High concentration oxygen therapy in acute respiratory disease

---

A thesis submitted in partial fulfilment

of the requirements for the Degree of

Doctor of Philosophy in Health Sciences

at the University of Canterbury

Kyle Perrin

University of Canterbury

2010

Table of Contents

List of Figures

List of Tables

Acknowledgements

First I would like to acknowledge financial support from the Health Research Council of New Zealand in the form of a Clinical Research Training Fellowship, and thanks also to the New Zealand branch of the Royal Australasian College of Physicians for a grant towards equipment costs.

I had a great deal of help from many people over the time I was working on this thesis.

I want to thank the whole team at the Medical Research Institute of New Zealand, including Denise Fabian, Alison Pritchard, Maureen Stretch, Pip Shirtcliffe, Justin Travers and Tanya Baker. I am particularly indebted to the MRINZ research fellows who worked with us over recent years and supported these studies. Randomised controlled trials are a major undertaking and I couldn't have finished this work without them. So, in no particular order, many thanks to: Bridgette Healy, Kirsten Wadsworth, Jen Clay, Richard Bowditch, Llifon Edwards, Kate James, Sue Bibby, and Kelli Hart. Special thanks to Meme Wijesinghe and Mathew Williams.

For statistical matters I was very fortunate to have the invaluable support and advice of Mark Weatherall, who was unfailingly helpful and reliable from the earliest stages of study planning to the final analyses. Any remaining statistical errors are my own.

Thanks also to my family for their support, and especially to my wife Beth, who writes better than I ever will. She proof read the whole thesis, improving it significantly, and even managed to explain to me what the passive voice was. All remaining errors in the thesis are mine.

Finally thanks must go to my supervisors Professor Ian Town and Professor Richard Beasley. In particular I am deeply indebted to Richard, not only for supervising this thesis, but for being a great teacher, mentor and colleague for over 10 years. I have learnt an enormous amount from him over that time; his passion and excitement for clinical medicine and research continues to be a source of inspiration.

Abstract

Uncontrolled oxygen is often administered to breathless patients regardless of whether hypoxaemia is present. In acute exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) this may result in carbon dioxide (CO_2) retention and worsening respiratory failure in some patients. In AECOPD the main mechanism is the release of hypoxic pulmonary vasoconstriction and an increase in the physiological dead space to tidal volume ratio (V_D/V_T). Acute asthma and pneumonia have features in common with AECOPD, namely significant ventilation – perfusion mismatch; and there is the potential for CO_2 retention to occur if uncontrolled high concentration oxygen is given. There have been no randomised controlled trials of oxygen therapy in pneumonia and only one in asthma. The potential mechanisms of any change in arterial CO_2 that may occur with oxygen therapy in respiratory disorders other than COPD remain uncertain.

This thesis presents work from three clinical studies. In two randomised controlled trials, high concentration oxygen was compared to titrated oxygen therapy in patients with either acute severe asthma and suspected community acquired pneumonia. Oxygen was administered for one hour in conjunction with standard medical treatment. Transcutaneous CO_2 ($PtCO_2$) was continuously monitored and the number of patients with pre-specified increases in $PtCO_2$ were calculated. The proportion of patients with a rise in $PtCO_2$ ≥4 mmHg was significantly higher in the high concentration oxygen groups of both studies. In the pneumonia study 36/72 (50.0%) vs 11/75 (14.7%) met this endpoint, with a relative risk of 3.4 (95% CI 1.9 to 6.2; P <0.001), and in the asthma

study 22/50 (44%) vs 10/53 (18.9%) met this endpoint, with a relative risk of 2.3 (95% CI 1.2 to 4.3; P=0.009). Similarly, a rise in $PtCO_2$ ≥8 mmHg was more common with high concentration oxygen. In the pneumonia study 11/72 (15.3%) vs 2/75 (2.7%) of patients met this endpoint, with a relative risk of 5.7 (95% CI 1.3 to 25.0; P=0.007), and 10/50 (20%) vs 3/53 (5.7%) of asthma patients met this endpoint, with a relative risk of 3.6 (95% CI 1.1 to 12.3; P=0.03). A third study measured the physiological response to 20 minutes of 100% oxygen in chronic severe asthma, with comparison to a group of negative controls (normal subjects) and positive controls (COPD patients). There was a significant rise in $PtCO_2$ of similar magnitude in the asthma and COPD groups compared with the normal controls. The mechanism of the $PtCO_2$ rise was similar in asthma and COPD, with an increase in V_D/V_T but no change in minute ventilation.

These studies demonstrate than uncontrolled high concentration oxygen has the potential to cause CO_2 retention in respiratory diseases other than COPD, and that in asthma the mechanism of hypercapnia is similar to that in AECOPD. In acute asthma and community-acquired pneumonia oxygen should be administered only to those patients with evidence of arterial hypoxaemia in a dose that relieves hypoxaemia without causing hyperoxia, thereby achieving the benefits of oxygen therapy while reducing the potential for harm.

Abbreviations and symbols

Abbreviation/Symbol	**Definition**
ABG	Arterial Blood Gas
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
COPD	Chronic Obstructive Pulmonary Disease
CSF	Cerebrospinal fluid
ED	Emergency Department
EFL	Expiratory Flow Limitation
f	Respiratory frequency
F_ACO_2	Fraction of alveolar CO_2
F_ICO_2	Fraction of inspired CO_2
F_ECO_2	Fraction of expired CO_2
F_IO_2	Fraction of inspired O_2
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
HPV	Hypoxic Pulmonary Vasoconstriction
IC	Inspiratory Capacity
ICC	Intra-class Coefficient
MIGET	Multiple Inert Gas Elimination Technique
MV	Minute Ventilation
$P_{0.1}$	Inspiratory Mouth Occlusion Pressure

P_aCO_2	Arterial Partial Pressure of CO_2
P_ACO_2	Alveolar Partial Pressure of CO_2
P_ECO_2	Mixed expired CO_2
$PtCO_2$	Transcutaneous CO_2
PCO_2RT	CO_2 Recruitment Threshold
P_aO_2	Arterial Partial Pressure of O_2
P_ACO_2	Alveolar Partial Pressure of O_2
P_VCO_2	Mixed Venous Partial Pressure of CO_2
PEFR	Peak Expiratory Flow Rate
$\dot{Q}$	Perfusion
$\dot{V}$	Ventilation
V_A	Alveolar Tidal Volume
$V_{D\ (Alv)}$	Alveolar Dead Space Volume
$V_{D\ (Anat)}$	Anatomical Dead Space Volume
$V_{D\ (Phys)}$	Physiological Dead Space Volume
V_T	Tidal Volume
$\dot{V}\ CO_2$	Carbon Dioxide Production
$\dot{V}_A$	Alveolar Ventilation
$\dot{V}/\dot{Q}$	Ventilation Perfusion Ratio
V_D/V_T	Physiological Dead Space to Tidal Volume Ratio

Chapter 1: Introduction

1.1 The current approach to acute oxygen therapy

Of the many drugs administered on a daily basis to acutely unwell patients around the world, perhaps none is as over-prescribed as oxygen. Its primary indication, the treatment of arterial hypoxaemia, remains important, but the use of uncontrolled high flow oxygen in emergency care has become almost ubiquitous. Many health care workers considered it to be first line treatment for a variety of conditions ranging from sepsis, shock, chest pain and breathlessness, to childbirth, routine surgery and anxiety. Because it is perceived to be beneficial and without risk, oxygen therapy is often uncontrolled; that is, delivered in high concentration regardless of the presence or absence of hypoxaemia.

In the past, when arterial oxygenation could only be measured in the laboratory, it may have been reasonable to routinely administer oxygen to all breathless patients in case they were hypoxaemic. Now there is a reliable, accurate and non-invasive means of continuously assessing blood oxygenation, the pulse oximeter, which has been in use for decades. It should be a simple bedside process to assess the patient's requirement for oxygen with oximetry, and to monitor their response so that only the amount required to relieve hypoxia is given.

During the course of my medical training I often encountered patients receiving oxygen for no obvious reason, and found that on removing the oxygen mask that it either was not required or that the flow could be significantly reduced. How did this attitude to uncontrolled oxygen therapy come about? In part it may stem from the wide availability of supplementary oxygen in acute care settings over many decades. It is so familiar, and used with such regularity, that it is often not considered to be a drug, with risks, benefits and side effects.

There are also some myths associated with oxygen therapy which may have served to reinforce its widespread inappropriate use. First, it is widely believed to relieve breathlessness when the patient is not hypoxic, which is not the case (Clemens & Klaschik, 2007; Gallagher & Roberts, 2004; Philip et al., 2006). Second, there is a feeling among some emergency workers that if a patient has an acute cardiac or respiratory condition placing them at risk of hypoxia, that administering oxygen at high concentration will perhaps protect them from the effects of falling oxygenation if they should deteriorate. This rationale is flawed, for reasons which will be outlined Chapter 9. Third, there is a belief among some health care workers that even if a patient is not hypoxaemic, oxygen delivery to tissues may be increased by high concentration oxygen. This is incorrect, as can be seen by consideration of the oxy-haemoglobin dissociation curve in the next chapter. Finally, there may be an expectation among both the general public and health care workers that oxygen simply forms part of the standard treatment of a “sick” patient.

The studies in this thesis were prompted by my clinical experience, a review of the existing literature, and on consideration of whether this practice of routine oxygen administration was of benefit or harm to patients.

1.2 Uncontrolled oxygen in non-respiratory disease

Is there evidence that routine use of uncontrolled oxygen therapy is of benefit in the various situations in which it is currently used? The simple answer, for the majority of medical conditions, is no. On the contrary, the potential risks of uncontrolled oxygen have been described by a number of researchers since the mid 20th century (Daly & Behnke, 1963; Russek, Regan, & Naegle, 1950; Thomas, Malmcrona, & Shillingford, 1965).

In the field of cardiovascular medicine, oxygen has been routinely used as a first line treatment in ischaemic heart disease for decades, and this approach persists today (Antman et al., 2004; Van de Werf et al., 2003). The rationale is that in a patient with cardiac ischaemia, increasing the blood oxygen content might increase the supply of oxygen to hypoxic myocardium (Boland, 1940; Boothby, Mayo, & Lovelace, 1939). However, the administration of oxygen to non-hypoxaemic patients only increases the oxygen content of the blood by a small amount, and this is countered by a 20% fall in coronary blood flow induced by hyperoxia (Farquhar et al., 2009; McNulty et al., 2005). The net effect may be an overall reduction in oxygen delivery. High flow oxygen has also been shown to reduce cardiac output (Daly & Behnke, 1963), reduce cerebral (Kety &

Schmidt, 1948), retinal (Dollery, Hill, Mailer, & Ramalho, 1964) and renal blood flow (Aber, Harris, & Bishop, 1964) and increase peripheral vascular resistance (Kenmure, Murdoch, Beattie, Marshall, & Cameron, 1968).

There is only one randomised controlled trial comparing uncontrolled oxygen therapy to air in acute myocardial infarction. In this study the group receiving oxygen showed a non-significant three-fold increase in mortality. The oxygen group also had a significantly higher average cardiac enzyme level, suggestive of greater infarct size (Rawles & Kenmure, 1976). This study, done in 1976, has never been repeated; yet high flow oxygen continues to be given as standard treatment for acute myocardial infarction and is recommended by a number of international guidelines (Antman et al., 2004; Van de Werf et al., 2003).

This theme of continued oxygen use in the absence of benefit also appears in other fields of medicine. Recent evidence has emerged that the use of 100% oxygen in neonatal resuscitation results in higher mortality (Davis, Tan, O'Donnell, & Schulze, 2004), as well as being linked with retro-lental fibroplasia, a retinal disease of premature infants (Chow, Wright, & Sola, 2003). However, in contrast to the situation with myocardial infarction, guidelines in neonatology have been changed to reflect these recent findings (AHA, 2006). There are also studies which suggest that uncontrolled oxygen causes harm in the setting of acute stroke (Ronning & Guldvog, 1999), and in acute sepsis (Garner et al., 1989).

1.3 Uncontrolled oxygen in respiratory disease

What is the situation with regard to acute respiratory disease? As with the conditions discussed above, there is little evidence to show that routine uncontrolled oxygen is beneficial in the absence of hypoxaemia. There is however evidence of potential for harm in one common condition: acute exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD). Some patients with AECOPD develop increasing hypercapnia and worsening acidosis if uncontrolled oxygen therapy is administered. However, unlike cardiovascular disease, there is widespread awareness of this risk and it is perhaps the only acute medical illness where the dangers of uncontrolled oxygen are well recognised by most clinicians.

The pathophysiology of acute severe asthma has much in common with AECOPD, specifically the presence of widespread airflow obstruction, lung hyperinflation and ventilation-perfusion mismatch. If this is the case, why is there not the same caution with regard to uncontrolled oxygen therapy in acute severe asthma? First, the commonly held view of the main mechanism of carbon dioxide retention in AECOPD is incorrect. Most clinicians believe that worsening hypercapnia is due to oxygen administration suppressing the “hypoxic drive to breathe”, that it only occurs in patients with chronic CO_2 retention, and that it therefore does not occur in asthma. However, the main driver of oxygen-induced hypercapnia in AECOPD is the release of hypoxic pulmonary vasoconstriction and a resultant increase in physiological dead space, a mechanism that

could also operate in acute severe asthma. This concept will be addressed in detail in Chapter 3. Secondly, although CO_2 retention is less common in acute asthma compared to AECOPD (McFadden & Lyons, 1968; Tai & Read, 1967a), when it is present it is often thought to be solely due to the severity of the asthma exacerbation, rather than the uncontrolled oxygen treatment that these patients are almost invariably receiving.

These presumptions run contrary to preliminary evidence from two studies that suggest high concentration oxygen therapy may cause hypercapnia in acute severe asthma (Chien et al., 2000; G. J. Rodrigo, Rodriquez Verde, Peregalli, & Rodrigo, 2003). Similarly, there has been little research on oxygen therapy in community acquired pneumonia. Like asthma, this condition is associated with significant ventilation-perfusion mismatch and therefore potential harm from routine uncontrolled oxygen exists.

Rather than delivering uncontrolled high concentration oxygen to all patients regardless of hypoxaemia, an alternative approach is to titrate or adjust the flow of oxygen according to need. This is easily achieved in the emergency department and the ambulance with the widespread availability of pulse oximetry. Indeed, it is currently the standard of care for AECOPD (BTS, 2004), although studies show that guidelines are often not followed (Durrington, Flubacher, Ramsay, Howard, & Harrison, 2005; Joosten, Koh, Bu, Smallwood, & Irving, 2007; Plant, Owen, & Elliott, 2000).

Although there is widespread understanding of the need to control oxygen flow in AECOPD, the routine administration of high concentration oxygen in acute asthma and

pneumonia is thought to be not only safe but desirable ("British Guideline on the Management of Asthma," 2008; Hargreave, Dolovich, & Newhouse, 1990; Inwald, Roland, Kuitert, McKenzie, & Petros, 2001). There is no current evidence to support this approach. In fact, there is an urgent need to define the correct approach to oxygen use in these common and potentially life threatening disorders.

1.4 Thesis aim

The aim of this thesis is to investigate the physiological and clinical effects of uncontrolled high concentration oxygen in patients with acute severe asthma and acute pneumonia. Specifically it will address two questions:

1. Does the administration of uncontrolled high concentration oxygen increase arterial CO_2 tension (P_aCO_2) in asthma and pneumonia?
2. What is the mechanism of the increases in P_aCO_2 that occur?

The results will help to provide evidence based recommendations for the rational and safe use of oxygen therapy in these diseases.

1.5 Thesis outline

The background chapters begin with a summary of the history of oxygen, and then present aspects of respiratory physiology relevant to the research questions and methods in this thesis. This will include a discussion of pulmonary ventilation, gas exchange, hypoxic pulmonary vasoconstriction (HPV), and the concept of physiological dead space to tidal volume ratio (V_D/V_T).

Chapter 3 reviews the literature regarding the use of oxygen in AECOPD, particularly the mechanisms of CO_2 retention when high flow oxygen is delivered. A review of the pathophysiology of acute asthma and pneumonia follows, with an emphasis on gas exchange and CO_2 retention, and a comparison to the mechanisms in AECOPD. The chapter ends with a summary of the current evidence for oxygen use in these disorders and presents possible approaches to investigating the effects of oxygen therapy in asthma and pneumonia with a valid research methodology.

Chapters 4 and 5 describe the design and methodology of two randomised controlled trials comparing high concentration with titrated oxygen therapy in patients with severe asthma and pneumonia. The methodology of a third study based in the pulmonary function laboratory is described in Chapter 6. This work investigates the potential mechanisms of CO_2 retention in asthma. It compares the response to oxygen of patients with chronic severe asthma with a group of COPD patients (positive controls) and normal

subjects (negative controls). Chapter 7 describes the validation of the methods, in particular the use of transcutaneous carbon dioxide recordings as a measure of arterial carbon dioxide.

The results are presented in Chapter 8 and the final chapters comprise a discussion of the data, the practical implications of the results for the treatment of patients with acute asthma and pneumonia, and conclusions including recommendations for the use of oxygen in acute respiratory disease.

1.6 Definitions

For the purposes of the discussion in this thesis the following phrases are used, as there are no widely accepted definitions in the medical literature. Hyperoxia refers to an elevation of the arterial oxygen tension (P_aO_2) to levels above the normal physiological range of 80 – 100 mmHg. By implication, this generally occurs when oxygen is administered without regard to the patient's oxygen saturation level. The term "uncontrolled oxygen" in the context of this thesis refers to the administration of oxygen without titration, by any device, at flow rates high enough to result in hyperoxia. Uncontrolled oxygen is contrasted with titrated oxygen therapy; in this case the flow, and consequently concentration, is adjusted to relieve hypoxaemia without producing hyperoxia.

Although the terms “high flow oxygen” and “high concentration oxygen” are often used interchangeably, this can result in confusion. In the case of most commonly used oxygen delivery devices (nasal prongs, medium concentration masks, and non-rebreathing masks) increasing the flow of oxygen in litres per minute generally results in higher inspired concentrations of oxygen. However, in the case of Venturi masks, high oxygen flows are used but are diluted with room air by the mask to deliver a fixed, and usually low, oxygen concentration. In this thesis the term high concentration oxygen will be used, and refers to flow rates of oxygen resulting in high inspired oxygen concentrations. It should be noted that although high concentration oxygen therapy is often given in an uncontrolled fashion, the terms are not necessarily equivalent. In some critically ill patients with severe hypoxaemia, high concentrations of oxygen may be required to relieve it, and in that case would be considered appropriate.

Chapter 2: Background history and respiratory physiology

The introductory chapter presented a broad outline of the current position of oxygen use in acute respiratory medicine and how the potential harms of a routine and uncontrolled approach to oxygen administration will be addressed in this thesis. The purpose of this chapter is to give an overview of the history of oxygen as a medical therapy and to describe some aspects of respiratory physiology that pertain to the aims and methods of this research.

2.1 The history of oxygen as a medical therapy

2.1.1 Discovery

As with many major scientific findings, the discovery of oxygen was the result of observations by a number of individuals over the course of more than a century. The first important contribution came from John Mayow, an Englishman born in the 1640s who studied civil law at Oxford University. Although not trained as a scientist, he undertook a number of scientific experiments, a practice that was not uncommon among educated men in the 17th century. In particular he was interested in the composition of air and the nature of respiration which he investigated using jars inverted over water. When he placed both an animal and a candle under an inverted jar he noted that the candle extinguished first and the animal died soon after, much more quickly than if it was placed

under the jar by itself. In a 1668 publication he wrote “Animals and fire draw particles of the same kind from the air” (Sternbach & Varon, 2004, p. 235).

At the time it was known that combustion required air to sustain it but Mayow’s observations led him to link the seemingly unrelated processes of respiration and combustion. He was the first to postulate that only a specific component of the air, which he called “nitro-aerius”, was required to sustain life. Moreover, he proposed that this substance was extracted from the air by the lungs and transferred to the blood, a significant departure from previous notions that breathing was primarily required to cool the heart. Mayow died in 1679 with little recognition of his theories during his lifetime (Sternbach & Varon, 2004). Indeed, not long after his death a new and completely erroneous theory was to dominate the fields of combustion and respiration for the next 100 years.

In the latter part of the 17th century a German chemist, Johann Joachim Becher, proposed ideas that were later modified by another German, Georg Ernst Stahl, to become known as the “phlogiston theory” (Wilkinson, 2004). At the time it was still commonly believed that all matter was made up of four elements: fire, water, air and earth; a belief that had persisted from pre-Socratic Greek philosophy. Stahl proposed the existence of an additional element “phlogiston” in an attempt to explain the phenomena of burning, rusting and respiration. The theory stated that all flammable materials contained phlogiston which was released into the air during combustion, leaving the material in a "dephlogisticated" form. If a substance was burned in a confined space the emitted gas

was regarded as "phlogisticated air", or air which had become saturated with phlogiston and therefore less able to support further combustion (Wilkinson, 2004).

In the early 1770s Joseph Priestly, an English chemist and minister, began experiments into the nature of gases, eventually discovering a total of nine, including nitrous oxide, nitrogen dioxide and hydrogen chloride. His breakthrough came during an experiment in 1774 heating mercuric oxide. The gas he isolated not only supported combustion to a much greater degree, it resulted in a confined mouse living longer. Priestly commented that "I have discovered an air five or six times as good as common air" (Wilkinson, 2004, p. 250). As a firm supporter of the phlogiston theory he reasoned that this newly discovered gas must have an ability to absorb extra phlogiston released from burning material or a breathing animal, and therefore referred to it as "de-phlogisticated air".

Priestly was probably the first human to ever inhale oxygen in concentrations higher than ambient air. He noted "The feeling of it to my lungs was not sensibly different from that of common air, but I fancied that my breast felt peculiarly light and easy for some time afterwards" (Grainge, 2004, p. 489). Regarding its potential as a treatment for disease he wrote "It may be conjectured that it might be salutary to the lungs in certain morbid cases" (Grainge, 2004, p. 489). However, he also gave voice to the first ever warning on inappropriate oxygen administration: "It might not be so proper for use in the usual healthy state of the body…A moralist, at least, may say that the air which nature has provided for us is as good as we deserve" (Grainge, 2004, p. 489). This note of

reservation, although perhaps based more on his religious convictions than science, would nevertheless be ignored for centuries to come.

Although the discovery of oxygen is historically attributed to Priestly, a Swedish pharmacist, Carl Wilhelm Scheele, had made an identical but independent discovery while heating mercuric oxide in 1772. Unfortunately for Scheele his work was not published until years later, and consequently he has received less credit than Priestly. He called the gas “fire air” from its ability to augment combustion, but also recognized its importance to respiration (Severinghaus, 2002).

Despite their experimental findings neither Priestly nor Scheele understood that the substance they had identified was a chemical element. In 1778 Priestly traveled to Paris and discussed his findings with the French chemist Antoine Lavoisier, who years earlier had actually received correspondence from Scheele. It was Lavoisier who recognised the new gas was an element, and finally discredited the century old phlogiston concept (Sternbach & Varon, 2005). In fact by this time the phlogiston theory had already begun to unravel. It had become apparent to a number of scientists that some materials, such as magnesium, gained weight when they burned. This was attributed to phlogiston having a “negative weight” in some substances. Lavoisier considered the whole theory to be flawed and objected to the fact that the proponents of the phlogiston theory changed its properties to fit with the outcome of inconsistent experiments. Ironically, Priestly remained a firm supporter of the phlogiston theory until his death in 1804, by which time

it had been essentially discredited by the international scientific community (Severinghaus, 2002).

Lavoisier called the new element “oxygen” from a Greek root for "acid forming", due to his incorrect belief that the tart taste of acidic solutions was due to oxygen. In 1790 he published results from a series of experiments showing that the metabolism of animals involved a slow form of combustion. He hypothesized that atmospheric oxygen supplied by breathing enabled this slow combustion to proceed and that it was the source of body heat. Lavoisier had a profound effect on the understanding of chemistry in the late 18th century. In addition to advancing the understanding of respiration he made significant contributions to other fields such as public health. Despite holding liberal political and social views he was beheaded during the French Revolution, probably due to his affluence and involvement in tax collection (Wilkinson, 2004).

2.1.2 Early attempts at therapy

One of the earliest recorded attempts to use the new gas as a medical therapy came in the 1790s when Thomas Beddoes, a lecturer in chemistry at Oxford University, established the Pneumatic Institute. Based in Bristol, its purpose was to investigate the potential medical benefits of the many recently discovered gases, a practice known as “pneumatic medicine”. He and his colleagues felt that oxygen might be particularly beneficial in the treatment of “consumption” or tuberculosis, but were discouraged when repeated administrations failed to cure the disease (Leigh, 1973).

In the 19th century many physiologists turned their attention to oxygen research. A number of discoveries were made including the mechanisms of oxygen uptake in the lung, and the fact that oxygen seemed to interact in a reversible way with haemoglobin resulting in a change in the colour of blood. Unfortunately this progress in basic physiology was not replicated in the field of practical therapeutics. The clinical administration of oxygen in the 19th century was characterised by numerous individual case reports and opinion pieces published in leading medical journals, but little in the way of systematic study. It was also a source of significant entrepreneurial activity; astute businessmen advertised oxygen as a panacea for a variety of medical complaints (Grainge, 2004). A key limitation during this period was the lack of a reliable means to produce large amounts of oxygen of adequate purity.

In 1886 Arthur and Leon Brin formed Brin's Oxygen Company (now BOC) and began the commercial manufacture of oxygen using a high temperature barium oxide process (Leigh, 1974). Although most of the oxygen produced at this time was used for industrial purposes, it was also made available for personal use. In the late 1800s many self proclaimed experts recommended oxygen administration by a variety of routes including intravenous, subcutaneous and even as an enema to cure liver disorders.

The first edition of Sir William Osler's seminal textbook "The principles and practice of medicine" was published in 1892. At that time Osler was considered one of the most influential physicians in the English speaking world, but the first edition of the text is notable for the absence of any significant discussion of oxygen therapy. It was not until

the third edition in 1898 that he made reference to the role of oxygen in the treatment of pneumonia:

> It is doubtful whether the inhalation of oxygen in pneumonia is really beneficial. Personally, when called in consultation to a case, if I see the oxygen cylinder at the bedside I feel the prognosis to be extremely grave. (Warren, 2005, p. 83)

However, he did concede that

> It does sometime [sic] seem to give transitory relief and to diminish cyanosis. It is harmless, its exhibition is very simple, and the process need not be at all disturbing to the patient. (Warren, 2005, p. 83)

In 1899 Lorrain Smith, a British pathologist, exposed a variety of animals to high concentration oxygen for prolonged periods which resulted in damage to the pulmonary tissues (Smith, 1899). The publication of this study was the first scientific report to warn of the potential harms of oxygen use. Osler was aware of Smith's work, and in the next edition of his text published in 1901 stated "That it [oxygen] may under certain circumstances be positively harmful…oxygen can be a serious irritant, actually producing inflammation in the lungs" (Warren, 2005, p. 83).

2.1.3 The modern era

There was a rapid advancement in the understanding of oxygen physiology in the early years of the 20th century. The most important work was done by Adolph Fick and Paul Bert who were the first to introduce units of partial pressure to describe oxygen tension in the alveoli and blood. They also demonstrated a fall in oxygen tension between arterial and venous blood and showed how it related to cardiac output and tissue oxygen consumption (Grainge, 2004).

It was on the background of this research that the physician and physiologist John Haldane published his seminal work "The therapeutic administration of oxygen" and ushered in the era of modern oxygen therapy (Haldane, 1917). Haldane had extensive experience treating World War I soldiers exposed to chemical agents, particularly chlorine gas, which produced widespread lung inflammation. Therapy for chlorine inhalation was predominantly supportive and supplementary oxygen was a crucial element in the treatment of the resultant hypoxaemia. He was the first well respected physician to advocate the prompt treatment of hypoxaemia by the administration of supplementary oxygen, which was counter to both the pessimistic views of Osler a decade previously, and his colleagues at the time. His view, which marked a turning point in the general attitude to oxygen, is summarised by the following statement from his 1917 paper:

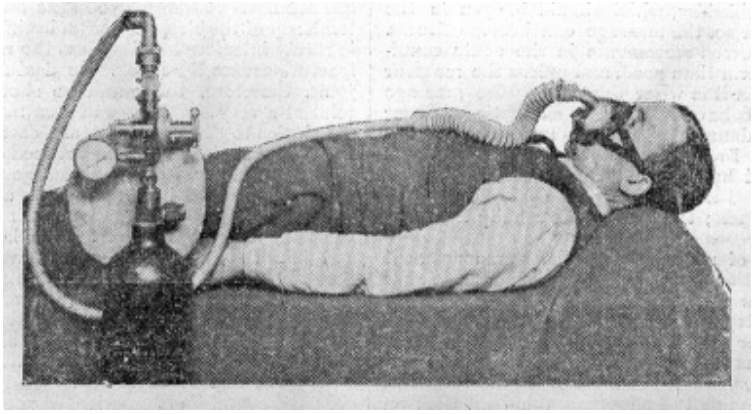
> It may be argued that such measures as the administration of oxygen are at best only palliative and are of no real use, since they do not remove the pathological condition. As a physiologist, I cannot for a moment agree with this reasoning. The living body is no machine, but an organism constantly tending to maintain or revert to the normal, and the respite afforded by such measures as the temporary administration of oxygen is not wasted, but utilized for recuperation (Haldane, 1917, p. 182).

In other words, Haldane realized that the there was a role for supplementary oxygen as a supportive therapy, and that if patients could be prevented from dying of hypoxaemia then natural recovery might be possible.

On a practical level, he strongly advised against intermittent administration of oxygen. This was common practice at the time; physicians would often prescribe oxygen for five to ten minutes every hour. Haldane characterised the futility of this approach: "Intermittent oxygen therapy is like bringing a drowning man to the surface of the water – occasionally" (Grainge, 2004, p. 493).

Importantly, he was also the first to recommend that oxygen only be given in amounts sufficient to relieve hypoxaemia, to both reduce the potential for harm and to preserve limited supplies. Haldane felt that "Existing methods of giving oxygen are nearly always very crude and wasteful"(Haldane, 1917, p. 183). He designed a facemask and tubing system to improve delivery, and used adjustable oxygen cylinders to control the flow (Figure 2.1). He recognized that the fractional concentration of oxygen administered was important, although there was no means to accurately measure this at the time. In terms of physiology, he noted that there were three fundamental causes of poor oxygen delivery to the tissues: lack of oxygen, lack of haemaglobin and lack of adequate circulation (Haldane, 1919). Haldane's recommendations on oxygen therapy became widespread when he published them in a book "Respiration" in 1922.

Figure 2.1: Haldane's oxygen apparatus (Haldane, 1917)



Another important study was published in 1919 by William Stadie, describing his experience with multiple cases of severe pneumonia associated with the Spanish influenza epidemic (Stadie, 1919). He used the recently developed technique of radial artery puncture and arterial blood gas (ABG) analysis to determine the relationship of clinical cyanosis to the amount of de-saturated arterial blood in patients with acute pneumonia. At the time it was widely accepted that cyanosis was associated with a worse prognosis in a variety of cardiac and respiratory conditions. Despite this there was considerable debate as to the precise cause of cyanosis, with theories ranging from excess carbon dioxide to the presence of methaemaglobin. The confusion was partly due to the almost exclusive use of venous blood sampling to determine the saturation of blood. Stadie was the first to study a large number of arterial samples, and to link the presence of de-saturated arterial blood to the degree of cyanosis. He found the average arterial level of de-saturated blood to be 5% in healthy subjects, 13% in non-fatal pneumonia and 32% in fatal pneumonia (Stadie, 1919). He was also able to correlate the depth of

cyanosis to the degree of de-saturation. The importance of this finding was that physicians had not previously been aware of the severe degree of arterial hypoxaemia that could be present once patients became visibly cyanosed.

In 1920 Jonathan Meakins, a professor at McGill University who had worked extensively with Haldane, published work showing that continuous oxygen therapy could reverse the arterial hypoxaemia seen in severe pneumonia (J. C. Meakins, 1920). Further case reports of the efficacy of oxygen in pneumonia followed in the 1920s and by the end of the decade it was widely accepted as part of standard therapy for that disease.

In 1932 Potts published his "Critical resume of oxygen therapy" in which he declared oxygen therapy to be 10 years old, dating its birth from the publication of Haldane's "Respiration" in 1922. Despite the advances made in the previous two decades, Potts summarised the difficulties physicians at the time faced with regard to the assessment of hypoxaemia:

> Facilities for the determination of the degree of anoxaemia are not to be found in the ordinary clinical laboratory, but the time will come, I venture, when the degree of anoxaemia will be considered as regularly as the leucocyte count now is in acute appendicitis (Potts, 1932, p. 631).

As antibacterial medicines became available in the middle decades of the 20th century, pneumonia came to be seen as a less serious illness, and the emphasis on oxygen therapy switched to its use in another increasingly common condition: COPD. The use of oxygen in COPD, and indeed acute asthma, received little attention in the medical literature

during the first decades of the 20th century. Early research reports on oxygen in chronic bronchitis and emphysema began to appear in the 1930s and focused predominantly on the growing awareness of its side effects (Barach, 1938; Barach & Richards, 1931). These problems, and further literature related to the causes of carbon dioxide retention in asthma and COPD, will be discussed in detail in chapter 3.

2.2 Respiratory physiology

"Respiration" refers to the transfer of oxygen from the atmosphere into the lungs, via haemoglobin molecules in the circulation, to metabolically active tissues where it is used for energy production in cellular mitochondria. The carbon dioxide produced during oxidative metabolism moves in the opposite direction and is excreted from the body through the lungs. The role of the respiratory system in this process can best be understood by dividing it into two main components:

1. Ventilation - the movement of air between the atmosphere and alveoli
2. Gas exchange - the exchange of oxygen and carbon dioxide molecules between alveoli and the blood

Pulmonary disease can result in problems with one or both of these processes, and manifests as either hypoxaemia (due to abnormalities of ventilation or gas exchange) and/or hypercapnia (due to abnormalities of ventilation alone).

2.2.1 Pulmonary ventilation

The *tidal volume* (V_T) refers to the volume of air entering the lungs in a normal breath and in the average adult is approximately 500ml. A proportion of this inspired gas remains in the pharynx, trachea and bronchial passages, never reaches the alveoli, and is exhaled without contributing to gas exchange. This volume, known as *anatomical dead space* or $V_{D\,(anat)}$, is fixed for a given individual at around 2.2ml/Kg of body weight, or about one third of the tidal volume. In addition to anatomical dead space *alveolar dead space* or $V_{D\,(alv),}$ refers to alveolar units that are adequately ventilated, and therefore have the potential to contribute to gas exchange, but for various reasons have either absent or reduced blood flow. Unlike anatomical dead space, alveolar dead space is not fixed. The combination of alveolar and anatomical dead space is referred to as *physiological dead space* or $V_{D\,(phys)}$:

$$V_{D\,(phys)} = V_{D\,(anat)} + V_{D\,(alv)}$$

In healthy individuals the alveolar dead space is negligible, as most alveoli have normal or near normal blood flow. However, in many pulmonary diseases the alveolar dead space volume increases to the extent that it has significant effects on overall ventilation. The assessment and measurement of changes in dead space ventilation are explained in more detail below.

Using the concept of physiological dead space we can refer to the volume of atmospheric air that reaches functional alveoli and contributes to gas exchange. This is known as the *alveolar tidal volume* or V_A, and is expressed by the following equation:

$$V_A = V_T - V_{D\,(phys)}$$

Minute ventilation ($\dot{V}$) refers to the total volume of air expired from the lungs per unit time, and is derived from the tidal volume (V_T) and the respiratory breath frequency or respiratory rate (f):

$$\dot{V} = f \times V_T$$

Of more importance physiologically is the rate at which new atmospheric air reaches the alveolar spaces and is therefore available for gas exchange. Alveolar tidal volume (V_A) is used to derive the *alveolar minute ventilation* ($\dot{V}_A$):

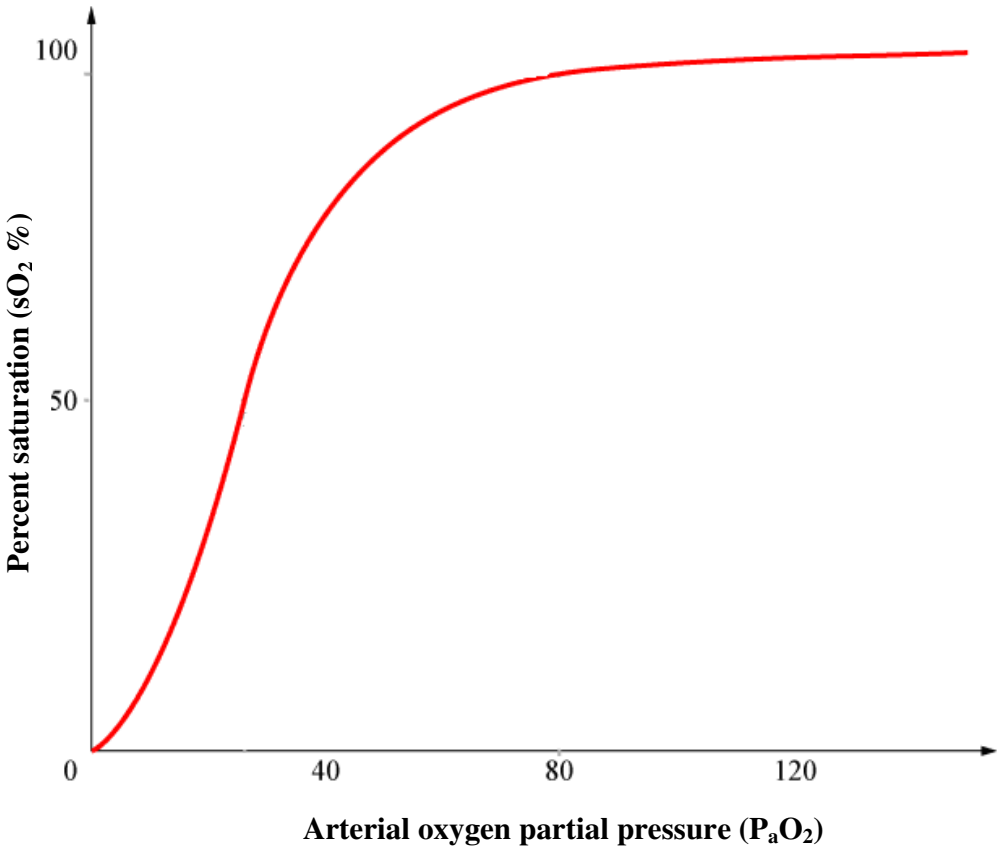
$$\dot{V}_A = f \times V_A$$
$$= f \times (V_T - V_D)$$

2.2.2 Gas exchange

Once the alveoli have been ventilated with fresh atmospheric air, the second function of the respiratory system is to exchange oxygen and carbon dioxide with blood flowing through the pulmonary circulation. This process is accomplished by diffusion, the movement of molecules from a region of high concentration to a region of low concentration. While breathing room air, the partial pressure of oxygen in the alveoli (P_AO_2) is approximately 100 mmHg compared with the partial pressure of oxygen in blood returning to the lungs from the venous circulation (P_vO_2) of 40 mmHg. Although this pressure gradient drives the transfer, oxygen is poorly soluble in solution and its diffusion is significantly enhanced by the physiological properties of the haemoglobin molecule.

Each haemoglobin molecule can bind four molecules of oxygen. The binding of oxygen is a co-operative process; as each additional molecule is added it becomes progressively easier for the remaining binding sites to be filled. This is due to a conformational change that occurs in the structure of haemoglobin; adding oxygen molecules changes its shape making it more receptive to further binding. This chemical property facilitates the uptake of oxygen in the lungs and its release in the tissues, as well as producing the characteristic sigmoid shape of the oxy-haemoglobin dissociation curve (Figure 2.2).

Figure 2.2: The oxy-haemoglobin dissociation curve



The total oxygen content of blood is determined principally by two variables: the quantity of haemoglobin in g/L, and the percentage of haemoglobin molecules saturated with oxygen. This has important implications for oxygen administration. Oxygen dissolves poorly in plasma; consequently once haemoglobin molecules are 100% saturated, increasing the P_AO_2 by increasing the fraction of inspired oxygen has little effect on total blood oxygen content.

A pressure gradient also exists to drive carbon dioxide diffusion in the opposite direction. In contrast to oxygen however, carbon dioxide readily diffuses across the alveolar-capillary membrane such that alveolar and arterial pressures usually equalise rapidly. Hence the removal of carbon dioxide from the blood is primarily dependent on alveolar ventilation. This relationship is important when considering mechanisms of CO_2 retention.

Aside from a reduction in inspired oxygen concentration (such as that occurring at altitude), there are only four possible mechanisms by which arterial hypoxaemia can develop:

1. A reduction in minute ventilation
2. A shunt which delivers blood directly from the right side of the heart to the left, bypassing the alveoli
3. A reduction in oxygen diffusion due to an abnormality of the alveolar-capillary membrane
4. Abnormal matching of perfusion and ventilation.

The fourth mechanism is the most common and because plays an important role in COPD, asthma and pneumonia it will be discussed in more detail below.

2.2.3 Ventilation-perfusion matching

The major determinant of the efficiency of gas exchange within the lung is the degree to which ventilation and perfusion are matched. So called "ventilation-perfusion mismatch" is the most common cause of hypoxaemia in respiratory disease.

Conceptually, when discussing ventilation-perfusion matching it is helpful to consider the lung to be comprised of a number of individual alveolar units each having a supply of atmospheric air, or ventilation ($\dot{V}$) and a supply of blood, or perfusion ($\dot{Q}$). The relationship between them is expressed as the ratio $\dot{V}/\dot{Q}$.

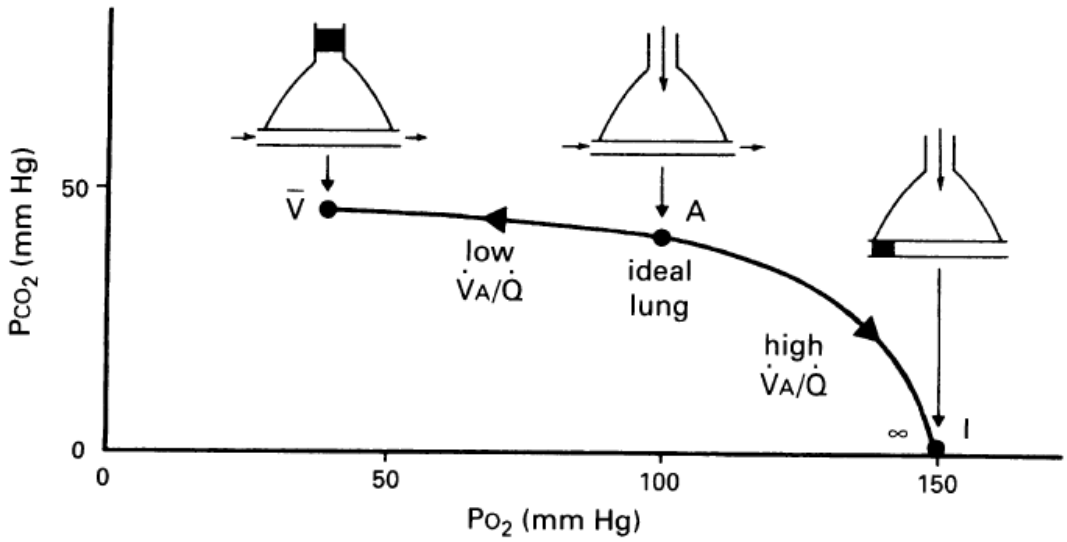
In an ideal alveolar unit ventilation exactly matches perfusion giving a $\dot{V}/\dot{Q}$ ratio of one. Theoretically, the $\dot{V}/\dot{Q}$ ratio can vary between the following two extremes depending on the underlying conditions in a given lung unit:

1. Normal ventilation with complete absence of blood flow results in a $\dot{V}/\dot{Q}$ ratio of infinity. This is equivalent to alveolar dead space as described above.

2. Normal perfusion with complete absence of ventilation results in a $\dot{V}/\dot{Q}$ ratio of zero. This is known as a shunt, blood moves from the right to the left side of the heart without being exposed to oxygen-containing alveoli.

The theoretical extremes of $\dot{V}/\dot{Q}$ mismatching are represented graphically in Figure 2.3 along with the partial pressures of carbon dioxide and oxygen and that exist there.

Figure 2.3: The three compartment model showing an ideal lung unit (A) where ventilation and perfusion are equally matched, Dead Space (I) with no perfusion, and Shunt (V) with no ventilation. (Roca & Wagner, 1994)



In practice, abnormal gas exchange in respiratory disease tends to result from lung units which have partial ventilation-perfusion mismatching rather than these extremes. In lung units with reduced ventilation but normal perfusion, the $\dot{V}/\dot{Q}$ ratio is less than one (but not zero). Although this does not represent a true shunt as defined above, it is possible to quantitatively calculate the total contribution of these units as the "physiological shunt".

Similarly, lung units with reduced perfusion but normal ventilation have a $\dot{V}/\dot{Q}$ ratio greater than one (but not infinity) and therefore ventilation to these units can be quantified as contributing to "physiological dead space".

2.2.4 Hypoxic pulmonary vasoconstriction

When mismatches in ventilation and perfusion arise they are partially corrected by an auto-regulatory mechanism known as hypoxic pulmonary vasoconstriction (HPV). In most vascular beds in the body, tissue hypoxia provokes a strong vasodilator response in order to increase the delivery of oxygenated arterial blood. In contrast, pulmonary capillaries respond to alveolar hypoxia with vasoconstriction. This effectively diverts blood away from lung units with poor ventilation (low $\dot{V}/\dot{Q}$ ratios) to lung units with better ventilation, thus maximising oxygen transfer. The phenomenon was first described in 1946, although the exact mechanism remains controversial (Von Euler & Liljestrand, 1946). The increase in vascular pressure begins within seconds of reducing the inspired oxygen concentration (Hauge, 1968), reaches a peak within minutes, and can be sustained for long periods of time (Malik & Kidd, 1973). The threshold for the onset of HPV in the human pulmonary circulation is reached when the P_AO_2 falls to around 60 mmHg (Cutaia & Rounds, 1990).

2.2.5 Carbon dioxide elimination

The partial pressure of carbon dioxide in the blood (P_aCO_2) is determined by two factors: cellular metabolic activity (production) and pulmonary ventilation (elimination). In a

steady state situation the quantity of CO_2 exhaled per unit time must equal the quantity produced in the body ($\dot{V}\ CO_2$). This relationship is expressed in the following way:

$$\dot{V}\ CO_2 = CO_2 \text{ elimination}$$
$$= \text{alveolar } CO_2 \text{ concentration x alveolar ventilation}$$
$$= P_ACO_2 \times \dot{V}_A$$

Because CO_2 production ($\dot{V}\ CO_2$) is essentially constant, and arterial and alveolar CO_2 levels are essentially equal due to complete and rapid diffusion in the lung, the equation can be rearranged to show that P_aCO_2 is inversely proportional to alveolar ventilation:

$$P_aCO_2 = 1 / \dot{V}_A$$

Furthermore, because alveolar minute ventilation is determined by the respiratory frequency and the alveolar tidal volume the equation can be modified:

$$P_aCO_2 = 1 / f\ (V_T - V_D)$$

An alternative way to express the above equation is:

$$P_aCO_2 = 1 / \dot{V}_E (1 - V_D/V_T)$$

The physiological dead space to tidal volume ratio V_D/V_T, also known as the dead space fraction, and can be derived from clinical measurements. From the equation above it can be seen that if CO_2 production is constant there are only two mechanisms by which P_aCO_2 can increase:

1. A reduction in overall minute ventilation (by a reduction in respiratory rate and/or tidal volume)
2. An increase in physiological dead space volume (V_D) and consequently an increase in V_D/V_T

2.2.6 Physiological dead space

The Danish physiologist Christian Bohr first proposed the concept of measuring physiological dead space in 1891 (Bohr, 1891). His approach was to express the elimination of CO_2 mathematically based on the following principles:

1. The total volume of air expired in a single breath is equal to the sum of the dead space volume and the alveolar volume.
2. Because CO_2 in atmospheric air is essentially zero, the CO_2 in the anatomical dead is zero.
3. The total quantity of CO_2 in a measured expired tidal volume can only come from ventilated alveoli, but is mixed with and diluted by air in the dead space volume.

He expressed the relationship as follows:

$$V_T \times F_ECO_2 = (V_D \times F_ICO_2) + (V_A \times F_ACO_2)$$

Where F_ECO_2 represents the total fraction of mixed expired CO_2 in a complete tidal breath, F_ICO_2 represents the fraction of CO_2 contained in the dead space volume and F_ACO_2 represents the fraction of CO_2 in ventilated alveoli. Because F_ICO_2 is close to zero the equation becomes:

$$V_T \times F_ECO_2 = (V_A \times F_ACO_2)$$

If V_A is substituted by $V_T - V_D$ (as described above) and we convert fractions of CO_2 to partial pressures, the equation becomes:

$$V_T \times P_ECO_2 = (V_T - V_D) \times P_ACO_2$$

Solving this equation for V_D:

$$V_D = (P_ACO_2 - P_ECO_2 / P_ACO_2) \times V_T$$

This is the original form of the Bohr equation; however physicians and researchers initially found it problematic to use. Although mixed expired gas could be collected to

derive P_ECO_2 there was difficulty, and much controversy, in obtaining accurate estimates of the alveolar CO_2 despite a variety of methods. In 1938 Enghoff proposed substituting P_aCO_2 for P_ACO_2 on the basis that the rapid transfer of CO_2 from blood to alveoli meant the two were essentially equivalent (Enghoff, 1938). Using this substitution, and expressing the equation as a V_D/V_T ratio produces:

$$V_D/V_T = (P_aCO_2 - P_ECO_2 / P_aCO_2)$$

This in known as the Bohr-Enghoff equation and is the form most often used in research and clinical practice when the physiological dead space to tidal volume ratio is measured (Fletcher, Jonson, Cumming, & Brew, 1981).

Chapter 3: Oxygen therapy in acute respiratory disease

Following a description of some relevant aspects of general respiratory physiology in Chapter 2, this chapter begins by outlining the pathophysiology of acute exacerbations of COPD (AECOPD) and literature regarding the effects of uncontrolled oxygen administration in COPD, specifically oxygen induced hypercapnia. The evidence regarding possible mechanisms of CO_2 retention in COPD is then discussed. Section 3.3 describes similarities in the pathophysiology of acute asthma and AECOPD, reviews the existing literature on oxygen use in acute asthma, and raises the potential for similar mechanisms of CO_2 retention to operate in asthma and pneumonia. Finally, a case is made that a significant gap in medical knowledge exists regarding the potential for oxygen induced hypercapnia in acute asthma and pneumonia.

3.1 COPD

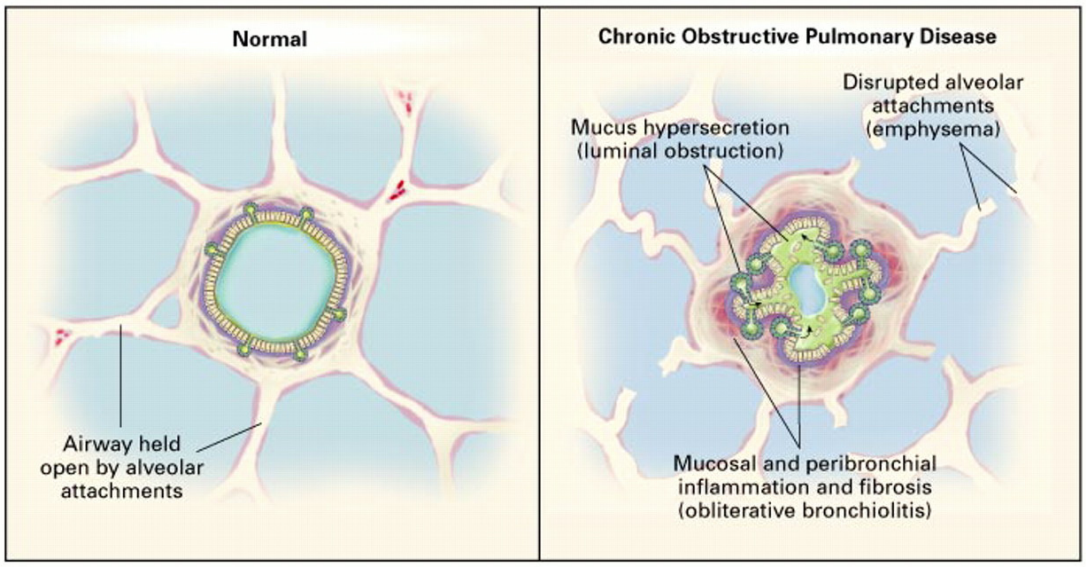
3.1.1 Pathophysiology of acute exacerbations of COPD

Over time, progression in the severity of airflow obstruction in COPD is associated with an increased frequency of acute exacerbations (Miravitlles et al., 2000; Niewoehner et al., 2007). For some patients they are a significant component of the overall burden of the illness, and may also be life threatening (Seemungal et al., 1998). Both the Australasian

COPD-X guideline document (Abramson, Crockett, Frith, & McDonald, 2006) and the British Thoracic Society guidelines (BTS, 2004) define an acute exacerbation as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication.

The ventilation and gas exchange abnormalities that occur during AECOPD are primarily due to an acute increase in airflow obstruction which results in increased expiratory flow limitation (EFL). The underlying cause of EFL in stable COPD varies from patient to patient but usually results from a mixture of airway inflammation and mucous hyper-secretion, and the loss of alveolar attachments due to destruction of parenchymal lung tissue (Figure 3.1).

Figure 3.1: Mechanisms of airflow limitation in COPD (Barnes, 2000)

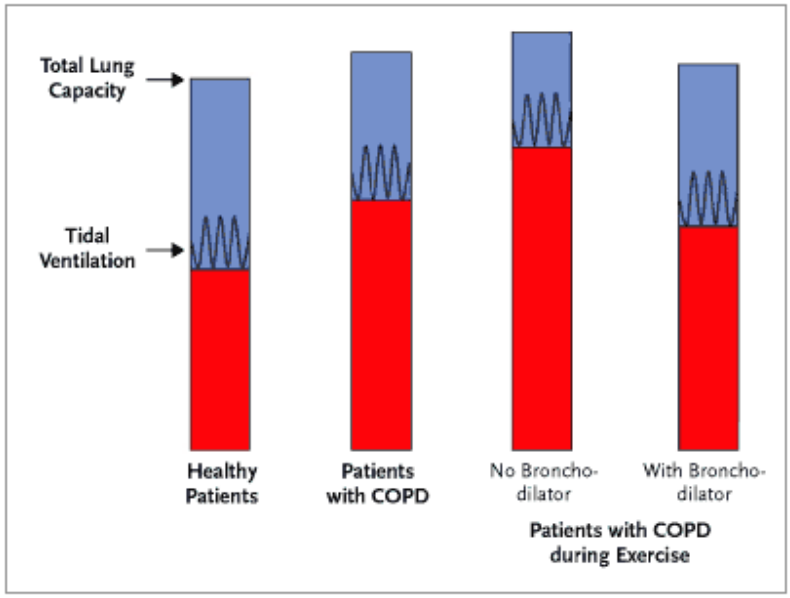


In the majority of patients the major cause of COPD is chronic inhalation of tobacco smoke, although exposure to other airborne particulate matter such as indoor biomass fires is important in some cases (Dennis et al., 1996; S. Liu et al., 2007; Orozco-Levi et al., 2006). Finally, longstanding asthma can lead to airway remodeling and chronic narrowing (Marsh et al., 2008).

The acute deterioration in airflow obstruction that characterises AECOPD is usually the result of increased airway inflammation due to either viral or bacterial infection, although environmental pollutants and allergens may play a role in some cases (Bhowmik, Seemungal, Sapsford, & Wedzicha, 2000). This usually manifests as a change in sputum volume or colour, and an increase in wheeze and breathlessness.

During tidal breathing at rest the Functional Residual Capacity (FRC) represents the lung volume at which the elastic recoil forces of the pulmonary parenchyma and chest wall are equal. In normal subjects this also represents the lung volume at which the respiratory muscles are at their optimal functional length. Hyperinflation is defined as an increase in the FRC above the normal range (Roussos & Macklem, 1982). In AECOPD, the increased EFL means that during spontaneous breathing the time for expiration may be insufficient to allow the lung volume to fall to its natural relaxation position, resulting in progressive hyperinflation. This dynamic increase in FRC, and concomitant reduction in the Inspiratory Capacity (IC), is strongly correlated with the degree of perceived dyspnoea during AECOPD (Stevenson, Walker, Costello, & Calverley, 2005). The effects of hyperinflation in COPD during exercise are shown graphically in Figure 3.2; a similar process occurs during an acute exacerbation.

Figure 3.2: Pulmonary hyperinflation in COPD (Sutherland & Cherniack, 2004)



As a consequence of progressive hyperinflation, the operating tidal volume of the lungs in patients with AECOPD moves closer to the region of total lung capacity, and away from the more favourable volumes for respiratory muscle function. Although hyperinflation has some positive physiological effects, such as a small increase in airway calibre and elastic recoil, these are countered by flattening of the diaphragm and consequent reduction in muscle function and strength (Tobin, 1988). The result is that higher pressure changes are required to maintain the same tidal volume, and thus more energy is expended.

The combination of an acute increase in airflow obstruction and the changes in pulmonary mechanics outlined above often result in abnormalities of gas exchange. The

most common arterial blood gas abnormality is hypoxaemia, which can be severe, and there may be varying degrees of hypercapnia and respiratory acidosis. Three studies which documented the degree of arterial hypoxaemia in patients presenting with AECOPD prior to receiving any oxygen therapy are shown in Table 3.1. Although hypoxaemia is relatively common, the strongest predictor of mortality and the need for invasive ventilation is the arterial pH, which is in turn determined by the degree of acute hypercapnia (Ambrosino et al., 1995; Jeffrey, Warren, & Flenley, 1992; Plant et al., 2000).

Table 3.1: Three studies of room air P_aO_2 in patients presenting with AECOPD

Study	Patients (n)	Mean P_aO_2 (mmHg)	Range (mmHg)
(King, Ali, & Briscoe, 1973)	40	40.4	24 - 68
(Warrell, Edwards, Godfrey, & Jones, 1970)	7	29.8	25 - 28
(Rudolf, Banks, & Semple, 1977)	3	33.6	31 - 39

As noted in Chapter 2, there are only four possible mechanisms of arterial hypoxaemia: an isolated reduction in minute ventilation, pure right to left shunt, a limitation of diffusion across the alveolar-capillary membrane, or mismatch of ventilation and perfusion. Although these can all potentially play a role in the hypoxaemia of AECOPD,

the importance of $\dot{V}/\dot{Q}$ mismatch became apparent through physiological studies beginning in the 1970s.

An important development in the field of pulmonary physiology occurred in 1974 when Wagner and colleagues developed the Multiple Inert Gas Elimination Technique, or MIGET (Wagner, Saltzman, & West, 1974). The technique is based on the intravenous infusion of a mixture of six inert gases with a range of solubility coefficients. By simultaneously measuring arterial blood, mixed venous blood and expired air, the retention and secretion of each gas can be plotted graphically to express the degree of ventilation and perfusion matching (Figures 3.3). In the graphical representation, each data point represents a particular amount of blood flow (●) or ventilation (o) to the corresponding pulmonary compartment, and is plotted against the $\dot{V}/\dot{Q}$ ratio on a logarithmic scale. In a normal individual it can be seen that both curves are centered on an ideal $\dot{V}/\dot{Q}$ ratio of 1 and are narrow. Note the absence of shunt and a normal anatomical dead space fraction of 30% (Figure 3.4)

Figure 3.3: The Multiple Inert Gas Elimination Technique. Six inert gases are infused intravenously while samples of arterial blood (a) mixed venous blood (v) and mixed expired gases (E) are obtained. (Roca & Wagner, 1994)

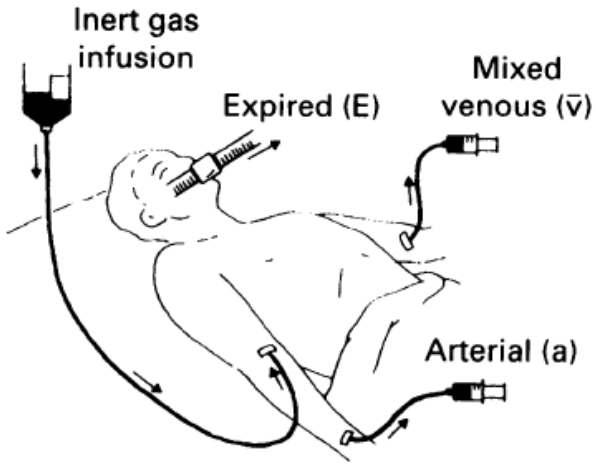
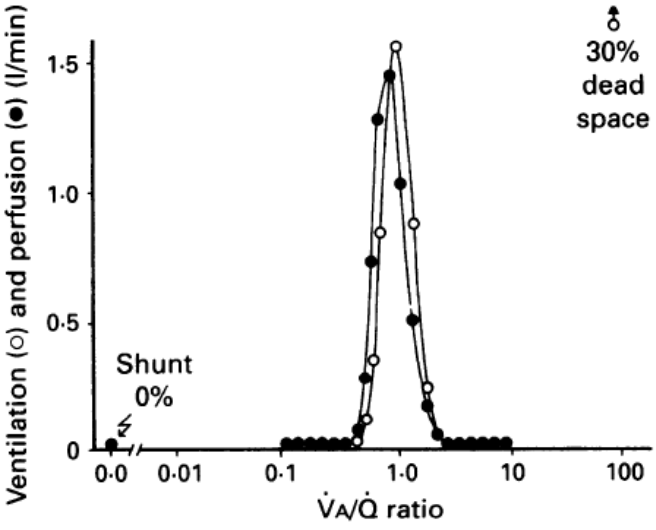
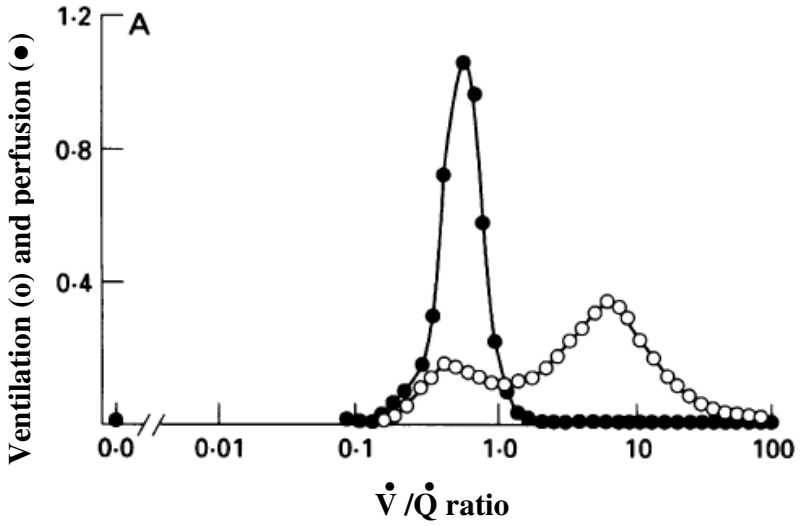


Figure 3.4: Example of a MIGET graph from a normal individual breathing room air. (Roca & Wagner, 1994)



Barbera et al described the mechanisms of worsening gas exchange during AECOPD using MIGET (1997). They studied 13 hospitalised patients with AECOPD during their admission and then again one month after discharge. Exacerbations were characterised by very severe airflow obstruction (mean FEV1 0.74L), severe hypoxaemia (mean P_aO_2 44 mm Hg) and hypercapnia (mean P_aCO_2 55 mm Hg). Inequality of $\dot{V}/\dot{Q}$ was significantly abnormal (Figure 3.5), but measured shunt was negligible. During recovery, improvements in hypoxaemia, gas exchange and airflow obstruction followed a more or less parallel course.

Figure 3.5: $\dot{V}/\dot{Q}$ distribution in a patient with COPD. Note the bimodal appearance of ventilation compared to perfusion due to areas of the lung with significantly elevated $\dot{V}/\dot{Q}$ ratios (Agusti & Barbera, 1994).



In summary, during AECOPD patients develop significant abnormalities in pulmonary physiology, principally increased airflow limitation and hyperinflation. MIGET has revealed that the abnormal gas exchange and hypoxaemia associated with AECOPD can be almost entirely explained by severe $\dot{V}/\dot{Q}$ mismatch, with little contribution from either shunt or diffusion limitation (Barbera et al., 1997; Wagner, Dantzker, Dueck, Clausen, & West, 1977). The next section will review the clinical effects of oxygen administration in AECOPD with particular reference to the mechanisms of oxygen induced hypercapnia.

3.1.2 Oxygen therapy in AECOPD

As noted in Chapter 2, the use of oxygen therapy became widespread during the years 1920 to 1950, particularly in the setting of pneumonia. However, oxygen was also frequently given to cyanotic patients with acute exacerbations of COPD. It was noted by clinicians at an early stage that adverse effects were associated with this approach.

As early as 1905 it had been demonstrated that in humans the principle stimulus to breathe was the level of arterial carbon dioxide (Haldane & Priestley, 1905). Administering CO_2 to volunteer subjects increased the depth of respiration, while reducing CO_2 by over-ventilation resulted in hypopnoea or temporary apnoea. Unfortunately a number of physicians misinterpreted these findings, and by 1919 many had come to the erroneous conclusion that the main cause of hypoxaemia in patients with respiratory infection was abnormally rapid shallow respirations (Haldane, Meakins, &

Priestley, 1919). This led to an enthusiasm in the medical community for the therapeutic administration of CO_2 mixed with oxygen in an effort to stimulate the respiratory effort of breathless patients. As late as 1932 Haldane was advocating the therapeutic use of CO_2 and demonstrating apparatus for delivering it ("Reports of Societies," 1932).

In 1933 the first case report describing papilloedema in an acutely breathless patient with emphysema was published in the British Journal of Ophthalmology, and was given little consideration at the time by internal medicine physicians (Cameron, 1933). Further reports followed, with most clinicians ascribing the papilloedema to either polycythaemia or raised central venous pressure as both were common findings in advanced emphysema.

Thomas Simpson further elaborated on the phenomenon in 1948 when he documented three cases of papilloedema associated with acute emphysema. By documenting that none of his patients had raised venous pressure or polycythaemia, Simpson dismissed these as possible mechanisms (Thomas Simpson, 1948). He considered it more likely that gas exchange abnormalities were influencing the pressure of cerebrospinal fluid (CSF). In 1925 a study had established that elevated CO_2 sometimes occurred in emphysema (J. Meakins & Davies, 1925). Simpson linked this observation to other work involving the direct observation of the pial vessels of cats through a trephine hole in the skull. This study had found that inhalation of just 5% CO_2 increased the diameter of cerebral blood vessels by 17% (Wolff & Lennox, 1930). Simpson went further and documented the

CSF pressure by lumbar puncture in six patients who were administered 7% inhaled CO_2 mixed with oxygen. He noted prompt rises in CSF pressure within one to two minutes to at least twice baseline levels in all six patients (Thomas Simpson, 1948).

The following year a study linked Simpson's observations on CSF pressure in emphysema with the effects of oxygen therapy by directly measuring the response of CSF pressure to oxygen administration at a flow rate of 6 L/min in four patients with severe emphysema and five subjects with no respiratory disease (Davies & Mackinnon, 1949). All four cases in the emphysema group had higher than normal resting CSF pressure and demonstrated a prompt rise which resolved on cessation of oxygen inhalation. None of the normal subjects had a change in CSF pressure. Although they did not measure CO_2 directly they surmised, with reference to Simpson's work, that the mechanism seemed to be oxygen induced increases in CO_2.

In parallel with these studies on CSF pressure and papilloedema, a number of investigators had been reporting that oxygen administration in severe emphysema occasionally resulted in mental state changes, specifically varying degrees of stupor and coma. One of the earliest to document this effect was Alvan Barach in the 1930's. He noted that "A profound disturbance of mental functioning may take place in patients suffering from longstanding arterial anoxaemia after inhalation of 50% oxygen…In some patients lassitude and mental depression take place accompanied by severe headache" (Barach & Richards, 1931, p. 336). Initially he attributed these symptoms to sudden changes in arterial oxygen tension, but in fact he was writing an accurate description of

CO_2 narcosis. In a later paper he recognised the link between elevation of P_aCO_2 and oxygen therapy (Barach, 1938). Other reports and case series followed (Donald, 1949; Taquini, Fasciolo, Suarez, & Chiodi, 1948).

By 1950 there was widespread acceptance that oxygen therapy could induce mental state changes in patients with chronic hypoxia, but debate remained as to the exact cause, and it had not yet been linked only to emphysema. In 1950 a paper accurately summarised the current state of knowledge (Comroe, Bahnson, & Coates, 1950). It presented a series of 65 consecutive patients given oxygen therapy: 43 had emphysema and the rest comprised patients with asthma, bronchiectasis, pulmonary vascular disease and congenital heart disease. They noted the development of mental changes in eight patients; all of whom had emphysema as well as a P_aCO_2 of greater than 50 mmHg and oxygen saturations of less than 90% at baseline. Oxygen administration increased the P_aCO_2 in all patients, ranging from 10 to 52 mmHg. Despite their consistent finding of oxygen induced hypercapnia, and the previous work by Simpson, Comroe et al remained uncertain as to the underlying mechanism. They proposed and discussed four potential mechanisms of the observed mental changes: carbon dioxide narcosis, cerebral vasospasm, increased CSF pressure and cerebral depression by high oxygen tension. Interestingly, this lack of mechanistic certainty did not prevent them concluding the paper with a recommendation on oxygen administration that was in some respects ahead of its time. They essentially reinforced comments that Barach had made in his earlier work: that patients with emphysema rarely require 100% oxygen to relieve their hypoxaemia and that the safest

approach is to administer oxygen at lower concentrations initially and to increase it gradually should the patient tolerate it.

In 1952 a study measured minute ventilation, CSF pressure and arterial blood gases before and after oxygen in four patients with emphysema and three normal controls (Mithoefer, 1952). It demonstrated a rise in P_aCO_2 and CSF pressure, and falls in minute ventilation in all emphysema patients but none of the controls. Despite these results the author was reluctant to be definitive about a link between oxygen, CO_2 and CSF changes. However, the report is one of the earliest to describe the role of the hypoxic drive to breathe in emphysema, a concept that would become firmly entrenched over the following decades. In reference to the fall in ventilation after oxygen was given the paper states:

> It indicates that in these patients anoxia was an important respiratory stimulant…which had assumed much of the function of stimulation normally carried by carbon dioxide. When the anoxic stimulus was removed, respiratory depression ensued despite a rising arterial carbon dioxide tension. (Mithoefer, 1952, p. 1118)

Two years later, firmer opinions began to appear in the literature. In 1954 Simpson published a case series of acute respiratory infections in emphysema, along with a general review of management. With regard to oxygen administration he states: “Mental symptoms or even coma may ensue when oxygen is given to these patients. Studies at this hospital suggest that the mental symptoms are due to CO_2 narcosis” (T. Simpson, 1954, p. 300). A similar study investigated the effect on ventilation of 100% oxygen in 35

emphysematous patients. In 26 patients there was a fall in ventilation accompanied by a mean increase in P_aCO_2 of 8.6 mmHg and a fall in pH (Prime & Westlake, 1954). Regarding the fall in ventilation the authors stated: "This appears to be the effect of the relief of anoxia since it occurred only in anoxic emphysematous subjects and did not occur in those with normal saturation or in normal controls" (Prime & Westlake, 1954, p. 323). They also demonstrated that patients with emphysema and baseline elevations of P_aCO_2 demonstrated a reduced and blunted response to 7% inhaled CO_2 suggesting altered sensitivity of the respiratory control centre. The authors of a review article the same year agreed "The decrease in ventilation results from the elimination of the hypoxic stimulus to the respiratory mechanism. Drowsiness, which may progress to coma if oxygen therapy is prolonged, is related to the increasing severity of respiratory acidosis" (Cohn, Carroll, & Riley, 1954, p. 449). Their recommendations on practical management echoed those of Comroe from four years previously, specifically, that patients be given oxygen only if arterial saturations were below 85% and that a low initial concentration of around 40% should be used.

Further work in the 1950s did little to advance the overall understanding of CO_2 narcosis but did help to clarify more precisely the relationship between the degree of acidosis, CO_2 retention and the severity of lung disease (Bickerman & Barach, 1955; Westlake, Simpson, & Kaye, 1955) and the prognostic value of arterial blood gases in emphysema (Platts & Greaves, 1957).

In 1960 E.J.M. Campbell published two articles in the Lancet which made significant advances to the understanding of oxygen administration in emphysema. In the first, he studied four patients with acute exacerbations of emphysema and measured their response to varying concentrations of inspired oxygen. Despite the patients having extremely deranged gas exchange (mean P_aCO_2 79 mmHg and mean P_aO_2 23 mmHg) he was able to determine the precise arterial oxygen response to inspired fractions of oxygen ranging from 21 to 35% (E. J. Campbell, 1960b). He demonstrated that the arterial oxygen tension of patients with severe respiratory failure was very sensitive to even small degrees of oxygen enrichment. He advocated continuous rather than intermittent oxygen therapy (which was still considered by some clinicians to be the appropriate approach to minimising CO_2 retention), and recommended inspired oxygen concentrations in the range of 24 to 35%.

In his second paper he outlined the problem with existing modes of oxygen delivery, namely that wide patient variations in minute ventilation meant that the exact concentration delivered to a patient could not be determined with any degree of accuracy (E. J. Campbell, 1960a). He described a new oxygen delivery system comprising a mask connected to bottles of both compressed room air and oxygen. A baseline flow of room air at 40 L/min was administered and oxygen was added at a specific flow rate to produce a precise gas mixture which could be varied between 24 and 35% oxygen. The overall flow rate of the mixture was much higher than the patient's peak inspiratory air flow, regardless of the level of minute ventilation, and consequently the concentration remained accurate. Unfortunately the fact that the compressed air bottles were exhausted

in one to two hours limited its practical application. Campbell experimented with a variety of alternative designs, including the use of large pumps which attempted to produce the same effect but were limited by their size. Eventually he designed a mask based on his knowledge of the Venturi effect, which would be his most important contribution to practical therapeutics, and which is still in widespread use today.

The Venturi effect refers to the reduction in pressure that occurs when any gas or fluid flows through a constricted section of a tube. As a consequence of this drop in pressure, gas flowing through a narrow aperture in the base of a mask entrains air at a fixed rate from the surrounding environment. Campbell's "Venturi mask" used a jet of oxygen fixed at a flow of 3 L/min through a small aluminium orifice into a mask with side holes. He calculated that this design would entrain room air at a rate of 50 L/min and produce an oxygen concentration of 24%. In order to achieve higher concentrations, a second oxygen inlet was added to the mask which was supplied by the same bottle. This setup proved to be somewhat complex and less accurate than initially thought, and Campbell had soon modified the mask design to its modern form, a single aperture with an accurate diameter designed to deliver a precise, but fixed, inspired oxygen concentration (E.J. Campbell, 1963).

In his recommendations for the management of emphysema, Campbell emphasised the importance of early measurement of P_aCO_2 in all patients due to the unreliability of clinical features of hypercapnia. However, in the majority of his patients this was not done by ABG analysis, but instead using a bedside re-breathing technique which would

now be considered somewhat unreliable (E. J. Campbell, 1967). He considered that measurements of the pH and P_aO_2 were less important, on the basis that his oxygen delivery method would increase the P_aO_2 of most patients to above 40 mmHg, the level he considered safe. This opinion was based on data published the previous year showing that patients with emphysema arriving at hospital prior to treatment with oxygen were often conscious despite a P_aO_2 as low as 30 mmHg (Refsum, 1963). It is worth noting that at the time of these publications laboratory methods for determining ABG tensions were somewhat difficult and time consuming. In fact the assays were only available at large tertiary hospitals or those with a research focus, and even then often during office hours only (Thomas Simpson, 1964).

Hutchison et al had a contrasting view, and suggested that the Campbell's approach was potentially dangerous, as ABG data from their series of patients indicated that a significant number were under-oxygenated using his method (Hutchison, Flenley, & Donald, 1964). They considered measurement of the P_aO_2 important to ensure adequate oxygenation had been achieved, and that a higher level of 50 mmHg should be considered a safe minimum. They recommended measuring the pH routinely as it provided important information about the chronicity of P_aCO_2 changes.

A number of other published series followed in the 1960s, which essentially demonstrated the same findings: that hypoxia could usually be relieved by relatively low concentration oxygen administration, and that serious hypercapnia was uncommon (Cherniack & Hakimpour, 1967; Eldridge & Gherman, 1968; Mithoefer, Karetzky, &

Mead, 1967). There was minor disagreement regarding the so-called safe level of P_aO_2 with some American researchers recommending 60 mmHg as an adequate target (Eldridge & Gherman, 1968). In any event, it was generally accepted that uncontrolled high concentration oxygen therapy led to significant CO_2 narcosis in a proportion of patients with acute exacerbations of emphysema, and therefore should be avoided. In terms of the mechanism, most investigators agreed that because many of these patients had chronic hypoxia and CO_2 retention, they must rely on their hypoxic drive to breathe, and that oxygen therapy abolished this resulting in a decrease in minute ventilation.

However, evidence began to appear which contradicted this accepted mechanism. A study published in 1960 reported that oxygen administered to stable emphysema patients increased the P_aCO_2 significantly, even when the baseline level was normal (Brodovsky, Macdonell, & Cherniack). If a reduction in the hypoxic drive to breathe was the main driver of oxygen induced hypercapnia, then the observed rise in P_aCO_2 should be related both to the initial level of P_aO_2, and to the degree of increase with oxygen therapy, however a case series in 1968 showed that there was no relationship (Eldridge & Gherman).

In 1965 the first study to directly address the question of the mechanism of oxygen induced CO_2 retention was published (Pain, Read, & Read). It was prompted by the authors' clinical observation that in a number of patients there appeared to be no relationship between ventilation changes and the degree of CO_2 elevation when oxygen was administered. They pointed out that "there have been very few reports of the

response to breathing oxygen in which sufficient data are given to allow comparison of the relative changes in ventilation and arterial PCO_2" (Pain et al., 1965, p. 195). They studied 38 stable patients with chronic airflow obstruction, measuring ABGs and minute ventilation while breathing air and then after 10 minutes breathing 100% oxygen. In 24 patients the P_aCO_2 rose by 5 to 24%. Changes in minute ventilation ranged from a rise of 15% to a fall of 58% but there was no correlation between the changes in ventilation and change in P_aCO_2. To explain their findings the authors referred to the relationship between overall minute ventilation and P_aCO_2.

As discussed in Chapter 2, if production of CO_2 remains constant, then P_aCO_2 is solely determined by overall minute ventilation and the relationship is inversely proportional:

$$P_aCO_2 \quad = \quad 1 / \dot{V}_E$$

Consequently, for P_aCO_2 to double overall minute ventilation must be halved. The only other way P_aCO_2 can be raised is by an increase in the physiological dead space, or specifically the physiological dead space to tidal volume ratio, V_D/V_T:

$$P_aCO_2 \quad = \quad 1 / \dot{V}_E (1 - V_D/V_T)$$

From this equation it can be seen that an increase in V_D/V_T will increase P_aCO_2 even if $\dot{V}_E$ remains the same.

The authors note in their discussion:

> In the present group of experiments, the only discernable factor which might produce blood flow redistribution is the administration of oxygen. If there are regions in the diseased lung where vasoconstriction has produced local reductions of blood flow (of a "compensatory" nature), high alveolar oxygen tensions may reverse this vasoconstriction and lead to a worsening of blood flow distribution (in relation to ventilation), with a resulting increase in the V_D/V_T ratio. (Pain et al., 1965, p. 200)

Pain and Read were the first researchers to demonstrate the effect of oxygen administration on pulmonary blood flow in emphysema patients, and propose that this might have a significant influence on gas exchange.

The fact that pulmonary artery pressures were sensitive to alveolar oxygen tensions, referred to as hypoxic pulmonary vasoconstriction (HPV), had been demonstrated as far back as 1946 (Von Euler & Liljestrand). In 1959 it was shown that giving vasodilator drugs to patients with chronic pulmonary disease induced hypoxaemia, presumably by the reversal of HPV and increased blood flow to poorly ventilated lung units (Halmagyi & Cotes). A 1961 study confirmed this finding by administering the potent intravenous vasodilator priscoline to 14 patients with chronic lung disease. Not only did blood oxygen content fall in 13 subjects, but eight subjects showed an increase in P_aCO_2 (Stern & Braun). The fact that oxygen administration could produce similar effects to those seen with vasodilator drugs was demonstrated in a 1962 study which demonstrated that

inhalation of 100% oxygen for 10 minutes by 11 healthy volunteers resulted in an almost twofold increase in the arterial-alveolar CO_2 gradient (Larson & Severinghaus). The authors noted that this was most likely due to oxygen increasing blood flow to less ventilated alveoli in the lung bases, thereby increasing alveolar dead space.

The 1965 work by Pain et al was extended in 1967. This study involved 58 patients with stable COPD breathing air and then 100% oxygen for 10 to 15 minutes. Frequent measurements of minute ventilation were made, and V_D/V_T ratios were calculated (Lee & Read). Although changes in P_aCO_2 in response to oxygen were not reported, their findings correlated well with earlier studies. Two-thirds of the 58 patients showed a significant rise in V_D/V_T from baseline while breathing oxygen; however the increases had no relationship with minute ventilation. They concluded that the increases in physiological dead space resulted from oxygen induced changes in blood flow distribution, with perfusion redirected to lung units with lower ventilation.

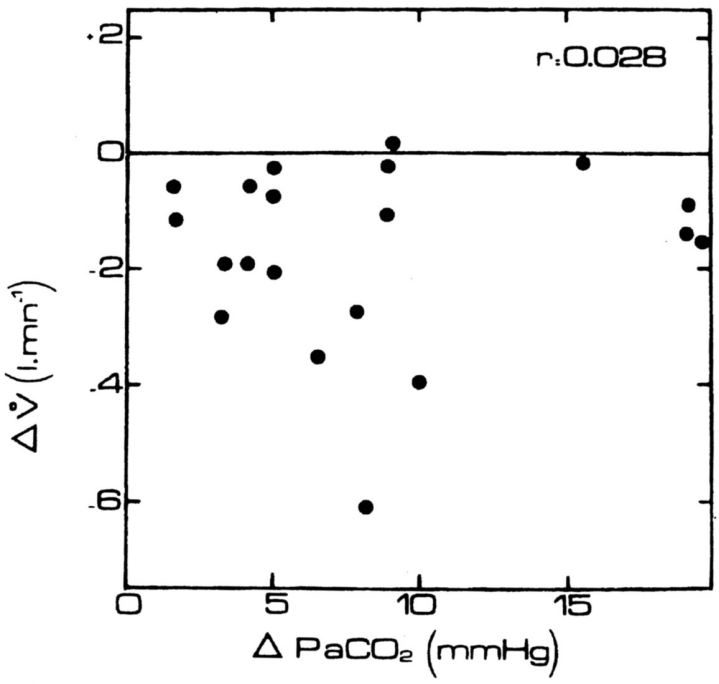
In 1973 a large study reported the responses of 151 patients with stable emphysema to 100% oxygen for 20 minutes (Lopez-Majano & Dutton). It found that 35 of 151 patients had a rise in P_aCO_2 greater than 10 mmHg, and that the incidence and severity of hypercapnia was strongly linked to a lower baseline P_aO_2. The authors contrasted this with findings from earlier studies in which the degree of baseline hypercapnia or hypoxia did not closely relate to the degree of P_aCO_2 rise breathing oxygen (Brodovsky et al., 1960; Miller et al., 1968; Penman, 1962; Swain, Park, & Williams, 1968). In their discussion the authors state that the P_aCO_2 changes they observed were due to decreases

in minute ventilation, despite not measuring it, and proposed that the variable responses to oxygen they observed may be due to patients having greater or lesser degrees of emphysema or chronic bronchitis. They made no reference to the alternative mechanisms proposed by Lee and Read in 1967. Their discussion highlights the fact that by the 1970s most researchers were still of the view that oxygen induced hypercapnia was due to the removal of the hypoxic drive to breathe (Mithoefer, Karetzky, & Mead, 1967; Rudolf et al., 1977).

In 1980 Michel Aubier and co-workers published two important studies on the pathophysiology of acute respiratory failure in COPD. The first study was designed to determine changes in respiratory drive, minute ventilation, tidal volume, and respiratory frequency in response to oxygen breathing (Aubier, Murciano, Fournier et al., 1980). As an estimate of neuromuscular respiratory drive they recorded inspiratory mouth occlusion pressures. This technique was first described in 1975 (Whitelaw, Derenne, & Milic-Emili), and measures the pressure generated against a closed airway 100 milliseconds after the onset of inspiration during normal tidal breathing ($P_{0.1}$). Aubier et al studied 20 severe COPD patients during an episode of acute respiratory failure with a mean P_aO_2 of 37.6 mmHg and a mean P_aCO_2 of 61 mmHg at baseline. After recording on room air, subjects breathed oxygen at a flow rate of 5L/min for 30 minutes. This resulted in a mean increase in P_aCO_2 of 10 mmHg, and a final level exceeding 80 mmHg in 13 patients. In terms of respiratory drive, $P_{0.1}$ was significantly elevated while breathing room air with a mean of 8.3 cmH_2O compared to 1.7 cmH_2O in normal controls. Although $P_{0.1}$ decreased by 40% with oxygen breathing, confirming previous findings in stable COPD patients

(Bradley, Fleetham, & Anthonisen, 1979; Sorli, Grassino, Lorange, & Milic-Emili, 1978), the final value was still significantly higher than normal controls. This decrease in respiratory drive translated into a small decrease in minute ventilation of 14%, comprised of a reduced respiratory frequency but a preserved tidal volume. The authors noted that not only was the overall magnitude of change in minute ventilation insufficient to account for the observed rise in P_aCO_2, but when changes in minute ventilation for each subject were correlated with the changes in P_aCO_2 no relationship was found (Figure 3.6).

Figure 3.6: Data showing no relationship between changes in minute ventilation and P_aCO_2 after oxygen at 5L/min for 30 minutes (Aubier, Murciano, Fournier et al., 1980)



The authors' interpretation of these findings was to agree with Lee and Read that oxygen induced rises in V_D/V_T must have made a significant contribution to hypercapnia. Although the observed decrease in the drive to breathe (as estimated by the $P_{0.1}$) when oxygen was administered suggested that hypoxia was contributing, the $P_{0.1}$ remained significantly elevated such that minute ventilation changes were only small.

A second study by the same group later that year investigated this theory and extended their findings (Aubier, Murciano, Milic-Emili et al., 1980). This work investigated the time course of changes in ventilation and gas exchange in 22 patients with AECOPD breathing oxygen for 15 minutes, but used a higher concentration of 100%. As in the first study they measured the P_aCO_2 response to oxygen, as well as respiratory frequency, tidal volume and minute ventilation. However, rather than recording $P_{0.1}$ they collected mixed expired CO_2 and were thus able to calculate V_D/V_T ratios. The effects of 100% oxygen on arterial blood gases are shown in Table 3.2.

Table 3.2: Mean (± SE) arterial blood gas data before and after 15 minutes of 100% oxygen (Aubier, Murciano, Milic-Emili et al., 1980)

	P_aO_2 (mmHg)	P_aCO_2 (mmHg)	pH
Air	38 ± 2	65 ± 3	7.34 ± 0.01
O_2	225 ± 23	88 ± 5	7.25 ± 0.02
Air versus O_2	$P < 0.001$	$P < 0.001$	$P < 0.001$

During the first three minutes oxygen administration resulted in a transient decrease in minute ventilation in all patients, with a mean fall of 18 ± 2%. However, for the remainder of the study period minute ventilation slowly increased, and by the end of the study was 93 ± 6% of the baseline value. Data on ventilation, breathing patterns and dead space to tidal volume ratios are shown in Table 3.3. In keeping with the results from the first study, the magnitude of the changes in minute ventilation did not adequately explain the rise in P_aCO_2 observed. However a significant rise in V_D/V_T ratio was noted and the authors considered that this was likely to be the most important mechanism. They considered the possibility of the Haldane effect, but previous research had found this to be a minor contributor to the increases in P_aCO_2 (Lenfant, 1966).

Table 3.3: Mean (± SE) minute ventilation and V_D/V_T before and after 15 minutes of 100% oxygen (Aubier, Murciano, Milic-Emili et al., 1980)

	$\dot{V}_E$ (L/min)	f (b/min)	V_T (ml)	V_D/V_T
Air	10.2 ± 20.5	32 ± 2	341 ± 26	77 ± 2
O_2	9.5 ± 0.07	31 ± 2	323 ± 21	82 ± 2
Air versus O_2	P < 0.01	NS	NS	P < 0.01

As noted in section 3.1, the multiple inert gas elimination technique developed by Wagner in 1974 was critical in advancing the understanding of gas exchange abnormalities in COPD and other pulmonary diseases. In conjunction with the work by Aubier and colleagues, a number of studies began to use MIGET to confirm that the administration of oxygen to COPD patients, even at concentrations as low as 26%, caused increased mismatching of perfusion to ventilation, particularly in under-ventilated lung units (Castaing, Manier, & Guenard, 1985; Wagner et al., 1974).

The next paper to substantially address the issue of oxygen induced hypercapnia studied 17 patients with moderately severe but stable COPD before and after 15 minutes of 100% oxygen (Sassoon, Hassell, & Mahutte, 1987). The authors of this study approached the question of potential mechanisms in two ways. First, they noted that individual patient responses to oxygen administration varied considerably. They proposed that if the hypoxic drive theory was solely responsible, then patients who demonstrated hyperoxic induced hypercapnia should have a blunted hypercapnic drive, but patients who did not should have a normal hypercapnic drive. Second, although previous studies had assumed that CO_2 production ($\dot{V}CO_2$) remained constant, they elected to measure it directly, along with respiratory drive and other ventilation variables, so an attempt could be made to estimate the proportional contributions of $\dot{V}CO_2$, minute ventilation, V_D/V_T and $P_{0.1}$ to the observed changes in P_aCO_2. Although the mean increase in P_aCO_2 of 4.4 mmHg in their subjects was smaller than that noted in previous studies, they confirmed the results of both studies by Aubier et al: a significant increase in the V_D/V_T ratio was the dominant

mechanism. Small and non-significant falls in both minute ventilation and $\dot{V}CO_2$ were seen, which the authors noted may have canceled each other out in terms of the effect on P_aCO_2. Hypercapnic respiratory drive was measured in all patients and found to have no correlation to the likelihood of a P_aCO_2 increase or its magnitude; further evidence that hyperoxic hypercapnia was not due to impaired CO_2 sensitivity.

In 1991 a study based in an intensive care unit administered 100% oxygen to 13 intubated patients and analysed changes in V_D/V_T and the "CO_2 recruitment threshold" (PCO_2RT) (Dunn, Nelson, & Hubmayr). PCO_2RT measures the response of a mechanically unloaded respiratory system to graduated increases in inspired CO_2, and is a surrogate measurement of respiratory drive. Although the authors found a significant increase in V_D/V_T with oxygen, the PCO_2RT also increased, which was interpreted as being consistent with a suppression of the hypoxic drive to breathe. However, there are a number of problems with their interpretation. First, all patients had been ventilator dependent for at least a week, and six had been ventilated for a month. The majority had had recent major surgical procedures, and significant co-morbidities were common including congestive heart failure, sepsis and renal failure. The patients were classified as having airflow obstruction based on ventilator-derived passive expiratory flow recordings rather than spirometry and clinical history. Finally, the measurement of PCO_2RT as an estimate of the degree of hypoxic drive to breathe had not been validated in other groups of patients.

Another study based in an intensive care unit measured the ventilatory CO_2 response using the re-breathing technique as an estimate of the CO_2 drive to breathe (Tardif et al., 1993). Patients were studied on the fifth day of admission with the ventilator set to maintain ABGs at a near normal range. During the experiment patients were disconnected from the ventilator and allowed to breathe 100% oxygen from a closed eight litre Douglas bag. In addition to the minute ventilation response to increasing inspired CO_2, inspiratory occlusion pressures ($P_{0.1}$) were measured as marker of neuromuscular respiratory drive. They compared 25 well defined and selected severe COPD patients with 26 controls and found that although the ventilatory response to increasing inspiratory CO_2 was lower in COPD patients, the slope was sufficiently steep to indicate that CO_2 drive still accounted for a significant proportion of their minute ventilation. Likewise, the occlusion pressure recordings indicated that the neural drive to breathe was well above normal.

A 1997 study examined respiratory control during oxygen induced hypercapnia by comparing observed changes in minute ventilation, arterial oxygen saturation and P_aCO_2 with the ventilation change predicted by the baseline ventilatory drive of each patient (Dick, Liu, Sassoon, Berry, & Mahutte). They measured both the hypercapnic and hypoxic respiratory drive in 11 stable hypoxic COPD patients and then administered 100% oxygen for 15 minutes. The mean P_aCO_2 increased by 6.6 ± 3.3 mmHg after oxygen, but no significant change in minute ventilation occurred. They calculated that the predicted fall in minute ventilation due to the loss of hypoxic drive was balanced by the predicted increase due to the stimulatory affects of hypercapnia. They concluded that

there was no evidence of failure of respiratory control mechanisms in the maintenance of P_aCO_2 homeostasis.

The most recent study of the respective roles of hypoventilation and $\dot{V}/\dot{Q}$ mismatch in AECOPD investigated the response to oxygen of 22 COPD patients studied within 72 hours of hospital admission (Robinson, Freiberg, Regnis, & Young, 2000). This study used MIGET to assess ventilation perfusion relationships and V_D/V_T, and documented minute ventilation at baseline and after oxygen. After breathing room air for at least 20 minutes to ensure a steady state, 100% oxygen was administered for 20 minutes. For the purposes of analysis the subjects were divided into two groups: 10 "non-retainers" who showed no increase in P_aCO_2, and 12 "retainers" defined as subjects whose P_aCO_2 increased by >3 mmHg from baseline.

At baseline breathing room air the retainers were significantly more hypoxic (mean P_aO_2 54.5 mmHg compared to 62.7 mmHg) and more hypercapnic (mean P_aCO_2 56.3 mmHg compared to 49.7 mmHg) than the non-retainers. The mean increase in P_aCO_2 in the retainer group was 8.8 ± 5.6 mmHg. All subjects demonstrated significant $\dot{V}/\dot{Q}$ inequality breathing room air and in both retainers and non-retainers it worsened significantly after 20 minutes of oxygen, with no difference between the groups. Detailed analysis of the $\dot{V}/\dot{Q}$ distribution patterns indicated that the main change in both groups was an increase in blood flow to lung units with low $\dot{V}/\dot{Q}$ ratios, consistent with the release of hypoxic pulmonary vasoconstriction. There was a small increase in the V_D/V_T

in the retainer group but not in the non-retainers. There was a significant decrease in minute ventilation in the retainer group (from 9.0 ± 2.0 L/min to 7.2 ± 1.6L/min) and not in the non-retainers; however comparison of the change in ventilation between the groups was non-significant. The authors interpreted their data as demonstrating that the major mechanism differentiating CO_2 retainers from non-retainers was a fall in minute ventilation rather than increasing V_D/V_T, because oxygen induced changes in $\dot{V}/\dot{Q}$ mismatch occurred equally in both groups.

Although this study seems to contradict earlier work, there are a number of methodological problems with respect to their data. First, their definition of CO_2 retainers as patients with a P_aCO_2 increase of more than 3 mmHg seems arbitrary and perhaps lacks clinical significance as a means of discriminating the two groups. In fact, of the 12 retainers, one third had rises in P_aCO_2 of only 3 to 4 mmHg. Secondly, although the retainer group was more hypoxic than the non-retainer group, neither group was particularly hypoxic in comparison with the data from Aubier et al (Table 3.2). Because HPV is not thought to be active until the P_AO_2 falls to 55-60 mmHg (Cutaia & Rounds, 1990), it could be argued that there was little opportunity for reversal of HPV in the non-retainer group whose mean baseline P_aO_2 was 62.7 mmHg.

In summary it can be seen that there is considerable heterogeneity in the data from a number of COPD studies over several decades. This is likely to be due to variability in methodology, physiological endpoints and the severity and acuity of patients studied.

Despite this, the available evidence points towards a mechanism of oxygen induced carbon dioxide retention that is dominated largely by changes in pulmonary blood flow and V_D/V_T ratio, rather than suppression of the hypoxic drive to breathe. The popularisation of the concept of the hypoxic drive to breathe and its role in oxygen induced hypercapnia is frequently attributed to an influential and often cited article by Campbell (1967). In the paper he does refer to the hypoxic drive to breathe, but he also later states that changes in $\dot{V}/\dot{Q}$ matching could also contribute to hypercapnia. For whatever reason, the latter theory has received less attention.

3.2 Asthma

This section outlines the pathophysiology of acute exacerbations of asthma and reviews the literature on the effects of oxygen treatment. The similarities between AECOPD and asthma exacerbations are described, emphasising the potential for a similar mechanism of CO_2 retention to occur.

3.2.1 Pathophysiology of acute severe asthma

Asthma is generally defined as a disease of the airways in which inflammation of the bronchial mucosa leads to variable degrees of airway hyper-responsiveness and airflow limitation (Gustavo J. Rodrigo, Rodrigo, & Hall, 2004). The mechanism, severity and duration of inflammation varies from patient to patient, as does the degree of airflow obstruction, resulting in a number of different clinical phenotypes (Wenzel, 2006).

Like COPD, asthma is primarily a disease of the airways and thus can broadly be classified as an obstructive lung disease. However there are a number of important differences between the two conditions. First, asthma is typically intermittent and many patients demonstrate little in the way of symptoms or lung function abnormalities between exacerbations. In a minority of patients however, chronic poorly controlled bronchial inflammation can lead to airway remodeling, and in some, fixed airflow obstruction develops similar to that seen in COPD. Second, many COPD patients have disease of the pulmonary parenchyma in addition to the airways. This destruction of alveolar attachments and connective tissue (Figure 3.1) does not occur in asthma. Third, in advanced stages COPD results in more severe airflow obstruction than in asthma. Despite these differences, the changes in pulmonary physiology and gas exchange that occur during severe acute asthma and AECOPD are similar.

Acute exacerbations of asthma (also referred to as asthma attacks or acute asthma) are characterised by a progressive deterioration in symptoms over hours or days, although a small number of patients have a rapid deterioration over the course of a few minutes (Gustavo J. Rodrigo & Rodrigo, 2000). The characteristic symptoms of cough, wheeze and shortness of breath result from an increase in bronchial inflammation, and airflow obstruction. There are a variety of triggers for the increased inflammatory response in the airways (Singh & Busse, 2006). The increase in airflow obstruction results from a combination of bronchial wall oedema, increased secretions and constriction of bronchial smooth muscle (McFadden, 2003). Fatal or near fatal exacerbations are characterised by

extensive plugging of the small airways with impacted mucus, epithelial cells and inflammatory cells (Dunnill, 1960; Hogg, 1987).

If the airflow obstruction and expiratory flow limitation is not relieved by therapy with bronchodilator and anti-inflammatory drugs, a series of abnormalities in lung mechanics and gas exchange occurs, similar to that observed in AECOPD. The increase in airway resistance leads to a reduced expiratory flow rate, premature airway closure and progressive hyperinflation (McFadden, 2003). As with AECOPD, the perceived degree of breathlessness in patients with acute asthma is closely linked to hyperinflation with a direct correlation to changes in end-expiratory volumes, specifically an increasing FRC (Lougheed, Lam, Forkert, Webb, & O'Donnell, 1993). The extent of hyperinflation and gas-trapping in acute asthma can be significant, and in some individuals residual volume approaches 400% of normal and FRC can be twice predicted values (McFadden, Kiser, & DeGroot, 1973). Like AECOPD, these changes in lung volumes result in flattening of the diaphragm and progressive worsening of the length-tension relationship of respiratory muscles.

3.2.2 Oxygen therapy in acute severe asthma

As noted earlier in this chapter, case reports of COPD patients developing delirium, confusion and coma in response to high concentration oxygen therapy began to appear in the literature as early as the 1930s. By contrast, administration of uncontrolled oxygen to patients with acute asthma was felt to be relatively safe.

In 1951 the first report on oxygen induced hypercapnia in a patient with acute asthma was published in the New England Journal of Medicine (Beale, Schiller, Halperin, Franklin, & Lowell). It describes a 53 year old man with recent onset asthma who was admitted with acute dyspnoea and wheeze. Due to the presence of cyanosis he was given oxygen at 6L/min; however over the following hours he was noted to become increasingly drowsy and then unresponsive. An ABG showed that his P_aCO_2 had increased from 83 mmHg on room air to 142 mmHg breathing oxygen with a concomitant fall in pH from 7.22 to 7.11. When oxygen was withdrawn his mental state and hypercapnia improved. Although it is possible that the man had underlying emphysema in addition to asthma, as his smoking status is not mentioned, he eventually fully recovered from the episode and attained relatively normal lung function. Despite this case report appearing in a widely read international journal there was nothing else of note published on the issue of oxygen therapy in asthma for another decade.

By the 1960s most investigators agreed that the hypoxia associated with acute asthma was predominantly the result of $\dot{V}/\dot{Q}$ mismatch (Field, 1967; Rees, Borthwick, Millar, & Donald, 1967; Rees, Millar, & Donald, 1967). Moreover, a number of reports began to appear in which the administration of vasodilator agents, such as acetyl-choline and isoprenaline, worsened arterial oxygen saturation and increased $\dot{V}/\dot{Q}$ mismatch (Irnell & Nordgren, 1966; Knudson & Constantine, 1967; Palmer & Diament, 1967; Tai & Read,

1967b). This was thought to be due to the vasodilator effect of the drugs increasing blood flow to lung units with low ventilation, thus reversing the compensatory effects of HPV.

In 1967 the first study looking specifically at the effects of oxygen on $\dot{V}/\dot{Q}$ relationships in asthma was published (Field). It involved 26 asthmatic hospital in-patients who were administered 100% oxygen for 20 minutes. Changes in minute ventilation, V_D/V_T and P_aCO_2 were measured. It found a statistically significant increase in P_aCO_2 of 3.0 mmHg which was associated with a small but statistically significant increase minute ventilation of 0.84L/min, but no change in tidal volume. The V_D/V_T increased significantly by 8.7%. The authors interpretation was that oxygen inhalation attenuated HPV and resulted in redistribution in pulmonary blood flow. The increase in blood flow to poorly ventilated lung units diverts blood away from well ventilated areas, resulting in a net increase in alveolar dead space and thus increased V_D/V_T.

There are a number of methodological issues with Field's study. First, although subjects had airflow obstruction at the time of the study, there was no record of smoking history, no requirement for a previous formal diagnosis of asthma, and the group included a number of elderly patients. Hence it is possible that COPD may not have been adequately excluded. Second, there was no control group, and the study incorporated a number of other elements, such as changes in posture from lying to sitting and the administration of

isoproterenol and atropine, which may have influenced the effects of oxygen on the physiological variables measured.

The following year another small uncontrolled study of 12 in-patients with asthma used a similar methodology to assess the effects of 100% oxygen administered for 20 minutes (Valabhji, 1968). In this sample there was a similar rise in the V_D/V_T of 8.8%, but no significant change in P_aCO_2 was observed.

In addition to physiological studies, 1967 saw the publication of the first large systematic case series of ABG abnormalities in 76 patients with acute asthma. The patients were divided into two groups; 12 with life threatening asthma and 64 with less severe asthma (Tai & Read, 1967a). Data for the 12 severe asthma patients are shown in Table 3.4.

It can be seen that all seven of the subjects receiving high flow oxygen were hypercapnic compared with only one of five receiving room air, although this may be related to disease severity as data on FEV1 were not provided for these patients. Five of the seven subjects receiving oxygen had a P_aO_2 greater than 80 mmHg, and three were significantly hyperoxic with a P_aO_2 of 150, 200, and 265mmHg respectively. Among the 64 patients with less severe asthma, significant abnormalities in ABG results were less common; only nine (14%) had a P_aCO_2 greater than 45 mmHg and only four (6%) had a P_aO_2 less than 60 mmHg.

Table 3.4: ABG results from 12 patients with life threatening asthma (Tai & Read, 1967a)

Subject	P_aCO_2 (mmHg)	P_aO_2 (mmHg)	pH
1	200*	200	6.81
2	138*	150	7.00
3	79*	71	7.25
4	74	39	7.31
5	66*	59	7.29
6	65*	265	7.24
7	57*	88	7.27
8	55*	88	7.24
9	41	60	N/A
10	40	59	7.32
11	39	60	7.38
12	34	62	N/A

* Subjects receiving high concentration oxygen at the time of ABG

The alveolar gas equation describes the relationship between alveolar oxygen and arterial carbon dioxide. In its simplified form, for a patient breathing room air at sea level with a respiratory quotient of 0.8, it is represented as:

$$P_AO_2 = 147 - (P_aCO_2 / 0.8)$$

It follows from this equation that the highest P_aCO_2 possible while breathing room air is around 80 mmHg. Levels above this would result in alveolar and arterial oxygen tensions that are theoretically incompatible with life. Therefore a P_aCO_2 higher than 80 mmHg, as in the Tai study and other case series of acute severe asthma (Molfino, Nannini, Martelli, & Slutsky, 1991; Mountain & Sahn, 1988; Wasserfallen, Schaller, Feihl, & Perret, 1990), must be partly attributable to the administration of oxygen. In these reports the degree of hypercapnia in some patients with life-threatening asthma is often noted, but is usually ascribed to the severity of airflow obstruction. Little mention is made of the potential contribution of the high concentration oxygen the patients are almost invariably receiving at the time.

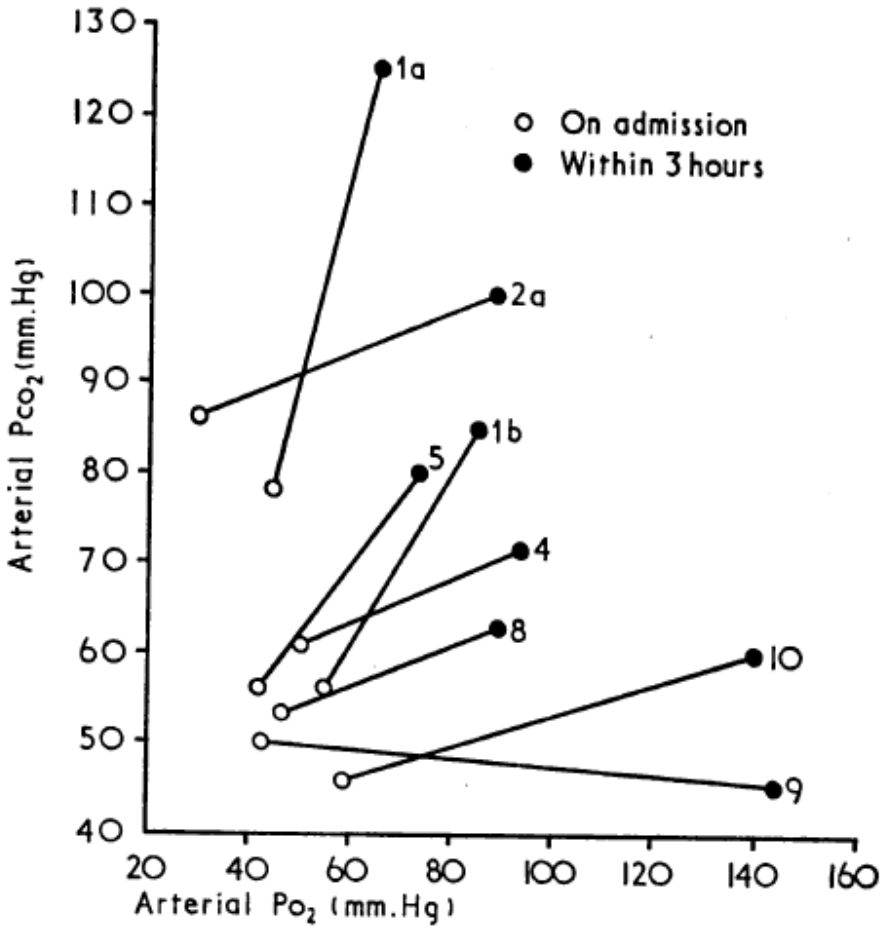
The following year a large study presented ABG and FEV1 data for a group of 101 acute asthmatics (McFadden & Lyons, 1968). In this series all ABG samples were taken on room air and the most common gas exchange abnormality was mild to moderate hypoxaemia associated with hypocapnia. Hypercapnia occurred in 11 subjects and was associated with increasing airflow obstruction, with the majority of hypercapnic patients having an FEV1 less than 15% predicted.

Rees, Millar and Donald (1968) studied 25 episodes of acute severe asthma, but unlike previous work they took ABG samples on room air, and again after delivering controlled

oxygen therapy at concentrations of 28 to 35% to assess the response. Moderate to severe hypoxaemia was present at baseline with a mean P_aO_2 of 53 mmHg, and the administration of low concentration oxygen increased this to a mean of 73mmHg without any significant rise in P_aCO_2. This study was the first to demonstrate that low concentration oxygen therapy was usually sufficient to relieve hypoxaemia in the majority of patients with acute severe asthma.

A case series of ABG abnormalities in acute childhood asthma reported baseline data on 24 exacerbations in 21 children aged between two and 12 years, and described the response to the administration of oxygen at a flow rate of 4 – 10L/min for three hours (H. Simpson, Forfar, & Grubb, 1968). On admission, hypoxaemia was common with a P_aO_2 less than 75 mmHg in all cases and less than 50 mmHg in four. Hypercapnia, defined as P_aCO_2 greater than 50 mmHg, was present at baseline in eight cases. In response to oxygen therapy, respiratory failure worsened in seven of these eight cases (Figure 3.7).

Figure 3.7: Change in gas exchange after three hours of oxygen administration in eight presentations of acute severe childhood asthma (H. Simpson et al., 1968).



In 1976 an editorial in the British Medical Journal directly addressed the question of appropriate oxygen therapy in acute severe asthma ("Editorial: Oxygen in bronchial asthma," 1976). With reference to the report by Shiller in 1951, and the pediatric series from Simpson et al in 1968, it emphasized the risks of oxygen induced hypercapnia and gave the following opinion, in contradiction to current practice at the time:

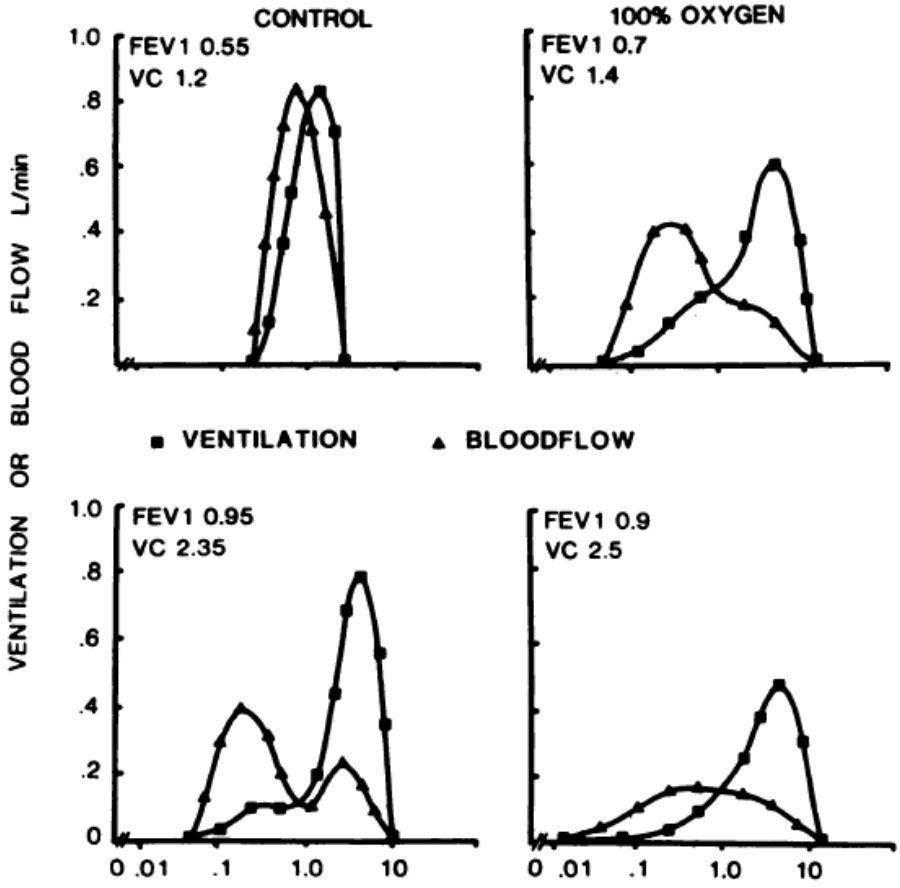
> It seems prudent, then, in the severe asthmatic first to give controlled oxygen therapy (24% through a Venturi-type mask). If this fails to maintain an arterial oxygen saturation of 80-90%, then 28% or even35% oxygen should be given. The effect of oxygen in the individual asthmatic can be judged properly only by careful clinical assessment and frequent measurements of arterial blood gas tensions. ("Editorial: Oxygen in bronchial asthma," 1976, p. 609)

Another case series on oxygen therapy in acute asthma aimed to document the baseline status of 14 consecutive patients before any oxygen was delivered, and then the response to a relatively low flow oxygen regime (Rudolf, Riordan, Grant, Maberly, & Saunders, 1980). Moderate to severe hypoxaemia was present on arrival with a P_aO_2 range of 43 – 71 mmHg and a mean of 56 mmHg. Hypercapnia (defined as $P_aCO_2 > 45$ mmHg) was present in five of the 14 subjects. After one hour of oxygen at 4L/min, all patients had relief of hypoxia with a minimum P_aO_2 of 74 mmHg. Of the five hypercapnic patients, only two still had elevated P_aCO_2 after one hour, and in both cases it returned to normal with a decrease in oxygen concentration to 24%.

In the 1980s the use of MIGET enabled investigators to further clarify the ventilation perfusion relationships in asthma and the response to oxygen. Corte and Young demonstrated a significant worsening of $\dot{V}/\dot{Q}$ mismatch in 10 subjects with chronic asthma (FEV1 < 60% predicted) after breathing 100% oxygen for 20 minutes (1985). There was a spectrum of baseline $\dot{V}/\dot{Q}$ abnormalities ranging from mild changes in six subjects to moderately severe in four. Although all subjects had airflow obstruction, there was poor correlation between FEV1 and $\dot{V}/\dot{Q}$ mismatch. The six subjects with only

mildly abnormal $\dot{V}/\dot{Q}$ changes showed the largest increase in mismatch in response to oxygen. Changes were also seen in the remaining four, but were of a smaller magnitude. The $\dot{V}/\dot{Q}$ distributions before and after 100% oxygen for two representative subjects are shown in Figure 3.8.

Figure 3.8: $\dot{V}/\dot{Q}$ distributions before and after 100% oxygen in two subjects with mild (top) and severe (bottom) baseline $\dot{V}/\dot{Q}$ abnormalities (Corte & Young, 1985).



The authors considered that the wide variation in $\dot{V}/\dot{Q}$ ratios at baseline reflected different degrees of HPV, and that those with less $\dot{V}/\dot{Q}$ mismatch had compensated for areas of poor ventilation more completely. Previous work in normal subjects has demonstrated that there is significant inter-individual variability in the response of local HPV to alveolar hypoxia (Fowler & Read, 1963). Consequently, if the subjects with mild $\dot{V}/\dot{Q}$ abnormalities at baseline had more active HPV as a compensatory mechanism, then the change seen in response to 100% oxygen might be expected to be larger.

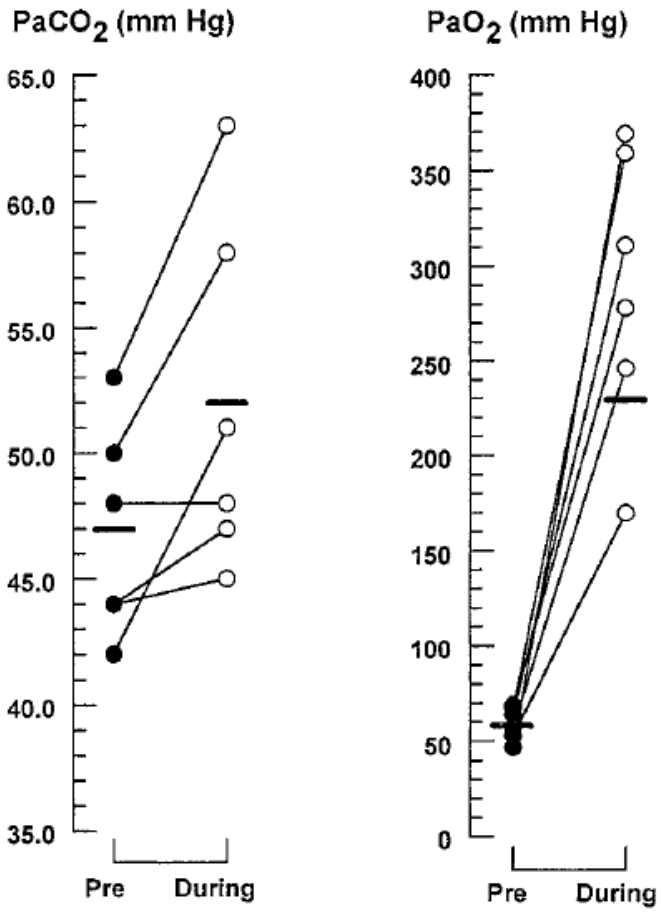
Later studies using MIGET confirmed Corte and Young's findings that the dominant mechanism for hypoxaemia is $\dot{V}/\dot{Q}$ mismatch, with little contribution from either shunt or alveolar-capillary diffusion limitation (Ballester et al., 1989; Ferrer, Roca, Wagner, Lopez, & Rodriguez-Roisin, 1993; Roca et al., 1988; Rodriguez-Roisin, Ballester, Roca, Torres, & Wagner, 1989). Moreover, as with AECOPD, $\dot{V}/\dot{Q}$ mismatch substantially worsened when patients were administered 100% oxygen in both acute severe asthma (Ballester et al., 1989; Rodriguez-Roisin, Ballester, Roca, Torres, & Wagner, 1989) and chronic severe asthma (Ballester, Roca, Ramis, Wagner, & Rodriguez-Roisin, 1990) as a consequence of a reduction in HPV.

An uncontrolled prospective interventional study of oxygen treatment in acute asthma assessed the effect of fixed dose low concentration oxygen via a 35% Venturi mask during pre-hospital treatment (Ford & Rothwell, 1989). The 45 episodes of acute asthma

were associated with significant airflow obstruction with a mean Peak Expiratory Flow Rate (PEFR) of 28% predicted. An arterial blood gas (ABG) was taken a mean of 20 minutes following the commencement of oxygen, and found that all patients had adequate relief of hypoxaemia with a P_aO_2 range of 66 to 160 mmHg. One quarter of patients had a P_aCO_2 greater than 45 mmHg with an upper range of 58mmHg. Unfortunately there was no control group in this study, baseline ABG results breathing room air were not available and the subjects were not followed longitudinally in a systematic way following the first ABG. However, it provided further evidence of the ability of relatively low concentrations of oxygen to relieve the hypoxaemia in most patients with acute severe asthma.

A similar prospective interventional trial studied 37 subjects presenting with severe asthma and a mean FEV1 of 49% predicted (Chien et al., 2000). A baseline ABG was taken on room air and repeated after 20 minutes of 100% oxygen, with no other asthma treatment administered during the study period. As expected, mean P_aO_2 increased substantially from 70.2 mmHg to 303.5 mmHg. The P_aCO_2 remained stable in five subjects, fell in seven and increased in 25. There was a small but statistically significant increase in mean P_aCO_2 of 2.3 mmHg. Of the 25 subjects who had an increase in P_aCO_2, hypercapnia developed in seven subjects who had previously normal CO_2, and worsened in six patients who had hypercapnia at baseline (Figure 3.9).

Figure 3.9: Changes in gas exchange before and during 100% oxygen therapy in asthmatics with hypercapnia at baseline (Chien et al., 2000).



The authors considered that the changes were likely due to oxygen therapy, given that they occurred without any significant change in respiratory rate or FEV1. However, a major weakness of the study was the lack of a control group, and the fact that no other asthma medications were given concurrently with oxygen.

The first, and currently only, randomised controlled trial of oxygen therapy in acute severe asthma was published in 2003 (G. J. Rodrigo et al.). In this study subjects were randomised to receive either 28% or 100% oxygen for 20 minutes, and as with the study by Chien et al, other asthma treatments were withheld for the duration of the study. The 74 patients had severe airflow obstruction (mean PEFR 41%), moderate hypoxaemia (mean P_aO_2 77.8 mmHg) and hypocapnia (mean P_aCO_2 36.4 mmHg) at baseline. There was a statistically significant increase in mean P_aCO_2 of 2.7 mmHg in the 100% oxygen group compared to the 28% group. The authors considered a P_aCO_2 increase of more than 2 mmHg to be greater than that expected by the Haldane effect and therefore physiologically significant. In the 100% oxygen group, 16/38 (42%) subjects had an increase in $P_aCO_2 > 2$ mmHg, averaging 5 mmHg (range 2.4 to 14.3 mmHg) compared to only 6/36 (16%) of subjects in the 28% oxygen group. Figure 3.10 shows the relationship between P_aCO_2 before and after 20 minutes of oxygen in the two groups. Patients receiving 100% oxygen had a tendency to increase their P_aCO_2 in contrast to the 28% group where it tended to fall. P_aCO_2 had a significant inverse relationship to PEFR in the 100% group but not in the 28% group (Figure 3.11).

Figure 3.10: P_aCO_2 before and after 20 minutes of oxygen therapy in the 28% and 100% oxygen groups (G. J. Rodrigo et al., 2003).

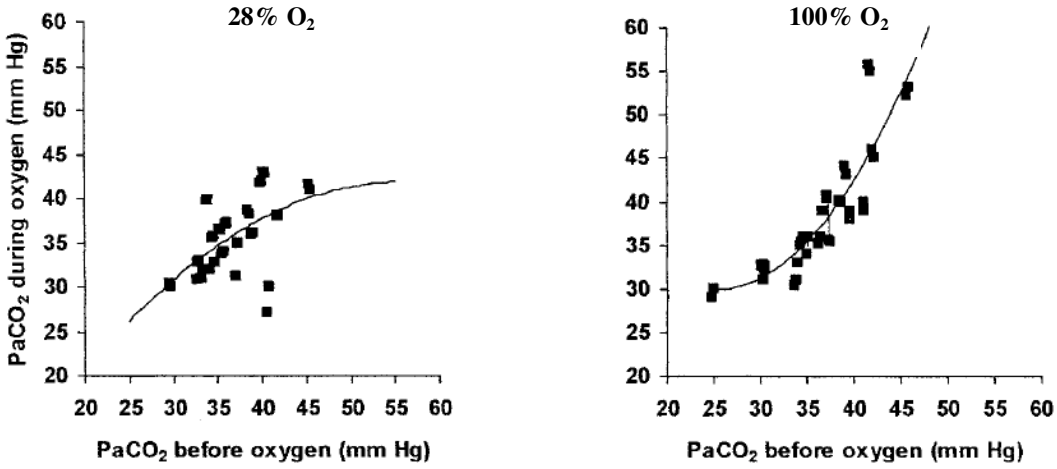
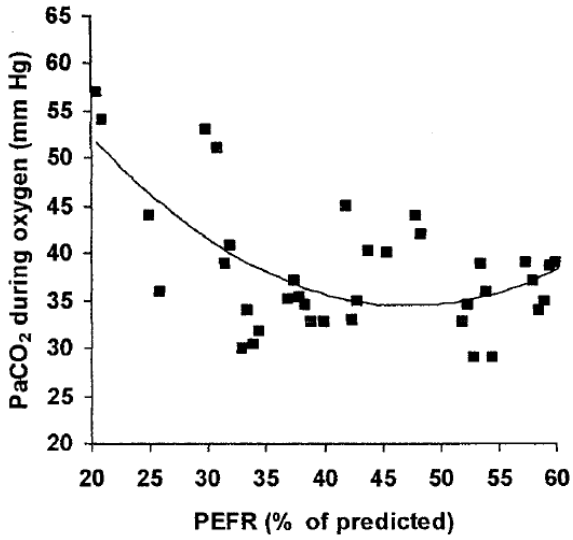


Figure 3.11: Relationship between initial PEFR and P_aCO_2 in the 100% group (G. J. Rodrigo et al., 2003)



Although this study has the strength of a randomised controlled design, as with the study by Chien et al there are a number of methodological issues. First, although 100% oxygen via a non-rebreather mask is occasionally administered to asthmatics, the commonest delivery device is a medium concentration mask with flow rates of 6-8 L/minute, similar to that used for the delivery of nebulised bronchodilators. Second, the duration of oxygen delivery was shorter than in general clinical practice, and no other asthma medications were administered during the study. Finally, two subjects were excluded after randomisation and enrollment, due to being unable to maintain oxygen saturations above 90%. It is likely that these patients had severe airflow obstruction and therefore may have had a higher risk of an increase in P_aCO_2 during the period of oxygen treatment.

In summary, although the studies by Chien et al and Rodrigo et al provide the best available evidence to date on the effect of high concentration oxygen in acute severe asthma, their methodological weaknesses and poor generalisability to routine clinical practice limit their interpretation.

3.3 Pneumonia

Community-acquired pneumonia is a common respiratory condition associated with significant morbidity and mortality ("BTS Guidelines for the Management of Community Acquired Pneumonia in Adults," 2001). It is caused by the accumulation of inflammatory cells and exudate in alveolar spaces, giving rise to consolidation (Wunderink & Waterer,

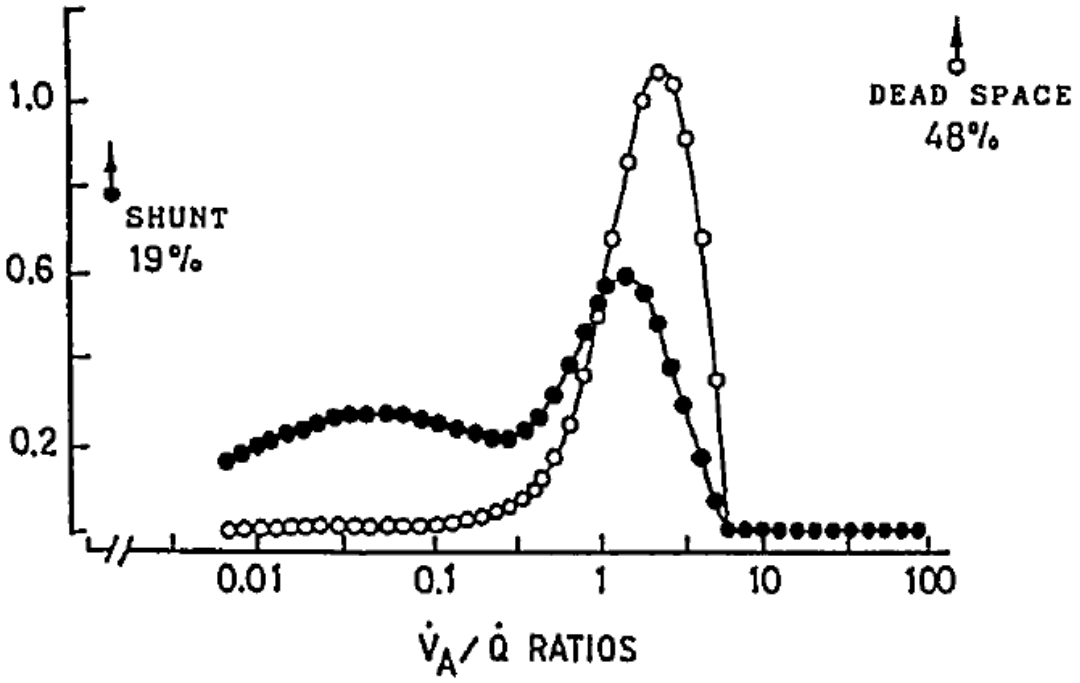
2004). In terms of the pathophysiology of gas exchange, pulmonary infection can result in both V/Q mismatch or shunt, depending on the degree of ventilation to the lung units affected by consolidation (Light, 1999).

As outlined in Chapter 2, the early history of oxygen administration saw a great deal of interest in its use for the treatment of cyanosis and hypoxaemia associated with severe pneumonia. Unfortunately, in the 100 years since it was first used there have been no randomised controlled trials on oxygen therapy in pneumonia. Despite this, routine use of oxygen is recommended in international guidelines ("BTS Guidelines for the Management of Community Acquired Pneumonia in Adults," 2001). Although there is a paucity of clinical research on the effects of oxygen treatment in acute pneumonia, physiological studies have demonstrated the gas exchange abnormalities that exist in moderate and severe pneumonia, as well as changes that occur when oxygen is administered.

Early work on the gas exchange abnormalities during experimental pneumonia in anaesthetised dogs found significant abnormalities including both V/Q mismatch and shunt (Wagner, Laravuso, Goldzimmer, Naumann, & West, 1975), findings that were later advanced with studies using MIGET. These found that while shunt was a common finding in mechanically ventilated patients with pneumonia, in spontaneously breathing subjects, V/Q mismatch was the dominant cause of hypoxaemia (Gea et al., 1991; Lampron et al., 1985; Walmrath et al., 1995). A typical V/Q dispersion graph from a patient mechanically ventilated with life threatening pneumonia is shown in Figure 3.10.

Note the presence of a significant shunt fraction and the bimodal perfusion pattern indicating increased blood flow to regions with low V/Q ratio. In general, increasing pneumonia severity results in worsening of both the shunt fraction and the degree of V/Q mismatch (Gea et al., 1991).

Figure 3.12: V/Q distribution of a mechanically ventilated pneumonia patient (Gea et al., 1991).



Among mechanically ventilated patients, the administration of 100% oxygen does not significantly increase the degree of shunt. However, V/Q mismatch is markedly worsened by oxygen administration in both ventilated and spontaneously breathing patients,

suggesting the release of hypoxic pulmonary vasoconstriction (Lampron et al., 1985; Lemaire, Matamis, Lampron, Teisseire, & Harf, 1985).

These studies show that the pathophysiology of gas exchange in pneumonia is similar acute asthma and AECOPD, in that all patients demonstrate a significant degree of V/Q mismatch. Moreover, the administration of oxygen worsens V/Q dispersion in pneumonia. Consequently there is the potential for a significant increase in V_D/V_T and thus oxygen induced hypercapnia, although no studies to date have assessed the effect of oxygen on P_aCO_2 in acute pneumonia.

3.4 Summary

The aim of this chapter was to outline the pathophysiology of AECOPD, acute severe asthma and pneumonia, and to draw parallels between the mechanisms of abnormal gas exchange in the three conditions. Previous studies in acute asthma and pneumonia suggest that high concentration oxygen can worsen gas exchange, and that the most likely mechanism, as with AECOPD, is the reversal of HPV and in increase in V_D/V_T. This provides a physiological basis for a potential risk of carbon dioxide retention in respiratory conditions other than AECOPD. In addition there is preliminary evidence from a small number of clinical studies that high concentration oxygen may cause significant hypercapnia in acute asthma.

Previous studies on the physiological response to oxygen in asthma and pneumonia have been limited by small size, poorly defined enrollment and selection criteria, and the lack of control groups. In addition they have often included interventions other than oxygen, such as the administration of vasodilator or bronchodilator drugs. Some have measured the change in $\dot{V}/\dot{Q}$ mismatch or the change in P_aCO_2 but not both simultaneously. Finally, few studies have recorded minute ventilation in conjunction with $\dot{V}/\dot{Q}$ data, to assess its contribution as an alternative mechanism of carbon dioxide retention. Importantly, there is no clinical data from large randomised controlled trials in either asthma or pneumonia which adequately assesses the effect of uncontrolled high concentration oxygen on P_aCO_2 in a routine clinical setting.

To address these questions, chapters 4 and 5 outline the methodology of two randomised controlled trials on the effect of high concentration oxygen therapy in patients with acute asthma and pneumonia. Chapter 6 describes a physiological study, with both positive and negative control groups, to assess the response of P_aCO_2, V_D/V_T and minute ventilation to 100% oxygen in chronic severe asthma.

Chapter 4: A randomised controlled trial of high concentration versus titrated oxygen in acute asthma- methods

4.1 Outline of the study

As discussed in chapter 3, there is currently little evidence to guide the appropriate use of oxygen in acute severe exacerbations of asthma. The studies that have been conducted are limited by the lack of a control group (Chien et al., 2000), a short duration of oxygen therapy (Chien et al., 2000; G. J. Rodrigo et al., 2003), and the exclusion of some patients with more severe disease (G. J. Rodrigo et al., 2003). In addition, no concurrent asthma therapy was given during the time of oxygen administration, making them less applicable to routine clinical practice.

This study protocol was designed to extend earlier work and provide evidence on which to base rational guidelines for oxygen therapy in acute asthma by comparing continuous high concentration administration with titrated oxygen flow.

The study was designed as an open, randomised, controlled, parallel group trial. It was not possible to blind the participants or the investigators due to the requirement for patients in the titrated oxygen group to change delivery devices according to the flow of oxygen required (see the titration protocol below). Although blinding is desirable when

possible, it is less important in studies such as this which assess objective physiological endpoints.

Compared to earlier studies, there are design differences in this study which aim to more closely replicate clinical practice in the emergency department. These are:

1. The duration of oxygen administration was increased from 20 to 60 minutes
2. Standard therapy for acute asthma, including bronchodilators and corticosteroids, was given concurrently with oxygen
3. The oxygen flow rate was set at 8 L/min via a medium concentration mask in the high concentration group, rather than attempting to deliver 100% oxygen. 8 L/min is the flow rate recommended to drive nebulised medications ("Current best practice for nebuliser treatment, British Thoracic Society," 1997).

4.2 Study objective and hypothesis

The objective of the study was to investigate the effects of high concentration oxygen on P_aCO_2 in patients with acute severe asthma in the emergency department. The hypothesis was that administration of high flow oxygen in acute severe asthma may result in worse outcomes when compared to titrated oxygen, as defined by an increase in P_aCO_2.

4.3 Study participants

Subjects were recruited between July 2007 and September 2009. The study was conducted in the emergency departments of three metropolitan hospitals in Wellington, New Zealand: Wellington Hospital (tertiary public, catchment 250,000), Hutt Hospital (secondary public, catchment 140,000) and Kenepuru Hospital (secondary public, catchment 100,000).

Patients arriving at the emergency department either by ambulance or self presentation were approached by the investigator to assess potential eligibility. Patients aged between 18 and 65 years were eligible for inclusion if they met the following criteria:

- A previous doctor diagnosis of asthma
- A history consistent with a current acute exacerbation of asthma
- An FEV1 $\leq$ 50% predicted at the time of first assessment by the investigator.

Patients were excluded if they met any of the following criteria:

- A history of COPD
- A history of more than 20 pack years of tobacco smoking
- Patient unconscious, unable to speak or unable to perform spirometry
- Requirement for mechanical ventilation

- Presence of other risk factors for hypercapnic respiratory failure: Significant neuromuscular disease, severe chest wall restriction, or morbid obesity.

4.4 Randomisation

A computer generated randomised allocation schedule was provided by a biostatistician. To ensure allocation concealment, the schedule was imbedded into a specially designed enrolment database (Microsoft Access) by a third party. This was done without the involvement of the clinical investigators responsible for enrolment and was therefore concealed from them. This database was then accessed by a secure password. Once an eligible patient had provided written informed consent the investigator entered their details into the database. A field then appeared prompting the entry of the next available subject number. After clicking a button marked “randomise” the database would then reveal the allocation for that patient (either “high flow” or “titrated”) based on the imbedded randomisation schedule.

4.5 Interventions

Subjects who met the enrolment criteria and gave written informed consent were randomly assigned to one of two oxygen regimes for a total of 60 minutes:

4. Oxygen delivered at 8 litres per minute via a medium concentration mask (Hudson RCI, Durham NC, USA)

5. Oxygen delivered at a flow rate titrated to achieve transcutaneous oxygen saturations between 93 and 95%.

The oxygen adjustment protocol for patients in the titrated oxygen group is shown in Table 4.1. Oxygen flow rates up to 4L/min were delivered via nasal prongs (Hudson RCI, Durham NC, USA). Flow rates higher then 4L/min were delivered by medium concentration mask.

Table 4.1: Oxygen titration protocol

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

In both groups, if an oxygen flow rate of 8L/min was insufficient to maintain the oxygen saturation above 90% the patient was withdrawn from the study.

4.6 Clinical measurements

4.6.1 Transcutaneous partial pressure of carbon dioxide ($PtCO_2$)

The transcutaneous measurement of P_aCO_2 functions on the principle that carbon dioxide diffuses extremely well through tissues. A probe is attached to the earlobe and warms to 42°C which dilates and "arterialises" the underlying capillaries. The CO_2 diffusing through the skin changes the pH of an electrolyte membrane in the probe and the resulting signal is converted to an estimate of the P_aCO_2. The device used in this study (TOSCA 500; Linde Medical Sensors AG, Basel, Switzerland) has a Stow-Severinghaus electrode. The probe membrane was replaced every 14 days as per manufacturer guidelines. The device automatically calibrates every four hours using an internal canister containing 7% carbon dioxide.

4.6.2 Heart rate and oxygen saturation

The TOSCA 500 incorporates both pulse oximetry and $PtCO_2$ measurement in the same probe, so the monitor was used to record heart rate and oxygen saturation.

4.6.3 Spirometry

All spirometry was performed using a handheld spirometer (Micro Spirometer, Micro Medical Ltd, Rochester, U.K.) which was regularly calibrated, and standard reference tables for predicted values were used.

4.7 Study protocol

Potential participants were screened by the investigator with baseline spirometry. If the FEV1 was less than or equal to 50% predicted and the inclusion/exclusion criteria were met, the patient was asked to provide written informed consent and then randomised. The patient's earlobe was cleaned with an alcohol swab and allowed to dry. The $PtCO_2$ probe was attached using the provided attachment clips and contact gel. If the oxygen saturations were less than 92%, oxygen was given to achieve a saturation of 93-95% (Table 4.1). A minimum of 10 minutes was allowed for arterialisation to occur and $PtCO_2$ readings to stabilise, at which point (Time = 0) baseline data were recorded and the oxygen protocol started. The FEV1, $PtCO_2$, respiratory rate, heart rate and oxygen saturations were recorded at baseline and then at 20 minute intervals for the duration of the study. The timing of the study procedures is summarised in Table 4.2.

Table 4.2: Summary of asthma study procedures

Procedure	T = - 10	T = 0	T = 20	T = 40	T = 60
Consent	X				
Randomise	X				
Attach ear probe	X				
Spirometry	X		X	X	X
Start oxygen regime		X			
$PtCO_2$		X	X	X	X
Heart rate		X	X	X	X
Respiratory Rate		X	X	X	X
Pulse oximetry	X	X	X	X	X

4.8 Asthma treatment protocol

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 (FEV1 30 to 50% predicted) received salbutamol 2.5mg via a nebuliser every 20 minutes and prednisone 40mg orally. Those with very severe asthma (FEV1 < 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. Additional doses of salbutamol were given if the investigator felt they

were warranted for reasons of clinical severity. The need for ABG testing and chest radiology was at the discretion of the investigator. Patients randomised to the titrated oxygen group had all nebulised medications administered via an air driven nebuliser while continuing with titrated oxygen via nasal prongs if required. Patients in the high flow oxygen group had all nebulised medications driven by 8L/min of oxygen.

4.9 Outcome measures and statistical analysis

The primary outcome variable was the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg. Secondary outcome variables included the proportion of patients with a $PtCO_2$ rise of ≥8 mmHg, the proportion with both a rise in $PtCO_2$ ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes, and the mean change from baseline $PtCO_2$. 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. Variables for which normality assumptions were not met were analysed by a Mann-Whitney test. Analysis was by intention to treat. SAS version 9.1 and Minitab version 14 were used.

4.10 Sample size

Using data from a previous study (G. J. Rodrigo et al., 2003), 75 participants were required in each group to detect a difference in the main outcome variable (the proportion

of patients with a rise in $PtCO_2$ of ≥ 4 mmHg) of 20% in the high concentration oxygen group and 5% in the titrated group with power of 80% and a type 1 error rate of 5%.

4.11 Ethical approval and trial registration

The main ethical issue that arose during the planning phase of the study was the acknowledgement that the protocol would involve approaching patients in the emergency department with an acute medical illness, some of whom would be distressed and/or significantly breathless.

Clinical research is governed by the ethical and quality standards of Good Clinical Practice (GCP), which are in turn based on the Declaration of Helsinki (Williams, 2008). One of the clear obligations of the researcher is to provide comprehensive information about the clinical study to all potential participants. However, previous research has demonstrated that patients enrolled into clinical trials of acute medical interventions have limited capacity to retain and remember important aspects of the study at a later date (Chenaud, Merlani, Luyasu, & Ricou, 2006; Gammelgaard, Mortensen, & Rossel, 2004). Despite this, there is an ethical imperative to study patients with acute medical illness so that future therapies can be improved or made safer.

For the studies in this thesis the full information sheet submitted to the ethics committee for approval was four pages long, and the full consent form (to be signed after reading

the information sheet) was two pages long with 16 individual statements to tick (See appendices). The disclosure of this much information is appropriate and desirable when subjects are considering enrolment into a study on an outpatient or ambulatory basis. However, in this case it was felt to potentially be a barrier not only to participation in the study, but also to the prompt institution of appropriate medical treatment.

I met personally with the Central Regional Ethics Committee to discuss possible solutions. My proposal was to prepare a separate single page document with a short statement describing the key features of the study, including the fact that participation was voluntary and the subject could withdraw at any time, followed by a space for written consent (see appendices). The intention was that this "short information and consent form" would be supplemented by a clear verbal explanation and the offer to answer any questions. The ethics committee agreed that this was a reasonable approach to take on the basis that the study was conceptually easy to describe and involved no invasive monitoring. We also agreed that there would be a requirement for the patient to read the full information sheet and sign the full consent form at an appropriate time during the study, and that they could withdraw their consent at that point if they wished.

The study was approved by the Central Regional Ethics Committee, Wellington, New Zealand (CEN 06/11/101) on 18th January 2007 and prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN 12607000131459). The study was approved by Capital and Coast District Health Board and Hutt Valley District Health Board.

4.12 Study organisation

All investigators involved in the study were qualified medical practitioners with at least three years post-graduate clinical experience. I was responsible for the training and supervision of all participating research staff. Staff levels permitting, an investigator was usually onsite and available to recruit patients at the emergency departments of the participating hospitals from 0800 to 2200 Monday to Friday.

4.13 Data management

Each patient's results were recorded on a study worksheet which was stored in a secure locked location near the emergency department. Collected data sheets were then transferred to the offices of the Medical Research Institute of New Zealand for data entry and secure storage. The data was entered into the study database (Microsoft Access) and stored on a secure server.

Chapter 5: A randomised controlled trial of high concentration versus titrated oxygen in pneumonia-methods

5.1 Outline of the study

Although international guidelines recommend the use of supplementary oxygen in pneumonia ("BTS Guidelines for the Management of Community Acquired Pneumonia in Adults," 2001), there have been no randomised controlled trials investigating the role of oxygen therapy in this condition. As with acute asthma, uncontrolled oxygen use is considered by most clinicians to be safe and without risk. However, as outlined in Chapter 3, there are a number of potential complications of high flow oxygen therapy in acute pneumonia. The presence of significant ventilation perfusion mismatch in most patients indicates that the same mechanisms of carbon dioxide retention that occur in acute COPD and asthma could occur also in pneumonia (Gea et al., 1991; Lampron et al., 1985; Lemaire et al., 1985).

5.2 Study objective and hypothesis

The objective of the study was to investigate the effects of high concentration oxygen on P_aCO_2 in patients with suspected community acquired pneumonia in the emergency department. The hypothesis was that administration of high flow oxygen in acute

community acquired pneumonia may result in worse outcomes, when compared to titrated oxygen, as defined by an increase in P_aCO_2.

5.3 Study participants

Subjects were recruited between July 2007 and April 2009. The study was conducted in the emergency departments of three metropolitan hospitals in Wellington, New Zealand: Wellington Hospital (tertiary public, catchment 250,000), Hutt Hospital (secondary public, catchment 140,000) and Kenepuru Hospital (secondary public, catchment 100,000).

Patients arriving at the emergency department either by ambulance or self presentation were approached by the investigator to assess potential eligibility. Patients aged between 18 and 75 years were eligible for inclusion if they reported the recent onset of all the following symptoms

1. Cough
2. At least one systemic feature: sweating, rigors or fever > 37.8°
3. Dyspnoea (respiratory rate > 18 breaths per minute).

Patients were excluded if they met any of the following criteria:

- History of chronic obstructive pulmonary disease
- History of greater than 20 pack years of tobacco smoking

- Requirement for mechanical ventilation
- Presence of other risk factors for hypercapnic respiratory failure: Significant neuromuscular disease, severe chest wall restriction, or morbid obesity
- Suspected neutropenic sepsis.

5.4 Randomisation

A computer generated randomised allocation schedule was provided by a biostatistician. To ensure allocation concealment, the schedule was imbedded into a specially designed enrolment database (Microsoft Access) by a third party. This was done without the involvement of the clinical investigator responsible for enrolment and was therefore concealed from them. This database was then accessed by a secure password. Once an eligible patient had provided written informed consent the investigator entered their details into the database. A field then appeared prompting them to enter the next available subject number. After clicking a button marked “randomise” the database would then reveal the allocation for that patient (either “high flow” or “titrated”) based on the imbedded randomisation schedule.

5.5 Interventions

Subjects who met the enrolment criteria and gave written informed consent were randomly assigned to one of two oxygen regimes for a total of 60 minutes:

1. Oxygen delivered at 8 L/min via a medium concentration mask (Hudson RCI, Durham NC, USA)

2. Oxygen delivered at a flow rate titrated to achieve transcutaneous oxygen saturations between 93 and 95 percent.

The oxygen adjustment protocol for patients in the titrated group is shown in Table 5.1. Oxygen flow rates up to 4L/min were delivered via nasal prongs (Hudson RCI, Durham NC, USA). Flow rates higher then 4L/min were delivered by medium concentration mask.

Table 5.1: Oxygen titration protocol

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

In both groups, if an oxygen flow rate of 8L/min was insufficient to maintain the oxygen saturation above 90% the patient was withdrawn from the study.

5.6 Clinical measurements

5.6.1 Transcutaneous partial pressure of carbon dioxide ($PtCO_2$)

See section 4.6.1.

5.6.2 Heart rate and oxygen saturation

The TOSCA 500 incorporates both pulse oximetry and $PtCO_2$ measurement in the same probe, so the monitor was used to record heart rate and oxygen saturation.

5.6.3 CRB-65 score

The CRB-65 score was calculated for all subjects at baseline and again at the end of the study period. The score is recommended by international guidelines for the assessment of severity in pneumonia ("BTS Guidelines for the Management of Community Acquired Pneumonia in Adults," 2001) and an increasing CRB-65 score indicates an increasing risk of mortality (Lim et al., 2003). One point is scored for each of the following:

1. New onset confusion (defined as an Acute Mental Test score $\leq$ 8/10)
2. Respiratory rate $\geq$ 30 breaths per minute
3. Blood pressure < 90 mmHg systolic or < 60 mmHg diastolic

4. Age ≥ 65 years.

5.6.4 Chest x-ray

All chest films were formally reported by a consultant radiologist blinded to the treatment allocation. The presence or absence of an infiltrate consistent with pneumonia was recorded.

5.7 Study protocol

Potential participants identified by the investigator were asked to provide written informed consent and randomised. The patient's earlobe was cleaned with an alcohol swab and allowed to dry. The $PtCO_2$ probe was attached using the provided attachment clips and contact gel. If the oxygen saturations were less than 92%, oxygen was given to achieve a saturation of 93-95% (see Table 5.1). A minimum of 10 minutes was allowed for arterialisation to occur and $PtCO_2$ readings to stabilize, at which point (Time = 0) baseline data were recorded and the oxygen protocol started. The $PtCO_2$, respiratory rate, heart rate and oxygen saturations were recorded at baseline and then at 20 minute intervals for the duration of the study. The timing of the study procedures is summarised in Table 5.2.

Table 5.2: Summary of study procedures

Procedure	T = - 10	T = 0	T = 20	T = 40	T = 60
Consent	X				
Randomise	X				
Attach ear probe	X				
Start oxygen regime		X			
$PtCO_2$		X	X	X	X
Heart rate		X	X	X	X
Respiratory Rate		X	X	X	X
Pulse oximetry	X	X	X	X	X

5.8 Pneumonia treatment protocol

A full history and physical examination was undertaken on each patient. Empirical antibiotics were administered in accordance with published guidelines ("BTS Guidelines for the Management of Community Acquired Pneumonia in Adults," 2001). Other treatments such as analgesia and intravenous fluids were administered at the discretion of the investigator. All patients underwent a chest radiograph and routine blood tests including a full blood count, creatinine and electrolytes.

5.9 Outcome measures and statistical analysis

The primary outcome variable was the proportion of patients with a $PtCO_2$ rise of ≥4 mmHg. Secondary outcome measures included the proportion of patients with a $PtCO_2$ rise of ≥8 mmHg, the proportion with both a rise in $PtCO_2$ ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes, and the mean change from baseline $PtCO_2$. The rate of change of $PtCO_2$ was determined using a mixed linear model with random intercept and slope terms. Whether the risk of a $PtCO_2$ rise 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. Continuous outcome variables were analysed as a change from baseline using independent sample t-tests. Variables for which normality assumptions were not met were analysed by a Mann-Whitney test. Analysis was by intention to treat. SAS version 9.1 and Minitab version 14 were used.

5.10 Sample size

Using data from a previous study (G. J. Rodrigo et al., 2003), 75 participants were required in each group to detect a difference in the main outcome variable (the proportion of patients with a rise in $PtCO_2$ of ≥ 4 mmHg) of 20% in the high concentration oxygen group and 5% in the titrated group with power of 80% and a type 1 error rate of 5%.

5.11 Ethical approval and trial registration

As with the acute asthma study, subjects initially signed a short information and consent form supplemented by a clear verbal explanation and the offer to answer any questions. All subjects subsequently read the information sheet and signed the full consent form during the study.

The study was approved by the Central Regional Ethics Committee, Wellington, New Zealand (CEN 06/11/101) on 18th January 2007 and prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN 012607000196448). The study was approved by Capital and Coast District Health Board and Hutt Valley District Health Board.

5.12 Study organisation

All investigators involved in the study were qualified medical practitioners with at least three years post-graduate clinical experience. I was responsible for training and supervision of all participating research staff. Staff levels permitting, an investigator was usually onsite and available to recruit patients at the emergency departments of the participating hospitals from 0800 to 2200 Monday to Friday.

5.13 Data management

Each patient's results were recorded on a study worksheet and stored in a secure locked location near the emergency department. Collected data sheets were then transferred to the offices of the Medical Research Institute of New Zealand for data entry and secure storage. The data was entered into the study database (Microsoft Access) and stored on a secure server.

Chapter 6: A study of the physiological response to oxygen in chronic asthma - methods

6.1 Outline of the study

As noted in Chapter 3 there is little existing literature regarding the mechanisms of oxygen induced hypercapnia in asthma. In contrast, a number studies in COPD have attempted to examine the different contributions of changes in minute ventilation and the role of reversal of HPV on ventilation-perfusion matching. On balance the main factor involved in oxygen induced hypercapnia appears to be an increase in the physiological dead space to tidal volume ratio.

The hypothesis of this study is that because $\dot{V}/\dot{Q}$ mismatching is a predominant physiological feature of both asthma and COPD, the mechanism of any increase in P_aCO_2 seen with high concentration oxygen is likely to be similar in these two disorders. The original design elements of this study are the inclusion of both positive (COPD subjects) and negative (normal subjects) control groups, the continuous measurement of $PtCO_2$ and the simultaneous measurement of both minute ventilation and dead space to tidal volume ratio.

The aim was to investigate the physiological changes that occur when patients with asthma and severe airflow obstruction are administered 100% oxygen. While some of the methods used in this study, such as measurement of minute ventilation, could be applied to asthma patients with an acute exacerbation, it is logistically difficult to adequately control all potential variables in the emergency department setting including the effects of concomitant bronchodilator therapy. Additionally, previous studies on responses to oxygen in COPD have proved to be valid when conducted on patients in the stable state as well as during an exacerbation (Aubier, Murciano, Fournier et al., 1980; Dick et al., 1997; Sassoon et al., 1987).

6.2 Aims and objectives

The objective of the study was to investigate the physiological effect of high concentration oxygen in patients with chronic asthma and severe airflow obstruction, compared to subjects with COPD and a group of normal controls.

The hypothesis was that administration of 100% oxygen in chronic asthma with airflow obstruction would result in similar physiological changes to patients with COPD, specifically:

- An increase in P_aCO_2
- An increase in V_D/V_T

- Minimal change in minute ventilation.

6.3 Study participants

Subjects were recruited between December 2008 and September 2009. The study was conducted at the MRINZ pulmonary function laboratory based at Bowen Hospital, Crofton Downs, Wellington. Potentially eligible subjects were identified through existing study databases and referral by local respiratory physicians.

Asthma patients aged between 18 and 65 years were eligible for inclusion if they met the following criteria:

- Diagnosis of asthma ("British Guideline on the Management of Asthma," 2008)
- Pre-bronchodilator FEV1 $\leq$ 60% predicted
- No history of COPD
- No history of cigarette smoking greater than 5 pack years
- Absence of other risk factors for hypercapnic respiratory failure: Significant neuromuscular disease, severe chest wall restriction, or morbid obesity.

COPD patients aged over 18 years were eligible for inclusion if they met the following criteria:

- Diagnosis of COPD ("BTS guidelines: Diagnosing COPD," 2004)

- Pre-bronchodilator FEV1 ≤ 50% predicted
- Absence of other risk factors for hypercapnic respiratory failure: Significant neuromuscular disease, severe chest wall restriction, or morbid obesity.

Normal subjects aged over 18 years were eligible for inclusion if they met the following criteria:

- No history of COPD, asthma or other cardio-respiratory disease
- No history of cigarette smoking
- No current symptoms of dyspnoea, cough or wheeze
- Absence of other risk factors for hypercapnic respiratory failure: Significant neuromuscular disease, severe chest wall restriction, or morbid obesity
- FEV1/FVC ratio ≥ 0.7 and FEV1 percent predicted ≥ 80%.

6.4 Study protocol

All subjects read the information sheet and signed written informed consent (see appendices). Asthma and COPD patients were instructed to withhold short and long acting bronchodilator medication on the morning of the study, and withhold long acting bronchodilator medication on the evening prior to the study. All subjects were studied seated at 90° upright in a chair and all recordings were made between 9am and 12pm.

A transcutaneous carbon dioxide sensor was attached to an earlobe for continuous monitoring of both $PtCO_2$ and arterial oxygen saturation. An appropriate sized nose and mouth Continuous Positive Airway Pressure (CPAP) mask (FlexiFit 431, Fisher and Paykel Healthcare, Auckland, New Zealand) was fitted with head straps to ensure a satisfactory seal on the face with no mask leak. A combined pneumotachygraph and infrared CO_2 gas analyser (COSMO Respiratory Profile Monitor, Respironics, Murrysville, PA USA) was fitted to the outflow port of the CPAP mask. Signals from both the pneumotachygraph flow meter and the infrared gas analyser were displayed on the COSMO Respiratory Profile Monitor.

To administer 100% oxygen a 200L Douglas bag was filled from an oxygen cylinder at least two hours before the subject was studied to allow the oxygen in the bag to come to room temperature. The connection valve from the Douglas bag incorporated a three way tap so that flow through the tubing to the mask could be switched between room air and oxygen from the bag. The Douglas bag was connected by flexible tubing to the inflow port of a T-piece incorporating a one way valve. The second arm of the T-piece connector was attached to the pneumotachygraph and the mask. The third arm of the T-piece connector incorporated a one way valve and acted as the expiratory port. The valves in both the inflow and outflow ports of the T-piece ensured that expiratory gases vented out of the circuit after passing the pneumotachygraph.

After fitting the mask and transcutaneous carbon dioxide sensor subjects were instructed to breathe normally through the mask, with the three way tap on the Douglas bag open to

room air. A minimum of 15 minutes was allowed to give the subject sufficient time to accommodate to the circuit and to confirm reliable and steady signals from the transcutaneous CO_2 sensor, flow monitor and gas analyser. The resistance of the mask, valve and tubing was not directly measured as it did not change between air and oxygen breathing, and the outcome variables of interest were all measured as a change from baseline. During the study subjects were not permitted to talk or interact with family members. Although the investigator was present throughout, there was no feedback or interaction given to subjects. All monitor displays were hidden from the subject's view.

During the final minute of room air breathing the following data were recorded

- $PtCO_2$ (mmHg)
- Minute ventilation (L/min)
- V_D/V_T
- Heart rate (beats/min) and respiratory rate (breaths/min).

The $PtCO_2$ and a simultaneously recorded mixed expired carbon dioxide (P_ECO_2) measurement were used to calculate the V_D/V_T according to the Bohr-Enghoff equation:

$$V_D/V_T = (P_aCO_2 - P_ECO_2 / P_aCO_2)$$

After recording baseline measurements on room air the three-way tap was connected to the Douglas bag and the subjects breathed 100% oxygen for 20 minutes. During the final minute of oxygen breathing the same data was recorded. The mask and recording

equipment was then removed and a final FEV1 was recorded. The timing of the study procedures is summarised in Table 6.1.

Table 6.1: Summary of study procedures

Procedure	T = -15	T = -1	T = 0	T = 10	T = 20
Consent	X				
Spirometry	X				X
Start breathing through mask	X				
Start 100% oxygen			X		
$PtCO_2$		X		X	X
Heart rate		X		X	X
Respiratory Rate		X		X	X
V_D/V_T		X		X	X
Minute ventilation		X		X	X

6.5 Study procedures

6.5.1 Transcutaneous partial pressure of carbon dioxide ($PtCO_2$)

See section 4.6.1.

6.5.2 Heart rate and oxygen saturation

The TOSCA 500 incorporates both pulse oximetry and $PtCO_2$ measurement in the same probe, so the monitor was used to record heart rate and oxygen saturation.

6.5.3 Spirometry

All spirometry was performed using a handheld spirometer (Micro Spirometer, Micro Medical Ltd, Rochester, U.K.) which was regularly calibrated and standard reference tables for predicted values were used.

6.5.4 Mixed expired CO_2

The real time infra-red gas analyser of the COSMO Respiratory Profile Monitor continuously measures the partial pressure of expired CO_2 and combines this with flow recordings to express the data in the form of volumetric capnography. The volume weighted three minute average expired CO_2 is updated every 15 seconds and mixed expired CO_2 is calculated by dividing the volume of CO_2 for a one minute interval by the total expired volume for the same interval.

6.5.5 Minute ventilation and respiratory rate

The pneumotachygraph of the COSMO Respiratory Profile Monitor continuously measures flow and pressure across the expiratory port of the mask mouth piece. Minute ventilation is calculated by the rolling average tidal volume divided by respiratory rate over two minutes. Respiratory rate is measured by the flow meter and computed as an eight breath moving average updated breath to breath.

6.6 Outcome measures

The primary outcome variable was the change in $PtCO_2$ from baseline. Secondary outcome variables included change in minute ventilation, change in dead space to tidal volume ratio and change in FEV1.

6.7 Sample size

In a previous randomised study 17 patients with stable but severe COPD were compared breathing 94% oxygen or room air (Sassoon et al., 1987). It detected a significant difference of 4.4 mmHg in the transcutaneous PCO_2 between the two treatments. With a standard deviation of the change in P_aCO_2 breathing oxygen in COPD of 5.6 (Robinson et al., 2000), a sample size of 18 has 80% power to detect a difference between air and oxygen breathing greater than 4 mmHg with a type I error rate of 5%.

6.8 Ethical approval and trial registration

The study was approved by the Central Regional Ethics Committee, Wellington, New Zealand (Ethics reference: CEN/08/04/013) on 20th May 2008 and prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12608000549325) on 30/10/08.

6.9 Data management

Each patient's results were recorded on a study worksheet and stored in a secure locked location. Collected data sheets were then transferred to the offices of the Medical Research Institute of New Zealand for data entry and secure storage. The data was entered into the main study database (Microsoft Excel) and stored on a secure server.

Chapter 7: Validation of methods

This chapter presents data demonstrating the accuracy and repeatability of the clinical measurements used in this thesis and the equipment used to obtain them. 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 by the same operator. 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.

The following analyses were undertaken:

1. The validity and precision of the TOSCA 500 monitor in the estimation of P_aCO_2
2. The repeatability of the TOSCA 500 monitor in the measurement of $PtCO_2$
3. The repeatability of the COSMO Respiratory Profile Monitor in the measurement of V_D/V_T
4. The repeatability of the COSMO Respiratory Profile Monitor in the measurement of minute ventilation
5. The repeatability of spirometry in the measurement of FEV1.

7.1 A validation study on the accuracy of transcutaneous carbon dioxide recordings

7.1.1 Introduction

Portable devices to measure the transcutaneous partial pressure of carbon dioxide ($PtCO_2$) are a non-invasive alternative to an ABG in the assessment and monitoring of P_aCO_2. They function on the principle that CO_2 diffuses extremely well through tissues. A probe is attached to an area of skin (usually the earlobe) and warms to 42°C which "arterializes" the underlying capillaries. The CO_2 diffusing through the skin changes the pH of an electrolyte membrane in the probe and the resulting signal is converted to an estimate of the P_aCO_2. Although end-tidal carbon dioxide monitors are an alternative method of non-invasive P_aCO_2 monitoring, their major limitation is that they become inaccurate in the setting of changing alveolar dead space (Liu, Lee, & Bongard, 1992; Sanders et al., 1994; Stock, 1988).

Transcutaneous CO_2 devices have been studied in a variety of clinical settings including invasive and non-invasive ventilation in intensive care units and overnight studies of sleep disordered breathing (Bendjelid et al., 2005; Cox et al., 2005; Cuvelier, Grigoriu, Molan, & Muir, 2005; Janssens, Howarth-Frey, Chevrolet, Abajo, & Rochat, 1998; Senn, Clarenbach, Kaplan, Maggiorini, & Bloch, 2005). When compared to ABG, studies have shown variable accuracy depending on the device used and the clinical setting.

The aim of this study was to assess the accuracy of a $PtCO_2$ device in the assessment of P_aCO_2 by comparing it to the gold standard of ABG analysis.

7.1.2 Method

This study formed part of the two randomised controlled trials of high concentration versus titrated oxygen therapy in acute severe asthma and community-acquired pneumonia. The aim was to collect 25 paired P_aCO_2 and $PtCO_2$ recordings in patients attending the ED and enrolled into either of the two studies.

A detailed description of the two study protocols has already been given, but in brief, patients were assessed by the study investigators on arrival and if the enrolment criteria were met, written informed consent was obtained. An earlobe was cleaned with an alcohol swab and allowed to dry. The $PtCO_2$ probe was attached to the earlobe using an attachment clip and contact gel. A minimum of 10 minutes was allowed for arterialisation to occur and $PtCO_2$ readings to stabilise, at which stage the randomised oxygen treatment regime was started. The $PtCO_2$ was monitored continuously as part of the study protocol and subjects had an ABG taken during the course of their routine assessment and treatment if the investigator felt it was clinically indicated, hence the data obtained represents a convenience sample.

The ABG samples were obtained by radial artery puncture with a 22 gauge needle and blood was collected into a heparinised syringe. Samples were analyzed immediately with

an arterial blood gas analyser (Radiometer ABL800 FLEX, Copenhagen, Denmark) and a simultaneous $PtCO_2$ reading was recorded with the transcutaneous CO_2 monitor (TOSCA 500; Radiometer Basel AG; Switzerland).

Data were analysed using the Bland-Altman method of $P_aCO_2 - PtCO_2$ versus the mean of P_aCO_2 and $PtCO_2$, along with limits of agreement representing plus or minus two standard deviations of the difference.

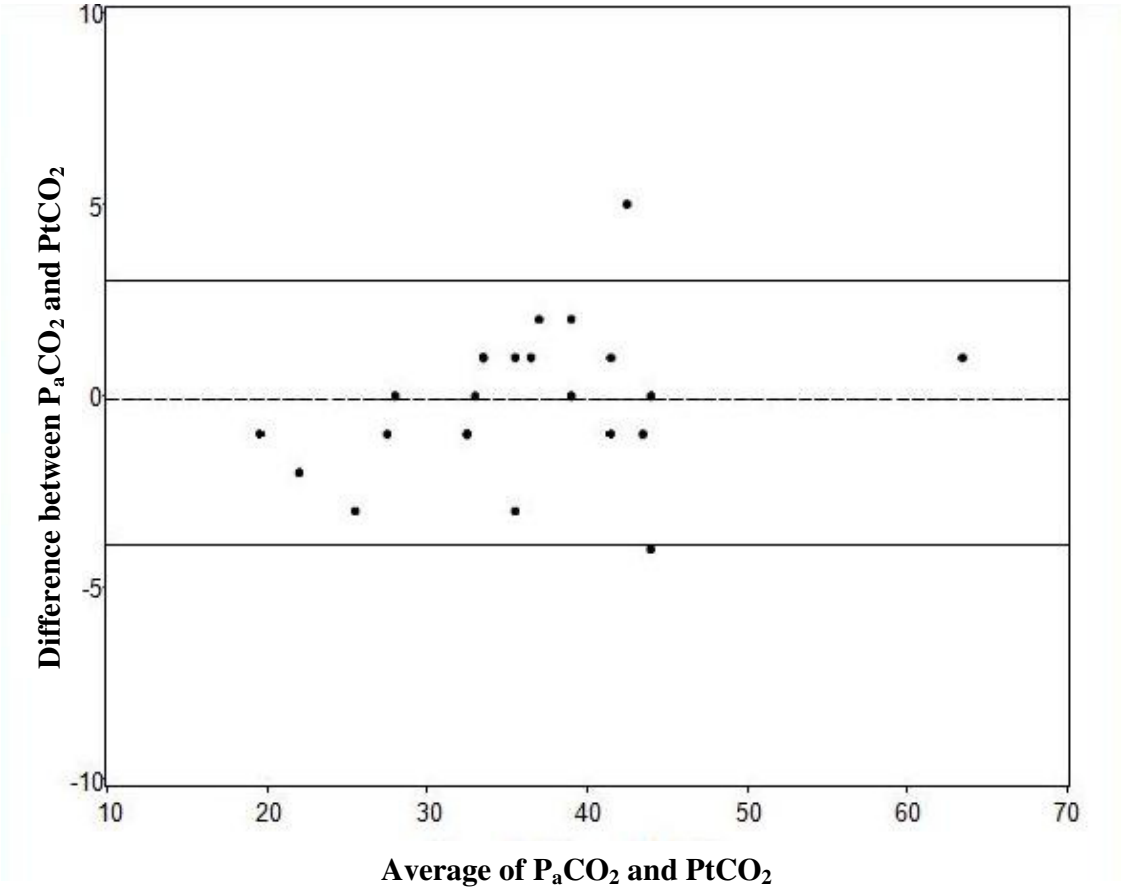
7.1.3 Results

There were 25 pairs of data in total but one patient was excluded because of difficulty attaching the probe to the earlobe. This resulted in a lack of signal from the ear probe and therefore 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 mean FEV_1 % predicted in the asthma patients was 25.5%. The mean respiratory rate for the whole group was 27 breaths per minute. The P_aCO_2 range for the group was 19 to 64 mmHg with a mean of 34.9 mmHg. The mean time ABG samples were taken was 39.5 minutes after starting the randomized oxygen treatment regime. The mean (SD) $P_aCO_2 - PtCO_2$ difference was -0.13 (1.9) mmHg with limits of agreement of plus or minus 3.8 mmHg (-3.9 to +3.7). Complete data for both recording methods is shown in Table 7.1 and the Bland-Altman plot is shown in Figure 7.1.

Table 7.1: Summary of data comparing paired P_aCO_2 and $PtCO_2$ measurements

Variable	Mean (SD)	Median (Inter-quartile range)	Range (mmHg)
P_aCO_2	36.2 (9.3)	36.5 (32.0 to 41.5)	19 to 64
$PtCO_2$	36.3 (8.7)	36 (33 to 40.5)	20 to 63
Difference ($P_aCO_2 - PtCO_2$)	-0.13 (1.9)	0 (-1 to 1)	-4 to 5
Average (P_aCO_2 and $PtCO_2$)	36.2 (8.9)	36 (32.5 to 41.5)	19.5 to 63.5

Figure 7.1 A Bland-Altman plot of the difference between the P_aCO_2 and $PtCO_2$, against the average of P_aCO_2 and $PtCO_2$ (mmHg). Horizontal lines indicate plus or minus 2 standard deviations of the differences.



7.1.4 Conclusion

The data demonstrate that when compared to the gold standard of an ABG, transcutaneous carbon dioxide measurements demonstrate minimal bias and acceptable limits of agreement.

7.2 A repeatability study of the measurement of $PtCO_2$, minute ventilation, V_D/V_T and FEV1

7.2.1 Method

For the full study protocol refer to the study procedures section of chapter 6. All 18 normal subjects returned to the pulmonary function laboratory for a repeat study. The second set of data was recorded using an identical study protocol and the same equipment. The subjects were studied between three and seven days from their initial visit, and within one hour of the time of the original study. I undertook all testing on both visits. Normal subjects were used for test repeatability analysis, as they were unlikely to have significant changes in the study parameters over time, unlike subjects with asthma and COPD.

7.2.2 Statistical analysis

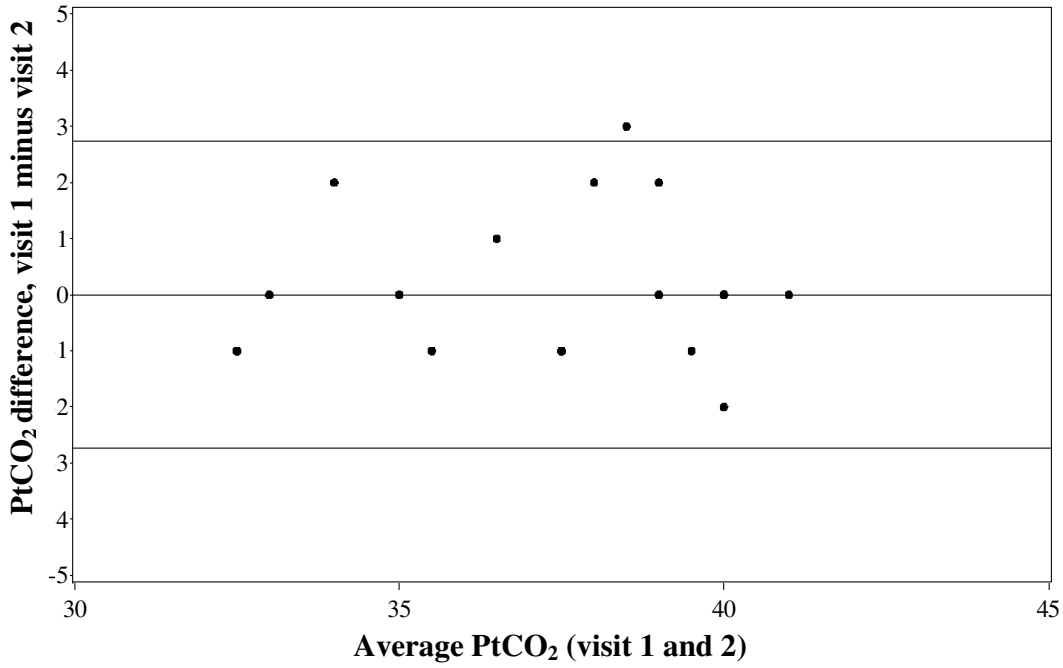
Mixed linear models were used to estimate the intra-class correlation coefficients (ICC) for the variables measured twice in the normal group ($PtCO_2$, MV, V_D/V_T and FEV1)

supplemented by Bland-Altman calculation of their limits of agreement. SAS 9.1 was used.

7.2.3 Results

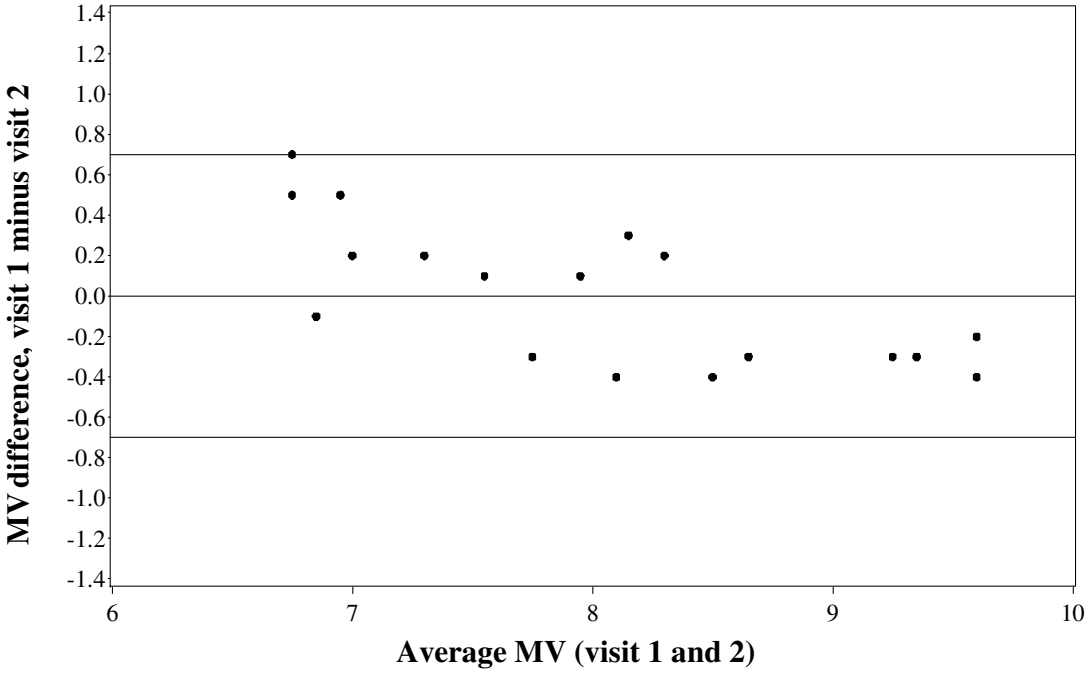
For transcutaneous carbon dioxide the mean (SD) difference between visit one and two was 0.10 (1.37) mmHg with limits of agreement of plus or minus 2.74 mmHg (-2.64 to +2.8). A Bland-Altman plot of limits of agreement for $PtCO_2$ results of the two visits is shown in Figure 7.2. The ICC was 0.89.

Figure 7.2: Bland-Altman plot of the difference between $PtCO_2$ (mmHg) at visits one and two against the mean value of the two visits. Horizontal lines indicate plus or minus 2 standard deviations of the differences.



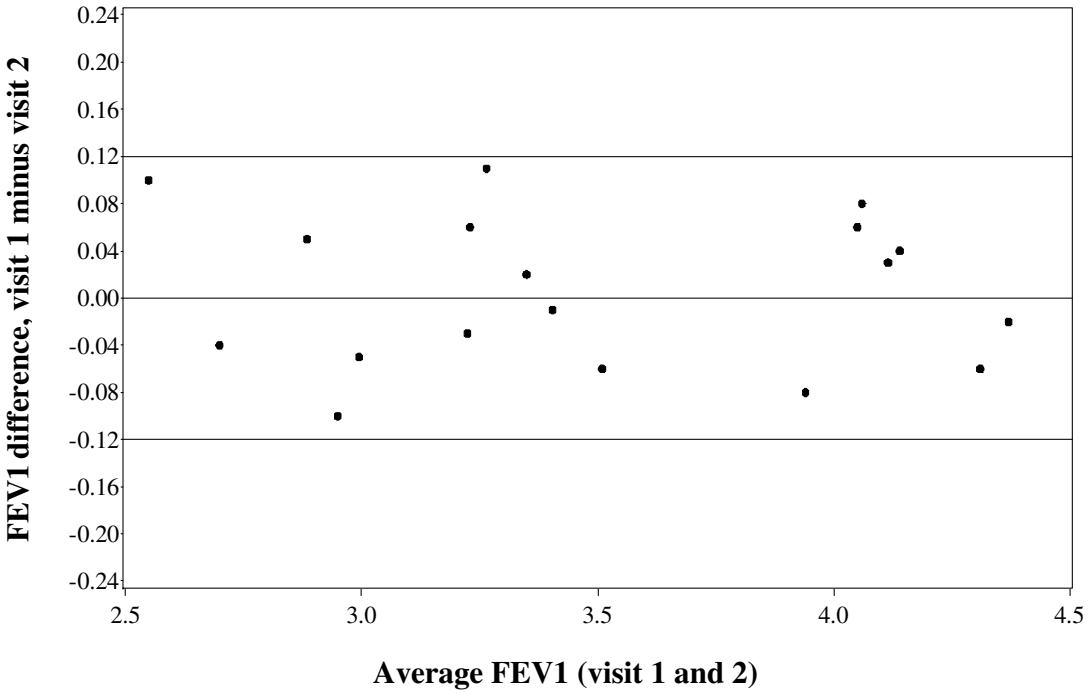
For the measurement of minute ventilation the mean (SD) difference between visit one and two was 0.006 (0.35) L/min with limits of agreement of plus or minus 0.7 L/min (Figure 7.3). The ICC was 0.94.

Figure 7.3: Bland-Altman plot of the difference between MV (L/min) at visits one and two against the mean value of the visits. Horizontal lines indicate plus or minus 2 standard deviations of the differences



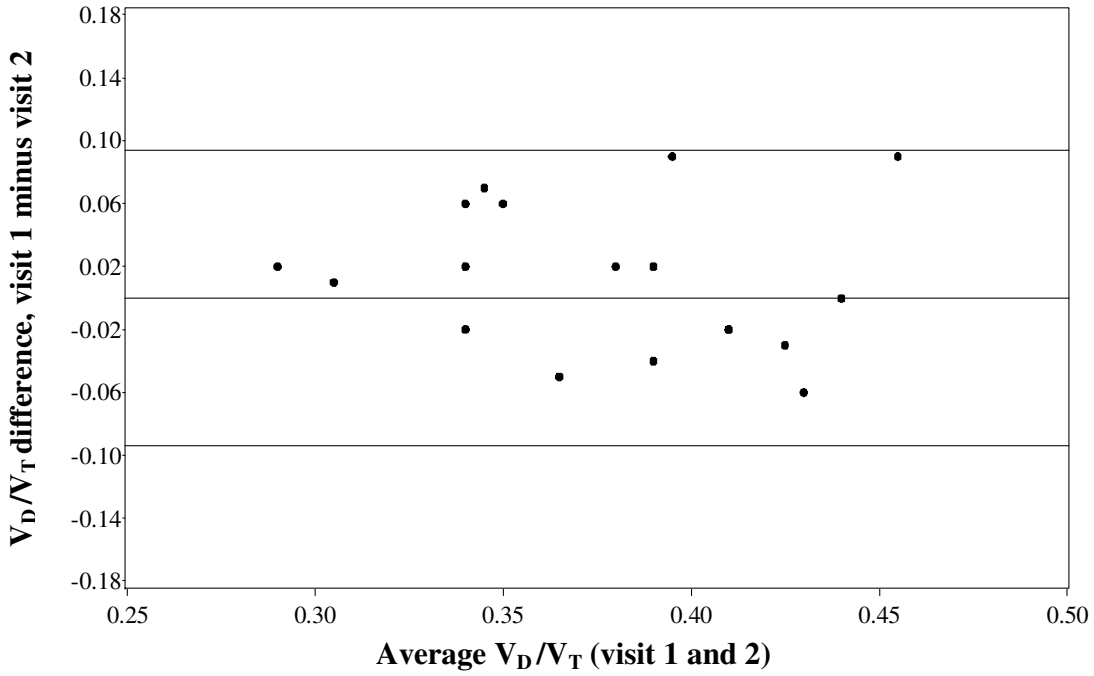
For the measurement of FEV1 the mean (SD) difference between visit one and two was 0.006 (0.06) L with limits of agreement of plus or minus 0.12 L (Figure 7.4). The ICC was 0.99.

Figure 7.4: Bland-Altman plot of the difference between FEV1 (L) at visits one and two against the mean value of the visits. Horizontal lines indicate plus or minus 2 standard deviations of the differences



For the measurement of V_D/V_T the mean (SD) difference between visit one and two was 0.012 (0.047) with limits of agreement of plus or minus 2.74 (Figure 7.5). The ICC was 0.59.

Figure 7.5: Bland-Altman plot of the difference between V_D/V_T at visits one and two against the mean value of the visits. Horizontal lines indicate plus or minus 2 standard deviations of the differences



7.2.4 Conclusion

Bland-Altman analysis of the data demonstrates that all four measurements had minimal bias and acceptable limits of agreement between the two visits. ICC analysis indicates high reliability between recordings for visits one and two for FEV1, $PtCO_2$ and minute ventilation. The measurement of V_D/V_T was moderately reliable.

Chapter 8: Results

8.1 High concentration versus titrated oxygen in acute severe asthma

8.1.1 Subjects

Eligible patients were recruited from July 2007 to December 2009. A total of 106 patients were randomised, 53 to the titrated group and 53 to the high flow group. Three patients were withdrawn from the high concentration oxygen group: two were enrolled and randomised but met exclusion criteria (one patient with COPD and one with obesity hypoventilation syndrome), and in one patient a $PtCO_2$ signal could not be obtained. This left 50 patients in the high concentration group and 53 in the titrated group for final analysis. Figure 8.1 shows the flow of the patients through the study.

The two groups were well matched with respect to age, sex, respiratory rate, oxygen saturation, and mean $PtCO_2$ at baseline as outlined in Table 8.1, although there was a lower mean FEV1 in the high flow group of 1.15L compared to 1.29L in the titrated group.

Figure 8.1: Flow of asthma patients through the study.

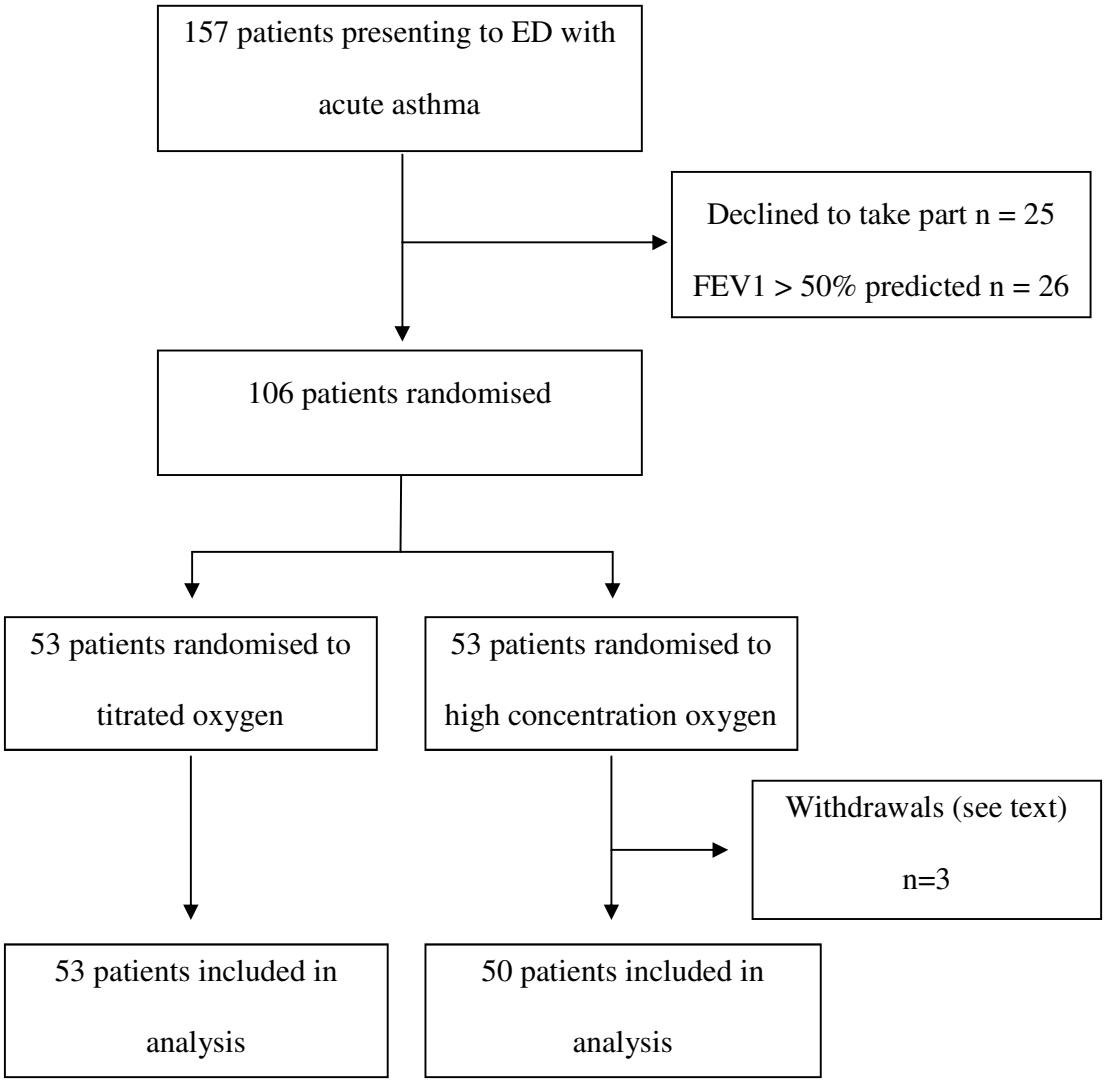


Table 8.1: Baseline characteristics of asthma patients.

	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)
$PtCO_2$ ≥38 mmHg	20 (40.0)	15 (28.3)	35 (34.0)
FEV1, L	1.15 (0.43)	1.29 (0.44)	1.22 (0.44)
FEV1 % predicted	32.1 (9.9)	36.9 (9.7)	34.6 (10.1)

Values for age, respiratory rate, heart rate, SpO_2, $PtCO_2$ FEV1 and FEV1 % predicted are mean (SD). Values for sex and $PtCO_2$ ≥38 mmHg are number of participants (percentage).

$PtCO_2$ levels at baseline ranged from 14 to 50 mmHg (Figure 8.2). The majority of patients were hypocapnic at baseline with only 35/103 (34%) having a $PtCO_2 \geq 38$ mmHg. Mild to moderate hypoxia was common, and only eight patients had oxygen saturations < 93% at baseline. 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.

8.1.2 Changes in $PtCO_2$

Results for the main primary and secondary outcome variables are shown in Table 8.2. 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, 22/50 (44%) vs 10/53 (18.9%) with a relative risk of 2.3 (95% CI 1.2 to 4.3; P=0.009). The proportion of patients with a rise in $PtCO_2$ ≥8 mmHg was significantly greater in the high concentration, 10/50 (20%), compared with the titrated group, 3/53 (5.7%), with a relative risk of 3.6 (95% CI 1.1 to 12.3, P=0.03). The proportion of patients with both a rise in $PtCO_2$ ≥4 mmHg and a $PtCO_2$ ≥38 mmHg at 60 minutes was 16/50 (32%) and 4/53 (7.6%), in the high concentration and titrated oxygen groups respectively, with a relative risk of 4.3 (95% CI 1.6 to 12.0, P=0.001).

Figure 8.2: $PtCO_2$ levels in asthma patients at baseline and after 60 minutes in the high concentration (o) and titrated (●) oxygen groups.

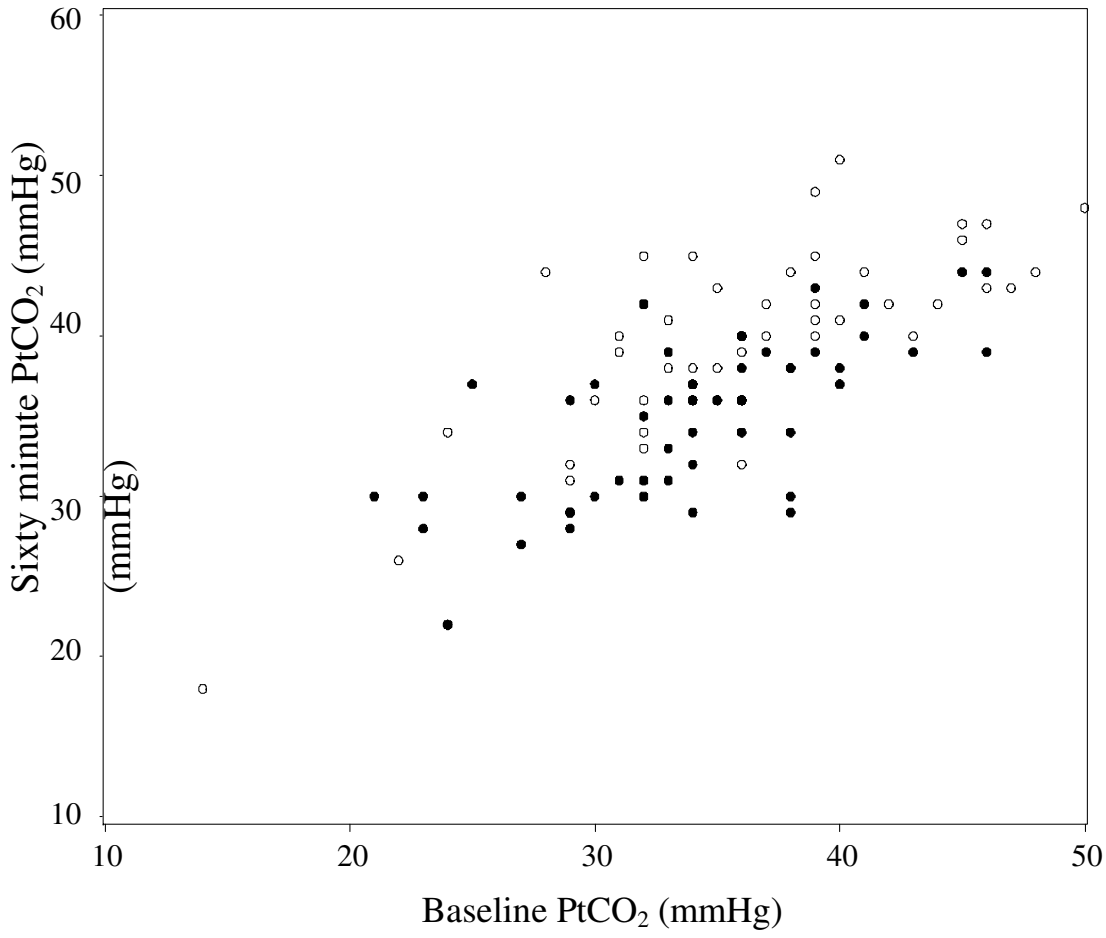


Table 8.2: The proportion of asthma patients with a predetermined rise in $PtCO_2$ from baseline at 60 minutes.

	High flow O_2 n (%)	Titrated O_2 n (%)	Relative risk (95% CI)	P value
Change in $PtCO_2$ ≥4 mmHg	22 (44%)	10 (18.9%)	2.3 (1.2 to 4.3)	P=0.009
Change in $PtCO_2$ ≥4 mmHg and $PtCO_2$ ≥38 mmHg	16 (32%)	4 (7.6%)	4.3 (1.6 to 12.0)	P=0001
Change in $PtCO_2$ ≥8 mmHg	10 (20%)	3 (5.7%)	3.6 (1.1 to 12.3)	P= 0.003

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 8.3).

Table.8.3: Time course of change in $PtCO_2$: proportion of asthma patients with a rise of ≥4 mmHg at three time points.

Time	High concentration n (%)	Titrated n (%)	Relative risk (95% CI)	P value
20 minutes	15 (30%)	7 (13.2%)	2.3 (1.0 to 5.1)	P=0.038
40 minutes	20 (40.8%)	8 (15.1%)	2.7 (1.3 to 5.6)	P=0.004
60 minutes	21 (42.9%)	10 (18.9%)	2.3 (1.2 to 4.3)	P=0.001

The mean change in $PtCO_2$ from baseline (Table 8.4) was significantly greater in the high concentration group compared with the titrated group, with a mean difference at 60 minutes of 2.6 mmHg (95% CI 0.9 to 4.3; P<0.003). The rate of increase in the high concentration group was 0.054 mmHg/min (95% CI 0.035 to 0.074) and the titrated group was 0.012 mmHg/min (95% CI -0.0065 to 0.031). The difference in the rate of change was 0.042 mmHg/min (95% CI 0.069 to 0.15, P=0.003).

Table.8.4: Time course of mean change in $PtCO_2$ in asthma patients.

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

8.1.3 Clinical variables

The high flow oxygen group had a higher rate of hospital admission with 26/50 (52%) admitted compared to 17/53 (32%) in the titrated group, a relative risk of 1.6 (95% CI 1.0 to 2.6, P=0.04).

There was no difference between the treatment groups in the mean change from baseline to 60 minutes of the three main clinical variables. The mean changes in respiratory rate, pulse rate, and FEV1 are shown in Table 8.5.

Table 8.5: Mean change from baseline to 60 minutes of clinical variables in asthma patients.

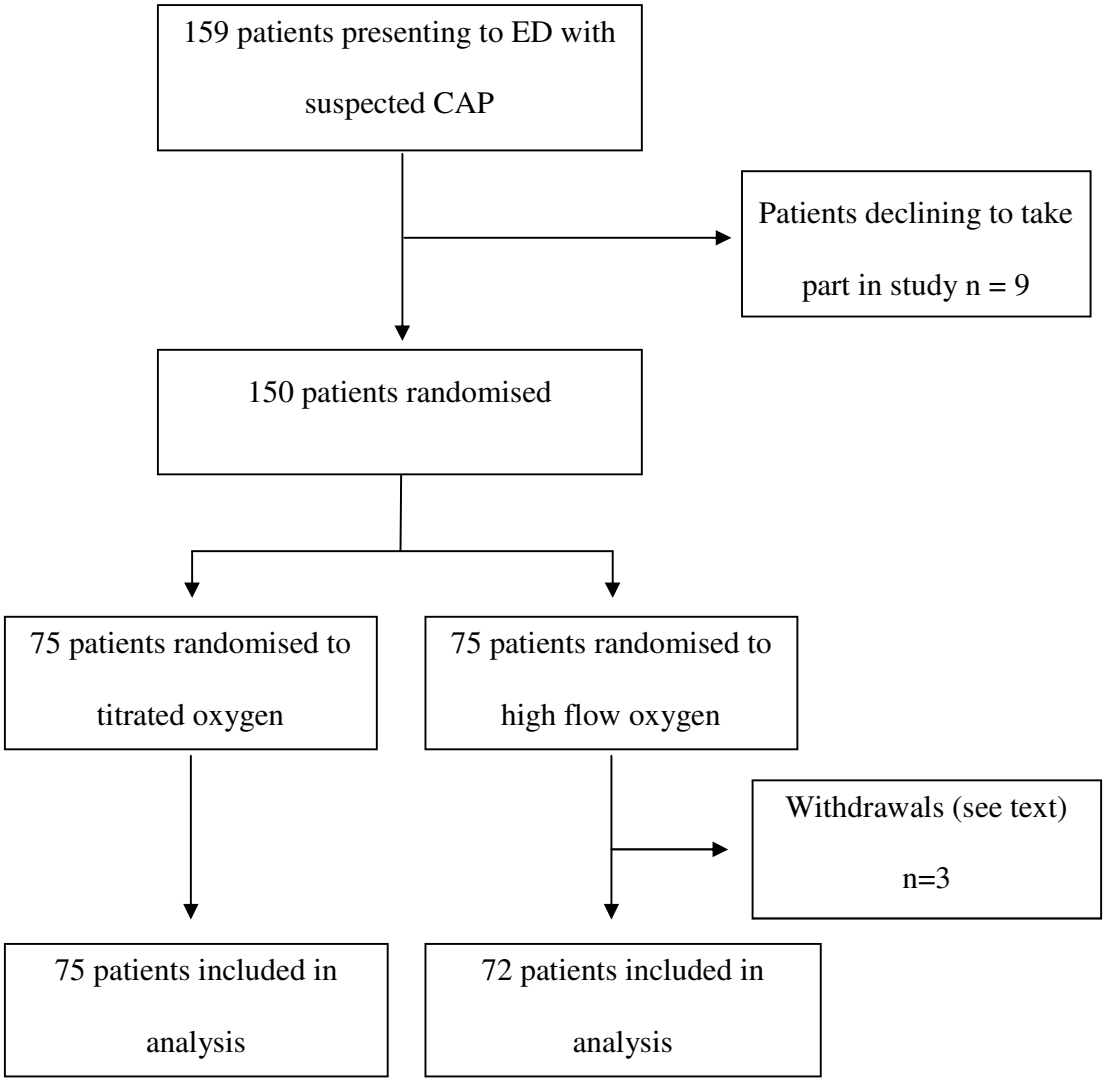
Variable	High concentration mean (SD)	Titrated mean (SD)	Difference (95% CI)	P value
Resp. rate, breaths/min	-3.1 (4.5)	-3.1 (4.3)	0.0 (-1.7 to 1.7)	P=0.97
Heart rate, beats/min	0.04 (11.7)	3.4 (9.4)	-3.3 (-7.0 to 0.3)	P=0.08
FEV1, L/min	0.36 (0.38)	0.35 (0.38)	0.0 (-0.14 to 0.15)	P=0.93

8.2 High concentration versus titrated oxygen in acute pneumonia

8.2.1 Subjects

Eligible patients were recruited from July 2007 to April 2009. Figure 8.3 shows the flow of the 150 patients through the study, with 75 randomised to high concentration oxygen and 75 randomised to titrated oxygen.

Figure 8.3: Flow of pneumonia patients through the study.



Three patients were withdrawn from the high concentration oxygen group prior to the administration of oxygen. In one patient this was due to the inability to obtain stable and reliable $PtCO_2$ recordings, and two patients (one with COPD and one with obesity

hypoventilation syndrome) were inadvertently enrolled but subsequently found to meet exclusion criteria. As a result there were 72 and 75 patients included in the high concentration and titrated oxygen groups respectively.

The two groups were well matched with respect to age, sex, respiratory rate, oxygen saturation, $PtCO_2$, and CRB-65 score at baseline, and also well matched for the radiological confirmation of pneumonia (Table 8.6).

The 74/146 (50.7%) patients in which there was radiological confirmation of pneumonia had lower oxygen saturations than those without radiological confrimation: mean (SD) 95.7% (3.7) vs 96.8% (2.8) and a higher proportion had 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 8.4). In 29/147 (19.7%) patients the baseline $PtCO_2$ at presentation was ≥38 mmHg. 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 6/72 (8.3%) patients required oxygen between one to four litres per minute via nasal prongs and 1/72 (1.4%) patient required >4 litres per minute via medium concentration mask to achieve oxygen saturations ≥93%. In the high concentration

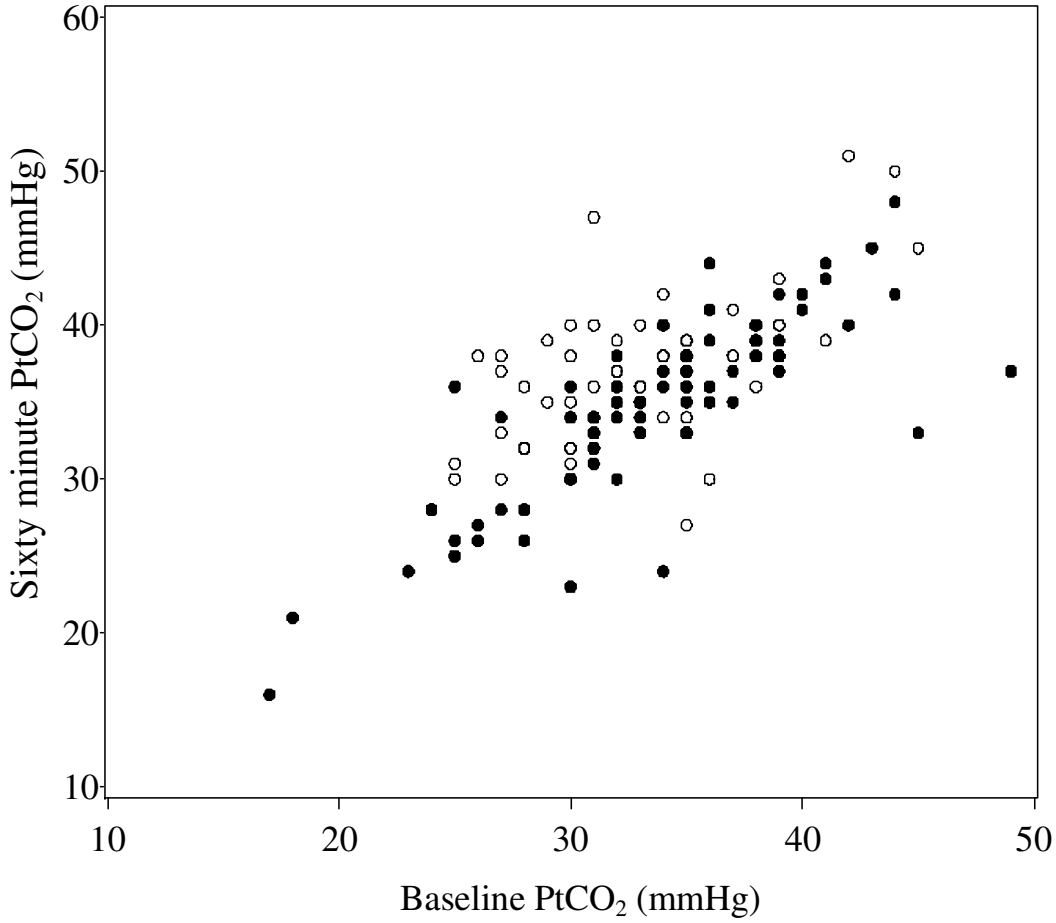
oxygen group the oxygen saturation at 60 minutes was ≥99% in 65/72 (90.3%) of patients and was between 93 and 98% in the remaining 7/72 (9.7%) patients.

Table 8.6: Baseline characteristics of pneumonia patients.

	High flow O_2 n=72	Titrated O_2 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)
$PtCO_2$ ≥38 mmHg	11 (15.3)	18 (24.0)	29 (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).

Figure 8.4: $PtCO_2$ levels in pneumonia patients at baseline and after 60 minutes in the high concentration (o) and titrated (●) oxygen groups.



8.2.2 Changes in $PtCO_2$

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, 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). 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 8.7).

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 8.8).

The mean change in $PtCO_2$ from baseline (Table 8.9) was significantly greater in the high concentration oxygen group compared with the titrated oxygen group, with a mean difference of 2.7 mmHg (95% CI 1.5 to 3.9; P<0.001). The rate of increase in the high concentration group was 0.058 mmHg/min (95% CI 0.044 to 0.072) compared to 0.017 mmHg/min (95% CI 0.0031 to 0.031) in the titrated group. The difference in the rate of change was 0.041 mmHg/min (95% CI 0.022 to 0.06, P<0.001).

Table 8.7: The proportion of pneumonia patients with a predetermined rise in $PtCO_2$ 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	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

Table 8.8: Time course of change in $PtCO_2$: proportion of pneumonia patients with a rise of ≥4 mmHg at three time points.

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

Table 8.9: Time course of mean change in $PtCO_2$ in pneumonia patients.

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

In patients with radiological confirmation of pneumonia, 20/35 (57.1%) of the high concentration oxygen group had a rise in $PtCO_2$ ≥4 mmHg compared with 5/39 (12.8%) in the titrated group, relative risk 4.5. In those without consolidation 16/37 (43.2%) of the high concentration oxygen group had a rise in $PtCO_2$ ≥4 mmHg compared with 6/36 (16.7%) in the titrated group, relative risk 2.6. However this interaction was not statistically significant (P=0.28).

8.2.3 Clinical variables

There were similar rates of hospital admissions between the two treatment groups with 36/72 (50%) admitted in the high concentration group compared with 37/75 (49.3%) in the titrated group, relative risk 1.01 (95% CI 0.74 to 1.39, P=0.94).

There was no significant difference in the change in respiratory rate between the treatment groups (-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). There was no significant difference in the change in CRB-65 score between the two groups after 60 minutes (P=0.99).

8.3 The physiological response to oxygen in chronic asthma

8.3.1 Subjects

Subjects were recruited between December 2008 and December 2009. The baseline characteristics of the three groups are summarised in Table 8.10.

Table 8.10 The baseline characteristics of asthma, COPD and normal subjects.

	Normal n=18	Asthma n=18	COPD n=18
Sex, male N (%)	9 (50)	8 (44)	11 (61)
Age (yr)	33.4 (10.4)	36.4 (9.4)	73.9 (7.1)
Respiratory rate (breaths/min)	12 (2.2)	13.4 (2.5)	14.3 (3.3)
BMI (kg/m^2)	25.9 (2.2)	28.1 (30.1)	22.7 (2.6)
SpO_2 %	97.9 (1.1)	97.1 (1.4)	95.8 (2.2)
FEV1 (L)	3.50 (0.58)	1.52 (0.39)	0.98 (0.22)
FEV1 % predicted	99.1 (2.9)	46.7 (6.0)	38.8 (6.8)
$PtCO_2$ (mmHg)	37.1 (2.8)	37.6 (3.0)	39.9 (4.9)
MV (L/min)	8.0 (1.1)	8.9 (1.6)	10.8 (1.9)
V_D/V_T	0.37 (0.06)	0.47 (0.1)	0.59 (0.07)

Values for age, respiratory rate, BMI, SpO_2, $PtCO_2$ FEV1 and FEV1% predicted are mean (SD). Values for sex are number of participants (percentage).

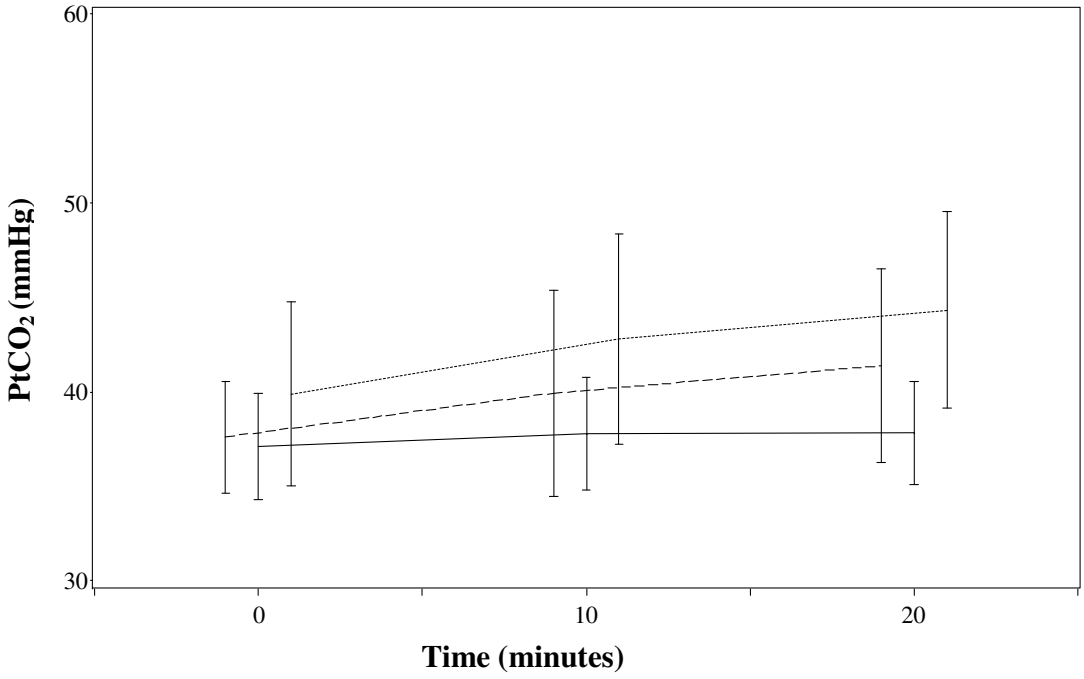
Compared to asthmatics and normal controls, patients with COPD were older and had a lower mean BMI. The asthma and COPD groups had severe airflow obstruction, compared with the normal controls in which the mean FEV1 was 99% of predicted normal values. Compared to the normal controls the asthma group had a higher V_D/V_T ratio and MV, and the COPD group had a higher V_D/V_T ratio and MV than the asthma group.

8.3.2 Changes in $PtCO_2$

After 20 minutes of 100% oxygen there was a significant increase in $PtCO_2$ from baseline in both the asthma and COPD groups with a mean rise of 3.8 and 4.4 mmHg respectively. No significant rise in $PtCO_2$ was observed in the normal group, with a change from baseline of 0.7 mmHg.

When compared to the normal controls, the change in $PtCO_2$ in both the asthma and COPD groups was significantly different when adjusted for baseline, with an asthma minus normal difference of 3.1 mmHg (95% CI 1.3 to 4.8, P<0.001) and a COPD minus normal difference of 3.7 mmHg (95% CI 1.9 to 5.5, P<0.001) at 20 minutes (Table 8.11). The time course of the changes in $PtCO_2$ is shown in Figure 8.5.

Figure 8.5: $PtCO_2$ versus time in patients with asthma (short dash line), COPD (long dash line) and normal controls (solid line). Data points are mean plus or minus one standard deviation.



8.3.3 Changes in MV, V_D/V_T, FEV1 and respiratory rate

There was no significant change in minute ventilation from baseline in the asthmatics, COPD patients or normal controls with a mean (SD) difference of -0.06 (0.5), -0.3 (1.0) and 0.06 (0.4) respectively (Table 8.11). There was no evidence of a change in respiratory rate or FEV1 at 20 minutes after adjusting for baseline, in the three patient groups.

Table 8.11: Changes in physiological variables at 20 minutes after adjusting for baseline.

	Asthma minus normal (95% CI)	COPD minus normal (95% CI)	P value
$PtCO_2$ (mmHg)	3.1 (1.3 to 4.8)	3.7 (1.9 to 5.5)	< 0.001
Minute ventilation (L/min)	0.0 (-0.5 to 0.4)	-0.1 (-0.7 to 0.4)	0.87
V_D/V_T	0.03 (-0.005 to 0.065)	0.07 (0.02 to 0.12)	0.03
Respiratory rate (breaths per min)	0.4 (-0.7 to 1.5)	-0.04 (-1.2 to 1.1)	0.63

The V_D/V_T increased more in the COPD and asthma groups than in the normal controls, with a mean (SD) rise after 20 minutes of 0.10 (0.05), 0.07 (0.06), and 0.04 (0.02) respectively. After adjusting for baseline, the change was significantly higher in the COPD group compared to normal controls. Although the point estimate of the difference

between the asthma group and normal controls was 0.3, the 95% confidence interval crossed zero (Table 8.11).

Chapter 9: Discussion

9.1 Introduction

This chapter discusses the key findings of the studies in this thesis, their clinical significance, their strengths and limitations, and compares the results to previous work. Given their similar methodology and results, the studies on acute asthma and pneumonia will be considered together followed by the physiological study of oxygen in chronic asthma and COPD.

9.2 Randomised controlled trials of high concentration versus titrated oxygen in acute asthma and pneumonia

9.2.1 Key findings

These studies show 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 suspected community-acquired pneumonia or acute severe asthma. The relative risk of an increase in $PtCO_2$ of more than 4 mmHg with high concentration oxygen therapy was 2.3 in asthma and 3.4 in pneumonia. Similarly, a rise in $PtCO_2$ of at least 8 mmHg was three-fold more likely in asthma and five-fold more

likely in pneumonia with high concentration oxygen therapy, compared with the titrated oxygen regime.

These results are physiologically and clinically significant as indicated by the magnitude and frequency of the $PtCO_2$ changes in the groups receiving high concentration oxygen. Although no subjects experienced symptomatic hypercapnia, there was a clear signal that uncontrolled oxygen administration resulted in an increased risk of carbon dioxide retention.

It is likely that the increase in $PtCO_2$ seen with high concentration oxygen in these studies underestimates the magnitude of the effect seen in standard clinical practice. The mean change in $PtCO_2$, and the proportion of patients with a rise above the 4 mmHg and 8 mmHg thresholds, continued to increase in both high concentration groups throughout the 60 minute study period. In clinical practice, patients with severe asthma or suspected pneumonia often receive uncontrolled oxygen therapy in the ED for much longer than 60 minutes; hence it is possible that some patients would have continued to progressively retain CO_2 had the high concentration oxygen regime continued.

As noted above, in order to maintain the internal validity of the study it was necessary to exclude subjects with the potential to develop oxygen-induced hypercapnia, in particular COPD and obesity hypoventilation syndrome. In clinical practice however, high concentration oxygen is routinely given to such patients if they present in a non-specific

fashion with symptoms of wheeze, cough and breathlessness. As a result, in an unselected group the likelihood of significant hypercapnia may be increased further.

Finally, although an attempt was made to include all potential subjects with severe or life threatening asthma, there are difficulties in performing clinical studies in subjects with critical illness. Asthma patients who were moribund, unable to speak, unable to perform spirometry, or so distressed that they could not consent, were not approached. Consequently, those with the most severe airflow obstruction, and hence the highest risk of hypercapnia, were not able to be studied. Similarly, pneumonia patients with more severe disease who were too unwell to provide consent were not included, and they are likewise at higher risk of oxygen induced CO_2 retention due to higher degrees of $\dot{V}/\dot{Q}$ mismatch. The danger for such patients is compounded by the fact that a more severe illness makes it more likely they will be given high concentrations of oxygen, and for longer periods of time.

There was a significant difference in admission rates in the asthma study with 26/50 (52%) admitted in the high flow group compared to 17/53 (32%) in the titrated group, a relative risk of 1.6 (95% CI 1.0 to 2.6, P=0.04). This may be the result of apparent differences in the baseline severity of patients in the two groups, with a lower FEV1 and higher initial $PtCO_2$ in the high concentration group. Although a genuine effect of oxygen treatment on asthma admission rates cannot be ruled out, the baseline differences

between the groups and lack of a similar finding in the pneumonia study makes it less likely.

As well as the risk of worsening hypercapnia, uncontrolled oxygen therapy poses another potential risk to patients with acute respiratory disease: masking the ability to detect a clinical deterioration (Beasley, Aldington, & Robinson, 2007; Downs & Smith, 1999). If a patient with acute asthma or pneumonia is prescribed oxygen in excess of their requirements and becomes hyperoxic, a clinical decline is less likely to be detected at the bedside by the use of routine pulse oximetry. Conversely, if oxygen is titrated to maintain oxygen saturations in the normal range (93-96%) a clinical deterioration will become apparent earlier as the oxygen saturations fall, enabling more rapid medical re-assessment and intervention.

This concept is supported by the oxygen saturation data from these trials. In the pneumonia study, the oxygen saturations were ≥99% in 90% of subjects in the high concentration oxygen group. Because they were likely to be significantly hyperoxic, a progressive clinical deterioration in these patients may result in little or no change in oxygen saturation until a potentially life-threatening situation had developed. In contrast, 90% of patients in the titrated oxygen group required no supplementary oxygen at all, as their oxygen saturations remained >92%. A clinical deterioration in this titrated group is likely to be recognised sooner through the detection of falling oxygen saturations, giving the option of increasing oxygen concentration as supportive care while more definitive intervention is undertaken.

The only clinical variable which was significantly altered was heart rate which demonstrated a greater reduction in the high concentration arm of the pneumonia study, a change that might be interpreted as a beneficial effect of oxygen therapy. However, a number of studies have demonstrated significant cardiovascular effects from hyperoxia, including a reduction in cardiac output and stroke volume, and increases in mean arterial pressure and mean systemic vascular resistance (Kenmure et al., 1968; Loeb et al., 1971; Mackenzie et al., 1964; Shillingford & Thomas, 1967; Sukumalchantra et al., 1969; Thomas et al., 1965). It is possible that the independent cardiovascular effects of hyperoxia were responsible for this finding.

9.2.2 Comparison with previous studies

There are no previous trials comparing high concentration with titrated oxygen in pneumonia; consequently the findings of this study are novel and represent the first evidence of the potential for hypercapnic respiratory failure with the use of high concentration oxygen in this group of patients.

There has been only one previous randomised controlled trial comparing high and low concentration oxygen in acute severe asthma (G. J. Rodrigo et al., 2003). This study randomised 74 acute asthma patients to 100% or 28% oxygen for 20 minutes on arrival to the emergency department and prior to receiving any treatment for asthma. Their study endpoints were different, making it difficult to directly compare their results to this study.

However, the mean rise in $PaCO_2$ of 2.7 mmHg in the Rodrigo paper is similar to the 2.6 mmHg rise found in this study.

The weaknesses of the Rodrigo study include a short duration of oxygen administration of 20 minutes, the absence of any concurrent asthma therapy, and the use of 100% oxygen. The data in this thesis confirm the Rodrigo findings of a physiologically significant increase in carbon dioxide, but because this study protocol mimics clinical practice more closely, it extends their results in a number of ways.

First, most patients with acute severe asthma are administered bronchodilators concurrently with oxygen therapy from the time of arrival at hospital. My study protocol included routine asthma treatment according to international guidelines from the time of arrival, in conjunction with oxygen. Second, inspired oxygen concentrations of 100%, delivered using a non-rebreather mask in the Rodrigo study, are not routinely used in acute asthma. A flow of 8L/min, the recommended rate for the administration of bronchodilator drugs ("Current best practice for nebuliser treatment, British Thoracic Society," 1997), is a better reflection of clinical practice and delivers concentrations of inspired oxygen between 50 and 60% (Milross, Young, & Donnelly, 1989). Third, patients with acute severe asthma are often in the Emergency department for a few hours, and if they receive uncontrolled oxygen therapy it may be given for significantly longer than 20 minutes.

With regard to the duration of oxygen treatment, of particular note is the finding that the proportion of subjects in the high concentration group with a significant rise in $PtCO_2$ of ≥4 mmHg increased progressively at 20, 40 and 60 minutes in both the asthma and the pneumonia studies. It is possible that further progressive increases in carbon dioxide may occur if high concentration oxygen is given for longer than an hour, particularly among asthma patients whose airflow obstruction and clinical status is not improving with pharmacotherapy.

9.2.3 Methodological issues

9.2.3.1 Study participants

An important methodological issue in both studies was the need to exclude subjects that may have had alternative reasons for a rise in $PtCO_2$ aside from either asthma or pneumonia. A particular effort was made to exclude COPD patients on the basis of either a clinical history or doctor's diagnosis, or clinical suspicion of the investigator. In addition, access to hospital records which document previous admissions, out-patient consultations and spirometry where available, allowed further opportunities to exclude those with COPD. For the asthma study, a decision was made to exclude subjects over 65 years on the basis that a number of older patients who self report a diagnosis of asthma actually have COPD.

Because we did not perform spirometry on enrolment or prior to discharge in the pneumonia group, it is possible that some patients with COPD may have been included in

the study. However, in clinical practice when patients present with acute breathlessness and features consistent with pneumonia, spirometry is rarely done at the first point of oxygen therapy which is usually in the ambulance or Emergency Department, hence this study replicates what happens in clinical practice. It is likely that greater increases in $PtCO_2$ may occur in an unselected population of patients with acute respiratory infection or wheeze, as such a group would include those with concomitant unrecognised COPD, or other disorders associated with chronic respiratory failure.

Patients with other risk factors for oxygen induced carbon dioxide retention, including significant obesity, musculoskeletal disease and thoracic wall restriction, were also excluded, hence these disorders are unlikely to have contributed to the changes in $PtCO_2$ seen in the studies (Ellis, Grunstein, Chan, Bye, & Sullivan, 1988; Gay & Edmonds, 1995; Milross et al., 1989; Nowbar et al., 2004; Quint, Ward, & Davison, 2007).

In the pneumonia study, clinical rather than radiological inclusion criteria were used to select subjects. This was done to ensure that participants were enrolled before having received oxygen and antibiotics from clinical staff. In the ED there is often a delay after initial clinical assessment before an x-ray is performed in patients with suspected pneumonia, and oxygen therapy is usually administered to breathless patients on arrival rather than waiting for the results of chest radiography.

About half of the patients in the pneumonia study had radiological confirmation of consolidation. However, studies using high resolution computed tomography suggest that

plain chest radiography commonly misses consolidation, particularly bilateral changes and upper lobe disease (Syrjala, Broas, Suramo, Ojala, & Lahde, 1998). Consequently the true rate of pneumonia in the group as a whole may have been up to a third higher. This may explain why the presence or absence of radiologically confirmed pneumonia made no difference to the risk of raised $PtCO_2$ with high concentration oxygen therapy.

Finally, the enrolment target in the asthma trial was not met, despite opening the study to recruitment in a second hospital and extending the study duration by six months. Data from the Wellington Hospital Emergency Department indicate that there was an approximately 20% drop in asthma presentations over the period of the study, for reasons that are unclear. The proportion of subjects with a significant increase in $PtCO_2$ in the asthma study (44% in the high concentration group versus 19% in the titrated group) exceeded the estimates based on the randomised controlled trial used for the power calculation (G. J. Rodrigo et al., 2003). The magnitude of the effect found meant the result was still highly significant despite the reduction in numbers.

Despite these aspects of subject recruitment, the enrolment criteria in both the asthma and pneumonia groups were broad, and hence both studies can be considered to have good external validity and generalisability.

9.2.3.2 Clinical measurements

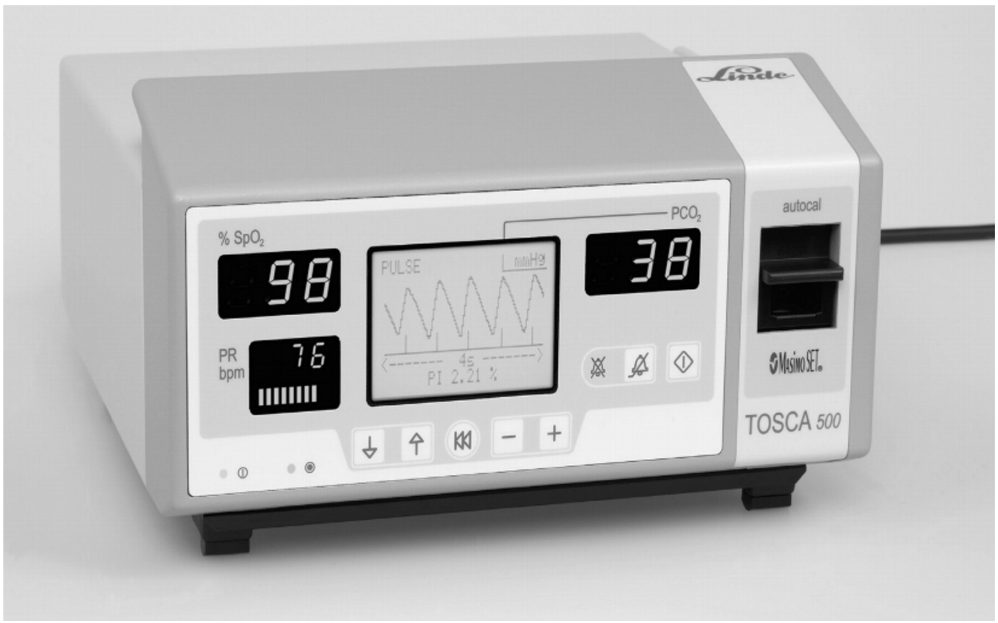
Early drafts of the study protocol for both the asthma and pneumonia trials specified an ABG at baseline and again at 60 minutes. However, during a short pilot of this protocol the first three potentially eligible asthma patients all refused a second ABG. In addition to what appeared to be a significant barrier to adequate recruitment, I considered that there were significant ethical issues in subjecting a large group of patients to an uncomfortable and potentially risky clinical procedure purely for research purposes. Although some Emergency Departments use venous blood gas assessments for estimation of P_aCO_2, this method still requires two separate venepunctures which would not be otherwise required in a large proportion of the potential subjects.

There are two methods to non-invasively estimate P_aCO_2. End-tidal carbon dioxide monitors are available in many emergency departments and are primarily used to detect the accurate placement of endotracheal tubes. However, in terms of their use in estimating P_aCO_2, the major limitation with capnography is that it becomes inaccurate in the setting of many pulmonary diseases, particularly when there is changing ventilation perfusion mismatch (S. Y. Liu, Lee, & Bongard, 1992; Sanders et al., 1994; Stock, 1988). By contrast, transcutaneous carbon dioxide monitor technology has advanced to the extent that its accuracy has been demonstrated in a variety of settings including healthy subjects (Eberhard, Gisiger, Gardaz, & Spahn, 2002; Fuke et al., 2009), AECOPD (Cox et al., 2005; Storre, Steurer, Kabitz, Dreher, & Windisch, 2007), sleep disorders (Maniscalco, Zedda, Faraone, Carratu, & Sofia, 2008; Rosner, Hannhart, Chabot, & Polu,

1999) and critical illness (Bendjelid et al., 2005; Rodriguez, Lellouche, Aboab, Buisson, & Brochard, 2006; Senn, Clarenbach, Kaplan, Maggiorini, & Bloch, 2005). There has also been a recent study demonstrating the accuracy of a transcutaneous device in a mixed group of 51 patients presenting to an ED (McVicar & Eager, 2009).

The decision was made to use transcutaneous monitoring to assess the main outcome measure in these studies, as it allowed continuous CO_2 monitoring without the discomfort of repeated arterial puncture or the risk of hand ischemia associated with an indwelling radial artery cannula. The TOSCA 500 device (Linde Medical Sensors AG, Basel, Switzerland), was selected because of its compact design, portability and ease of use, (Figure 9.1).

Figure 9.1: The display of a TOSCA 500 transcutaneous carbon dioxide monitor.



However, there are a number of factors that can impact on the accuracy of transcutaneous carbon dioxide monitoring (Kagawa & Severinghaus, 2005). First, correct placement of the probe is important. The skin of the earlobe must be cleaned with an alcohol swab and allowed to dry, then the probe is attached using attachment clips and contact gel supplied with the device. The entire probe must have contact with the gel because the presence of air between the probe and the skin significantly decreases the quality of the signal. Second, reliable recordings depend on adequate arterialisation of the capillaries underlying the probe. This is achieved by setting the probe to heat to 45°C initially before dropping to a temperature of 42°C to maintain a constant signal. Using this method the time taken for adequate arterialisation, and consequently a reliable and accurate percutaneous carbon dioxide signal, is stated by the manufacturers to be approximately five minutes. In these studies a longer warm up period of 10 minutes was allowed, and all tracings were deemed to be satisfactory and stable at T=0 when the oxygen regimen was started. In vitro response times for this device are typically less than 50 seconds and in vitro drift is less than 0.5% per hour (Bendjelid et al., 2005; Cox et al., 2005; Eberhard et al., 2002).

To ensure the accuracy of the device it regularly cleaned and checking, and the probe membrane was replaced every 14 days as per the manufacturer's guidelines. All research fellows involved in the recruitment of patients into the study were fully trained in the correct use of the device. As noted in chapter 7, the accuracy of the TOSCA 500 was validated in a sample of acute asthma and pneumonia subjects, and a Bland Altman

analysis indicated minimal bias and acceptable limits of agreement which exceed those of recent similar studies (Cox et al., 2005; Maniscalco et al., 2008; McVicar & Eager, 2009).

9.2.3.3 Potential sources of error and bias

Any measurements in a clinical study can introduce error unless the methods used are both valid and reliable. Validity refers to the accuracy with which a tool measures the "true" value of a clinical variable. In these studies, it is represented by how closely the $PtCO_2$ monitor is able to assess the true arterial partial pressure of carbon dioxide. As reported in Chapter 7, a validation study of the TOSCA 500 monitor indicated minimal bias and satisfactory validity. Reliability refers to the degree of agreement between different measurements on the same patient at different times using the same tool. In this case the reliability of the TOSCA 500 was assessed using two consecutive measurements by the same investigator on the same subject at different times, and analysis showed excellent agreement with an intra-class correlation coefficient of 0.89.

Bias can be introduced at any stage during the process of enrolment, randomisation and allocation of study subjects to a treatment group. The low likelihood of enrolment bias in these studies is demonstrated by the subject flow diagrams in Chapter 8; low numbers of patients either refused to take part or did not meet inclusion criteria, and in the asthma

study exclusion was only due to insufficient airflow obstruction. Additionally there were low numbers of subject withdrawals in both studies.

Another source of enrolment bias can occur if the investigator is aware of, or can predict, what the next treatment allocation will be, as it may influence their decision on whether to enrol the next potential participant. Allocation concealment, a critical part of the randomisation process, helps to avoid this. Randomisation in these studies was by way of a computer generated schedule supplied by a statistician. The schedule was sent to a third party, who had no involvement in the conduct of the study, and embedded into a Microsoft Access database purpose designed so that the schedule was concealed from those participating in the conduct and analysis of the studies. The investigators accessed the database via a secure login code, and the allocation of a participant to a treatment group was only revealed after the decision to enrol and informed consent was completed and the patient details entered.

Finally, the issue of blinding is important in randomised controlled trials, particularly if subjective observations are used as outcome measurements, as it significantly reduces the likelihood of observer or subject bias. By necessity, the studies in this thesis were not blinded. Not only was there a clinical and ethical requirement for the investigator to have knowledge of the oxygen saturations in order to adjust oxygen therapy in the titrated group, but the fact that titrated oxygen is given using a variety of delivery devices means that it could not be concealed from the patient. However, the primary outcome variable in these studies, $PtCO_2$ displayed on a monitor, was sufficiently objective to make

significant observation bias unlikely. Subject bias was possible in these studies as participants were informed of the purpose of the study at enrolment and may have had an understanding of how to voluntarily influence their own $PtCO_2$. However, this seems unlikely; the monitor display was positioned out of view of the subjects and they were given no explanation of the potential reasons for carbon dioxide changes.

9.2.4 Interpretation and mechanisms

There are four potential physiological explanations for the oxygen induced increases in $PtCO_2$ shown in these studies:

1. The Haldane effect
2. Decreased minute ventilation
3. Increased shunt fraction
4. Increased V_D/V_T as a result of the release of HPV

The Haldane effect is due to a physiological property of haemoglobin molecules. A conformational change occurs when they become oxygenated in the pulmonary circulation which results in a release of carbon dioxide, facilitating gas exchange (Christiansen, Douglas, & Haldane, 1914; Tyuma, 1984). Because the administration of oxygen increases the amount of fully saturated haemoglobin, this could result in an increase in the release of transported carbon dioxide from those molecules, and hence theoretically the Haldane effect could be responsible for some of the effects induced by oxygen. A number of investigators have attempted to quantify the contribution of the

Haldane effect to arterial and venous partial pressures of carbon dioxide, with limited success. However, clinical studies and computer models have estimated that the effect is small, in the order of 1-2 mmHg increases in P_aCO_2 following oxygen administration (Lee & Read, 1967; Lenfant, 1966).

Minute ventilation was not formally measured in the ED based studies; hence it is possible that the increases in $PtCO_2$ were a result of oxygen administration suppressing the hypoxic drive to breathe. However, previous studies in acute and chronic asthma have failed to demonstrate any significant decline in minute ventilation when high concentration oxygen is delivered (Ballester et al., 1989; Corte & Young, 1985; Rodriguez-Roisin et al., 1989). Additionally, the majority of subjects in both the titrated and high concentration groups of both studies were hypocapnic at baseline and only mildly hypoxic, hence it is unlikely that subjects in either group were dependant on a hypoxic drive to breathe.

The presence of right to left shunt can result in increased alveolar dead space and therefore increased V_D/V_T (Mecikalski, Cutillo, & Renzetti, 1984). However, previous studies have demonstrated that there is minimal change in shunt when patients breathe 100% oxygen in COPD, asthma and pneumonia (Ballester et al., 1990; Corte & Young, 1985; Gea et al., 1991; Roca et al., 1988; Wagner et al., 1977)(Corte 1985, Roca 1988, Ballester 1990, Gea 1991). Consequently it is unlikely that increasing shunt is responsible for the results observed in these studies.

It is possible that the increases in $PtCO_2$ seen in the high concentration groups simply reflect a more rapid clinical resolution of their underlying condition and a consequent shift of their baseline hypocapnia towards the normal range as they recover. However, because the patients were randomised, this mechanism implies that there must be a specific beneficial therapeutic effect of high concentration oxygen on the underlying disease. This is not likely in the case of patients with suspected pneumonia, and has not been demonstrated previously in acute asthma. Moreover, oxygen has not been demonstrated to relieve breathlessness in non-hypoxaemic patients (Clemens & Klaschik, 2007; Gallagher & Roberts, 2004; Philip et al., 2006). This explanation is also contradicted by the fact that there were no significant changes in other clinical variables between the two oxygen groups over the course of oxygen treatment, aside from a lower heart rate in the pneumonia study. If high concentration oxygen were to hasten the clinical improvement in asthma one would expect to see differences between the groups in FEV1 or respiratory rate. However, results show that in the case of the asthma study there was no significant difference in the change in FEV1 during the study between the treatment groups.

The possibility of asthma therapy, specifically bronchodilator treatment, contributing to changes in gas exchange must also be considered. Bronchodilator administration is known to adversely affect $\dot{V}/\dot{Q}$ mismatch when given either intravenously or by nebuliser (Ballester et al., 1989; Field, 1967; Harris, 1972; Palmer & Diament, 1969). However, the randomisation of subjects and the standardisation of asthma treatment

across all participants mean that any effect of bronchodilators should have occurred equally in both groups.

Consequently the main underlying mechanism for the $PtCO_2$ elevation demonstrated in these studies is likely to be worsening $\dot{V}/\dot{Q}$ mismatching as a result of the release of hypoxic vasoconstriction and a consequent increase in physiological dead space. These physiological considerations are discussed further in section 9.3.

9.3 A study of the physiological response to oxygen in chronic asthma

9.3.1 Key findings

This study has demonstrated that breathing 100% oxygen results in an increase in $PtCO_2$ in subjects with chronic asthma. There was little difference in the magnitude of the increase or the mechanism when compared to subjects with COPD, and this is in contrast to the lack of change in normal controls. The increase in $PtCO_2$ seems likely to be related to a change in V_D/V_T which increased in both asthma and COPD patients but not in the normal controls. By contrast there was minimal change in minute ventilation in any of the three groups. This indicates that the most likely mechanism of an oxygen induced increase in P_aCO_2 in asthma is worsening of ventilation-perfusion mismatching due to the release of hypoxic pulmonary vasoconstriction.

9.3.2 Comparison with previous studies

This is the first controlled trial to measure the simultaneous response of carbon dioxide, minute ventilation and V_D/V_T to 100% oxygen in a well defined group of asthma patients, in the absence of confounding factors such as changes in posture and administration of vasodilator or bronchodilator drugs. The findings of this study are in line with previous work on the effects of oxygen on gas exchange in patients with asthma (Ballester et al., 1989; Ballester et al., 1990; Corte & Young, 1985; Field, 1967; Rodriguez-Roisin et al., 1989). It confirms that an increase in P_aCO_2 occurs, and establishes that the main mechanism is an increase in physiological dead space and not a decrease in minute ventilation.

9.3.3 Methodological issues

9.3.3.1 Study participants

The participants were selected in an attempt to ensure that no subjects in the asthma group had COPD, as that might have confounded any responses to oxygen seen. For this reason smokers were excluded, and an upper age limit of 65 years was used, given that patients over this age who self report a diagnosis of asthma have a higher likelihood of having COPD.

In order to replicate the effect of oxygen on patients with acute asthma, the chronic stable asthma patients needed to have at least moderately severe airflow obstruction, and for this

reason there was a requirement to have a pre-bronchodilator FEV1 of less than 60% predicted.

The other consideration in studying chronic asthma patients to replicate responses of those with acute exacerbations is whether the underlying gas exchange abnormalities are sufficiently similar to make them a valid study group. Previous work using MIGET has confirmed that although the $\dot{V}/\dot{Q}$ dispersion patterns in patients with chronic asthma are narrower than in those with acute exacerbations, reflecting better compensation by HPV, the $\dot{V}/\dot{Q}$ changes that occur when oxygen is administered are the same (Ballester et al., 1990; Rodriguez-Roisin & Roca, 1994).

9.3.3.2 Clinical measurement

P_aCO_2 was estimated using a TOSCA transcutaneous CO_2 monitor, and $PtCO_2$ was used to calculate the V_D/V_T according to the Bohr-Enghoff equation. This device allows continuous $PtCO_2$ monitoring without the discomfort of repeated arterial blood gas sampling. The issues regarding its accuracy and repeatability are discussed above.

The other variable required to calculate the V_D/V_T is the mixed expired carbon dioxide partial pressure. The COSMO Respiratory Profile Monitor uses a real time infra-red gas analyser which continuously measures the partial pressure of expired CO_2 and combines this with flow recordings to express the data in the form of volumetric capnography. The

volume weighted three minute average expired CO_2 is updated every 15 seconds and mixed expired CO_2 is calculated by dividing the volume of CO_2 for a one minute interval by the total expired volume for the same interval. This technique is accepted as the standard approach to the assessment of expired CO_2 for the purposes of dead space calculations, and has been shown to be equivalent to older methods such as Douglas Bag collection of expired gases (Lum, Saville, & Venkataraman, 1998; Mackinnon, Houston, & McGuire, 1997).

Minute ventilation is calculated by a flow sensor in the pneumotachygraph of the COSMO Respiratory Profile Monitor plus. It continuously measures flow and pressure across the inspiratory/expiratory port of the mask mouth piece. Minute ventilation is calculated by the rolling average tidal volume divided by respiratory rate over two minutes. Respiratory rate is measured by the flow meter and computed as an eight breath moving average updated breath to breath. These devices have established accuracy in clinical and research settings (Castle, Dunne, Mok, Wade, & Stocks, 2002).

Both the infra-red gas analyser and the flow meter were regularly calibrated as part of routine maintenance of the device.

The multiple inert gas elimination technique (MIGET) is considered the gold standard for measuring ventilation and perfusion matching, however it has the drawback of being highly invasive, requiring both arterial and central venous vascular access. Although MIGET can measure precise ventilation perfusion ratios, it is better suited to studies

where there is uncertainty about the types of $\dot{V}/\dot{Q}$ changes that will be found, for example it is able to measure the presence of a shunt fraction. However, previous work has shown shunt to be negligible in both asthma and COPD and that changing V_D/V_T is the dominant gas exchange abnormality (Ballester et al., 1989; Ballester et al., 1990; Barbera et al., 1997; Roca et al., 1988). Consequently a non-invasive method was used to determine the direction and magnitude of V_D/V_T ratios as a marker of changes in $\dot{V}/\dot{Q}$.

Although in clinical practice it would be uncommon to administer 100% oxygen to patients with asthma, this oxygen regime was used to ensure hyperoxia was achieved and to maximize the potential to determine an effect during the 20 minutes of administration. It is possible that the magnitude of the increase in $PtCO_2$ observed may have been less with lower oxygen concentrations.

Chapter 10: Summary and conclusions

The studies in this thesis show that uncontrolled high concentration oxygen causes an increase in P_aCO_2 in a significant proportion of patients presenting to the Emergency Department with severe asthma and suspected pneumonia. Additionally, a controlled trial of oxygen in chronic asthma shows that the main mechanism of carbon dioxide retention is similar to that observed in COPD; namely an increase in physiological dead space rather than a change in minute ventilation. In terms of potential harms to the patient, in addition to the hyperoxia induced gas exchange abnormalities demonstrated in these studies there is also the potential for hyperoxia to mask the ability to detect a clinical decline with pulse oximetry.

These findings extend the existing literature showing potential harm in the routine use of high concentration oxygen in a number of respiratory conditions for which it was previously considered safe and even desirable. There is now data to suggest that inappropriate high concentration oxygen therapy may have adverse effects on gas exchange across a wide range of respiratory conditions including stable COPD (Dick et al., 1997; Sassoon et al., 1987), exacerbations of COPD (Aubier, Murciano, Milic-Emili et al., 1980; Donald, 1949; Robinson et al., 2000; Westlake et al., 1955), asthma (Chien et al., 2000; Field, 1967; G. J. Rodrigo et al., 2003), obesity hypoventilation syndrome

(Barrera, Hillyer, Ascanio, & Bechtel, 1973; Said & Banerjee, 1963), and diffuse pulmonary fibrosis or infiltration (Said & Banerjee, 1963).

In October 2008 the British Thoracic Society (BTS) published the first ever comprehensive guidelines on the use of oxygen therapy for acute conditions in adult patients (O'Driscoll, Howard, & Davison, 2008). After an extensive review of the literature, and the production of a document running to around 60 pages, the vast majority of their recommendations had to be based on weak evidence, often at the level of expert opinion. As the authors' state in the executive summary "For most of the topics covered by the guideline there were either no randomised trials or just a handful of observational studies". Despite this, the guideline writing group took the perspective that a lack of evidence for any beneficial effects of routine high concentration oxygen should move practice towards a more cautious approach, and away from current opinion which assumes safety and benefit with oxygen therapy. Consequently, the general theme of the guideline can be summarised briefly: oxygen should only be given to patients with evidence of hypoxaemia and should be administered and monitored so that oxygen saturation stays within the normal range but no higher.

For most acutely ill patients with cardio-respiratory disease the BTS guidelines recommend a target oxygen saturation range of 94-98%. For those at risk of hypercapnic respiratory failure (such as patients with COPD, morbid obesity or chest wall restriction) a lower target range of 88-92% was recommended. However, for patients with critical or life threatening illness such as cardiac arrest, shock, sepsis or major trauma, the guideline

authors were more conservative and advised the routine use of high concentration oxygen through a reservoir mask at 15L/min. Again, the evidence grade for this recommendation was weak with few studies demonstrating a benefit of routine high flow oxygen in critical illness. In fact there is evidence to suggest that the presence of hyperoxia in the post-cardiac arrest setting is associated with a worse outcome. A recent multi-centre cohort study pooled data from over 6000 post-cardiac arrest patients. They demonstrated that hyperoxia (defined as a PaO_2 of > 300 mmHg) was associated with a higher mortality rate compared to both normoxic and hypoxic patients, with an odds ratio for death of 1.8 (CI, 1.5 – 2.2) after adjustment for pre-specified confounders (Kilgannon et al., 2010). In addition, data from animal models supports the notion that hyperoxia during and after cardiac arrest is detrimental, with studies demonstrating a decrease in brain function and less neurological recovery (Y. Liu et al., 1998; Richards, Fiskum, Rosenthal, Hopkins, & McKenna, 2007; Vereczki et al., 2006). As in the case with coronary blood flow, these adverse effects may represent vasoactive changes associated with hyperoxia, but there is also concern that reperfusion injury and an increase in oxygen free radicals may play a role.

The BTS guidelines have prompted a change in the recommendations contained in some disease-specific guidelines. For example, the BTS guidelines for pneumonia published in 2001 recommended continuous oxygen therapy for all patients with hypoxaemia, hypotension, metabolic acidosis, or a respiratory rate of >24 breaths/min ("BTS Guidelines for the Management of Community Acquired Pneumonia in Adults," 2001). This was modified in 2009 to state that “patients should receive oxygen therapy with

monitoring of oxygen saturations and inspired oxygen concentration with the aim to maintain arterial oxygen saturation 94–98%." (Lim et al., 2009)

In summary then, the BTS guideline for emergency oxygen use in adults is a significant advance, in that it clearly documents the currently available evidence, or lack of it, and moves clinical practice closer to what could be considered a safe approach. However there is also a clear need for further research to make these recommendations more robust, and until that occurs it is likely that widespread adoption of the guideline principles will be slow.

The studies in this thesis provide strong evidence that hyperoxia in patients with suspected pneumonia or severe asthma provides no clinical benefit and in fact is potentially harmful. What other areas require further research? Studies assessing the role of oxygen in acute cardiovascular disease are a priority, particularly its use in acute coronary syndromes and myocardial infarction. As noted in chapter one, there are a number of physiological studies which show the potent vasoactive properties of hyperoxia, most notably that it causes a significant decrease in coronary blood flow (Farquhar et al., 2009). The only randomised controlled trial of oxygen use in myocardial infarction showed a non-significant three-fold increase in mortality with routine high flow oxygen, and elevated cardiac enzymes suggesting larger infarct size (Wijesinghe et al., 2009). Another randomised controlled trial of high flow versus titrated oxygen in myocardial infarction is urgently needed. This would require a multicentre approach, as large numbers of subjects would be needed to detect changes in important outcomes such

as mortality. It is critical that the cardiology community collaborate on this as a research priority. In terms of acute respiratory disease, studies of high concentration oxygen use in AECOPD are required, particularly during the pre-hospital and ED stages of care. There are data from retrospective reviews and audits that suggest worse outcomes with over-oxygenation but there is a lack of high quality prospective data (Denniston, O'Brien, & Stableforth, 2002; Durrington, Flubacher, Ramsay, Howard, & Harrison, 2005; Joosten, Koh, Bu, Smallwood, & Irving, 2007; Wijesinghe et al., 2010). There also need to be further studies investigating the best approach to oxygen use in other acute respiratory diseases such as pulmonary embolism. Finally, the BTS recommendation that oxygen at 15L/min should be administered in cardiac arrest, severe sepsis and life threatening illness needs to be addressed. Although it can be problematic to undertake research in patients who are critically ill, the logistical concerns is this case are outweighed by the clinical and ethical imperative to accurately define the role of oxygen in these situations.

Oxygen therapy has evolved significantly over the 100 years since it was first introduced into routine clinical practice. Although initially there was a degree of scepticism about its value, there quickly developed an acknowledgement of its beneficial effect in hypoxaemic patients. Unfortunately, for a variety of reasons, the role of oxygen in the management of acute disease became ever broader and its use progressively moved away from an established evidence base. However, in recent years there has been a shift in clinical opinion, reinforced by the BTS guideline publication, towards a more cautious approach. Although further research is required, we can now state with some confidence

that there is likely to be little role for the routine use of high concentration oxygen in the vast majority of acute medical illnesses. The wide availability of pulse oximetry in pre-hospital and hospital settings means there is no reason why oxygen delivery cannot be titrated to target saturation levels. This approach increases the likelihood of patients receiving the benefits of oxygen therapy while reducing the potential for harm (Thomson, Webb, & Maxwell, 2002).

References

Aber, G. M., Harris, A. M., & Bishop, J. M. (1964). The effect of acute changes in inspired oxygen concentration on cardiac, respiratory and renal function in patients with chronic obstructive airways disease. *Clinical Science, 26*, 133-143.

Agusti, A. G., & Barbera, J. A. (1994). Contribution of multiple inert gas elimination technique to pulmonary medicine. 2. Chronic pulmonary diseases: chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Thorax, 49*(9), 924-932.

AHA. (2006). 2005 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) of Pediatric and Neonatal Patients: Neonatal Resuscitation Guidelines. *Pediatrics, 117*(5), e1029-1038.

Antman, E. M., Anbe, D. T., Armstrong, P. W., Bates, E. R., Green, L. A., Hand, M., et al. (2004). ACC/AHA guidelines for the management of patients with ST-Elevation myocardial infarction--executive summary: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol, 44*(3), 671-719.

Aubier, M., Murciano, D., Fournier, M., Milic-Emili, J., Pariente, R., & Derenne, J. P. (1980). Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease, 122*(2), 191-199.

Aubier, M., Murciano, D., Milic-Emili, J., Touaty, E., Daghfous, J., Pariente, R., et al. (1980). Effects of the administration of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *American Review of Respiratory Disease, 122*(5), 747-754.

Ballester, E., Reyes, A., Roca, J., Guitart, R., Wagner, P. D., & Rodriguez-Roisin, R. (1989). Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax, 44*(4), 258-267.

Ballester, E., Roca, J., Ramis, L., Wagner, P. D., & Rodriguez-Roisin, R. (1990). Pulmonary gas exchange in severe chronic asthma. Response to 100% oxygen and salbutamol. *Am Rev Respir Dis, 141*(3), 558-562.

Barach, A. L. (1938). Physiological methods in the diagnosis and treatment of asthma and emphysema. *Ann Intern Med, 12*(4), 454-481.

Barach, A. L., & Richards, D. W., Jr. (1931). Effects of treatment with oxygen in cardiac failure. *Arch Intern Med, 48*(2), 325-347.

Barbera, J. A., Roca, J., Ferrer, A., Felez, M. A., Diaz, O., Roger, N., et al. (1997). Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *European Respiratory Journal, 10*(6), 1285-1291.

Barnes, P. J. (2000). Chronic Obstructive Pulmonary Disease. *N Engl J Med, 343*(4), 269-280.

Barrera, F., Hillyer, P., Ascanio, G., & Bechtel, J. (1973). The distribution of ventilation, diffusion, and blood flow in obese patients with normal and abnormal blood gases. *Am Rev Respir Dis, 108*(4), 819-830.

Beale, H. D., Schiller, I. W., Halperin, M. H., Franklin, W., & Lowell, F. C. (1951). Delirium and coma precipitated by oxygen in bronchial asthma complicated by respiratory acidosis. *N Engl J Med, 244*(19), 710-714.

Beasley, R., Aldington, S., & Robinson, G. (2007). Is it time to change the approach to oxygen therapy in the breathless patient. *Thorax, 62*, 840-841.

Bendjelid, K., Schutz, N., Stotz, M., Gerard, I., Suter, P. M., & Romand, J. A. (2005). Transcutaneous PCO2 monitoring in critically ill adults: clinical evaluation of a new sensor. *Crit Care Med, 33*(10), 2203-2206.

Bhowmik, A., Seemungal, T. A. R., Sapsford, R. J., & Wedzicha, J. A. (2000). Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax, 55*(2), 114-120.

Bickerman, H. A., & Barach, A. L. (1955). The effect of breathing 100 per cent oxygen in pulmonary emphysema: correlation of clinical improvement with changes in pulmonary ventilation. *J Chronic Dis, 1*(2), 111-120.

Bohr, C. (1891). Ueber die Lungenathmung. *Skand. Archiv. Physiol, 2*, 236.

Boland, E. (1940). Oxygen in high concentrations for relief of paint. *Journal of the American Medical Association, 114*, 1512-1514.

Boothby, W., Mayo, C., & Lovelace, W. (1939). One hundred per cent oxygen. Indications for its use and methods of its administration. *Journal of the American Medical Association, 113*, 477-482.

British Guideline on the Management of Asthma. (2008). *Thorax, 63 Suppl 4*, iv1-121.

Brodovsky, D., Macdonell, J. A., & Cherniack, R. M. (1960). The respiratory response to carbon dioxide in health and in emphysema. *J Clin Invest, 39*, 724-729.

BTS. (2004). Management of exacerbations of COPD. *Thorax, 59*(90001), i131-156.

BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. (2001). *Thorax, 56*(90004), iv1-64.

BTS guidelines: Diagnosing COPD. (2004). *Thorax, 59*, i27-i38

Cameron, A. J. (1933). Marked Papilloedema in Pulmonary Emphysema. *Br J Ophthalmol, 17*(3), 167-169.

Campbell, E. J. (1960a). A method of controlled oxygen administration which reduces the risk of carbon-dioxide retention. *Lancet, 2*, 12-14.

Campbell, E. J. (1960b). Respiratory failure: the relation between oxygen concentrations of inspired air and arterial blood. *Lancet, 2*, 10-11.

Campbell, E. J. (1963). Apparatus for Oxygen Administration. *Br Med J, 2*(5367), 1269-c-1270.

Campbell, E. J. (1967). The J. Burns Amberson Lecture. The management of acute respiratory failure in chronic bronchitis and emphysema. *American Review of Respiratory Disease, 96*(4), 626-639.

Castle, R. A., Dunne, C. J., Mok, Q., Wade, A. M., & Stocks, J. (2002). Accuracy of displayed values of tidal volume in the pediatric intensive care unit. *Crit Care Med, 30*(11), 2566-2574.

Chien, J. W., Ciufo, R., Novak, R., Skowronski, M., Nelson, J., Coreno, A., et al. (2000). Uncontrolled Oxygen Administration and Respiratory Failure in Acute Asthma. *Chest, 117*(3), 728-733.

Chow, L. C., Wright, K. W., & Sola, A. (2003). Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics, 111*(2), 339-345.

Clemens, K. E., & Klaschik, E. (2007). Symptomatic treatment of dyspnoea in patients receiving palliative care: nasal delivery of oxygen compared with opioid administration. *Dtsch Med Wochenschr, 132*(38), 1939-1943.

Cohn, J. E., Carroll, D. G., & Riley, R. L. (1954). Respiratory acidosis in patients with emphysema. *Am J Med, 17*(4), 447-463.

Comroe, J. H., Jr., Bahnson, E. R., & Coates, E. O., Jr. (1950). Mental changes occurring in chronically anoxemic patients during oxygen therapy. *J Am Med Assoc, 143*(12), 1044-1048.

Corte, P., & Young, I. H. (1985). Ventilation-perfusion relationships in symptomatic asthma. Response to oxygen and clemastine. *Chest, 88*(2), 167-175.

Cox, M., Kemp, R., Anwar, S., Athey, V., Aung, T., & Moloney, E. (2005). Non-invasive monitoring of CO2 levels in patients using NIV for AECOPD. *Thorax, 61*, 363-364.

Current best practice for nebuliser treatment, British Thoracic Society. (1997). *Thorax, 52 Suppl 2*, S1-3.

Cutaia, M., & Rounds, S. (1990). Hypoxic pulmonary vasoconstriction. Physiologic significance, mechanism, and clinical relevance. *Chest, 97*(3), 706-718.

Daly, W. J., & Behnke, R. H. (1963). Hemodynamic consequences of oxygen breathing in left ventricular failure. *Circulation, 27*, 252-256.

Davies, C. E., & Mackinnon, J. (1949). Neurological effects of oxygen in chronic cor pulmonale. *Lancet, 2*(6585), 883-885, illust.

Davis, P. G., Tan, A., O'Donnell, C. P., & Schulze, A. (2004). Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet, 364*(9442), 1329-1333.

Dennis, R. J., Maldonado, D., Norman, S., Baena, E., Castano, H., Martinez, G., et al. (1996). Wood smoke exposure and risk for obstructive airways disease among women. *Chest, 109*(3 Suppl), 55S-56S.

Denniston, A. K., O'Brien, C., & Stableforth, D. (2002). The use of oxygen in acute exacerbations of chronic obstructive pulmonary disease: a prospective audit of pre-hospital and hospital emergency management. *Clin Med, 2*(5), 449-451.

Dick, C., Liu, Z., Sassoon, C., Berry, R., & Mahutte, C. (1997). O2-induced change in ventilation and ventilatory drive in COPD. *Am. J. Respir. Crit. Care Med., 155*(2), 609-614.

Dollery, C. T., Hill, D. W., Mailer, C. M., & Ramalho, P. S. (1964). High oxygen pressure and the retinal blood-vessels. *Lancet, 13*, 291-292.

Donald, K. (1949). Neurological effects of oxygen. *Lancet*, 1056-1057.

Downs, J. B., & Smith, R. A. (1999). Increased inspired oxygen concentration may delay diagnosis and treatment of significant deterioration in pulmonary function.[comment]. *Critical Care Medicine, 27*(12), 2844-2846.

Dunn, W. F., Nelson, S. B., & Hubmayr, R. D. (1991). Oxygen-induced hypercarbia in obstructive pulmonary disease. *American Review of Respiratory Disease, 144*(3 Pt 1), 526-530.

Dunnill, M. S. (1960). The pathology of asthma, with special reference to changes in the bronchial mucosa. *J Clin Pathol, 13*, 27-33.

Durrington, H. J., Flubacher, M., Ramsay, C. F., Howard, L. S., & Harrison, B. D. (2005). Initial oxygen management in patients with an exacerbation of chronic obstructive pulmonary disease. *Qjm, 98*(7), 499-504.

Eberhard, P., Gisiger, P. A., Gardaz, J. P., & Spahn, D. R. (2002). Combining transcutaneous blood gas measurement and pulse oximetry. *Anesth Analg, 94*(1 Suppl), S76-80.

Editorial: Oxygen in bronchial asthma. (1976). *Br Med J, 1*(6010), 609-610.

Eldridge, F., & Gherman, C. (1968). Studies of oxygen administration in respiratory failure. *Annals of Internal Medicine, 68*(3), 569-578.

Ellis, E. R., Grunstein, R. R., Chan, S., Bye, P. T., & Sullivan, C. E. (1988). Noninvasive ventilatory support during sleep improves respiratory failure in kyphoscoliosis. *Chest, 94*(4), 811-815.

Enghoff, H. (1938). Volumen inefficax. *Uppsala Lakaref. Forhand, 44*, 191.

Farquhar, H., Weatherall, M., Wijesinghe, M., Perrin, K., Ranchord, A., Simmonds, M., et al. (2009). Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J, 158*(3), 371-377.

Field, G. B. (1967). The effects of posture, oxygen, isoproterenol and atropine on ventilation-perfusion relationships in the lung in asthma. *Clinical Science, 32*(2), 279-288.

Fletcher, R., Jonson, B., Cumming, G., & Brew, J. (1981). The concept of deadspace with special reference to the single breath test for carbon dioxide. *British Journal of Anaesthesia, 53*(1), 77-88.

Ford, D. J., & Rothwell, R. P. (1989). 'Safe oxygen' in acute asthma: prospective trial using 35% Ventimask prior to admission. *Respiratory Medicine, 83*(3), 189-194.

Fowler, K. T., & Read, J. (1963). Effect of alveolar hypoxia on zonal distribution of pulmonary blood flow. *J Appl Physiol, 18*, 244-250.

Fuke, S., Miyamoto, K., Ohira, H., Ohira, M., Odajima, N., & Nishimura, M. (2009). Evaluation of transcutaneous CO2 responses following acute changes in PaCO2 in healthy subjects. *Respirology, 14*(3), 436-442.

Gallagher, R., & Roberts, D. (2004). A systematic review of oxygen and airflow effect on relief of dyspnea at rest in patients with advanced disease of any cause. *J Pain Palliat Care Pharmacother, 18*(4), 3-15.

Garner, W. L., Downs, J. B., Reilley, T. E., Frolicher, D., Kargi, A., & Fabri, P. J. (1989). The effects of hyperoxia during fulminant sepsis. *Surgery, 105*(6), 747-751.

Gay, P. C., & Edmonds, L. C. (1995). Severe hypercapnia after low-flow oxygen therapy in patients with neuromuscular disease and diaphragmatic dysfunction. *Mayo Clin Proc, 70*(4), 327-330.

Gea, J., Roca, J., Torres, A., Agusti, A. G., Wagner, P. D., & Rodriguez-Roisin, R. (1991). Mechanisms of abnormal gas exchange in patients with pneumonia. *Anesthesiology, 75*(5), 782-789.

Grainge, C. (2004). Breath of life: the evolution of oxygen therapy. *J R Soc Med, 97*(10), 489-493.

Haldane, J. S. (1917). The therapeutic administration of oxygen. *Br Med J, 1*(2928), 181-183.

Haldane, J. S. (1919). A Lecture on the Symptoms, Causes, and Prevention of Anoxaemia (Insufficient Supply of Oxygen to the Tissues), and the Value of Oxygen in its Treatment. *Br Med J, 2*(3055), 65-71.

Haldane, J. S., Meakins, J. C., & Priestley, J. G. (1919). The effects of shallow breathing. *J Physiol, 52*(6), 433-453.

Haldane, J. S., & Priestley, J. G. (1905). The regulation of the lung-ventilation. *J Physiol, 32*(3-4), 225-266.

Halmagyi, D. F., & Cotes, J. E. (1959). Reduction in systemic blood oxygen as a result of procedures affecting the pulmonary circulation in patients with chronic pulmonary disease. *Clin Sci, 18*, 475-489.

Harris, L. (1972). Comparison of the effect on blood gases, ventilation, and perfusion of isoproterenol-phenylephrine and salbutamol aerosols in chronic bronchitis with asthma. *J Allergy Clin Immunol, 49*(2), 63-71.

Hauge, A. (1968). Conditions governing the pressor response to ventilation hypoxia in isolated perfused rat lungs. *Acta Physiol Scand, 72*(1), 33-44.

Hogg, J. C. (1987). Varieties of airway narrowing in severe and fatal asthma. *J Allergy Clin Immunol, 80*, 417-419.

Hutchison, D. C., Flenley, D. C., & Donald, K. W. (1964). Controlled Oxygen Therapy in Respiratory Failure. *British Medical Journal, 2*(5418), 1159-1166.

Irnell, L., & Nordgren, L. (1966). Effects of acetylcholine infusion on the pulmonary circulation in patients with bronchial asthma. *Acta Med Scand, 179*(4), 385-393.

Joosten, S. A., Koh, M. S., Bu, X., Smallwood, D., & Irving, L. B. (2007). The effects of oxygen therapy in patients presenting to an emergency department with exacerbation of chronic obstructive pulmonary disease.[see comment]. *Medical Journal of Australia, 186*(5), 235-238.

Kagawa, S., & Severinghaus, J. W. (2005). Errors in monitoring transcutaneous PCO2 on the ear. *Crit Care Med, 33*(10), 2414-2415.

Kenmure, A. C., Murdoch, W. R., Beattie, A. D., Marshall, J. C., & Cameron, A. J. (1968). Circulatory and metabolic effects of oxygen in myocardial infarction. *British Medical Journal, 4*(5627), 360-364.

Kety, S., & Schmidt, C. (1948). The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *Journal of Clinical Investigation, 27*, 484-492.

Kilgannon, J. H., Jones, A. E., Shapiro, N. I., Angelos, M. G., Milcarek, B., Hunter, K., et al. (2010). Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA, 303*(21), 2165-2171.

King, T. K., Ali, N., & Briscoe, W. A. (1973). Treatment of hypoxia with 24 percent oxygen. A new approach to the interpretation of data collected in a pulmonary intensive care unit. *Am Rev Respir Dis, 108*(1), 19-29.

Knudson, R. J., & Constantine, H. P. (1967). An effect of isoproterenol on ventilation-perfusion in asthmatic versus normal subjects. *J Appl Physiol, 22*(3), 402-406.

Lampron, N., Lemaire, F., Teisseire, B., Harf, A., Palot, M., Matamis, D., et al. (1985). Mechanical ventilation with 100% oxygen does not increase intrapulmonary shunt in patients with severe bacterial pneumonia. *Am Rev Respir Dis, 131*(3), 409-413.

Larson, C. P., Jr., & Severinghaus, J. W. (1962). Postural variations in dead space and CO2 gradients breathing air and O2. *J Appl Physiol, 17*, 417-420.

Lee, J., & Read, J. (1967). Effect of oxygen breathing on distribution of pulmonary blood flow in chronic obstructive lung disease. *American Review of Respiratory Disease, 96*(6), 1173-1180.

Leigh, J. M. (1973). Variation in performance of oxygen therapy devices. Towards the rational employment of 'The dephlogisticated air described by Priestley'. *Ann R Coll Surg Engl, 52*(4), 234-253.

Leigh, J. M. (1974). Ideas and anomalies in the evolution of modern oxygen therapy. *Anaesthesia, 29*(3), 335-348.

Lemaire, F., Matamis, D., Lampron, N., Teisseire, B., & Harf, A. (1985). Intrapulmonary shunt is not increased by 100% oxygen ventilation in acute respiratory failure. *Bull Eur Physiopathol Respir, 21*(3), 251-256.

Lenfant, C. (1966). Arterial-alveolar difference in PCO2 during air and oxygen breathing. *Journal of Applied Physiology, 21*(4), 1356-1362.

Light, R. B. (1999). Pulmonary pathophysiology of pneumococcal pneumonia. *Semin Respir Infect, 14*(3), 218-226.

Lim, W. S., Baudouin, S. V., George, R. C., Hill, A. T., Jamieson, C., Le Jeune, I., et al. (2009). BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax, 64 Suppl 3*, iii1-55.

Liu, S., Zhou, Y., Wang, X., Wang, D., Lu, J., Zheng, J., et al. (2007). Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. *Thorax, 62*(10), 889-897.

Liu, S. Y., Lee, T. S., & Bongard, F. (1992). Accuracy of capnography in nonintubated surgical patients. *Chest, 102*(5), 1512-1515.

Liu, Y., Rosenthal, R. E., Haywood, Y., Miljkovic-Lolic, M., Vanderhoek, J. Y., & Fiskum, G. (1998). Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome. *Stroke, 29*(8), 1679-1686.

Lopez-Majano, V., & Dutton, R. E. (1973). Regulation of respiration during oxygen breathing in chronic obstructive lung disease. *American Review of Respiratory Disease, 108*(2), 232-240.

Lougheed, M. D., Lam, M., Forkert, L., Webb, K. A., & O'Donnell, D. E. (1993). Breathlessness during acute bronchoconstriction in asthma. Pathophysiologic mechanisms. *Am Rev Respir Dis, 148*, 1452-1459.

Malik, A. B., & Kidd, B. S. (1973). Time course of pulmonary vascular response to hypoxia in dogs. *Am J Physiol, 224*(1), 1-6.

Maniscalco, M., Zedda, A., Faraone, S., Carratu, P., & Sofia, M. (2008). Evaluation of a transcutaneous carbon dioxide monitor in severe obesity. *Intensive Care Med, 34*(7), 1340-1344.

Marsh, S. E., Travers, J., Weatherall, M., Williams, M. V., Aldington, S., Shirtcliffe, P. M., et al. (2008). Proportional classifications of COPD phenotypes. *Thorax, 63*(9), 761-767.

McFadden, E. R., Jr. (2003). Acute Severe Asthma. *Am. J. Respir. Crit. Care Med., 168*(7), 740-759.

McFadden, E. R., Jr., Kiser, R., & DeGroot, W. J. (1973). Acute bronchial asthma. Relations between clinical and physiologic manifestations. *New England Journal of Medicine, 288*(5), 221-225.

McFadden, E. R., Jr., & Lyons, H. A. (1968). Arterial-blood gas tension in asthma. *New England Journal of Medicine, 278*(19), 1027-1032.

McNulty, P. H., King, N., Scott, S., Hartman, G., McCann, J., Kozak, M., et al. (2005). Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *American Journal of Physiology Heart and Circulatory Physiology, 288*(3 57-3), H1057-H1062.

McVicar, J., & Eager, R. (2009). Validation study of a transcutaneous carbon dioxide monitor in patients in the emergency department. *Emergency Medicine Journal, 26*(5), 344-346.

Meakins, J., & Davies, H. (1925). *Respiratory function in disease*. Edinburgh: Oliver and Boyd.

Meakins, J. C. (1920). The therapeutic value of oxygen in pulmonary lesions: preliminary note. *Br Med J, 1*(3088), 324-326.

Mecikalski, M. B., Cutillo, A. G., & Renzetti, A. D., Jr. (1984). Effect of right-to-left shunting on alveolar dead space. *Bull Eur Physiopathol Respir, 20*(6), 513-519.

Milross, J., Young, I. H., & Donnelly, P. (1989). The oxygen delivery characteristics of the Hudson Oxy-one face mask. *Anaesth Intensive Care, 17*(2), 180-184.

Mithoefer, J. C. (1952). Increased intracranial pressure in emphysema caused by oxygen inhalation. *J Am Med Assoc, 149*(12), 1116-1120.

Mithoefer, J. C., Karetzky, M. S., & Mead, G. D. (1967). Oxygen therapy in respiratory failure. *New England Journal of Medicine, 277*(18), 947-949.

Nowbar, S., Burkart, K. M., Gonzales, R., Fedorowicz, A., Gozansky, W. S., Gaudio, J. C., et al. (2004). Obesity-Associated hypoventilation in hospitalized patients: Prevalence, effects, and outcome. *American Journal of Medicine, 116*(1), 1-7.

O'Driscoll, B. R., Howard, L. S., & Davison, A. G. (2008). British Thoracic Society guideline for emergency oxygen use in adult patients. *Thorax, 63 Suppl 6*, vi1-68.

Orozco-Levi, M., Garcia-Aymerich, J., Villar, J., Ramirez-Sarmiento, A., Anto, J. M., & Gea, J. (2006). Wood smoke exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J, 27*(3), 542-546.

Pain, M. C., Read, D. J., & Read, J. (1965). Changes of arterial carbon-dioxide tension in patients with chronic lung disease breathing oxygen. *Australasian Annals of Medicine, 14*(3), 195-204.

Palmer, K. N., & Diament, M. L. (1967). Effect of aerosol isoprenaline on blood-gas tensions in severe bronchial asthma. *Lancet, 2*(7528), 1232-1233.

Palmer, K. N., & Diament, M. L. (1969). Effect of salbutamol on blood-gas tensions in asthma. *Lancet, 2*(7619), 541.

Philip, J., Gold, M., Milner, A., Di Iulio, J., Miller, B., & Spruyt, O. (2006). A randomized, double-blind, crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. *J Pain Symptom Manage, 32*(6), 541-550.

Platts, M. M., & Greaves, M. S. (1957). Arterial blood gas measurements in the management of patients with chronic bronchitis and emphysema. *Thorax, 12*(3), 236-240.

Potts, W. H. (1932). Oxygen Therapy - a critical resume. *Americal journal of medical sciences, 184*(5), 616-631.

Prime, F. J., & Westlake, E. K. (1954). The respiratory response to CO2 in emphysema. *Clin Sci (Lond), 13*(3), 321-332.

Quint, J. K., Ward, L., & Davison, A. G. (2007). Previously undiagnosed obesity hypoventilation syndrome. *Thorax, 62*(5), 462-463.

Rawles, J. M., & Kenmure, A. C. (1976). Controlled trial of oxygen in uncomplicated myocardial infarction. *British Medical Journal, 1*(6018), 1121-1123.

Rees, H. A., Borthwick, R. C., Millar, J. S., & Donald, K. W. (1967). Aminophylline in bronchial asthma. *Lancet, 2*(7527), 1167-1169.

Rees, H. A., Millar, J. S., & Donald, K. W. (1967). Adrenaline in bronchial asthma. *Lancet, 2*(7527), 1164-1167.

Rees, H. A., Millar, J. S., & Donald, K. W. (1968). A study of the clinical course and arterial blood gas tensions of patients in status asthmaticus. *Quarterly Journal of Medicine, 37*(148), 541-561.

Refsum, H. E. (1963). Relationship between State of Consciousness and Arterial Hypoxaemia and Hypercapnia in Patients with Pulmonary Insufficiency, Breathing Air. *Clin Sci, 25*, 361-367.

Reports of Societies. (1932). *British Medical Journal, 1*(3707), 144-150.

Richards, E. M., Fiskum, G., Rosenthal, R. E., Hopkins, I., & McKenna, M. C. (2007). Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. *Stroke, 38*(5), 1578-1584.

Robinson, T. D., Freiberg, D. B., Regnis, J. A., & Young, I. H. (2000). The Role of Hypoventilation and Ventilation-Perfusion Redistribution in Oxygen-induced Hypercapnia during Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med., 161*(5), 1524-1529.

Roca, J., & Wagner, P. (1994). Contribution of multiple inert gas elimination technique to pulmonary medicine. 1. Principles and information content of the multiple inert gas elimination technique. *Thorax, 49*(8), 815-824.

Rodrigo, G. J., & Rodrigo, C. (2000). Rapid-Onset Asthma Attack. *Chest, 118*(6), 1547-1552.

Rodrigo, G. J., Rodrigo, C., & Hall, J. B. (2004). Acute Asthma in Adults: A Review. *Chest, 125*(3), 1081-1102.

Rodrigo, G. J., Rodriquez Verde, M., Peregalli, V., & Rodrigo, C. (2003). Effects of short-term 28% and 100% oxygen on PaCO2 and peak expiratory flow rate in acute asthma: a randomized trial. *Chest, 124*(4), 1312-1317.

Rodriguez-Roisin, R., Ballester, E., Roca, J., Torres, A., & Wagner, P. D. (1989). Mechanisms of hypoxemia in patients with status asthmaticus requiring

mechanical ventilation. *American Review of Respiratory Disease, 139*(3), 732-739.

Rodriguez, P., Lellouche, F., Aboab, J., Buisson, C. B., & Brochard, L. (2006). Transcutaneous arterial carbon dioxide pressure monitoring in critically ill adult patients. *Intensive Care Med, 32*(2), 309-312.

Ronning, O. M., & Guldvog, B. (1999). Should Stroke Victims Routinely Receive Supplemental Oxygen? : A Quasi-Randomized Controlled Trial. *Stroke, 30*(10), 2033-2037.

Rosner, V., Hannhart, B., Chabot, F., & Polu, J. (1999). Validity of transcutaneous oxygen/carbon dioxide pressure measurement in the monitoring of mechanical ventilation in stable chronic respiratory failure. *European Respiratory Journal, 13*, 1044-1047.

Roussos, C., & Macklem, P. T. (1982). The respiratory muscles. *N Engl J Med, 307*(13), 786-797.

Rudolf, M., Banks, R. A., & Semple, S. J. (1977). Hypercapnia during oxygen therapy in acute exacerbations of chronic respiratory failure. Hypothesis revisited. *Lancet, 2*(8036), 483-486.

Rudolf, M., Riordan, J. F., Grant, B. J., Maberly, D. J., & Saunders, K. B. (1980). Arterial blood gas tensions in acute severe asthma. *European Journal of Clinical Investigation, 10*(1), 55-62.

Russek, H., Regan, F., & Naegle, C. (1950). One hundred per cent oxygen in the treatment of acute myocardial infarction and severe angina pectoris. *Journal of the American Medical Association, 144*, 373-375.

Said, S. I., & Banerjee, C. M. (1963). Venous admixture to the pulmonary circulation in human subjects breathing 100 per cent oxygen. *J Clin Invest, 42*, 507-515.

Sanders, M. H., Kern, N. B., Costantino, J. P., Stiller, R. A., Strollo, P. J., Jr., Studnicki, K. A., et al. (1994). Accuracy of end-tidal and transcutaneous PCO2 monitoring during sleep. *Chest, 106*(2), 472-483.

Sassoon, C. S., Hassell, K. T., & Mahutte, C. K. (1987). Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. *American Review of Respiratory Disease, 135*(4), 907-911.

Seemungal, T. A., Donaldson, G. C., Paul, E. A., Bestall, J. C., Jeffries, D. J., & Wedzicha, J. A. (1998). Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med, 157*(5 Pt 1), 1418-1422.

Senn, O., Clarenbach, C. F., Kaplan, V., Maggiorini, M., & Bloch, K. E. (2005). Monitoring carbon dioxide tension and arterial oxygen saturation by a single earlobe sensor in patients with critical illness or sleep apnea. *Chest, 128*(3), 1291-1296.

Severinghaus, J. W. (2002). Priestley, the furious free thinker of the enlightenment, and Scheele, the taciturn apothecary of Uppsala.[see comment]. *Acta Anaesthesiologica Scandinavica, 46*(1), 2-9.

Simpson, H., Forfar, J. O., & Grubb, D. J. (1968). Arterial blood gas tensions and pH in acute asthma in childhood. *Br Med J, 3*(5616), 460-464.

Simpson, T. (1948). Papilloedema in Emphysema. *Br Med J, 2*(4578), 639-641.

Simpson, T. (1954). Acute Respiratory Infections in Emphysema. *Br Med J, 1*(4857), 297-301.

Simpson, T. (1964). Management of Respiratory Failure. *Br Med J, 2*(5422), 1462.

Singh, A. M., & Busse, W. W. (2006). Asthma exacerbations 2: Aetiology. *Thorax, 61*(9), 809-816.

Smith, J. L. (1899). The pathological effects due to increase of oxygen tension in the air breathed. *The Journal of Physiology, 24*(1), 19-35.

Stadie, W. C. (1919). The oxygen of the arterial and venous blood in pneumonia and its relation to cyanosis. *J. Exp. Med., 30*(3), 215-240.

Stern, S., & Braun, K. (1961). Blood gas changes following priscoline administration in mitral stenosis and chronic lung diseases. *American Journal of Cardiology, 7*, 188.

Sternbach, G. L., & Varon, J. (2004). Resuscitation Great. John Mayow and oxygen. *Resuscitation, 60*(3), 235-237.

Sternbach, G. L., & Varon, J. (2005). The discovery and rediscovery of oxygen. *Journal of Emergency Medicine, 28*(2), 221-224.

Stevenson, N. J., Walker, P. P., Costello, R. W., & Calverley, P. M. A. (2005). Lung Mechanics and Dyspnea during Exacerbations of Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med., 172*(12), 1510-1516.

Stock, M. C. (1988). Noninvasive carbon dioxide monitoring. *Crit Care Clin, 4*(3), 511-526.

Storre, J. H., Steurer, B., Kabitz, H. J., Dreher, M., & Windisch, W. (2007). Transcutaneous PCO2 monitoring during initiation of noninvasive ventilation. *Chest, 132*(6), 1810-1816.

Sutherland, E. R., & Cherniack, R. M. (2004). Management of Chronic Obstructive Pulmonary Disease. *N Engl J Med, 350*(26), 2689-2697.

Syrjala, H., Broas, M., Suramo, I., Ojala, A., & Lahde, S. (1998). High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clin Infect Dis, 27*(2), 358-363.

Tai, E., & Read, J. (1967a). Blood-gas tensions in bronchial asthma. *Lancet, 1*(7491), 644-646.

Tai, E., & Read, J. (1967b). Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma. *Thorax, 22*(6), 543-549.

Taquini, A. C., Fasciolo, J. C., Suarez, J. R. E., & Chiodi, H. (1948). Respiration and circulation in pulmonary anoxaemia. *Arch Intern Med, 82*(6), 534-577.

Tardif, C., Bonmarchand, G., Gibon, J. F., Hellot, M. F., Leroy, J., Pasquis, P., et al. (1993). Respiratory response to CO2 in patients with chronic obstructive pulmonary disease in acute respiratory failure.[see comment]. *European Respiratory Journal, 6*(5), 619-624.

Thomas, M., Malmcrona, R., & Shillingford, J. (1965). Haemodynamic effects of oxygen in patients with acute myocardial infarction. *British Heart Journal, 27*, 401-407.

Thomson, A., Webb, D., & Maxwell, S. (2002). Oxygen therapy in acute medical care: The potential dangers of hyperoxia need to be recognised. *British Medical Journal, 324*, 1406-1407.

Tobin, M. J. (1988). Respiratory muscles in disease. *Clin Chest Med, 9*(2), 263-286.

Valabhji, P. (1968). Gas exchange in the acute and asymptomatic phases of asthma breathing air and oxygen. *Clinical Science, 34*(3), 431-440.

Van de Werf, F., Ardissino, D., Betriu, A., Cokkinos, D. V., Falk, E., Fox, K. A. A., et al. (2003). Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J, 24*(1), 28-66.

Vereczki, V., Martin, E., Rosenthal, R. E., Hof, P. R., Hoffman, G. E., & Fiskum, G. (2006). Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *Journal of Cerebral Blood Flow & Metabolism, 26*(6), 821-835.

Von Euler, U. S., & Liljestrand, G. (1946). Observations on the Pulmonary Arterial Blood Pressure in the Cat. *Acta Physiologica Scandinavica, 12*(4), 301-320.

Wagner, P. D., Dantzker, D. R., Dueck, R., Clausen, J. L., & West, J. B. (1977). Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *Journal of Clinical Investigation, 59*(2), 203-216.

Wagner, P. D., Laravuso, R. B., Goldzimmer, E., Naumann, P. F., & West, J. B. (1975). Distribution of ventilation-perfusion ratios in dogs with normal and abnormal lungs. *J Appl Physiol, 38*(6), 1099-1109.

Wagner, P. D., Saltzman, H. A., & West, J. B. (1974). Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J Appl Physiol, 36*(5), 588-599.

Walmrath, D., Schneider, T., Pilch, J., Schermuly, R., Grimminger, F., & Seeger, W. (1995). Effects of aerosolized prostacyclin in severe pneumonia. Impact of fibrosis. *Am. J. Respir. Crit. Care Med., 151*(3), 724-730.

Warrell, D. A., Edwards, R. H., Godfrey, S., & Jones, N. L. (1970). Effect of controlled oxygen therapy on arterial blood gases in acute respiratory failure. *Br Med J, 1*(5707), 452-455.

Warren, C. P. (2005). The introduction of oxygen for pneumonia as seen through the writings of two McGill University professors, William Osler and Jonathan Meakins. *Canadian Respiratory Journal, 12*(2), 81-85.

Wenzel, S. E. (2006). Asthma: defining of the persistent adult phenotypes. *Lancet, 368*(9537), 804-813.

Westlake, E. K., Simpson, T., & Kaye, M. (1955). Carbon dioxide narcosis in emphysema. *Q J Med, 24*(94), 155-173.

Whitelaw, W. A., Derenne, J. P., & Milic-Emili, J. (1975). Occlusion pressure as a measure of respiratory center output in conscious man. *Respir Physiol, 23*(2), 181-199.

Wijesinghe, M., Perrin, K., Healy, B., Hart, K., Clay, J., Weatherall, M., et al. (2010). Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease. *Intern Med J*.

Wijesinghe, M., Perrin, K., Ranchord, A., Simmonds, M., Weatherall, M., & Beasley, R. (2009). Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart, 95*(3), 198-202.

Wilkinson, D. J. (2004). Resuscitation Great. The contributions of Lavoisier, Scheele and Priestley to the early understanding of respiratory physiology in the Eighteenth Century. *Resuscitation, 61*(3), 249-255.

Williams, J. R. (2008). The Declaration of Helsinki and public health. *Bull World Health Organ, 86*(8), 650-652.

Wolff, H. G., & Lennox, W. G. (1930). Cerebral circulation, XII: the effect on pial vessel of variations in the oxygen and carbon dioxide content of the blood. *Arch. Neurol., 23*, 1097-1120.

Wunderink, R. G., & Waterer, G. W. (2004). Community-acquired pneumonia: pathophysiology and host factors with focus on possible new approaches to management of lower respiratory tract infections. *Infect Dis Clin North Am, 18*(4), 743-759, vii.

Appendices

Appendix 1: Central Regional Ethics Committee approval for randomised controlled trials of oxygen in acute asthma and pneumonia

Appendix 2: Central Regional Ethics Committee approval for a study of oxygen in chronic stable asthma

Appendix 3: Information sheet, long consent form, and short consent form for randomised controlled trials of oxygen in acute asthma and pneumonia

Appendix 4: Information sheet and consent form for study of oxygen in chronic stable asthma

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.

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

20 May 2008

Dr Kyle Perrin
Medical Research Institute of New Zealand
PO Box 10055
The Terrace
Wellington

Dear Kyle

CEN/08/04/013
The effect of hyperoxia on carbon dioxide levels and ventilation in patients with chronic stable Asthma
Dr Kyle Perrin, Dr Meme Wijesinghe, Dr Mathew Williams
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
- Information sheet and consent form version 2, dated 1 May 2008.

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 **30 April 2009**. 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 **20 May 2009**. The report form is available on http://www.ethicscommittees.health.govt.nz. 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.

Final Report *(for studies less than 1 year)*
The study is approved until **30 April 2009**. A final report is required at the end of the study. The report form is available on http://www.ethicscommittees.health.govt.nz and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

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.