and patients could not be blinded to the treatment regimes, due to the requirement to titrate oxygen therapy in the control group.

A full history was taken and each patient underwent a physical examination. Empirical antibiotics were administered in accordance with published guidelines[160] and other therapies such as analgesia and intravenous fluids were administered at the discretion of the attending investigator. All patients underwent a chest radiograph and blood tests including a full blood count, creatinine and electrolytes.

Figure 14. Study protocol community acquired pneumonia



Measures

Transcutaneous carbon dioxide ($PtCO_2$) was used to estimate arterial $PaCO_2$ using a combined oxygen saturation/$PtCO_2$ monitor. Baseline measurements of $PtCO_2$ and oxygen saturation were recorded. Patients remained in a semi-recumbent position during the study protocol.

Measurements of $PtCO_2$, respiratory rate and heart rate were made at baseline (0 minutes) and at 20, 40 and 60 minutes. The oxygen saturation was measured continuously throughout the study period and recorded at 5 minute intervals.

The CRB-65 (confusion, respiratory rate >30 bpm, blood pressure systolic <90mmHg and/or diastolic ≤60mmHg and age over 65 years) was calculated at baseline and at 20, 40 and 60 minutes to determine the severity of pneumonia. Urea was omitted as this was unknown on arrival.

Arterial blood gas (ABG) measurements were performed according to clinical need and were not part of the study protocol. The ABG samples were obtained by radial puncture with a 22 gauge needle into a heparinized syringe. Samples were analyzed immediately with an arterial blood gas analyzer (Radiometer ABL800 FLEX, Copenhagen, Denmark). A simultaneous $PtCO_2$ reading was recorded.

All data was collected on a standardized data collection sheet shown in Appendix 1.

Statistical analysis

All statistical analysis was performed by Professor Mark Weatherall. The pre-specified primary outcome variable was the proportion of patients with a $PtCO_2$ >38 mmHg at 60 minutes. However after initial recruitment and clinical monitoring of patients it was apparent that this outcome was inappropriate to determine if a physiologically relevant increase in $PtCO_2$ had occurred. For this reason, the primary outcome was changed to the

proportion of patients with a $PtCO_2$ rise of ≥4 mmHg at 60 minutes and the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes was included as a secondary outcome variable. Other secondary outcome variables included the mean change from baseline $PtCO_2$, the mean change in respiratory rate and heart rate, and the need for hospital admission. The proportion of patients with a $PtCO_2$ rise of ≥8 mmHg was included as a post hoc analysis. Whether the risk of a $PtCO_2$ rise of ≥4 mmHg at 60 minutes was influenced by the presence or absence of a pulmonary infiltrate on the chest radiograph consistent with pneumonia, was tested by an interaction term in a logistic regression model.

The rate of change of $PtCO_2$ was determined using a mixed linear model with random intercept and slope terms. Continuous outcome variables were analysed as change from baseline using independent sample t-tests or for achieved oxygen saturation, for which normality assumptions were not met, by a Mann-Whitney test. Analysis was by intention to treat. SAS version 9.1 and Minitab version 14 were used.

Sample size calculation

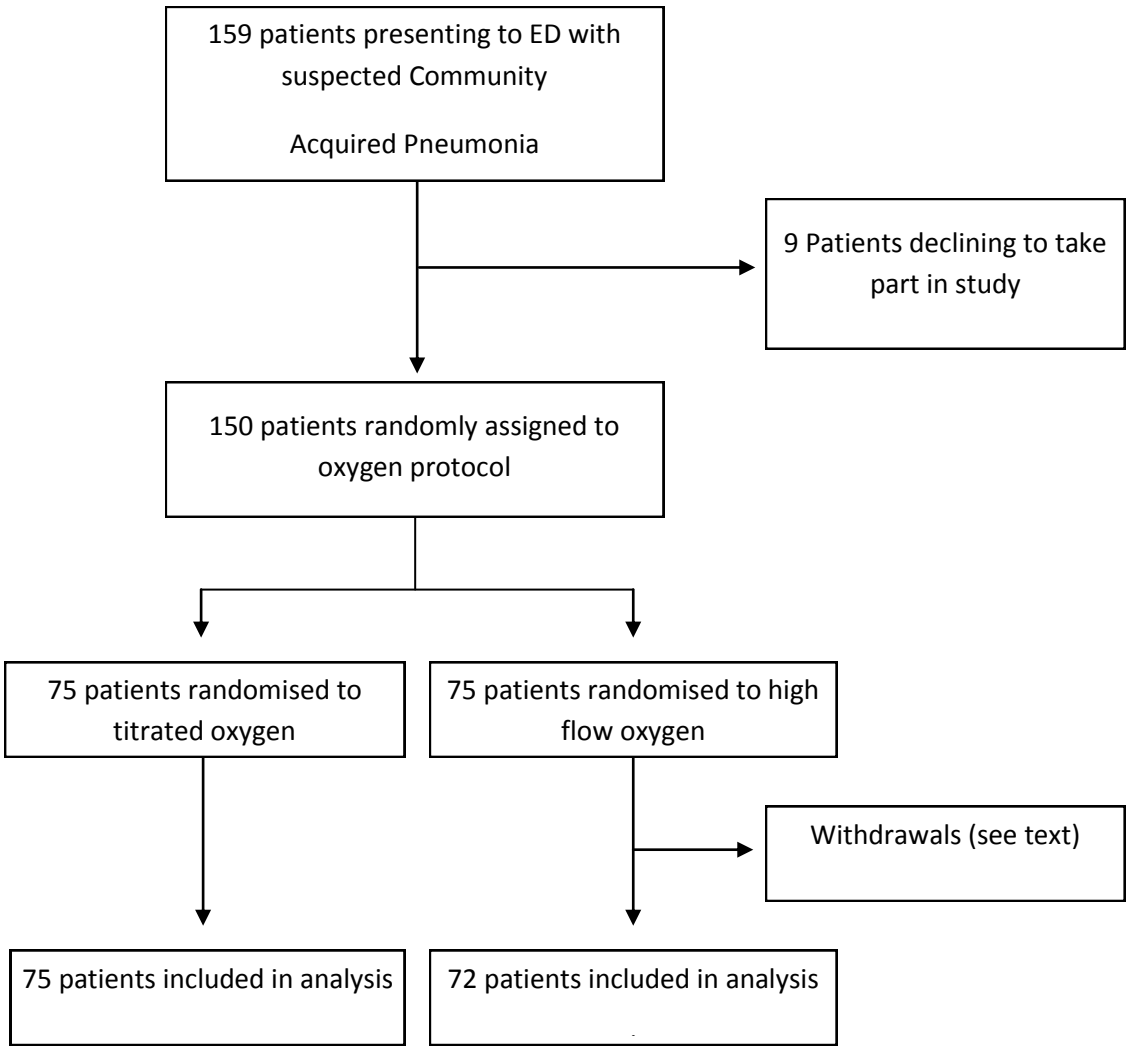
Based on previous research,[113] we calculated that to detect a difference in the main outcome variable of 20% in the high concentration oxygen group and 5% in the titrated group, with power of 80% at a type 1 error rate of 5%, 75 participants were required in each group.

3.3.4 Results

Patient Characteristics

Eligible patients were recruited from July 2007 to April 2009. Figure 16 shows the flow of the 150 patients through the study, with 75 randomized to high concentration oxygen and 75 randomized to titrated oxygen.

Figure 15. Flow of subjects through community acquired pneumonia study



Three patients were withdrawn from the high concentration oxygen group prior to the administration of oxygen due to the inability to obtain $PtCO_2$ recordings (n=1) and two protocol violations which included the inadvertent enrolment of a patient with COPD and another with obesity hypoventilation syndrome. As a result there were 72 and 75 patients included in the high concentration and titrated oxygen groups respectively. The two groups were similar in age, sex, respiratory rate, oxygen saturation, $PtCO_2$, CRB-65 score and radiological confirmation of pneumonia at baseline as outlined in Table 10.

Table 10. Characteristics of patients presenting with suspected community-acquired pneumonia, according to randomized oxygen treatment group

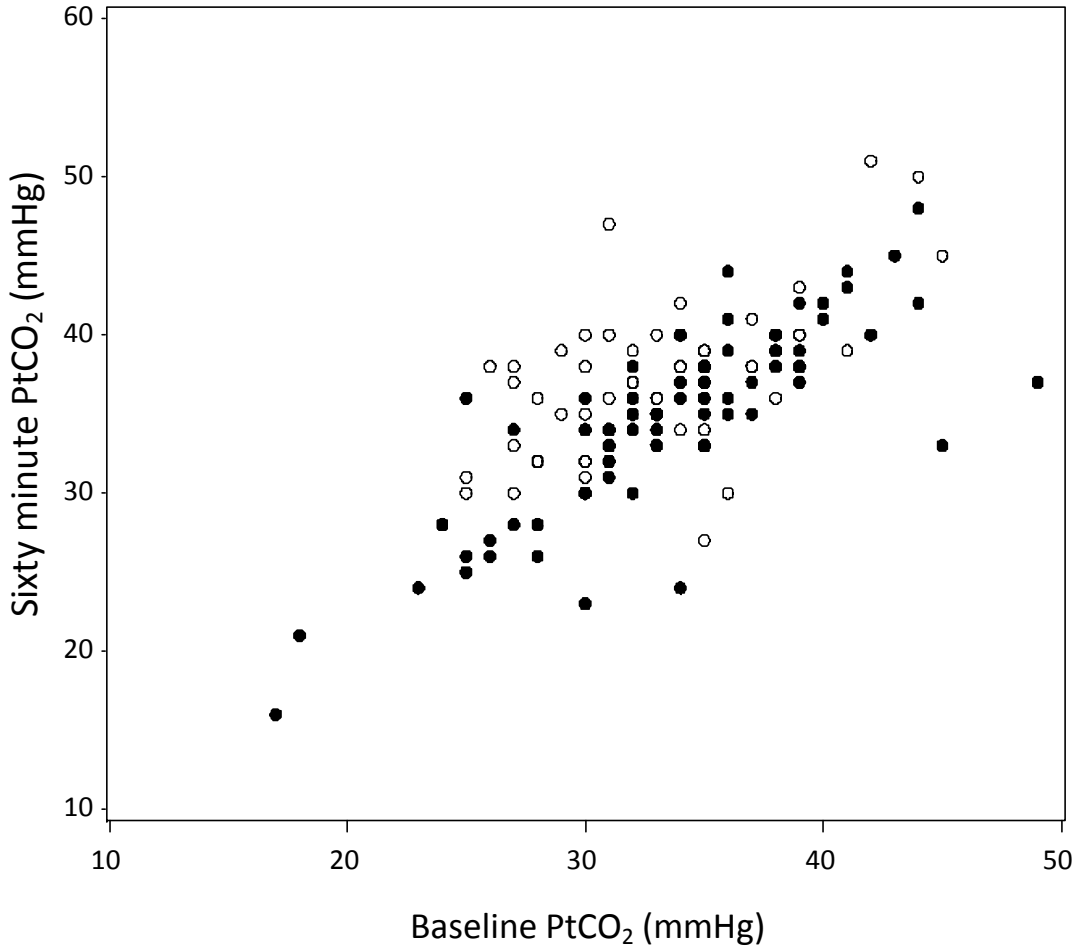
	High concentration n=72	Titrated n=75	All n=147
Sex, male	32	28	60
Age, yr	45.2 (16.3)	46.4 (16.3)	45.8 (16.2)
Respiratory rate, breaths/min	24.2 (6.0)	24.6 (6.6)	24.4 (6.3)
Heart Rate, beats/min	90.5 (16.8)	88.1 (18.2)	89.3 (17.5)
SpO_2, %	96.3 (3.4)	96.2 (3.2)	96.2 (3.3)
$PtCO_2$, mmHg	32.7 (4.6)	33.6 (5.9)	33.1 (5.3)
$PtCO_2 \geq 38$ mmHg	11/72 (15.3)	18/75 (24.0)	29/147 (19.7)
CRB-65 Score ≥2	7 (9.7)	7 (9.3)	14 (9.3)
Confirmed pneumonia	35/72 (48.6)	39/75 (52.0)	74/147 (50.3)

Values are mean (SD) for age, respiratory rate, heart rate, SpO_2 and $PtCO_2$, number of participants (percentage) for sex, confirmed pneumonia, $PtCO_2$ ≥38 mmHg and CRB-65 score ≥2

In 74/146 (50.7%) patients (one patient refused a chest radiograph), there was radiological confirmation of pneumonia, with the presence of a pulmonary infiltrate on the chest radiograph. Patients with confirmed pneumonia had lower oxygen saturations: mean (SD) 95.7% (3.7) vs 96.8% (2.8) and a greater proportion with a CRB-65 score ≥2: 12/74 (16.2%) vs 2/73 (2.7%).

There was a wide range of $PtCO_2$ levels at baseline ranging from 17 to 49 mmHg (Figure 17).

Figure 16. The $PtCO_2$ levels at baseline and after 60 minutes in the high concentration (o) and titrated (•) oxygen groups



Most (134/147) (91.2%) presented with an oxygen saturation >92% at baseline. In the titrated oxygen group 68/75 (90.7%) patients did not require oxygen therapy throughout the 60 minute treatment period as their oxygen saturations remained >92%. In the titrated oxygen group 6/75 (8.3%) patients required oxygen between 1 to 4 litres per minute via nasal prongs and 1/75 (1.4%) patient required >4 litres per minute via medium concentration mask to achieve oxygen saturations ≥93%. In the high concentration oxygen group the oxygen saturation at 60 minutes was ≥99% in 65/72 (90.3%) of patients and was between 93 and 98% in the remaining 7/72 (9.7%) patients.

Changes in $PtCO_2$

The proportion of patients with an increase in $PtCO_2$ of ≥4 mmHg at 60 minutes was significantly greater in the high concentration group, compared with the titrated oxygen group, 36/72 (50.0%) vs 11/75 (14.7%) with a relative risk of 3.4 (95% CI 1.9 to 6.2; P<0.001) (Table 11).

The proportion of patients with a rise in $PtCO_2$ ≥8 mmHg was significantly greater in the high concentration, 11/72 (15.3%), compared with the titrated group 2/75 (2.7%), with a relative risk of 5.7 (95% CI 1.3 to 25.0, P=0.007). The proportion of patients with both a rise in $PtCO_2$ ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes was 19/72 (26.4%) and 5/75 (6.7%), in the high concentration and titrated oxygen groups respectively, with a relative risk of 2.7 (95% CI 1.2 to 6.0, P=0.001)

Table 11. The proportion of patients with a predetermined rise in PtCO2 from baseline at 60 minutes

	High concentration n (%)	Titrated n (%)	Relative risk (95% CI)	P value
Change in $PtCO_2$ ≥4 mmHg	36 (50%)	11 (14.7%)	3.4 (1.9 to 6.2)	P<0.001
Change in $PtCO_2$ ≥4 mmHg and $PtCO_2$ ≥38 mmHg	19 (26.4%)	5 (6.7%)	2.7 (1.2 to 6.0)	P=0.01
Change in $PtCO_2$ ≥8 mmHg	11 (15.3%)	2 (2.7%)	5.7 (1.3 to 25.0)	P= 0.007

The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg was also greater in the high concentration group at the 20 and 40 minute time points (Table 12). In both groups the proportion of patients with a $PtCO_2$ ≥4 mmHg progressively increased throughout the 60 minute time course.

Table 12. The time course of the changes in PtCO2 in the treatment groups

(i) The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg

Time	High concentration n (%)	Titrated n (%)	Relative risk (95% CI)	P value
20 minutes	19 (26.4%)	4 (5.3%)	5.0 (1.8 to 13.8)	P<0.001
40 minutes	27 (37.5%)	8 (10.7%)	3.5 (1.7 to 7.2)	P<0.001
60 minutes	36 (50.0%)	11 (14.7%)	3.4 (1.9 to 6.2)	P<0.001

(ii) The mean change in $PtCO_2$ (mmHg)

Time	High concentration mean (SD)	Titrated mean (SD)	Difference (95% CI)	P value
20 minutes	1.9 (3.4)	-0.2 (2.7)	2.1 (1.1 to 3.1)	P<0.001
40 minutes	2.9 (3.7)	0.5 (3.6)	2.4 (1.2 to 3.6)	P<0.001
60 minutes	3.6 (3.9)	0.9 (3.7)	2.7 (1.5 to 3.9)	P<0.001

The change in $PtCO_2$ from baseline was significantly greater in the high concentration oxygen compared with the titrated oxygen group, with a mean difference of 2.7 mmHg (95% CI 1.5 to 3.9; P<0.001) at 60 minutes (Table 12ii). In both randomized groups the $PtCO_2$ increased with time (Table 12ii). The rate of increase in the high concentration group was 0.058 (95% CI 0.044 to 0.072) mmHg/min and the titrated group was 0.017 (95% CI 0.0031 to 0.031) mmHg/min. The difference in the rate of change was 0.041 mmHg/min (95% CI 0.022 to 0.06), P<0.001).

In patients with radiological confirmation of pneumonia, the high concentration oxygen group had a higher proportion with a rise in $PtCO_2$ $\geq$4 mmHg (20/35 (57.1%) vs 5/39 (12.8%), relative risk 4.5 (95% CI 1.9 to 10.6), compared to those without consolidation 16/37 (43.2%) vs 6/36 (16.7%), relative risk 2.6 (95% CI 1.1 to 5.9), however this interaction was not statistically significant, P=0.28.

Clinical variables

There was no significant difference in the change in respiratory rate (-2.9 vs -2.5 breaths per minute, high concentration vs titrated oxygen groups respectively, P=0.63). The reduction in heart rate was greater in the high concentration compared to the titrated oxygen group (-6.8 vs -2.6 beats per minute, mean difference -4.2, 95%CI -7.3 to -1.2, P=0.007). The CRB-65 did not differ between the two groups and there were similar rates of hospital admissions between the two treatment groups, 36/72 (50%) vs 37/75 (49.3%) for high concentration versus titrated oxygen respectively, relative risk 1.01 (95% CI 0.74 to 1.39, P=0.94). One patient in the titrated group required admission to the intensive care unit.

3.3.5 Discussion

This randomised controlled trial has shown that high concentration oxygen therapy results in a significant increase in $PtCO_2$ when administered to patients presenting to an emergency department with suspected community-acquired pneumonia. The three- to six-fold relative

risk of an increase in $PtCO_2$ of at least 4 mmHg or at least 8 mmHg suggests that this effect may be of both physiological and clinical significance.

There are a number of methodological issues relevant to the interpretation of the study findings. The first is that we used a TOSCA transcutaneous CO_2 monitor to measure $PaCO_2$ rather than the "gold standard" arterial blood gas (ABG) test. This method was chosen as it allowed continuous $PtCO_2$ monitoring without the discomfort of arterial blood gas sampling or the risk of hand ischemia associated with indwelling radial artery cannulae. The accuracy of transcutaneous carbon dioxide monitoring has been demonstrated in a variety of settings including healthy subjects,[161 162] AECOPD,[153 163] sleep disorders,[164 165] critical illness,[166] and in a mixed group of 51 patients presenting to an ED.[167] The accuracy of our device has been assessed in a subset of patients who had simultaneous ABG and $PtCO_2$ recordings[168]. The TOSCA accurately assessed $PaCO_2$ without significant bias and with clinically acceptable limits of agreement when compared to the ABG measurement, thus validating the methodology used.

By necessity the study was unblinded, as there was a clinical requirement for the investigator to have knowledge of the oxygen saturations in order to titrate the oxygen therapy in the "control" treatment group, and an ethical requirement for the investigator to monitor the patient's progress with knowledge of the oxygen administered. The objective display of $PtCO_2$ on the TOSCA monitor avoided subjective assessment of the primary outcome variable.

The decision to administer oxygen for 60 minutes was based on the evidence that CO_2 retention in COPD[74 76 78 82] and asthma[104 112] primarily occurs within 20 minutes of administration. However, further increases in $PaCO_2$ may occur beyond this time period and as a result the magnitude of the risk of an increased $PtCO_2$ with high concentration oxygen therapy may have been underestimated in our study. This was suggested by our observation that the difference in $PtCO_2$ between the high concentration and titrated

oxygen groups progressively increased throughout the 60 minute period. This is clinically relevant as relief of dyspnoea in pneumonia may take many days and oxygen therapy is often continued until the dyspnoea resolves.

The pre-specified analysis plan was to use the proportion of subjects with a $PtCO_2$ >38 mmHg at 60 minutes as the primary outcome variable. However, in the early phase of recruitment it was apparent that the pre-specified primary outcome variable did not reflect a physiological increase in $PtCO_2$ as it was primarily determined by the presenting $PtCO_2$. After a review of the records of the first 37 subjects (representing 25% of 150 participants contributing to the main outcome analysis) a change was registered in the primary outcome variable to the proportion of subjects with a $PtCO_2$ rise of $\geq$4 mmHg. We acknowledge that changing the primary outcome variable after the start of the study raises the possibility of creating a biased assessment of the outcome of the trial. However, no formal interim statistical analysis, of either the pre-specified outcome variable or the new main outcome variable, was carried out prior to this decision and although the study itself was not masked as to treatment allocation the decision was made without reference to the randomised allocation of the research participants.

Patients were excluded if they had a diagnosis of COPD due to the known effect of high concentration oxygen in exacerbations of this disorder[59 60 74 75 78 82]. Patients with established COPD were not included in this study based on their history. In addition, information was available from electronic medical records which documents any previous hospital admission, out-patients consultations and spirometry where available, allowing further investigation of a diagnosis of COPD. However, given that spirometry was not performed on enrollment or prior to discharge, patients with a new diagnosis of airway obstruction may have been included in the study. In clinical practice, when patients present with symptoms to suggest pneumonia, spirometry is rarely available at the first point of oxygen therapy which is usually in the ambulance or Emergency Department, thus this study replicates what happens in clinical practice. Indeed, it is probable that greater increases in $PtCO_2$ may occur in an unselected population of patients with community-acquired pneumonia, which is

more likely to include those with concomitant COPD or other disorders associated with chronic respiratory failure.

Patients presenting with suspected rather than confirmed community-acquired pneumonia were enrolled in the study, as oxygen therapy is usually administered to breathless patients presenting with suspected pneumonia rather than after the diagnosis is confirmed by chest radiography. About half of the patients had pneumonia subsequently confirmed by the presence of consolidation on the chest radiograph. Most of the other patients were likely to have had pneumonia without diagnostic changes on plain chest radiographs, which may occur in about one-third of patients with community-acquired pneumonia confirmed by high-resolution computed tomography.[169] This may explain why the presence of radiologically confirmed pneumonia made no significant difference to the risk of a raised $PtCO_2$ with high concentration oxygen therapy. When the analysis was restricted to subjects with radiologically confirmed pneumonia, there was a 4.5-fold increased risk of a rise in $PtCO_2 \geq 4$ mmHg with high concentration oxygen therapy.

In the absence of a clear view on what represents “physiologically” or “clinically” significant increase in $PtCO_2$ we chose levels of ≥ 4 mmHg and ≥ 8 mmHg respectively. The primary outcome variable was a rise of ≥ 4 mmHg which was considered to be physiologically significant, greater than the modest increase that might be expected from the Haldane effect. The secondary outcome variable, a rise of ≥ 8 mmHg, was considered to represent an effect of clinical significance. The findings of both the ≥ 8 mmHg rise in $PtCO_2$ in 15% of patients with community-acquired pneumonia treated with high concentration oxygen therapy and the associated six-fold relative risk compared with titrated oxygen therapy is of potential clinical importance. The study was not powered to investigate differences in clinical outcomes, in particular the adverse effects of severe hypercapnia. This issue needs to be addressed in a large study of an unselected group presenting with severe community-acquired pneumonia.

Both treatment groups were hypocapnic on presentation indicating a degree of hyperventilation. Over the course of the 60 minutes, there was a modest reduction in respiratory rate of <3 breaths per minute, with no significant difference between the two groups. This suggests that the greater increase in $PtCO_2$ in the high flow group could not be attributed to differential effects on minute ventilation. High flow oxygen resulted in a reduction in heart rate, which is a well recognized cardiovascular response to oxygen therapy.[39 45 46] This observed effect is not a marker of clinical benefit, as it is associated with an accompanying reduction in cardiac output and stroke volume, increases in mean arterial pressure and systemic vascular resistance, and reduction in coronary artery blood flow.[39 45 46]

In pneumonia, hypoxaemia is primarily due to intrapulmonary shunting and ventilation-perfusion inequalities.[170-172] Treatment with high concentration oxygen in pneumonia has minimal effect on intrapulmonary shunting, however it has the potential to significantly worsen ventilation-perfusion mismatch through release of hypoxic pulmonary vasoconstriction.[171-173] This would lead to an increase in the physiological dead space and is likely to represent the predominant mechanism responsible for the increase in $PtCO_2$ observed. Importantly, these data suggest that high concentration oxygen therapy may have the potential to cause an increase in $PaCO_2$ across a wide range of respiratory conditions with abnormal gas exchange. Indeed, this physiological response to high concentration oxygen therapy has now been reported in stable COPD,[75 78] exacerbations of COPD[59 60 74 82], asthma,[104 112 113] and obesity hypoventilation syndrome.[174]

Finally, this study reinforces concerns that the routine use of high concentration oxygen in pneumonia and other acute respiratory conditions has the potential to lead to a delay in the ability to recognize a subsequent progressive clinical deterioration.[55 56] In subjects in the high concentration oxygen group, the oxygen saturations were ≥99% in 90% of patients. If a progressive clinical deterioration were to occur in these patients, there may be little or no change in oxygen saturation until a potentially life-threatening situation has developed. At this stage there is limited opportunity to further increase the oxygen therapy while

interventions such as a medical review and transfer to the intensive care unit are undertaken. In contrast, 90% of patients in the titrated oxygen group required no supplementary oxygen at all as their oxygen saturations remained >92%. A subsequent clinical deterioration in these patients is likely to be recognized sooner through pulse oximetry, giving the option of increasing the oxygen therapy while further intervention is undertaken. This is contrary to the common assumption that administration of high concentration oxygen in a breathless patient will have a protective effect in the event that their clinical condition worsens.

In conclusion high concentration oxygen increases the $PtCO_2$ in patients with community acquired pneumonia. This suggests that the potential increase in $PaCO_2$ with high concentration oxygen therapy is not limited to COPD, but may also occur in other respiratory disorders with abnormal gas exchange. It also reinforces the importance of recognizing that oxygen is a drug that should be prescribed for defined indications in which the benefits outweigh the risks, that the prescription should specify the dose, method and duration of delivery, and that the patient's response to oxygen therapy should be monitored.[96] Based on the results of this study, It is recommended that in patients with suspected community-acquired pneumonia oxygen should be administered only to those patients with evidence of arterial hypoxemia in a dose that relieves the hypoxemia without causing hyperoxia, thereby achieving the benefits while reducing the potential for harm.[175]

Chapter 3.4 Randomised controlled trial of high concentration versus titrated oxygen therapy in acute severe asthma

3.4.1 Introduction

It is well recognised that high concentration oxygen therapy may lead to carbon dioxide (CO_2) retention when administered to patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD)[59 60] and that worsening ventilation-perfusion mismatch due to release of hypoxic pulmonary vasoconstriction with a resulting increase in physiological dead space is one of the major mechanisms causing this effect.[74 75 78 82 176] In contrast, the risks and benefits of oxygen therapy in acute severe asthma are less well understood. As with AECOPD, the dominant gas exchange abnormality in severe exacerbations of asthma is ventilation-perfusion mismatch, and oxygen administration has been shown to worsen the degree of mismatch.[104 105 109-111] As a result, it would be expected that high concentration oxygen therapy could also cause CO_2 retention in severe asthma, similar to its administration in AECOPD. There is preliminary data from case reports, case series and a single randomised controlled trial to suggest that high concentration oxygen therapy may cause CO_2 retention in acute severe asthma.[112 113 177 19 104 110 111 178 179] However, there are no randomised controlled trials comparing high concentration oxygen therapy with titrated oxygen administered only to hypoxaemic patients, to relieve hypoxaemia but avoiding hyperoxia, as recommended in recent British asthma[101] and oxygen guidelines.[13]

3.4.2 Objectives

- To investigate the effects of high concentration oxygen therapy on $PaCO_2$ in patients presenting to the ED with severe exacerbations of asthma.

3.4.3 Methods

Subjects

The study was conducted in the EDs of three metropolitan hospitals in Wellington, New Zealand: Wellington Hospital (tertiary public), Hutt Hospital (secondary public) and Kenepuru Hospital (secondary public).

Inclusion Criteria

Patients presenting to the emergency department with asthma either by ambulance or self presentation were approached by the investigator to assess potential eligibility.

- Aged between 18 and 65 years
- previous doctor diagnosis of asthma,
- history consistent with a current acute exacerbation of asthma,
- forced expiratory volume in one second (FEV_1) $\leq$50% of predicted values at the time of first assessment.

Exclusion Criteria

- Patients with a diagnosis of COPD,
- Patients with disorders associated with hypercapnic respiratory failure such as neuromuscular disease, chest wall restriction, or obesity hypoventilation syndrome
- Patients who were unconscious, unable to speak or unable to perform spirometry

Patients were provided with a patient information sheet (appendix 2) and written informed consent was obtained from each patient.

Study protocol

A detailed study protocol can be found in appendix 3. Patients were randomly assigned to one of two oxygen regimes for one hour. Patients in the high concentration group received oxygen at a flow rate of 8 L/min via a medium concentration mask (Hudson RCI, Durham NC, USA) which delivers a FiO_2 of between 0.4 and 0.78[180] Patients in the titrated group received oxygen only if their saturation was $\leq$92% on room air, with oxygen titrated as required at 5 minute intervals, to achieve an oxygen saturation of 93 to 95% according to the protocol outlined in chapter 3.1, table 9. Flow rates up to 4L/min were delivered via nasal prongs (Hudson RCI, Durham NC, USA). Flow rates higher than 4L/min were delivered by medium concentration mask.

A computerised randomisation sequence was generated by the biostatistician, Dr Mark Weatherall, and patients were enrolled and assigned to their treatment group by myself and the other clinical research fellows. Allocation concealment was achieved by using a secure database which contained the randomisation sequence. Allocation was only revealed to the researchers when the subjects were enrolled and their name entered in the database. Neither investigators or patients could be blinded to the treatment regimes due to the requirement to titrate oxygen therapy in the control group.

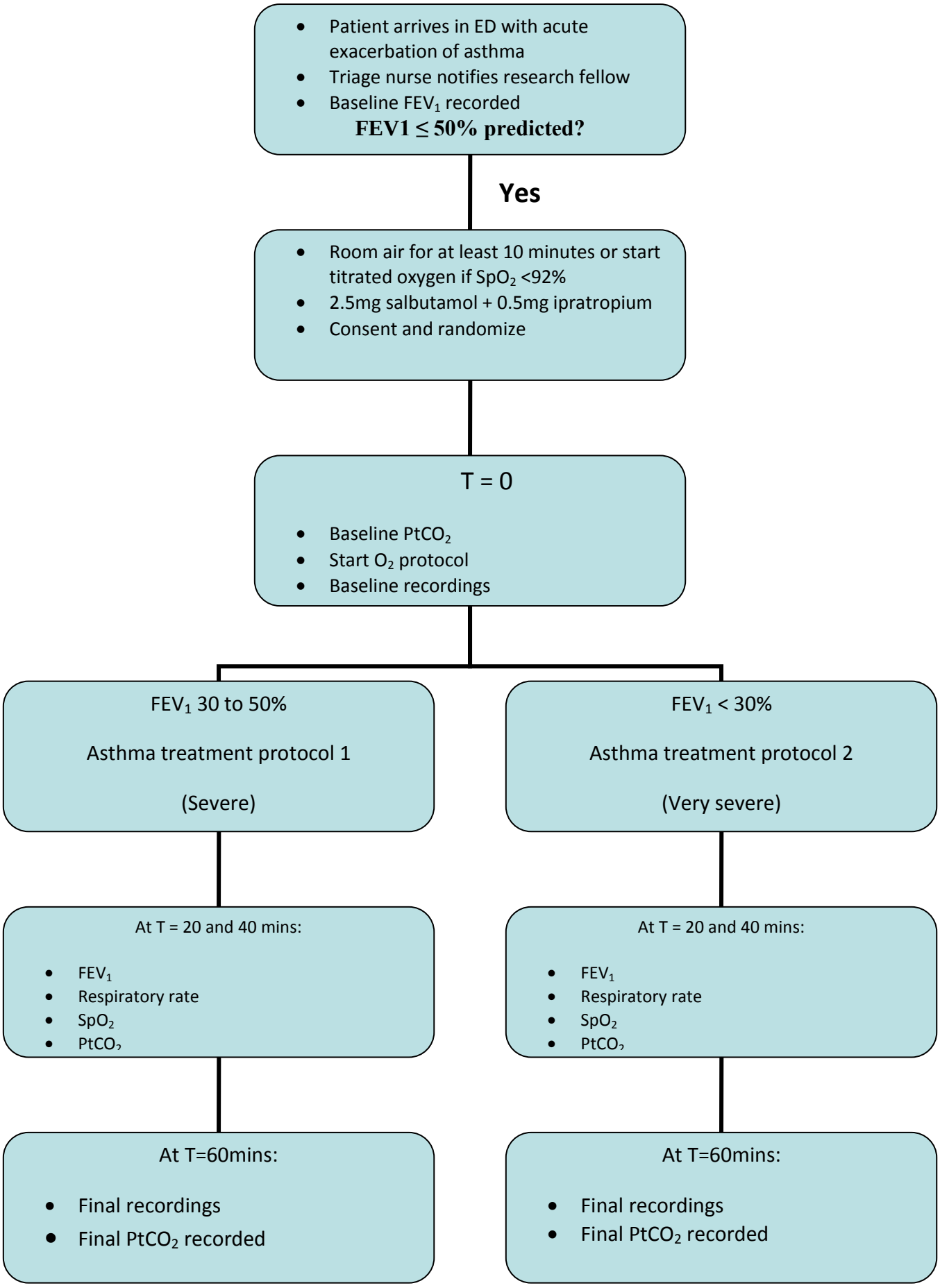
A medical history was taken, each patient underwent a physical examination, and asthma therapy was administered in accordance with published guidelines.[101] All patients received salbutamol 2.5mg and ipratropium bromide 0.5mg via air driven nebuliser (Portaneb, Respironics, Murrysville PA, USA) on arrival. Patients with severe asthma (FEV_1 30 to 50% predicted) received salbutamol 2.5mg via a nebuliser every 20 minutes and prednisone 40mg orally. Those with very severe asthma (FEV_1 <30% predicted) received salbutamol 2.5mg via nebuliser every 15 minutes, hydrocortisone 200mg intravenously and magnesium sulphate 2g in 100ml normal saline intravenously over 20 minutes.

Measures

Transcutaneous carbon dioxide ($PtCO_2$) was used to estimate arterial $PaCO_2$ using a combined oxygen saturation/$PtCO_2$ monitor (TOSCA, Radiometer, Basel, Switzerland) as

described in Chapter 3.1. Measurements of $PtCO_2$, FEV_1, respiratory rate and heart rate were made at baseline (0 minutes) and at 20, 40 and 60 minutes. The oxygen saturation was measured continuously throughout the study period and recorded at 5 minute intervals. Figure 18 shows the study protocol and measures taken.

Figure 17. Study protocol acute severe asthma



Statistical Analysis

The initial pre-specified primary outcome variable was the proportion of patients with a $PtCO_2$ >38 mmHg and FEV_1 ≤50% at 60 minutes. However, after recruitment of the initial 19 subjects it was apparent that the main determinant of this outcome was the baseline $PtCO_2$, rather than whether an increase in $PtCO_2$ had actually occurred. Specifically, of the 3/19 subjects who met the primary endpoint, two had a decrease in $PtCO_2$ (from 46mmHg to 39mmHg and from 45mmHg to 44mmHg) and the other had a minimal increase (from 39mmHg to 40mmHg). For this reason, the primary outcome was changed to the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg, and the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes included as a secondary outcome variable. Other secondary outcome variables included the mean change in $PtCO_2$ from baseline, changes in respiratory rate, heart rate and FEV_1, and the need for hospital admission at the end of the ED treatment period. The proportion of patients with a $PtCO_2$ rise of ≥8 mmHg was added as a post hoc outcome variable. The rate of change of $PtCO_2$ was determined using a mixed linear model with random intercept and slope terms. In the mixed linear model the fixed effects were the randomised treatment as a dichotomous variable, time as a continuous covariate, and a treatment times time interaction term. A random slope and intercept term with the individual participants as subjects and an unstructured covariance specified for the intercept and slope accounted for the correlation of repeated measurements on the same participants. Continuous outcome variables were analyzed as change from baseline using independent sample t-tests, or for achieved oxygen saturation for which normality assumptions were not met, by a Mann-Whitney test. Logistic regression was used to model the risk of admission, expressed as an odds ratio, both unadjusted for other variables and adjusted for baseline FEV_1, baseline oxygen saturation, and baseline $PtCO_2$. Analysis was by intention to treat. SAS version 9.1 and Minitab version 14 were used.

Sample size calculation

Based on previous research[113] we calculated that to detect a difference in the primary outcome variable of 20% in the high concentration oxygen group and 5% in the titrated group, with power of 80% at a type 1 error rate of 5%, 75 participants were required in each group.

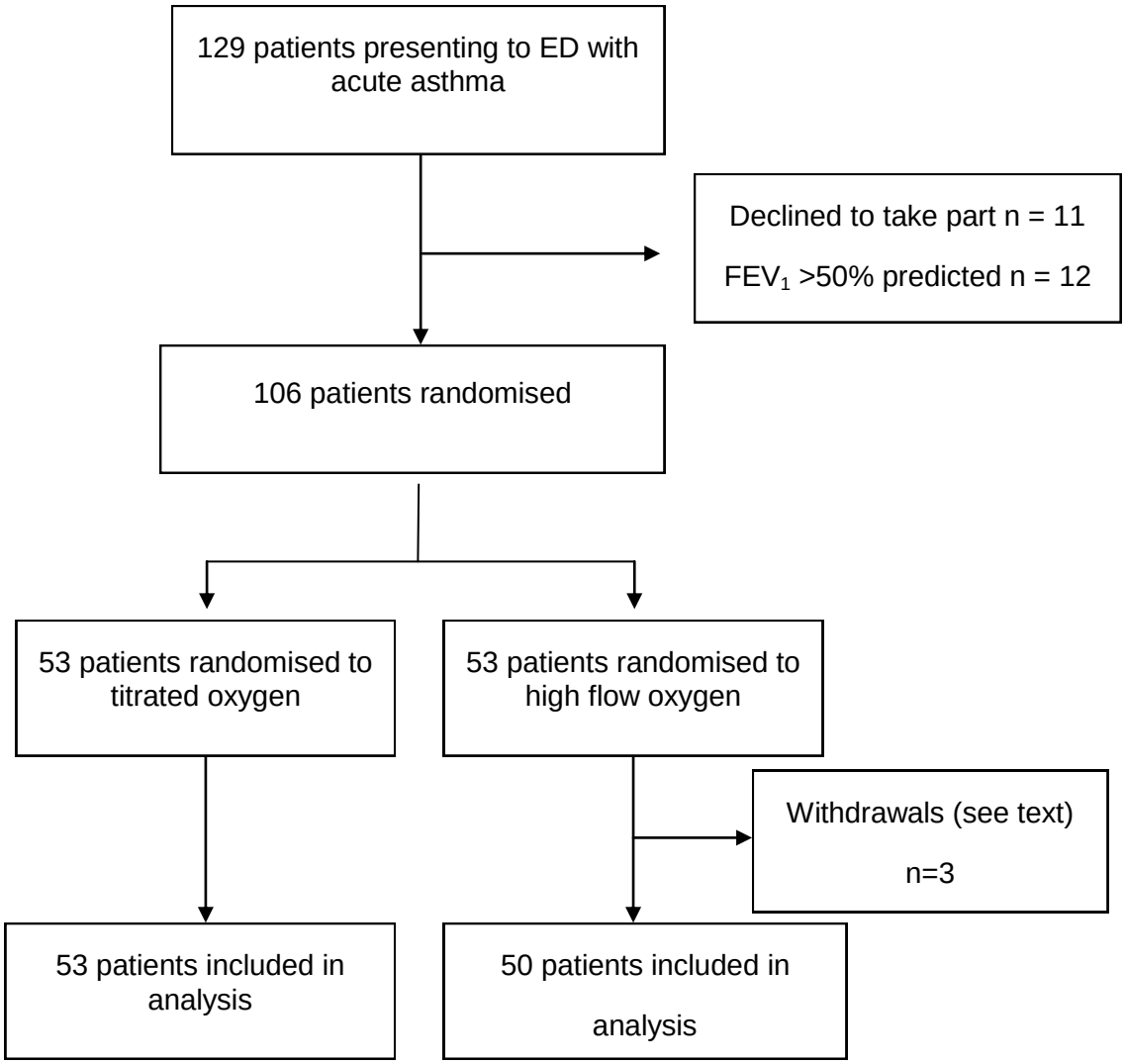
Ethics approval

Ethical approval was granted by the Central Regional Ethics Committee. See appendix 4.

3.4.4 Results

Eligible patients were recruited from July 2007 to December 2009. A total of 106 patients were randomised, 53 to the high concentration group and 53 to the titrated group. Three patients were withdrawn from the high concentration oxygen group, two due to protocol violations in which the subjects met an exclusion criteria after randomisation (one patient with COPD and one with obesity hypoventilation syndrome), and in one patient a reliable $PtCO_2$ signal could not be obtained. As a result there was data from 50 patients in the high concentration group and 53 in the titrated group for final analysis. Figure 19 shows the flow of the patients through the study.

Figure 18. Flow of patients through asthma study



The two oxygen treatment groups were well matched with respect to age, sex and respiratory rate (Table 13).

Table 13. Baseline characteristics of patients in asthma study

	High flow O_2 n=50	Titrated O_2 n=53	All n=103
Sex, male N (%)	27 (54)	18 (34)	45 (43.7)
Age, yr	35.0 (14.4)	32.6 (11.1)	33.8 (12.8)
Respiratory rate, breaths/min	23.4 (6.6)	22.7 (5.7)	23.0 (6.1)
Heart Rate, beats/min	97.7 (23.4)	100.7 (18.8)	99.2 (21.1)
SpO_2, %	95.1 (3.2)	96.4 (2.7)	95.8 (3.0)
$PtCO_2$, mmHg	36 (7.1)	34.1 (5.7)	35 (6.4)
$PtCO_2 \geq 38$ mmHg	20 (40.0)	15 (28.3)	35 (34.0)
FEV_1, L/min	1.15 (0.43)	1.29 (0.44)	1.22 (0.44)
FEV_1 % predicted	32.1 (9.9)	36.9 (9.7)	34.6 (10.1)

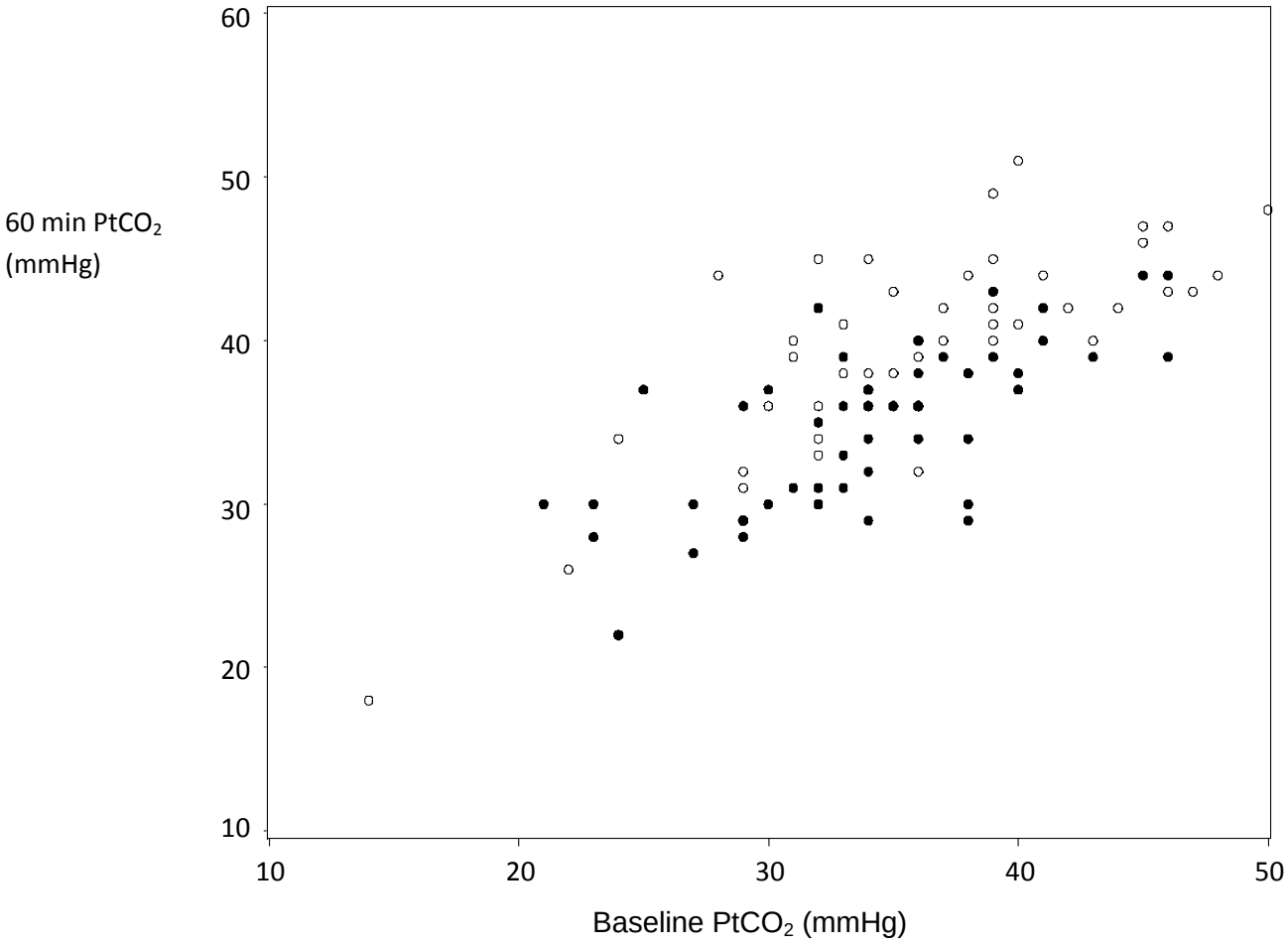
Values for age, respiratory rate, heart rate, SpO_2, $PtCO_2$ FEV_1 and FEV_1 % predicted are mean (SD). Values for sex and $PtCO_2 \geq 38$ mmHg are number of participants (percentage)

The baseline FEV_1 in the high concentration oxygen and titrated oxygen groups were 1.15L and 1.29L respectively.

$PtCO_2$ levels at baseline ranged from 14 to 50 mmHg (Figure 20).

Figure 19. The $PtCO_2$ levels at baseline and after 60 minutes in asthma study

The $PtCO_2$ levels at baseline and after 60 minutes in the high concentration (o) and titrated (•) oxygen groups. The subject who received high concentration oxygen and was withdrawn after 11 minutes due to safety concerns, following an increase in the $PtCO_2$ from 41 to 52 mmHg, is not presented in the figure.



The majority of patients were hypocapnic at baseline with 68/103 (66%) having a $PtCO_2$ <38 mmHg. There were eight patients with an oxygen saturation <93% at baseline while breathing room air. In the titrated oxygen group 48/53 (90%) patients did not require oxygen therapy throughout the 60 minute treatment period, four patients required 1-3L/min and one required more than 3L/min. In the high concentration oxygen group the oxygen saturation at 60 minutes was ≥99% in 39/50 (78%) of patients and was ≥95% in the remaining 11 patients.

The $PtCO_2$ levels at 60 minutes ranged from 18 to 52 mmHg (Figure 20). One patient who received high concentration oxygen was withdrawn after 11 minutes due to safety concerns, following an increase in the $PtCO_2$ from 41 to 52 mmHg. For the categorical outcome variables, the $PtCO_2$ value at 11 minutes was used as the final measurement in this patient. A total of 10 patients had a final $PtCO_2$ ≥45 mmHg. All 10 patients were in the high concentration oxygen group, and in five patients there was an increase in $PtCO_2$ ≥10 mmHg.

The proportion of patients with an increase in PtCO2 of ≥4 mmHg at 60 minutes was significantly greater in the high concentration group, compared with the titrated oxygen group, 22/50 vs 10/53 with a relative risk of 2.3 (95% CI 1.2 to 4.4; P=0.006) (Table 14). The proportion of patients with a rise in $PtCO_2$ ≥8 mmHg was significantly greater in the high concentration group, with a relative risk of 3.9 (95% CI 1.2 to 13.1, P=0.016). The proportion of patients with both a rise in $PtCO_2$ ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes was significantly greater in the high concentration group with a relative risk of 4.5 (95% CI 1.6 to 12.5, P=0.001). A total of 10 patients had a final $PtCO_2$ ≥45 mmHg. All 10 patients were in the high concentration oxygen group, and in five patients there was an increase in $PtCO_2$ ≥10 mmHg.

Table 14. The proportion of patients with a predetermined rise in PtCO2 from baseline at 60 minutes

	High flow O_2 n (%)	Titrated O_2 n (%)	Relative risk (95% CI)	P value
Change in $PtCO_2$ ≥4 mmHg	22 (44%)	10 (19%)	2.3 (1.2 to 4.4)	P=0.006
Change in $PtCO_2$ ≥4 mmHg and $PtCO_2$ ≥38 mmHg	17 (34%)	4 (8%)	4.5 (1.6 to 12.5)	P=0.001
Change in $PtCO_2$ ≥8 mmHg	11 (22%)	3 (6%)	3.9 (1.2 to 13.1)	P= 0.016

The proportion of patients with a rise in $PtCO_2$ ≥8 mmHg was significantly greater in the high concentration group, with a relative risk of 3.9 (95% CI 1.2 to 13.1, P=0.016). The proportion of patients with a $PtCO_2$ >38 mmHg and an FEV_1 percent predicted less than 50% after 60 minutes was 20/49 (40.8%) in the high concentration group and 6/53 (11.3%) in the titrated group, relative risk 3.6 (95% CI 1.6 to 8.2; P < 0.001).

The mean change in $PtCO_2$ from baseline was significantly greater in the high concentration group with a mean difference between the groups at 60 minutes of 2.6 mmHg (95% CI 0.9 to 4.3; P<0.003) (Table 15). The proportion of patients with a rise in $PtCO_2$ was greater in the high concentration group at the 20 and 40 minute time points (Table 15). The rate of increase in the high concentration group was 0.054 (95% CI 0.035 to 0.074) mmHg/min and the titrated group was 0.012 (95% CI -0.0065 to 0.031) mmHg/min. The difference in the rate of change was 0.042 mmHg/min (95% CI 0.069 to 0.15, P=0.003).

Table 15. Time course of changes in PtCO2 in the treatment groups

i) The mean change in $PtCO_2$ (mmHg)

Time	High concentration mean (SD)	Titrated mean (SD)	Difference (95% CI)	P value
20 minutes	2.8 (4.1)	0.3 (3.6)	2.5 (1.0 to 4.0)	P=0.001
40 minutes	3.0 (4.7)	0.4 (3.8)	2.6 (0.9 to 4.3)	P=0.002
60 minutes	3.4 (4.5)	0.8 (4.1)	2.6 (0.9 to 4.3)	P=0.003

ii) The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg

Time	High concentration N (%)	Titrated N (%)	Relative Risk (95% CI)	P value
20 minutes	15 (30%)	7 (13%)	2.3 (1.0 to 5.1)	P=0.038
40 minutes	21 (42%)	8 (15%)	2.8 (1.4 to 5.7)	P=0.002
60 minutes	22 (44%)	10 (19%)	2.3 (1.2 to 4.4)	P=0.006

There were 26/50 (52%) of the high concentration group admitted to hospital compared to 17/53 (32%) in the titrated group, odds ratio 2.3 (95% CI 1.0 to 5.1). P=0.042. After adjusting baseline FEV_1, oxygen saturation, and $PtCO_2$, this odds ratio was 1.7 (95% CI 0.68 to 4.26, P=0.26) (Table 16). In the adjusted analysis, a higher baseline FEV_1 and oxygen saturation were associated with a reduced risk of admission.

Table 16. Risk of hospital admission

i) Unadjusted analysis

	OR (95% CI)	**P-value**
High concentration oxygen	2.29 (1.03 to 5.10)	0.042

ii) Adjusted analysis

	OR (95% CI)	**P-value**
High concentration oxygen	1.70 (0.68 to 4.26)	0.257
Baseline oxygen saturation (per %)	0.80 (0.66 to 0.98)	0.028
Baseline $PtCO_2$ (per mmHg)	1.04 (0.96 to 1.12)	0.370
Baseline FEV_1 (per litre)	0.31 (0.10 to 0.94)	0.039

3.3.5 Discussion

This randomised controlled trial has shown that high concentration oxygen therapy results in a significant increase in $PtCO_2$ compared to titrated oxygen when administered to patients presenting to the emergency department with acute severe asthma. These results

are both physiologically and clinically significant, as indicated by the two- to four-fold relative risk of an increase in $PtCO_2$ of at least 4 mmHg or 8 mmHg respectively in the group receiving high concentration oxygen. Furthermore, all 10 patients in whom the final $PtCO_2$ was ≥45 mmHg had received high concentration oxygen therapy. Hypercapnia is an indication for admission to an ICU or HDU.[101] After adjustment for baseline predictors of severity, high flow oxygen was not statistically significant as a predictor of hospital admission, although the point estimate is consistent with increased risk.

The results in the current study extend those of previous reports.[112 113 178] There have been two prospective case series which have reported that oxygen therapy may lead to an increase in $PaCO_2$ in adults[112] with acute severe asthma. In the only previous randomised controlled trial comparing high and low concentration oxygen in acute severe asthma, 74 patients were given 100% or 28% oxygen for 20 minutes on arrival to the emergency department prior to receiving any asthma therapy.[113] The difference in the mean rise in $PaCO_2$ between the groups was 2.7 mmHg, similar to the 2.6 mmHg noted in the current study. However, the duration of oxygen therapy was 20 minutes and no concurrent asthma therapy was administered, limiting the generalisability of the study findings. Also, the administration of 28% oxygen rather than a titrated oxygen regime differed from the therapeutic approach currently recommended in guidelines[13 101 181]. Our study and others[182] have shown that most adult patients presenting to the ED with severe exacerbations of asthma do not have hypoxaemia, and as a result, do not require initial oxygen therapy.

There are a number of methodological issues relevant to the interpretation of the study findings. The first is that we used a TOSCA transcutaneous CO_2 monitor to measure $PaCO_2$ rather than the "gold standard" arterial blood gas test. This method was chosen as it allowed continuous $PtCO_2$ monitoring without the discomfort of arterial blood gas sampling or the risk of hand ischemia associated with indwelling radial artery cannulae. The accuracy of transcutaneous carbon dioxide monitoring has been demonstrated in a variety of settings including healthy subjects,[161 162] AECOPD,[153 163] sleep disorders,[164 165] critical illness,[166 183 184]and in a mixed group of 51 patients presenting to an ED.[167] The accuracy of our device

has been assessed in a subset of patients who had simultaneous ABG and $PtCO_2$ recordings.[168]The TOSCA accurately assessed $PaCO_2$ without significant bias and with clinically acceptable limits of agreement when compared to the ABG measurement, thus validating the methodology used.

By necessity the study was unblinded, as there was a clinical requirement for the investigator to have knowledge of the oxygen saturations in order to titrate the oxygen therapy in the "control" treatment group. The objective display of $PtCO_2$ on the TOSCA monitor avoided subjective assessment of the primary outcome variable.

The pre-specified analysis plan was to use the proportion of patients with a $PtCO_2$ >38 mmHg and FEV_1 ≤50% at 60 minutes as the primary outcome variable. However, in the early phase of recruitment it was apparent that the pre-specified primary outcome variable did not reflect a physiological increase in $PtCO_2$ as it was primarily determined by the presenting $PtCO_2$. After a review of the records of the first 19 patients (representing 17% of 106 patients contributing to the main outcome analysis) we registered a change in the primary outcome variable to the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg. Whilst changing the primary outcome variable after the start of the study raises the possibility of creating a biased assessment of the outcome of the trial there was no formal interim statistical analysis, of either the pre-specified outcome variable or the new main outcome variable, was carried out prior to this decision and although the study itself was not masked as to treatment allocation the decision was made without reference to the randomised allocation of the patients. In the event, for the original main outcome variable, $PtCO_2$ >38 mmHg and an FEV_1 percent predicted less than 50% after 60 minutes, the 3.6 fold increased risk associated with high concentration oxygen therapy was similar to the 2.3 and 3.9 fold increased risk observed with a $PtCO_2$ rise of ≥4 mmHg and ≥8 mmHg respectively.

It is unlikely that patients with established COPD were included in this study based on their history. In addition, immediate access to electronic medical records which documents any previous hospital admission, out-patients consultations and spirometry were available,

allowing further investigation of a diagnosis of COPD. The intention was to recruit 150 patients, based on the power calculation derived from the previous randomised controlled trial of oxygen therapy in asthma.[113] Due to difficulties with recruitment, the study sites were extended to include Hutt Hospital, and the planned 2 year study period by 6 months. With these measure 106 patients were enrolled which was less than the planned 150. However, as the study showed a statistically significant difference in risk the issue of type II error (and its complement statistical power) is not as important as it might have been if no statistically significant difference had been detected. It could be argued that the lower limit of the confidence interval for the risk includes a clinically irrelevant difference and that tighter confidence intervals arising from a larger sample size would give greater certainty than the achieved sample size. Patients with a diagnosis of COPD were excluded due to the known effect of high concentration oxygen in exacerbations of this disorder.[59 60 74 75 78 82 176]. It is probable that greater increases in $PtCO_2$ may occur in an unselected population of patients with acute asthma, which is more likely to include those with concomitant COPD or other disorders associated with chronic respiratory failure.

Although an attempt was made to include potential patients with severe or life threatening asthma, patients who were moribund, unable to speak, unable to perform spirometry, or so distressed that they could not consent, were not enrolled. Consequently, those with the most severe airflow obstruction, and hence the highest risk of hypercapnia at presentation, were not able to be studied. In this regard it is relevant that with progressively more severe hypercapnia, smaller falls in alveolar ventilation are required to produce a given further rise in $PaCO_2$[30].

The increase in $PtCO_2$ with high concentration oxygen is likely to be an underestimate of the magnitude of the effect that may be seen in standard clinical practice in which oxygen therapy may be administered for a longer period. The $PtCO_2$ progressively increased in the high concentration group throughout the 60 minute study period, suggesting that some patients may have had further increases in $PtCO_2$ had the high concentration oxygen regime continued.

The main mechanism for the elevation in $PtCO_2$ demonstrated in this study is likely to be worsening ventilation-perfusion mismatching as a result of the release of hypoxic pulmonary vasoconstriction and a consequent increase in physiological dead space, as has been demonstrated in studies of the effects of oxygen therapy in both acute severe and chronic asthma.[104 109-111] This is one of the main mechanisms which causes oxygen-induced CO_2 retention in AECOPD.[74 78 82 176] The important clinical implication of this data is that high concentration oxygen therapy may have the potential to cause an increase in $PaCO_2$ across a wide range of respiratory conditions with abnormal gas exchange due to ventilation perfusion inequality. In support of this interpretation, this physiological response to high concentration oxygen therapy has now been reported in stable COPD,[75 78], AECOPD,[59 60 74] asthma,[104 112 113] and obesity hypoventilation syndrome[174]. This response contrasts with that observed in normal subjects in whom high concentration oxygen therapy leads to a small decrease in $PaCO_2$[185 186] The observation that there was no difference in the change in FEV_1 between the two regimes suggests that the increase in $PtCO_2$ with high concentration oxygen therapy was not due to a bronchoconstrictor effect related to the low humidity of the delivered oxygen.

In conclusion, high concentration oxygen increases the $PtCO_2$ in patients with acute severe asthma. This suggests that the potential increase in $PaCO_2$ with high concentration oxygen therapy is not limited to COPD, but may also occur in other respiratory disorders with abnormal gas exchange. Consistent with recent guidelines,[13 101 187]this study recommends that in patients with acute severe asthma oxygen should be administered only to those with evidence of arterial hypoxemia in a dose that relieves the hypoxemia without causing hyperoxia, thereby achieving the benefits while reducing the potential for harm.[175]

Chapter 3.5 Randomised double-blind cross-over study of the effects of hyperoxia in obesity hypoventilation syndrome

3.5.1 Introduction

Obesity has reached epidemic proportions with more than one billion overweight adults worldwide, of whom at least 300 million are obese[188]. Obesity hypoventilation syndrome (OHS) is defined as a combination of obesity (body mass index (BMI) >30 kg/m^2) and awake hypercapnia ($PaCO_2$ ≥45mmHg) in the absence of other known causes of hypoventilation, accompanied by sleep disordered breathing[189-191]. The prevalence of OHS in the general population is unknown; but studies have found hypoventilation in 10-20% of patients with obstructive sleep apnoea[192] and as high as 31% in a cohort of obese hospitalised patients[193].

OHS is often under-diagnosed[191-194] and as a result, clinicians treating patients with OHS presenting with an acute respiratory or cardiac disorder are unlikely to be aware of the presence of chronic respiratory failure and hypercapnia. In this situation, the identification of hypoxaemia by pulse oximetry may lead to the administration of high concentration supplemental oxygen, which may have the potential to worsen the hypercapnia. This could occur if there was a reduction in minute ventilation or an increase in the physiological dead space due to worsening ventilation/perfusion mismatch, similar to the effects of oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease [70 74]. These concerns have led current guidelines[13] to recommend the judicious use of oxygen in patients with OHS, although to the best of our knowledge, there have been no randomised controlled trials to support this recommendation.

3.5.2 Objectives

To determine

- whether breathing 100% oxygen results in worsening hypercapnia in subjects with OHS

- the underlying mechanisms of any effect by the measurement of minute ventilation and physiological dead space.

3.5.3 Methods

Subjects

Subjects with newly diagnosed OHS were approached to participate in the study.

Inclusion criteria

- obesity (BMI >30 kg/m^2) and have
- evidence of daytime hypercapnia ($PtCO_2$ ≥45mmHg)

Exclusion criteria

- Subjects were excluded if they had a diagnosis of COPD (defined by a post-bronchodilator FEV_1 to FVC ratio <0.7, and FEV_1 <80% predicted and >10 pack year smoking history)
- Already receiving treatment with continuous or bilevel non-invasive positive pressure ventilation.

All potentially eligible obese subjects were screened for hypercapnia by myself. There were a number of different sources: tertiary hospital sleep clinic and obesity clinic, prior to bariatric surgery and from the community identified from general practice records. All patients were outpatients in a stable condition. The majority of subjects had full polysomnography, but this was not a requirement for entry into the study. Subjects who met the inclusion criteria were provided with a patient information sheet (appendix 2) and were invited to take part in the study.

The study was approved by the Wellington Regional Ethics Committee (appendix 4) and informed consent was obtained from each patient. The study was registered with the Australia New Zealand Clinical Trials Registry ACTRN 12608000592347.

Study Protocol

A detailed study protocol is shown in appendix 3. The study had a cross-over, AB/BA, design with a randomised order of administration of the experimental condition, 100% oxygen or room air. Subjects attended a respiratory physiology laboratory for testing on two occasions within 7 days. Each patient was fitted with a full face continuous positive airway pressure (CPAP) mask without positive airways pressure, held by elasticised straps around the head. Subjects sat upright at 90^{o} during the test. A Douglas Bag was filled with either 100% oxygen or room air which was attached to a three way tap and then connected via tubing to a one-way valve to the CPAP mask. Once the patient's respiratory rate and minute ventilation had reached a steady state whilst breathing room air, the three way valve was opened and the patient breathed the gas in the Douglas bag for 20 minutes.

To ensure an adequate wash out period, subjects were asked to return to the laboratory for a second test on a separate day, during which the study protocol was repeated with the other gas.

If the $PtCO_2$ rose by more than 10mmHg at any stage during the 20 minute treatment period, the study was terminated due to a risk of acidotic hypercapnic respiratory failure and coma.

Randomisation

A computerised randomisation sequence was generated by the statistician and held by the respiratory physiologist who prepared the Douglas bags to ensure allocation concealment.

Blinding

The study was double-blind. A respiratory physiologist and respiratory physician carried out the study protocol on each patient. The role of the respiratory physiologist was to prepare the laboratory on each study day including filling the 200 L Douglas bag with oxygen or air. The respiratory physician's role was to attend to the patient, attach the mask to the patient's face and record the physiological measurements. Oxygen saturations were not

recorded during the treatment period to ensure the patient and respiratory physician were blinded to the treatment throughout the duration of the study.

Measurements

Respiratory rate (RR), transcutaneous carbon dioxide tensions ($PtCO_2$), minute ventilation (MV) and dead space to tidal volume ratio (Vd/Vt) were measured at baseline. $PtCO_2$ was used to estimate $PaCO_2$ using a combined SpO_2/$PtCO_2$ monitor ("TOSCA", Radiometer, Basel, Switzerland). MV was measured using a flow sensor (CO_2SMO Plus! Respiratory Profile Monitor, Respironics, Murrysville, Pennsylvania, USA) attached to the expiratory port of the mask, calculated by expressing the eight breath moving average of expiratory volume in terms of volume per minute, updated every breath. The mixed expired CO_2 ($PeCO_2$) was measured using volumetric capnography (CO_2SMO Plus! Respiratory Profile Monitor, Respironics, Murrysville, Pennsylvania, USA). With measurements of the $PaCO_2$ and $PeCO_2$, the Vd/Vt was calculated by the machine, using the Bohr-Engoff equation[195]. The tidal volume (Vt) was calculated by the equation Vt = MV/RR, the physiological dead space volume (Vd) was calculated by the equation Vd = Vt x Vd/Vt, the alveolar volume (Va) was calculated by the equation Va = Vt - Vd, and the alveolar minute ventilation (MVa) was calculated by the MVa = Va x RR. The minute ventilation was used as a measure of ventilatory drive and the Vd/Vt as a measure of physiological dead space. All data were recorded on a data collection sheet (Appendix 1)

Statistical analysis

The main outcome variable was $PtCO_2$ and the primary analysis was a mixed linear model using the baseline value for the particular variable as a covariate, as well as a fixed term for the order of administration of the treatments. The mixed linear model takes into account the correlation between measurements on the same participants in the cross-over design. The secondary outcome variables were RR, MV, Vd/Vt, Vt, Vd, Va, MVa and change in $PtCO_2$ $\geq$4 mmHg. Analysis was by intention to treat. The association between the baseline oxygen saturation and change in $PtCO_2$ after oxygen use was assessed by regression analysis.

We calculated that a study recruiting 24 participants would give 80% power to detect a paired difference of 4mmHg in $PtCO_2$ based on a standard deviation of 6.5 for the paired difference from the study of Robinson et al[82].

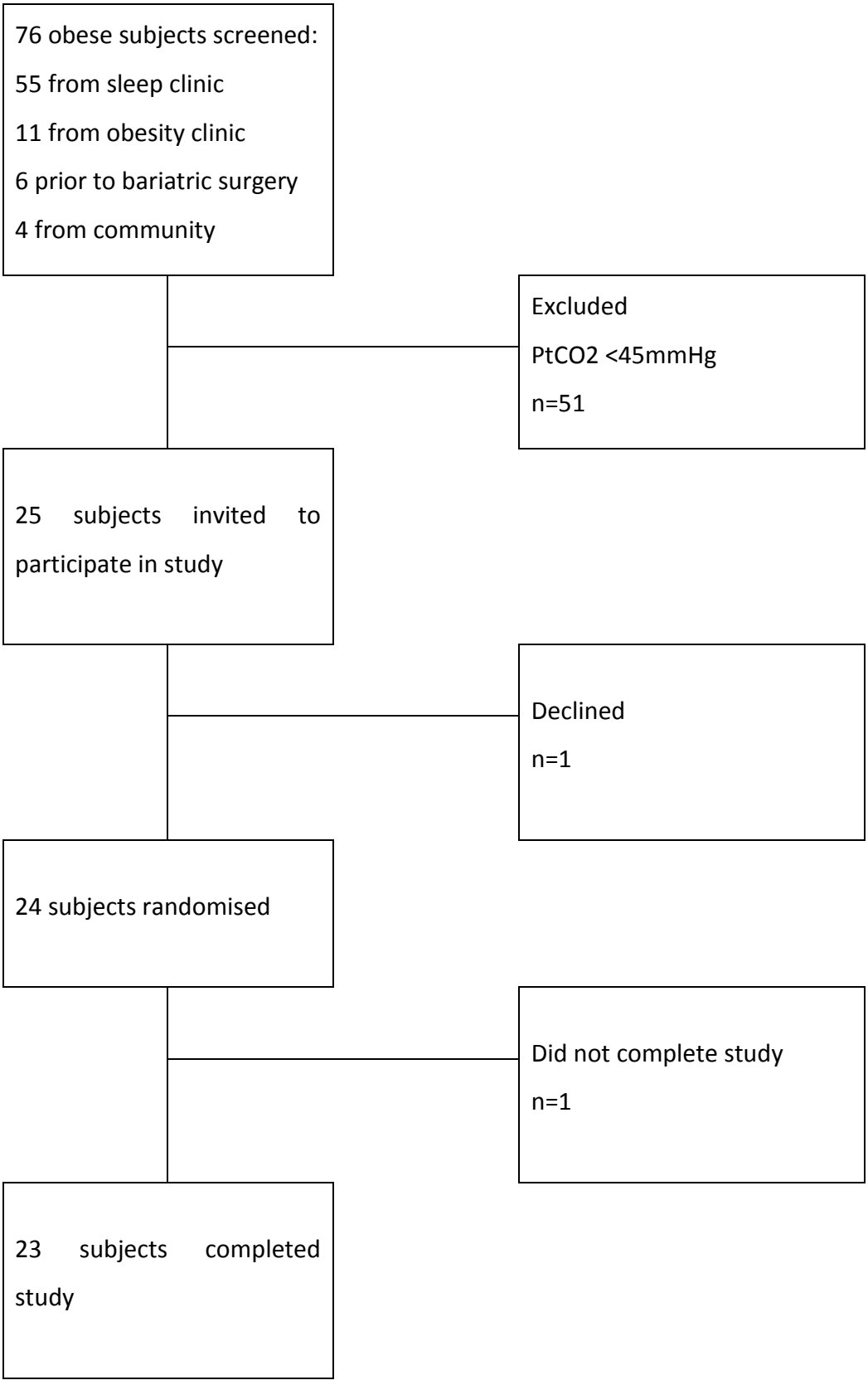
SAS version 9.1 was used.

3.5.3 Results

Characteristics of subjects

A total of 76 obese subjects (mean BMI 47.6 kg/m^2), without a history of COPD, were screened for evidence of daytime hypercapnia (Figure 21).

Figure 20. Flow of subjects through OHS study



Of these, 25 met the inclusion criteria and 24 consented to take part in the study. As a result, 24 subjects were randomised; one subject did not attend for the second test. The study took place between June 2008 and May 2009.

Table 17 shows the baseline characteristics of the subjects included in the study.

Table 17. Characteristics of subjects, OHS study

Age, years	47.3 (12.4)
Sex, male	14/24
Weight (kg)	154.7 (37.8)
BMI (kg/m^2)	52.4 (11.3)
$PtCO_2$ (mmHg)	49.2 (5.6)
SpO_2 (%)	95.5 (4.0)
FEV_1/FVC	0.80 (0.08)
Smoking history (pack years)	2.3 (3.3)

Values are mean (SD) for age, BMI, $PtCO_2$ SpO_2 and pack years;
number of subjects for sex

The 24 subjects were morbidly obese with a median BMI of 50.7 kg/m^{-2} (range 37.4 to 83.6). There was a wide range in the severity of chronic respiratory failure, with a median $PtCO_2$ of 47 mmHg (range 45 to 67) and median oxygen saturation of 97% (range 80 to 99). The median forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio was 0.80 (range 0.70 to 0.97). The median pack years of cigarette smoking was 0 (range 0 to 10).

Changes in $PtCO_2$

The mean $PtCO_2$ increased from 48.7 to 52.7 mmHg breathing oxygen, compared with a decrease in mean $PtCO_2$ from 48.6 to 47.7 mmHg in the room air group (Table 18).

Table 18: Changes in transcutaneous CO_2 and secondary outcome variables whilst breathing air and 100% oxygen

	AIR			OXYGEN		
	Baseline (n=24)	20 mins (n=24)	Difference	Baseline (n=23)	20 mins (n=23)	Difference
$PtCO_2$ (mmHg)	48.6 (4.0)	47.7 (5.4)	-1.0 (2.6)	48.7 (3.8)	52.7 (6.5)	4.0 (4.1)
RR (bpm)	15.8 (3.6)	15.7 (4.4)	-0.12 (2.6)	15.6 (3.8)	14.7 (3.8)	-0.91 (3.4)
MV (L/min)	9.6 (3.3)	9.0 (3.4)	-0.70 (2.3)	10.1 (2.9)	8.0 (3.3)	-2.1 (2.2)
Vd/Vt	0.58 (0.06)	0.59 (0.08)	0.01 (0.05)	0.57 (0.06)	0.65 (0.06)	0.09 (0.05)
Vt (L)	0.65 (0.31)	0.63 (0.34)	-0.02 (0.22)	0.69 (0.29)	0.56 (0.34)	-0.13 (0.18)
Vd (L)	0.37 (0.16)	0.36 (0.15)	-0.01 (0.10)	0.39 (0.16)	0.36 (0.21)	-0.03 (0.11)
Va (L)	0.28 (0.16)	0.28 (0.19)	-0.006 (0.12)	0.30 (0.14)	0.20 (0.14)	-0.10 (0.09)
MVa (L/min)	4.1 (1.6)	3.8 (1.9)	-0.32 (1.32)	4.4 (1.3)	2.8 (1.6)	-1.6 (1.2)

All values are mean (SD)

$PtCO_2$: Transcutaneous carbon dioxide tension (mmHg)

RR: Respiratory rate (breaths per minute)

MV: Minute ventilation (L/min)

Vd/Vt: Physiological dead space to tidal volume ratio

Vt: Tidal volume (L)

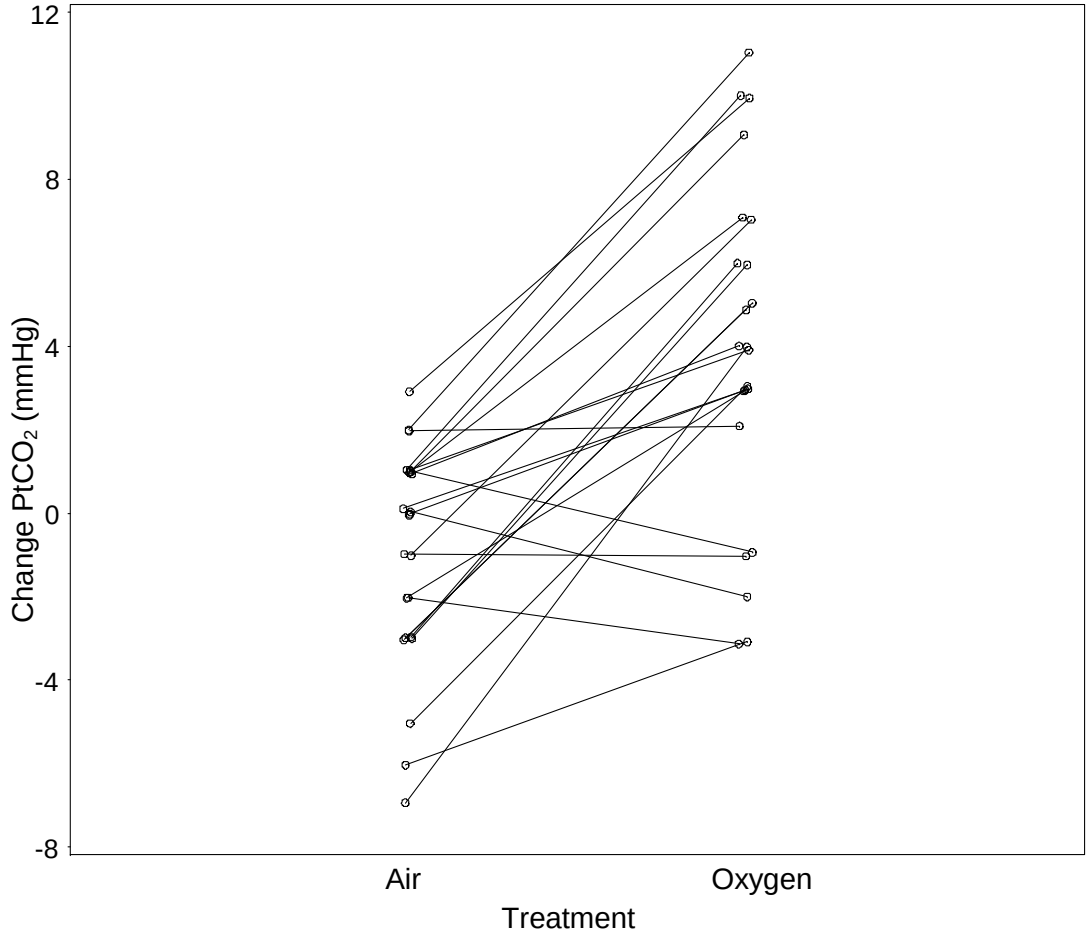
Vd: Physiological dead space volume (L)

Va: Alveolar volume (L)

MVa: Alveolar minute volume (L)

The $PtCO_2$ adjusted for baseline increased by 5.0 mmHg (95% CI 3.1 to 6.8; p<0.001) with oxygen compared with room air (Table 19). The number of subjects in whom the $PtCO_2$ increased by ≥4 mmHg was 10/23 (43.5%) when breathing 100% oxygen and 0/23 (0%) when breathing room air. There was a moderate association (r^2=0.25) between the baseline oxygen saturation and the change in $PtCO_2$ with oxygen therapy, with an increase in $PtCO_2$ of 0.50 mmHg (95% CI 0.11 to 0.89, P=0.014) for every 1% decrease in baseline oxygen saturation.

Figure 21. The change in $PtCO_2$ from baseline following breathing 100% oxygen or room air



The test was terminated in 3 subjects when breathing 100% oxygen, due to a rise in $PtCO_2$ of ≥10mmHg which occurred after 10:35, 13:20 and 15:51 minutes.

Changes secondary outcome variables

The mean MV decreased from 10.1 to 8.0 L/min breathing oxygen compared with 9.6 to 9.0 L/min breathing room air (Table 18). The mean MV adjusted for baseline decreased by 1.4 L (95% CI 0.11 to 2.6, P=0.03) with oxygen use compared with room air (Table 19). The mean MVa decreased by 1.17 L per minute (95% CI 0.54 to 1.81, P<0.001) breathing oxygen. The point estimate for the change in RR was 0.9 breaths per minute lower for the oxygen group; however this difference was not statistically significant.

The mean Vd/Vt increased from 0.57 to 0.65 breathing oxygen, compared with 0.58 to 0.59 breathing room air (Table 18). The mean Vd/Vt adjusted for baseline increased by 0.067 (95% CI 0.035 to 0.10, P<0.001) with oxygen use compared with room air (Table 19). The increase in Vd/Vt breathing oxygen was associated with a statistically significant mean reduction in Va of 0.085 L (95% CI 0.025 to 0.14, P=0.007), without a statistically significant mean change in Vd (-0.007 L, 95% CI -0.058 to 0.044, P=0.79).

Table 18. Mixed linear model estimates of the differences 100% oxygen minus air adjusted for baseline

	Estimate (95% CI)	P value
$PtCO_2$ (mmHg)	5.0 (3.1 to 6.8)	<0.001
RR (bpm)	-0.9 (-2.4 to 0.67)	0.25
MV (L/min)	-1.4 (-2.6 to -0.11)	0.03
Vd/Vt	0.067 (0.035 to 0.10)	<0.001
Vt (L)	-0.092 (-0.20 to 0.012)	0.08
Vd (L)	-0.007 (-0.058 to 0.044)	0.79
Va (L)	-0.085 (-0.14 to 0.025)	0.007
MVa (L/min)	-1.17 (-1.81 to -0.54)	<0.001

Although the point estimate for the change in RR was lower for the oxygen group, this was not statistically significant.

3.5.3 Discussion

This randomised, double-blind cross-over study has demonstrated that breathing 100% oxygen causes worsening hypercapnia in subjects with OHS. After 20 minutes breathing 100% oxygen, the $PtCO_2$ increased by a mean of 5 mmHg, with 3 of 24 subjects having to be withdrawn before completion of the study while breathing oxygen due to an increase in $PtCO_2$ of at least 10 mmHg. This indicates that subjects with stable OHS are at risk of an acute and marked decompensation of their respiratory failure with high flow uncontrolled oxygen therapy.

There are a number of methodological issues relevant to the interpretation of the study findings. Primarily, we used a TOSCA transcutaneous CO_2 monitor to measure $PtCO2_2$ rather than the "gold standard" arterial blood gas test. This method was chosen as it allowed continuous $PtCO_2$ monitoring without the discomfort of repeated arterial blood gas sampling or the risk of hand ischemia associated with indwelling radial artery cannulae[196]. The TOSCA has been shown to be an accurate means of estimating both $PaCO_2$ and SpO_2 from a single probe in healthy subjects[197 198], COPD [153] and obesity[164]

For the secondary outcome variables volumetric capnography was used to estimate Vd/Vt, using the Bohr-Enghoff equation, based on measurements of the mixed expired CO_2 and $PtCO_2$[195]. It would have been informative to have measured continuous distributions of ventilation-perfusion ratios by the multiple inert gas elimination technique [199]. However this involves the invasive measurement of cardiac output, which is technically difficult in this population and would have posed an unacceptable risk to our subjects. Furthermore, although MIGET has been used in COPD[82 200], it has not been validated in OHS. Given this study was primarily designed to investigate the effects of oxygen on $PtCO_2$ we used simple, non-invasive methods which provided validated measures of respiratory drive and physiological dead space to assess the mechanisms of the effect observed.

Although in clinical practice it would be uncommon to administer 100% oxygen to patients with OHS, this oxygen regime was chosen to ensure hyperoxaemia was achieved and to maximise the potential to determine an effect. As a result, the magnitude of the increase in $PtCO_2$ may have been greater than that which occurs with lower oxygen concentrations and further studies are required to examine this. There is evidence in COPD that the administration of oxygen may worsen hypercapnia across a range of concentrations from 28% to 100%.[74 68 70 72 75 82 201 202]Whilst the majority of these patients were studied during acute exacerbations, the latter two were performed in stable COPD and showed similar increases in $PaCO_2$ and Vd/Vt found in our group of patients with stable OHS.

The strengths of this study include the double-blind design, which minimised any voluntary changes in respiratory pattern which may have occurred with knowledge of the inspired gas. The cross-over design allowed each patient to act as his/her own control with an adequate washout period between each gas. The simple physiological methods used allowed continuous measurements to be made non-invasively without risk to the patient.

Subjects were recruited in whom the diagnosis of OHS had not previously been made, and who were not already receiving treatment with continuous or bilevel non-invasive positive pressure ventilation, which has the potential to reduce the severity of baseline hypercapnia [203-206], and the ventilatory response to hypercapnia[203 207]. Additionally, subjects with concomitant COPD were excluded, based on their smoking history and spirometry, to ensure that the response to oxygen therapy was not confounded by this condition. Other causes of daytime hypercapnia other than COPD and OHS were not considered, although this is unlikely. Seventy-six subjects from a number of sources including a tertiary hospital sleep clinic, obesity clinic, bariatric surgery waiting list and general practice, to enable 24 eligible subjects to be randomised. The observation that about one in three morbidly obese subjects (with a mean BMI of 47.6 kg/m^2) has OHS is in keeping with a study by Nowbar and colleagues[193] who found 31% of a sample of severely obese inpatients (with a mean BMI of 45 kg/m^2), had evidence of daytime hypoventilation. Other studies, have shown a lower prevalence in patients with obstructive sleep apnoea, ranging from 10-20%[191 208 209], which may be due to a lower range of BMI (33 to 43 kg/m^2) in comparison to this study in which the BMI range was from 37 to 84 kg/m^2.

A significant mean increase in $PtCO_2$ of 5 mmHg after 20 minutes of breathing 100% oxygen in OHS subjects has been demonstrated. This was similar to the original report of Barrera and colleagues in 1973[174], who demonstrated a rise in $PaCO_2$ from 58.3 mmHg to 63.4 mmHg with 100% oxygen in four obese patients with chronic hypoxemia and hypercapnia. Of clinical concern is that in 1 in 8 of our subjects, the test had to be stopped due to a rise in $PtCO_2$ of >10 mmHg, after 10 to 16 minutes of breathing 100% oxygen. This illustrates the short time period in which the $PaCO_2$ rises with oxygen therapy, similar to that observed with COPD[76 78 82]. It is likely that the $PaCO_2$ would have continued to rise if oxygen had been administered beyond the 20 minute time period, suggesting our findings are underestimates of the magnitude of the increase in hypercapnia that might occur with prolonged administration of high concentration oxygen therapy to OHS patients in clinical practice. Although pH was not measured, it is likely that subjects would have developed respiratory acidosis during this short period of oxygen administration.

A moderate association between baseline oxygen saturation and increase in $PtCO_2$ with oxygen therapy was observed, with an increase in $PtCO_2$ of 0.5 mmHg for every 1% lower in oxygen saturation on room air. This suggests that obese patients at greatest risk of worsening hypercapnia are those with the most marked hypoxaemia, that is, those most likely to receive high concentration oxygen therapy

This study suggests that the main mechanism which led to worsening hypercapnia when breathing oxygen was a reduction in MV leading to alveolar hypoventilation. The associated increase in Vd/Vt was associated with a reduction in Va, without a statistically significant change in Vd.

These findings provide support for the recommendations to treat all morbidly obese patients with oxygen therapy in the acute setting cautiously, similar to the approach in COPD.[13] Long-term supplemental oxygen is often administered in concurrence with domicillary bilevel positive airway pressure in patients with OHS, however oxygen therapy alone does not improve hypoventilation[210] and has recently been shown in a retrospective study[211] to be the only independent predictor of mortality. As shown, up to one-third of

morbidly obese patients may have coexisting OHS. Given that OHS is an under-recognized and under-treated condition[190] [191] [193] this study highlights the importance of adequate physiological assessment of morbidly obese patients, particularly on presentation to the Emergency Department, where high concentration oxygen is often administered to treat breathlessness

This is the first randomised double-blind controlled study of high concentration oxygen therapy in subjects with OHS. It has demonstrated that breathing 100% oxygen leads to worsening hypercapnia in subjects with OHS, and that the magnitude and speed of the effect may be striking. This physiological response is due to a reduction in MV resulting in alveolar hypoventilation, and an associated increase in Vd/Vt. In morbidly obese patients the possible presence of OHS needs to be recognized, as well as the potential for oxygen therapy to increase the $PaCO_2$. In morbidly obese patients it is recommended that oxygen therapy should be administered with caution.

SECTION 4 CONCLUSION

4.1 Summary of findings

Oxygen therapy remains a cornerstone of medical practice. It is widely used in a variety of clinical settings and is generally regarded as being safe. The British Thoracic Society has recently published guidelines on how to prescribe, administer and monitor oxygen safely which are being implemented and disseminated throughout the United Kingdom. The guidelines have demonstrated the lack of clinical trials to support this widely used drug.

In this thesis, I have presented a series of audits and randomised controlled trials on oxygen therapy in respiratory disorders with the overall aim to provide evidence for the use of oxygen therapy.

The main findings from each study are:

Oxygen Prescription Charts

- The prescription and administration of oxygen therapy is suboptimal in hospital inpatients.
- An oxygen prescription section on hospital drug charts improves the prescription of oxygen but not clinical practice.

Pre-Hospital Oxygen therapy in AECOPD

- A significant proportion of patients with AECOPD continue to receive high flow oxygen therapy on ambulance transfer to our Emergency Department, contrary to local and international guidelines
- The risk of adverse outcomes increases progressively with increased PaO_2

Randomised controlled trial of oxygen therapy in Community acquired pneumonia

- High concentration oxygen leads to a rise in arterial carbon dioxide tensions when administered to patients presenting acutely with community acquired pneumonia.
- There is a three fold relative risk increase in $PtCO_2$ of at least 4 mmHg when compared to titrated oxygen
- There is a six fold relative risk increase in $PtCO_2$ of at least 8 mmHg when compared to titrated oxygen
- There was no change in respiratory rate between the two groups, but the reduction in heart rate was greater in the high concentration group.
- CRB-65 score and rates of hospital admission did not differ between the two groups
- The rate of increase in $PtCO_2$ was significantly greater in the high concentration group.

Randomised controlled trial of oxygen therapy in acute severe asthma

- High concentration oxygen therapy results in a significant increase in $PtCO_2$ compared to titrated oxygen when administered to patients with acute severe asthma.
- There is a two fold relative risk increase in $PtCO_2$ of at least 4 mmHg when compared to titrated oxygen
- There is a four fold relative risk increase in $PtCO_2$ of at least 8 mmHg when compared to titrated oxygen
- All 10 patients who became hypercapnic ($PtCO_2$ ≥45mmHg) at the end of the study received high concentration oxygen.
- The rate of increase in $PtCO_2$ was significantly greater in the high concentration group.
- After adjustment for baseline predictors of severity, high concentration oxygen therapy was not statistically significant as a predictor of hospital admission.

Randomised controlled trial of hyperoxia in obesity hypoventilation syndrome

- Breathing 100% oxygen leads to worsening hypercapnia in subjects with obesity hypoventilation syndrome.
- After 20 minutes of breathing 100% oxygen, the $PtCO_2$ increased by a mean of 5mmHg
- Three of the 24 patients were withdrawn before completion from the study while breathing oxygen due to an increase in $PtCO_2$ of at least 10 mmHg
- Worsening hypercapnia is due to both an increase in the physiological dead space and a reduction in minute ventilation.

4.2 Implications of findings

The oxygen prescription chart audit has demonstrated that oxygen is a commonly used drug. Even after the introduction of a specific prescribing section on the drug chart, oxygen prescription remained substandard. Furthermore, clinical practice did not improve with oxygen prescription. The implications of poor oxygen practice have been highlighted in the recent NPSA alert which have resulted in serious adverse events, including deaths. This study endorses the mandatory requirement for a robust oxygen delivery policy in the hospital setting.

The AECOPD audit, once again highlights the continued practice of administering high flow oxygen in this vulnerable group of patients with respiratory disease. The implications of this, as demonstrated by our results, show that patients may unnecessarily be dying or requiring mechanical ventilation. This is despite these risks being clearly documented in national and international guidelines.

The findings of both the pneumonia and asthma study have demonstrated an increase in $PtCO_2$ in patients receiving high flow oxygen. The rise in $PtCO_2$ of ≥4mmHg and ≥8mmHg have potential physiological and clinical significance, particularly if occurring in patients with life-threatening episodes of respiratory failure. The higher rate of increase of $PtCO_2$ in the high concentration group is pertinent to clinical practice when oxygen is often delivered for several hours to days to relieve dyspnoea, which may result in even higher levels of $PaCO_2$ not seen in these studies. Additionally, asthma patients who develop hypercapnia require admission to a high dependency area which potentially could be avoided if oxygen was delivered to achieve a target saturation.

Both these studies have demonstrated a rise in $PtCO_2$ with high concentration oxygen therapy in respiratory disorders, other than COPD. This raises issues about the underlying mechanism of oxygen induced CO_2 retention which occurs with V/Q mismatch. The historical theory of “loss of hypoxic” drive is unlikely to contribute to this effect indicating that rises in

CO_2 with high flow oxygen may potentially occur in all patients with respiratory disease and V/Q mismatch.

Finally, although the BTS guidelines have highlighted a detrimental effect of high flow oxygen therapy in patients with OHS, this has not previously been supported with evidence from a randomised controlled trial. This study not only demonstrates the effects of 100% oxygen on $PtCO_2$ but also highlights how rapidly acute respiratory failure can ensue. OHS patients are often under-recognised and under-treated. The cautious administration of oxygen to all obese patients would potentially prevent this life-threatening complication.

4.3 Methodological Issues

The major methodological issues have been discussed in detail in the discussion sections of the relevant chapters and are listed below, to summarise:

- Retrospective nature of AECOPD audit
- Lack of blinding in pneumonia and asthma RCTs
- Short study time in pneumonia and asthma RCTs
- Use of transutaneous CO_2 monitoring to estimate $PaCO_2$ in all three RCTs
- Ability to exclude patients with COPD from pneumonia and asthma studies
- Measuring deadspace in OHS study

4.3 Future directions

Oxygen Prescription

We have shown from our audit that whilst a dedicated oxygen section on a drug chart improves the prescription of oxygen, this does not improve clinical practice. It would be relevant to know whether a prescription together with a specific observation chart recording respiratory rate, saturation and oxygen therapy facilitates monitoring and titration of oxygen therapy. A working example is from the BTS guidelines is shown below[13].

Figure 22. Working Example of respiratory section for Observation Chart[13]

Respiratory rate, oxygen saturation and oxygen therapy

Clinical review required if saturation is outside target range. Observation frequency_____

Continuous oxygen / PRN / Not on oxygen therapy Target range: 88–92% 94–98% Other____

Date	Example																				Date
Time	08.00																				Time
Respiratory rate	20																				Respiratory rate
Oxygen saturation %	94%																				Oxygen saturation %
Oxygen device or air	N																				Oxygen device or air
Oxygen flow rate l/min	4																				Oxygen flow rate l/min
Your initials*	LW																				Your initials*

*All changes to oxygen delivery systems must be initialled by a registered nurse or equivalent.

If the patient is medically stable and in the target range on two consecutive rounds, report to a registered nurse to consider weaning off oxygen.

*Codes for recording oxygen delivery on observation chart

A Air (not requiring oxygen, or weaning or on "PRN" oxygen)	H28 Humidified oxygen at 28% (also H35, H40, H60 for humidified oxygen at 35%, 40%, 60%)
N Nasal cannulae	RM Reservoir mask
SM Simple mask	TM Tracheostomy mask
V24 Venturi 24% V28 Ventri 28% V35 Venturi 35% V40 Venturi 40% V60 Venturi 60%	CP Patient on CPAP system
	NIV Patient on NIV system
	OTH Other device:_____ (specify which)

We have also shown from our audit that clinical practice was better in the ED. It would be beneficial to know whether there were specific wards or clinical areas which had deficiencies in their prescribing practices and administration of oxygen, so that staff education could be targeted in these areas.

In this audit, we did not look specifically at the other scenario involving the down-titration of oxygen in response to hyperoxia. As discussed throughout this thesis, the physiological effects of hyperoxia can potentially be detrimental.

The use of physiological monitoring "track and trigger" systems such as the modified Early Warning Score (MEWS) are useful for monitoring patients.[212] Oxygen saturation has been shown to be an important predictor of mortality[213] and the Standardised Early Warning Score (SEWS) (which incorporates oxygen saturation) has been shown to correlate with both in-hospital mortality and length of stay.[214] Further studies are required to show the benefits of such scoring system so that the measurement of SpO_2 can be incorporated as a mandatory observation by nursing and medical staff.

The BTS has appointed "Oxygen Champions" in most acute UK hospitals to help introduce the guidelines to improve oxygen use, enhance patient safety and audit usage

Oxygen therapy in AECOPD

AECOPD is one of the few conditions in which the potential dangers of oxygen therapy are widely accepted. There is a large body of evidence illustrating the mechanisms of oxygen induced hypercapnia [74 75 78 82] as well as the detrimental clinical outcomes [85-88 92]. Despite this, our audit has shown that oxygen continues to be administered to this group of vulnerable patients. Limitations of our study have been its retrospective nature and the inability to control for disease severity. The one randomised trial of oxygen therapy in the pre-hospital setting has shown better outcomes by targeting a saturation range of 88-92%. However, further trials are needed to define the ideal target oxygen saturation level for optimal outcome. The results of such studies need to be disseminated to not only nurses and medical staff but also paramedics who are invariably the first point of contact for patients.

Duration of study time

As discussed previously, the duration of the study was very short. Given that the difference in $PtCO_2$ between the high concentration and titrated oxygen groups progressively increased throughout the 60 minute period it would be useful to extend the study time to beyond 60 minutes and even up to several hours. This is clinically relevant as relief of dyspnoea in pneumonia may take many days and oxygen therapy is often continued until the dyspnoea resolves.

Clinical Outcomes

To our knowledge, this is the first study to investigate the effects of oxygen on carbon dioxide levels in patients with CAP. We did not look at clinical outcomes such as ICU admission or mortality. Clearly the results of this study need to be extended to investigate whether rises in CO_2 have clinical implications as occur in patients with AECOPD.

If adverse outcomes did occur, then further work would be required to determine the ideal target oxygen saturation which would treat hypoxaemia without causing hypercapnia.

Oxygen concentrations

It is rare for 100% oxygen to be given outside of intensive care units. We chose this concentration of oxygen to ensure the patients in the OHS study were hyperoxic. It would be informative to examine the effects of different FiO_2 levels on the CO2 level and on minute ventilation. Similarly to patients with AECOPD, an ideal target saturation range needs to be identified.

4.4 Overall Conclusion

Oxygen is a drug used widely in clinical practice. Despite this, there is a paucity of well-designed randomised clinical trials to support its use, as highlighted in the British Thoracic Society's "Emergency Oxygen use in Adult Patients"[13]. The UK's National Patients Safety Agency has recently reported nearly 300 adverse incidents and 9 deaths from poor oxygen management. The prescription of oxygen will help to reduce such untoward incidents, as well as the education of both hospital and pre-hospital staff.

The risks of administering uncontrolled oxygen to a subgroup of patients with COPD have been known for over 60 years and are well documented in international guidelines. Despite this, oxygen is continuously administered to patients with AECOPD without full appreciation of the risks. As highlighted by this thesis, the potential risks of oxygen induced hypercapnia and respiratory acidosis need to be extended to other common respiratory disorders in which abnormal gas exchange or respiratory drive are present. Oxygen should be administered according to documented low oxygen saturations rather than presumed need.

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APPENDICES

Data collection sheets

- Oxygen prescription charts
- Pre-Hospital Oxygen in AECOPD
- Oxygen and community-acquired pneumonia
- Oxygen and acute severe asthma
- Oxygen and Obesity Hypoventilation Syndrome

Patient Information sheets

- Oxygen and community-acquired pneumonia
- Oxygen and acute severe asthma
- Oxygen and Obesity Hypoventilation Syndrome

Study Protocols

- Oxygen and community-acquired pneumonia
- Oxygen and acute severe asthma
- Oxygen and Obesity Hypoventilation Syndrome

Ethics correspondence

- Oxygen and community-acquired pneumonia
- Oxygen and acute severe asthma
- Oxygen and Obesity Hypoventilation Syndrome

Equations

WELLINGTON HOSPITAL OXYGEN AUDIT

DATA COLLECTION FORM

2008

Patient Demographics

NHI

Age

M F

Sex

Ward

Date of admission

Date today

WARD

Y N

1. Is the patient on oxygen at the time of the audit?

If no, go to question 7

2. If yes, what is the

(a) Device

☐	Nasal Prongs	☐	Hudson Mask	☐	Venturi	☐	NRBM	☐	NIPPV

(b) Flow rate or FiO_2? ☐

	Y	N
3. Was oxygen started on the ward?	☐	☐
	Y	N
4. If yes, were the sats ≤ 92% prior to commencing oxygen?	☐	☐

PRESCRIPTION (if on oxygen)

	Y	N	D/K
5. Is O_2 prescribed in the drug chart?	☐	☐	☐

6. If yes, is there a specified:

	Y	N
(a) Device	☐	☐
	Y	N
(b) Flow rate or FiO_2	☐	☐
	Y	N
(c) O_2 sats target range	☐	☐

MONITORING AND TITRATION

(last 24 hrs)

Y	N
____	____

7. Were sats recorded on ≥ 2 occasions in the last 24 hours? ☐ ☐

Go to question 10 if <2

	Y	N	N/A
8. If sats were ≥ 96% on ≥2 occasions, was O_2 reduced or stopped?	☐	☐	☐
	Y	N	N/A
9. If O2 sats were ≤ 92% on ≥2 occasions was O_2 increased or commenced?	☐	☐	☐

AMBULANCE

	Y	N
10. Was the patient brought in by ambulance?	☐	☐

If no, go to question 15

INDICATION

	Y	N
11. Was oxygen administered in the ambulance?	☐	☐

If oxygen not administered, go to 15

	Y	N
12. Was oximetry documented prior to commencing oxygen?	☐	☐

	Y	N	D/K
13. Were the sats ≤ 92% prior to commencing oxygen?	☐	☐	☐

14. How much oxygen was administered? ☐

EMERGENCY DEPARTMENT

	Y	N
15. Was the patient admitted via ED?	☐	☐

If no, audit complete

INDICATIONS

	Y	N	D/K
16. Was oximetry/ABG documented on air on arrival?	☐	☐	☐

	Y	N	D/K
17. Was the patient on O_2 on arrival?	☐	☐	☐

Answer Qs 18-19 if on oxygen on arrival, Answer Qs 20-22 if on air on arrival

18. If documented, what were the sats?

☐ ≤ 92% ☐ 93-95% ☐ ≥96%

19. What was the next course of action?

☐ O_2 downtitrated ☐ O_2 uptitrated ☐ O_2 continued

	Y	N
20. Was oxygen administered at anytime in ED?	☐	☐

	Y	N
21. If yes, were the sats ≤ 92% prior to commencing?	☐	☐
22. If no, were the sats ≤ 92% at anytime?	☐	☐

PRESCRIPTION

	Y	N
23. Was O_2 prescribed in the drug chart?	☐	☐

24. If yes, was there a specified:

	Y	N
(a) Device	☐	☐

	Y	N
(b) Flow rate or FiO_2	☐	☐
(c) O_2 sats target range	☐	☐

MONITORING AND TITRATION

	Y	N	D/K
25. Were sats documented on ≥2 occasions?	☐	☐	☐
26. If sats were ≥ 96% on ≥2 occasions, was O_2 reduced or stopped?	☐	☐	☐
27. If sats were ≤ 92% on ≥2 occasions was O_2 increased or commenced?	☐	☐	☐

COPD AMBULANCE AUDIT

WELLINGTON HOSPITAL

2007

Audit number _____

Section 1: Demographics

1. NHI

2. Age

3. Sex M F

4. Date of presentation

Section 2: Current prescribed drug therapy

	Y	N	If yes
Long term oral steroids			mg/day

	Y	N
Current or recent (completed in the last 5 days) short course oral steroids		

	Y	N
Long term antibiotics		
Current or recent (completed in the last 5 days)short course antibiotics		
Inhaled corticosteroids		
Long acting beta agonist		
Tiotropium (Spiriva)		
Theophylline		

	DI		NEB	
	Y	N	Y	N
Short acting beta agonist				

	MDI		NEB	
	Y	N	Y	N
Ipratropium				

	MDI		NEB	
	Y	N	Y	N
Combivent				

	Y	N	If yes
Home oxygen	☐	☐	☐ l/min

Section 3: Background clinical details

	Y	N
Previous episode of CO2 retention? (PaCO2 > 45mmHg)	☐	☐

If yes:

Highest CO2	pH	Date
☐	☐	☐

CO2	Lowest pH	Date
☐	☐	☐

	Y	N
Previous acute BiPAP or CPAP?	☐	☐

	Y	N
Previous intubation?	☐	☐

Number of hospital admissions with COPD in the 12 months prior to this exacerbation	☐

	Y	N	Best result
	____	____	

Outpatient (stable) FEV1 in the 12 months prior to admission? [ ] [ ] [ ] litres

Comments

Section 4: Initial Ambulance Recordings

Time of arrival at scene [ ]

Time first recordings documented [ ]

	M	V	E	Total
First GCS				

	Resp rate	Heart rate	BP	O2 sats
First vital signs				

	Y	N
Were oxygen saturations clearly documented prior to commencing oxygen?		

O2 initiated by ambulance staff [ ] l/min

Time oxygen started

Section 5: Ambulance Management (From time located to triage, including initial recording and final recording)

	Y	N	D/K
Were sats documented on ≥ 2 occasions?			

	Y	N	N/A
If sats were ≥ 96% on ≥ 1 occasions, was O2 reduced or stopped?			
If sats were ≤ 92% on ≥ 1 occasions was O2 increased or commenced?			

	NEB		MDI	
Total dose of salbutamol in ambulance		mg		mcg
Total dose of ipratropium in ambulance		mg		mcg

Section 6: Final Ambulance Recordings (if more than one set done)

Time of final recordings

	M	V	E	Total
Final GCS				

	Resp rate	Heart rate	BP	O2 sats
Final vital signs				

O2 flow rate at time final sats recorded ☐ l/min

	scene	destination
Patient status at		

Comments

(including comments on mental status or consciousness level –direct quotes)

Section 7: ED Data (Triage)

Triage time and category ☐ Time ☐ Category

	M	V	E	Total
Triage GCS (if done)				

Resp rate	Heart rate	BP	O2 sats

Triage vital signs (if done)

Section 8: ED Data (first clinical assessment)

	M	V	E	Total	Time
ED GCS (if done)					

	Resp rate	Heart rate	BP	O2 sats	Time
First ED vital signs					

O2 flow rate at time first sats recorded ____ l/min

	Y	N	
ABG done?			If no go to **section 10**

Time of first ABG ____

Oxygen flow rate when ABG taken ____ l/min

	pH	pCO2	pO2	HCO3	Sats
ABG result					

Comment _____

Section 9: ED treatment prior to first ABG (ABG time _____)

(Excluding triage , from ED observation chart printout including the first clinical assessment)
If no ABG done treatment in the first 4 hours in ED from triage time.

	Y	N	D/K
Were sats documented on ≥ 2 occasions?	☐	☐	☐
	Y	N	N/A
If sats were ≥ 96% on ≥ 1 occasions, was O2 reduced or stopped?	☐	☐	☐
	Y	N	N/A
If sats were ≤ 92% on ≥ 1 occasions was O2 increased or commenced?	☐	☐	☐

	NEB	MDI
Total dose of salbutamol in ED	☐ mg	☐ mcg

	NEB	MDI
Total dose of ipratropium in ED	☐ mg	☐ mcg

Comments

(including comments on mental status or consciousness level –direct quotes)

_____

_____

Section 10: Outcome

	Y	N
ICU admission		

	Y	N
HDB required		

	Y	N
BiPAP or CPAP		

	Y	N
Intubated		

	D/C	Died
Patient discharged or died?		

	Date	Time
Date and time of discharge or death		

	DOA	ED or SSU	Ward or ICU
Place of death			

Data extraction by:

Name _____ Date_____

Comments:

Oxygen in acute community acquired pneumonia

Name:_____ ___ INITALS(_____) SEX: __ DOB: ___/____/_____

ID number: _____ Hospital Number _____

INCLUSION/EXCLUSION CRITERIA CHECKLIST

- ☐ Aged 18 – 65 years
- ☐ Cough
- ☐ Respiratory rate ≥ 18/min
- ☐ At least one systemic feature (sweating, rigors and/or fever >37.8° C)
- ☐ No previous diagnosis of COPD/emphysema

Consent signed ***Yes / No***

OXYGEN PROTOCOL:

- ☐ **High flow**
- ☐ **Titrated**

TIME (MINS)	**Resp Rate** (Beats/min)	**Blood Pressure**	**Heart Rate** (Beats/min)	**CRB score**	**tCO2** (mmHg)
T = 0					
T = 20					
T = 40					
T = 60					

ABG (if done) at T= ____min: pH_____ PCO2_____ PO2_____ HCO3_____ SATS_____

tCO2 at time ABG taken _____ mmHg

ADMITTED TO HOSPITAL (circle): YES NO UNKNOWN

Withdrawn from study? State reason below:

_____

_____

_____

_____

_____

MEDICATION ADMINISTERED

TIME GIVEN (T=X)	DRUG	DOSE

Evidence of consolidation on chest X-ray report?

- ☐ **YES**
- ☐ **NO**
- ☐ **UNKNOWN**

Final diagnosis:

- ☐ **Pneumonia**
- ☐ **Bronchitis**
- ☐ **Non-pneumonic viral illness (including influenza)**
- ☐ **Heart failure**
- ☐ **Pulmonary embolism**
- ☐ **Other**

Oxygen in severe acute asthma

Name:_____ ___ INITALS(_____) SEX: __ DOB: ___/____/____

ID number: _____ Hospital Number _____

INCLUSION/EXCLUSION CRITERIA CHECKLIST

- ☐ Aged 18 – 65 years
- ☐ History of asthma
- ☐ Current exacerbation of asthma and FEV1 ≤ 50% predicted
- ☐ No previous diagnosis of COPD/emphysema

Consent signed ***Yes / No***

OXYGEN PROTOCOL:

- ☐ **High flow**
- ☐ **Titrated**

FEV1 at baseline _____L/min AGE____ HEIGHT_____ PREDICTED FEV1:_____L/min

FEV1 % PREDICTED: _____

TIME (MINS)	**RESP RATE** (Beats/min)	**HEART RATE** (Beats/min)	**FEV1** (L/min)	**tCO2** (mmHg)
T = 0				
T = 20				
T = 40				
T = 60				

ABG (if done) at T= ____min: pH_____ PCO2_____ PO2_____ HCO3_____ SATS_____

tCO2 at time ABG taken _____ mmHg

ADMITTED TO HOSPITAL (circle): YES NO UNKNOWN

Withdrawn from study? State reason below:

_____

_____

_____

_____

_____

MEDICATION ADMINISTERED

TIME GIVEN **(T=X)**	**DRUG**	**DOSE**

Time (minutes)	Oxygen Saturation (%)	O_2 (L/min)
0		
5		
10		
15		
20		
25		
30		
35		
40		
45		
50		
55		
60		

Oxygen and Obesity Hypoventilation Syndrome

Name_____ DOB_____

NHI_____ Study ID_____

Wt_____Kg Ht_____cm BMI_____

Screening

O2 sats_____% tCO2_____mmHg

ABG (if known) PaO2_____mmHg PaCO2_____mmHg

Randomised Treatment

Visit	Date	Treatment A or B
1		
2		

Visit 1

	RR	tCO2	MV	Vd/Vt
Baseline				
20 minutes				

Visit 2

	RR	tCO2	MV	Vd/Vt
Baseline				
20 minutes				

Withdrawn from study? Y N

If Yes,

state reason, visit and time:_____

Investigator:_____

Date:_____

Participant Information Sheet

Full Study Title:

A COMPARISON OF HIGH FLOW VERSUS TITRATED OXYGEN THERAPY IN THE EMERGENCY DEPARTMENT TREATMENT OF RESPIRATORY DISORDERS

Introduction

You are invited to take part in a clinical research study. Please take the time to read this information sheet carefully to determine if the study is of interest to you. You may wish to discuss the information in this sheet with your family or whanau. Please ask us if you have any questions about the study. Your involvement in this study is voluntary and you have the right not to take part and to withdraw at any time.

Aim of the Study

It is currently standard treatment to prescribe high flow oxygen to people with severe asthma or pneumonia. However high flow oxygen may cause complications and it is now recognised that high flow oxygen can be detrimental to patients with emphysema. Few studies have looked at the use of high flow oxygen in asthma or pneumonia. An alternative regime is one where the amount of oxygen you receive is varied depending on the oxygen level in your blood (oxygen saturation). This can be measured by a probe which sits on your finger.

If you choose to participate in this study you will be randomly assigned to receive either high flow oxygen or have the flow of oxygen varied according to your oxygen saturation. During this study and throughout your admission you will receive the optimal treatment for your medical condition.

Where will the study be conducted?

The study will be conducted in the Emergency Department of Wellington Hospital, Riddiford Street, Wellington.

What tests and procedures will be carried out?

Once you have been randomised to either high flow or variable flow oxygen therapy, you will receive oxygen for 1 hour. During the 1 hour of the study you will have the following measurements made.

Carbon dioxide

Carbon dioxide is a waste gas produced by the body and it sometimes increases when people have problems breathing. It is measured with a device that attaches to the earlobe. It is painless.

Pulse oximetry

This is a test to measure the percentage of your blood that is saturated with oxygen (oxygen saturations). It involves wearing a probe on your finger for the duration of the 1 hour period. This will be monitored closely by the doctor and nurses looking after you. If you have been assigned to the variable oxygen regime, it is this test that will determine how much oxygen you need to be given. The probe simply clips on to your finger and does not hurt at all.

Respiratory rate, pulse and blood pressure

Your doctor or nurse will measure your rate of breathing, pulse rate and blood pressure throughout the study.

Forced expiratory volume in one second (FEV_1)

We will measure how well your lungs are working by asking you to blow into a machine as hard as you can. This enables us to assess how much air you can breathe out in one second and is a measure of how well your lungs are working.

These tests are the same ones you would receive if you were not participating in the study.

Possible Risks and Discomforts

You will receive optimal care for your condition while you are in the study, including any blood tests and x-rays that may be required. The extra tests done as part of the study are painless and do not present a risk to you.

Possible Benefits

The benefits to you of participating in this study are that you will be very closely monitored by an experienced doctor for the duration of the study. The level of monitoring will be more intensive than you would otherwise receive.

You will be contributing valuable information to an important study that may change the way we treat patients with asthma and pneumonia.

Alternative Therapy

You will remain on your usual medication during this study. Your medical care will not be compromised in any way by your participation in the study.

Participant Rights and Study Withdrawal

Participation in this study is entirely voluntary and you do not have to take part. Your decision whether or not to participate will not affect your health care in any way or your future relations with the hospital. If you agree to participate, you may withdraw from the study at any time. If you refuse to participate or if you choose to withdraw (at any time) this will not affect your health care or any benefits to which you are otherwise entitled. The study doctor, the sponsor or a government health authority may terminate your participation at any time.

Termination of Patient's Study Participation

Your participation in the study may be stopped for any of the following reasons:

- If you don't follow the investigator's instructions.

- The investigator decides it is in the best interest of your health and welfare to discontinue.

Compensation for Injury

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.

Confidentiality and Data Privacy

If you decide to participate in the study, the study doctor and MRINZ staff will collect medical and personal information about you as part of doing the study.

By agreeing to take part in this research, you will allow your medical information and results to be seen by people who check that the research was done properly.

Ethical Guidelines

This study has been reviewed and approved by the Central Ethics Committee in Wellington.

Patient's Rights

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate at telephone number: 0800 423 638.

Contact

If you have any questions about the study you can contact one of the study doctors:

Professor Richard Beasley

Telephone: 04-385 5999, pager 6794

Fax: 04-385 5550

Richard.Beasley@ccdhb.org.nz

Dr Kyle Perrin

Telephone: 04 4729120

Fax: 04 4729224

kyle.perrin@mrinz.ac.nz

Participant Information Sheet

Full Study Title:

A Study To Investigate The Effects Of Hyperoxia On Carbon Dioxide Levels And Ventilation In Patients With Obesity Hypoventilation Syndrome

Short Study Title:

A Study To Investigate The Effects Of Oxygen In Obesity Hypoventilation Syndrome

Introduction

You are invited to take part in a clinical research study. Please take the time to read this information sheet carefully to determine if the study is of interest to you. You may wish to discuss the information in this sheet with your family or whanau. Please ask us if you have any questions about the study. Your involvement in this study is voluntary and you have the right not to take part and to withdraw at any time.

Aim of the Study

It is currently standard treatment to administer high flow oxygen to patients with low levels of oxygen with obesity hypoventilation syndrome. However high flow oxygen may cause complications and it is now well recognised that this practice can be detrimental to patients with emphysema. To date, no studies have investigated the effects of high flow oxygen in patients with known or suspected obesity hypoventilation syndrome.

Where will the study be conducted?

The study will be conducted at the Medical Research Institute of New Zealand, Bowen

Hospital, Crofton Downs.

What tests and procedures will be carried out?

You will be asked to breathe through a mouthpiece for 20-25 minutes. This will be done in a comfortable, seated position. Oxygen will be delivered via the mouthpiece, but this will be no different from breathing air.

Carbon dioxide and Oxygen saturations

Carbon dioxide is a waste gas produced by the body and it sometimes increases when people have problems breathing. It is measured with a device (called a probe) that attaches to the earlobe. The device is painless. Oxygen saturations measure the percentage of your blood which is saturated with oxygen. These are also measured by the probe on your earlobe.

Forced expiratory volume in one second (FEV_1)

We will measure how well your lungs are working by asking you to blow into a machine as hard as you can. This enables us to assess how much air you can breathe out in one second and is a measure of how well your lungs are working.

Measurements of ventilation

We will also measure your tidal volume (the amount of air going in and out of your lungs) as well as your "dead space" (the amount of air that is inhaled, but does not take part in gas exchange). These measurements will be done by an experienced respiratory scientist whilst you are breathing through the mouthpiece, and you will not be aware that they are being taken.

What are the Possible Risks and Discomforts?

The oxygen delivered may cause a rise in your carbon dioxide levels. If the levels become too high, the oxygen will be stopped.

What are the Possible Benefits

You will be contributing valuable information to an important study that may change the way we treat patients with asthma and obesity hypoventilation syndrome.

Is there an Alternative to Participating?

You have the choice not to take part in this study. If you do decide to take part, you will remain on your usual medication during this study.

Will I have to Cost Me Anything to Participate?

Participation in this study is free; however, you may have travel expenses to get to Bowen Hospital and these will be reimbursed.

Participant Rights and Study Withdrawal

Participation in this study is entirely voluntary and you do not have to take part. Your decision whether or not to participate will not affect your health care in any way or your future relations with the hospital. If you agree to participate, you may withdraw from the study at any time. If you refuse to participate or if you choose to withdraw (at any time) this will not affect your health care or any benefits to which you are otherwise entitled. The study doctor, the sponsor or a government health authority may terminate your participation at any time.

Termination of Patient's Study Participation

Your participation in the study may be stopped for any of the following reasons:

- If you don't follow the study doctor's instructions.
- The study doctor decides it is in the best interest of your health and welfare to discontinue.

Compensation for Injury

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.

Confidentiality and Data Privacy

If you decide to participate in the study, the study doctor and MRINZ staff will collect medical and personal information about you as part of doing the study.

By agreeing to take part in this research, you will allow your medical information and results to be seen by people who check that the research was done properly.

No material which could personally identify you will be used in any reports on this study. Your subject data will be identified by a code number.

Ethical Guidelines

This study has been reviewed and approved by the Central Ethics Regional Committee in Wellington.

Patient's Rights

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate at telephone number: 0800 423 638.

Contact

If you have any questions about the study you can contact one of the study doctors:

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Telephone: 04-385 5999, pager 6794

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Richard.Beasley@ccdhb.org.nz

Dr Meme Wijesinghe

Telephone: 04 4729110 or 021 024 777 30

Fax: 04 4729224

Meme.wijesinghe@mrinz.ac.nz

Acute Pneumonia and High Flow Oxygen

Full Title

A randomised controlled trial of high flow versus titrated oxygen therapy in the emergency department management of patients with community acquired pneumonia.

Methods

Inclusion criteria:

1. Age 16-75 years
2. Cough
3. At least one systemic feature (sweating, rigors and/or fever >37.8° C)
4. Respiratory Rate >18 breaths/min

Exclusion criteria:

1. Respiratory failure requiring mechanical ventilation
2. Diagnosis of COPD/emphysema
3. Acute ECG changes suggesting ischaemia
4. Suspected neutropaenic sepsis
5. Known or suspected chronic hypercapnic respiratory failure as a result of any of the following disorders:
    - Neuromuscular disease
    - Chest wall disease
    - Obesity hypoventilation syndrome

Intervention:

Patients will be randomly assigned to receive one of two oxygen regimes for 1 hour:

1. Continuous high flow oxygen (8L/min via Hudson mask)
2. Oxygen titrated to achieve an oxygen saturation of 93-95% via nasal prongs or Hudson mask as required. See oxygen titration protocol below.

(The clinical assessment and management of the patient for the time they are under the trial protocol lies with the attending research registrar. At the end of the trial period the patient's management is handed over to an E.D. doctor. The research registrars have full staff status

and are working as E.D. doctors under the clinical supervision of the duty E.D. consultant for the purposes of this trial).

Primary outcome variables:

1. Proportion of patients with an increase in $PaCO_2 \geq 4$mmHg at 1hour

Secondary outcome variables:

1. Proportion of patients with a $PaCO_2 \geq 38$mmHg and an increase of ≥ 4mmHg at 1hour
2. Mean change in respiratory rate and heart rate
3. Mean change in $PaCO_2$
4. Need for hospital admission
5. Combined primary endpoint with asthma/oxygen study

Detailed study protocol:

1. The on duty triage nurse will notify the on-duty/on-call research registrar via a designated cell phone when any patient presents to the emergency department between 0800 and 1700 with symptoms of a chest infection or suspected pneumonia (this includes patients who self-present, arrivals via ambulance and patients referred for assessment by the medical registrar).
2. If the patient meets the above inclusion criteria, the trial is discussed with the patient and the short consent form signed (the long information sheet and consent will be read and signed at an appropriate time during the trial period).
3. If the patients oxygen saturations are >92% whilst breathing room air, they will remain off oxygen for at least 10 minutes, If the saturations are <92%, titrated oxygen will be commenced according to the protocol below.
4. The patient is randomised and an initial transcutaneous CO2 (TCO2) level is recorded (Time = 0) and the oxygen protocol is started.
5. At 20 minute intervals oxygen saturations, TCO2 level and CRB score will be recorded. The final TCO2 recording is made at Time=60
6. If a patient requires any nebulised medication, those randomised to the titrated oxygen group will have them driven with room air while continuing with oxygen via nasal prongs (if required). Patients in the high flow oxygen group will continue to receive 8l/min of oxygen through the nebuliser.
7. Patients will be removed from the trial if they require more than 8l/min of oxygen via a Hudson Mask to maintain oxygen saturations above 90%
8. Patients will receive the usual investigations including a CXR, blood tests and arterial blood gases where indicated.
9. If the CRB score is ≥2 at any time, the ED consultant will be notified and decide if the patient should continue in the trial
10. The treating clinician can withdraw the patient from the trial at any time if there are any other clinical concerns

Treatment Protocol

1. History and physical examination. Calculation of the CRB score:

   Confusion: new mental confusion defined as an Abbreviated Mental Test score of 8 or less

   Respiratory rate: raised ≥ 30/min

   Blood pressure: Systolic <90mmHg *and/or* diastolic ≤ 60mmHg

   65 Aged 65 or over

(1 feature present = non-severe CAP, 2 or more features present = severe CAP)

2. If the clinical suspicion of community acquired pneumonia is high, empirical antibiotic treatment will be administered as follows (BTS guidelines):

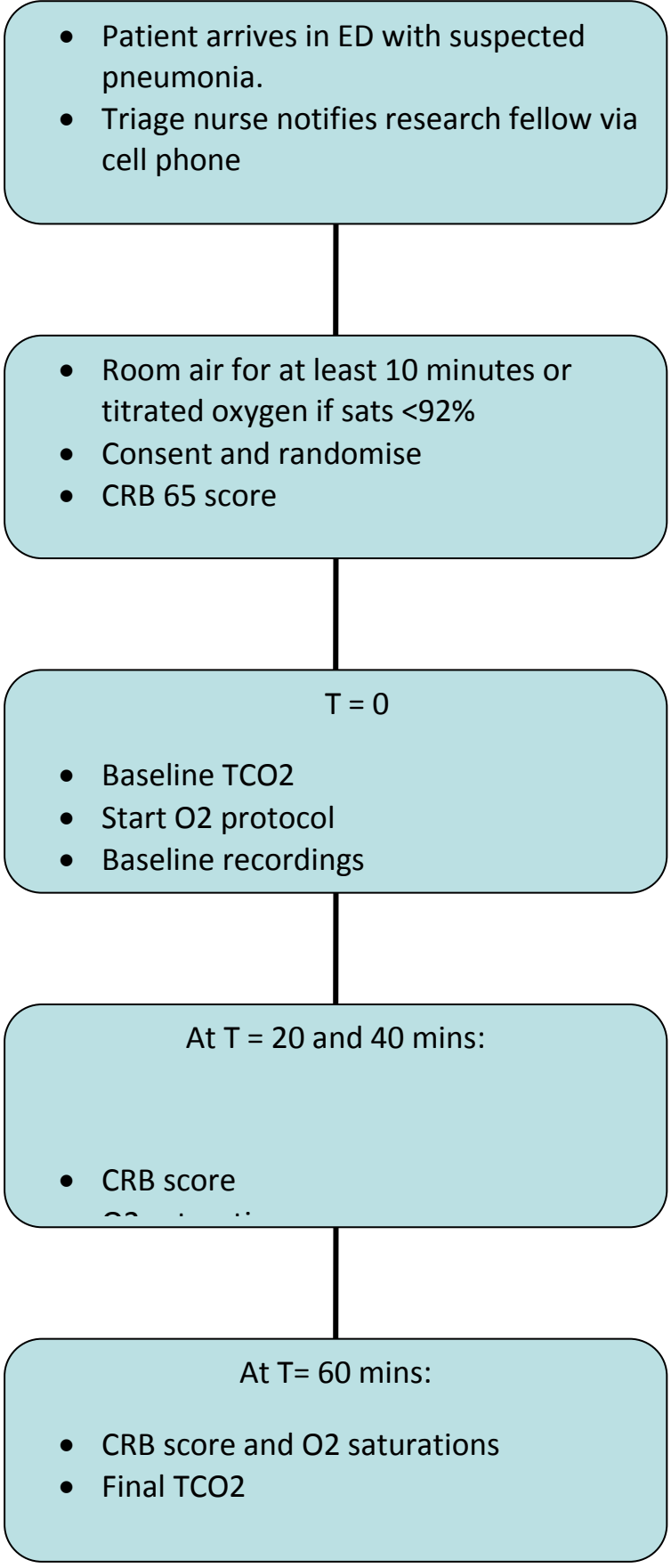
Severity	Antibiotic Regimen
Non-severe (previously untreated in community)	Amoxycillin 500mg-1.0g tds po
Non-severe	Amoxycillin 500mg-1.0g tds po plus erythromycin 500mg qds po Or if intravenous required: Co-amoxiclav 1.2g iv qds plus erythromycin 500mg qds iv
Severe	Cefuroxime 1.5g tds iv plus erythromycin 500mg qds iv

3. All patients will have a chest x-ray. Other therapies (intravenous fluids and analgesia) are administered at the discretion of the attending registrar.

Oxygen Dose Adjustment for the titrated oxygen group

Oxygen Saturation	**Dose Adjustment L/min**	**Next Saturation Check**
> 98%	Reduce by 2 L	In 5 minutes
96% - 97%	Reduce by 1L	In 5 minutes
93% - 95%	No change	In 5 minutes
91% - 92%	Increase by 1L	In 5 minutes

89% - 90%	Increase by 2L	In 5 minutes
86% - 88%	Increase by 4L	In 5 minutes
<86% withdraw		


Patient arrives in ED with suspected pneumonia.
Triage nurse notifies research fellow via cell phone
Room air for at least 10 minutes or titrated oxygen if sats <92%
Consent and randomise
CRB 65 score
T = 0
Baseline TCO2
Start O2 protocol
Baseline recordings
At T = 20 and 40 mins:
CRB score
At T= 60 mins:
CRB score and O2 saturations
Final TCO2

Severe Asthma and High Flow Oxygen

Full Title

A randomised controlled trial of high flow versus titrated oxygen therapy in the emergency department management of patients with severe asthma.

Methods

Inclusion criteria:

1. History of asthma
2. Presentation to the emergency department with an acute exacerbation of asthma
3. Age 16-65 years
4. FEV1 ≤ 50% predicted

Exclusion criteria:

6. Diagnosis of COPD/emphysema
7. Asthma attack requiring mechanical ventilation
8. Patient unconscious, unable to speak or unable to perform spirometry on arrival
9. Known or suspected chronic hypercapnic respiratory failure as a result of any of the following disorders:
    - Neuromuscular disease
    - Chest wall disease
    - Obesity hypoventilation syndrome

Intervention:

Patients will be randomly assigned to receive one of two oxygen regimes for 1 hour:

3. Continuous high flow oxygen (8L/min via Hudson mask)
4. Oxygen titrated to achieve an oxygen saturation of 93-95% via nasal prongs or Hudson mask as required. See oxygen titration protocol below.

(The clinical assessment and management of the patient for the time they are under the trial protocol lies with the attending research registrar. At the end of the trial period the patient's management is handed over to an E.D. doctor. The research registrars have full staff status and are working as E.D. doctors under the clinical supervision of the duty E.D. consultant for the purposes of this trial).

Primary outcome variables:

2. Proportion of patients with an increase in $PaCO_2 \geq 4$mmHg at 1hour

Secondary outcome variables:

6. Proportion of patients with a $PaCO_2 \geq 38$mmHg and an increase of ≥ 4mmHg at 1hour
7. Change in respiratory rate, heart rate, and FEV_1 during the treatment period
8. Mean change in $PaCO_2$
9. Need for hospital admission
10. Combined primary endpoint with pneumonia/oxygen study

Detailed study protocol:

11. The on duty triage nurse will notify the on-duty/on-call research registrar via a designated cell phone when any patient presents to the emergency department with acute asthma (this includes patients who self-present, arrivals via ambulance and patients referred to the medical registrar for assessment).
12. The research fellow will attend and obtain initial spirometry (if not already done by triage nurse).
13. If FEV1 < 50% predicted: the patient given 2.5mg salbutamol and 0.5mg ipratropium via air driven nebuliser. If the oxygen saturations are <92%, oxygen will be given via nasal prongs to achieve a saturation of 93-95% (see titration protocol below).
14. The trial is discussed with the patient and the short consent form signed (the long information sheet and consent will be read and signed at an appropriate time during the trial period).
15. The patient is randomised, and after at least 10 minutes of breathing room air or titrated oxygen if initially hypoxaemic, the transcutaneous CO2 (TCO2) level is recorded (Time = 0) and the oxygen protocol is started.
16. At 20 minute intervals FEV1, TCO2, respiratory rate, heart rate and oxygen saturations will be recorded. A questionnaire regarding recent beta-agonist use will be administered. The final TCO2 recording is made at Time=60.
17. Patients randomised to the titrated oxygen group will have all nebulised medications driven with room air while continuing with oxygen via nasal prongs (if required). Patients in the high flow oxygen group will continue to receive 8l/min of oxygen through the nebuliser.
18. Patients will receive the usual investigations including a CXR, blood tests and arterial blood gases where indicated.
19. Patients will be removed from the trial if they require more than 8l/min of oxygen via a Hudson Mask to maintain oxygen saturations above 90%
20. The treating clinician can withdraw the patient from the trial at any time if there are clinical concerns
21. The E.D. physician will be consulted regarding any patient with:
    - An FEV1 that decreases despite treatment
    - An FEV1 < 30% that fails to increase despite treatment

- An initial PaCO2 above 45mmHg
- Saturations of less than 90% despite oxygen at 8L/min (withdraw from trial)

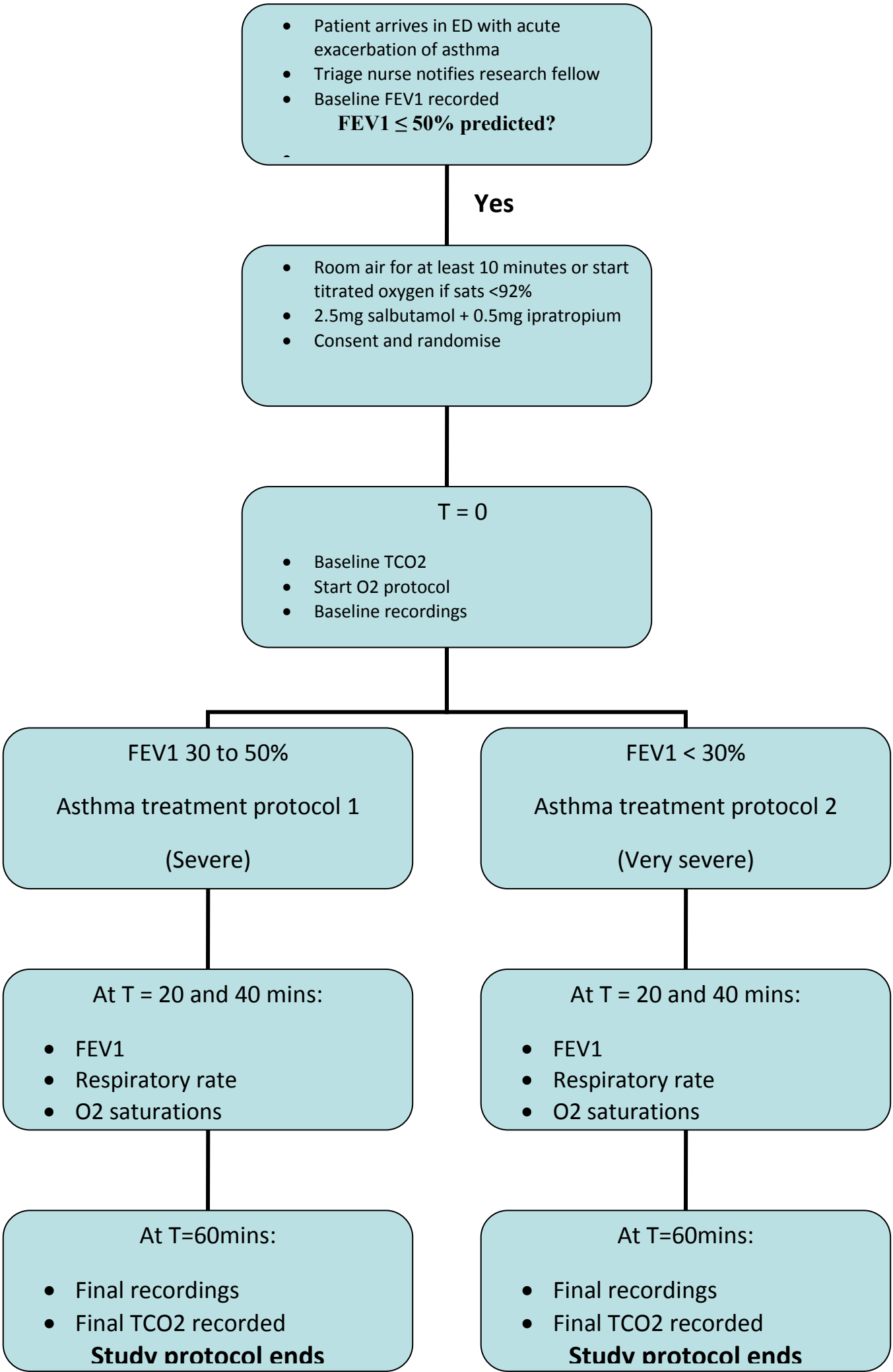
Treatment protocols:

1. Severe asthma (FEV1 30 to 50% predicted)
    - Salbutalmol 2.5mg and ipratropium bromide 0.5mg via nebuliser on arrival
    - Salbutamol 2.5mg via nebuliser every 20 minutes
    - Prednisone 40mg P.O.

2. Very severe asthma (FEV1 < 30% predicted)
    - Salbutalmol 2.5mg and ipratropium bromide 0.5mg via nebuliser on arrival
    - Salbutamol 2.5mg via nebuliser every 15 minutes
    - Prednisone 40mg P.O. and hydrocortisone 100mg I.V.
    - Magnesium sulphate 2g in 100ml normal saline over 20min

Oxygen Dose Adjustment for the titrated oxygen group

Oxygen Saturation	**Dose Adjustment L/min**	**Next Saturation Check**
> 98%	Reduce by 2 L	In 5 minutes
96% - 98%	Reduce by 1L	In 5 minutes
93% - 95%	No change	In 5 minutes
91% - 92%	Increase by 1L	In 5 minutes
89% - 90%	Increase by 2L	In 5 minutes
86% - 88%	Increase by 4L	In 5 minutes
<86% withdraw		


Patient arrives in ED with acute exacerbation of asthma
Triage nurse notifies research fellow
Baseline FEV1 recorded
FEV1 ≤ 50% predicted?
Yes
Room air for at least 10 minutes or start titrated oxygen if sats <92%
2.5mg salbutamol + 0.5mg ipratropium
Consent and randomise
T = 0
Baseline TCO2
Start O2 protocol
Baseline recordings
FEV1 30 to 50%
Asthma treatment protocol 1
(Severe)
FEV1 < 30%
Asthma treatment protocol 2
(Very severe)
At T = 20 and 40 mins:
FEV1
Respiratory rate
O2 saturations
At T = 20 and 40 mins:
FEV1
Respiratory rate
O2 saturations
At T=60mins:
Final recordings
Final TCO2 recorded
Study protocol ends
At T=60mins:
Final recordings
Final TCO2 recorded
Study protocol ends

Obesity Hypoventilation Syndrome and High Flow Oxygen

Full Title

A Randomised Double-Blind Cross-Over Study To Investigate The Effects Of Hyperoxia On Carbon Dioxide Levels And Ventilation In Patients With Obesity Hypoventilation Syndrome.

Methods

Inclusion criteria:

1. Patients with a new diagnosis of Obesity Hypoventilation Syndrome:
    - BMI >30kg/m2,
    - Daytime hypercapnia (pCO2 >45mmHg)

Exclusion criteria:

1. Diagnosis of chronic airflow obstruction post-bronchodilator FEV1 to FVC ratio <0.7 and FEV1 <80% predicted and > 10 pack year smoking history

2. Patients already receiving treatment with CPAP or non-invasive positive pressure ventilation

Intervention

24 patients will be recruited

Patients will attend the laboratory on two occasions within 7 days.

Patients will have the following measured as baseline on room air whilst breathing into a pneumotachygraph via a mouthpiece:

- Heart rate and respiratory rate
- Transcutaneous carbon dioxide levels and oxygen saturations
- Minute ventilation
- Dead space to tidal volume ratio

The patient will be randomized, in a double-blind fashion, to receive 100% oxygen or room air delivered for 20 minutes.

The following measurements will be made during the last 2 minutes of each treatment period

- Heart rate, respiratory rate and oxygen saturations
- Transcutaneous carbon dioxide levels
- Minute ventilation
- Dead space to tidal volume ratio

Oxygen saturations, transcutaneous carbon dioxide and heart rate will be monitored continuously

On the patient's second visit, the study protocol will be repeated with the other gas.

Outcome Measures

Primary:

1. Change in PaCO2 from baseline

Secondary Outcome Measures:

1. Change in minute ventilation
2. Change in dead space to tidal volume ratio
3. Change in PaCO2 from baseline of ≥ 4mmHg

Health and Disability Ethics Committees

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
PO Box 5013
Wellington
Phone (04) 496 2405
Fax (04) 496 2191

18 January 2007

Prof. Richard Beasley
Dept of Respiratory Medicine
Wellington Hospital
Private Bag 7902
Wellington

Dear Richard

CEN/06/11/101 - Comparison of high flow versus titrated oxygen therapy in the emergency department management of respiratory disorders
Prof. Richard Beasley

The above study has been given ethical approval by the **Central Regional** Ethics Committee.

Approved Documents
Participant Short Information Sheet and Consent Form version 1, dated 17 May 2006
Participant Information Sheet and Participant Informed Consent Form, Version 1, dated 12 May 2006

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until **June 2008**. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator's responsibility to forward a progress report covering all sites prior to ethical review of the project in **January 2008**. The report form is available on http://www.newhealth.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:

- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator or sponsor breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. If the adverse event is local and does not have the sponsor's report attached, an opinion on whether the event is thought to be related to the study should be given along with any other pertinent information. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

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

Yours sincerely

Claire Yendoll
Central Ethics Committee Administrator
Email: claire_yendoll@moh.govt.nz

Health and Disability Ethics Committees

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
PO Box 5013
Wellington
Phone (04) 496 2405
Fax (04) 496 2191

18 December 2007

Prof Richard Beasley
Medical Research Institute of New Zealand
3rd Floor, 99 The Terrace
PO Box 10055
Wellington

Dear Prof Beasley

CEN/07/10/068
A study to investigate the effects of hyperoxia on carbon dioxide levels and ventilation in patients with obesity hypoventilation syndrome
Prof Richard Beasley, Dr. Kyle Perrin, Dr. Mark Weatherall, Mr Mathew Williams, Dr Meme Wijesinghe
Medical Research Institute of New Zealand

The above study has been given ethical approval by the **Central Regional** Ethics Committee. A list of members of this committee is attached.

Approved Documents
- **Protocol Oxygen & OHS Study Version 1, dated 20 September 2007**.
- Participant Information Sheet Version 2, dated 29 November 2007
- Participant Consent Form Version 2, dated 29 November 2007

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until **21 November 2008**. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator's responsibility to forward a progress report covering all sites prior to ethical review of the project in **18 December 2008**. The report form is available on http://www.newhealth.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:
- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

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Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

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

Yours sincerely

Jiska van Bruggen
Central Regional Ethics Committee Administrator

Email: jiska_van_bruggen@moh.govt.nz

Health and Disability Ethics Committees

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
PO Box 5013
Wellington
Phone (04) 496 2405
Fax (04) 496 2191

18 December 2007

Dear Prof Beasley

CEN/07/10/068

A study to investigate the effects of hyperoxia on carbon dioxide levels and ventilation in patients with obesity hypoventilation syndrome

Prof Richard Beasley, Dr. Kyle Perrin, Dr. Mark Weatherall, Mr Mathew Williams, Dr Meme Wijesinghe
Medical Research Institute of New Zealand

Central Regional Ethics Committee Members		
Name	**Member category**	**Term (Appointed)**
Trevor James (Chair)	Community representative	3 years (Dec 04)
Helen Colebrook	Lawyer	3 years (Dec 06)
Matire Harwood	Biostatistician	3 years (Dec 04)
John Kleinsman	Ethicist	3 years (Dec 04)
Elaine Papps	Health practitioner	3 years (Dec 06)
Jacqueline Virtue	Health practitioner	3 years (Dec 04)
Joe Asghar	Pharmacist/pharmacologist	3 years (Dec 06)
Maureen Holdaway	Researcher	2 years (Dec 06)
Guy Taylor	Researcher	3 years (Dec 04)
Jacqueline Renouf	Consumer Representative	3 years (July 05)
Dianne Wepa	Consumer Representative	3 years (Dec 04)
Anne Tuffin	Community Representative	3 years (Dec 06)

Bohr Equation

Expired CO_2 = inspired CO_2 + CO_2 given out by lungs

Or: $F_E \times V_T = (F_I \times V_T) + (F_A \times V_A)$

Where F_E = fractional concentration of CO_2 in expired gas

F_I= fractional concentration of CO2 in inspired gas

F_A = fractional concentration of CO2 in alveolar gas

V_T =tidal volume

V_A = alveolar component of tidal volume

Since inspired CO2 is negligible, it may be ignored:

I.e. $F_E \times V_T = F_A \times V_A$

But $V_A = V_T - V_D$

Therefore $F_E \times V_T = F_A \times (V_T - V_D)$

$= (F_A \times V_T) - (F_A \times V_D)$

Or: $F_A \times V_D = (F_A \times V_T) - (F_E \times V_T)$

$= V_T (F_A - F_E)$

Therefore $\frac{VD}{VT} = \frac{FA-FE}{FA}$

Since partial pressure is proportional to concentration:

$$\frac{VD}{VT} = \frac{PACO2 - PECO2}{PAO2}$$

Where PAO2= alveolar partial pressure of CO2

PECO2=mixed expired partial pressure of CO2

Since alveolar PCO2 approximately equals arterial PCO2,

$$\frac{VD}{VT} = \frac{PaCO2 - PECO2}{PaO2}$$

Where PaO2= arterial partial pressure of CO2