An auto-titrating (intelligent) oxygen system in patients with chronic respiratory failure

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Abstract

Long-term oxygen therapy (LTOT) improves survival in patients with chronic obstructive pulmonary disease (COPD) and chronic hypoxaemia with international guidelines recommending LTOT for patients with chronic hypoxaemia secondary to respiratory failure. LTOT is prescribed at a fixed-flow rate aiming to maintain the partial pressure of oxygen ≥8 kilopascals or oxygen saturations (SpO_2) >90% at rest.

However, many patients on domiciliary LTOT continue to experience episodes of intermittent hypoxia (SpO_2 <90%) during rest, exercise, activities of daily living (ADL) and sleep with the potentially harmful consequences of arrhythmias, ischaemic heart disease, transient increases in pulmonary pressures and reduced cerebral oxygenation. The aim of this thesis was to explore whether a novel smartphone based auto-titrating oxygen system (the intelligent oxygen therapy system [iO_2Ts]), could reduce intermittent hypoxia by delivering variable flow oxygen to maintain a pre-set SpO_2 target during various activities which typically take place over a period of 24 hours.

In the first study, the iO_2Ts significantly reduced intermittent hypoxia compared to ambulatory oxygen in patients with COPD on LTOT during a 6-minute walk test (6MWT). The second study showed that the iO_2Ts is equivalent to ambulatory oxygen in reducing intermittent hypoxia during a 6MWT in patients with interstitial lung disease (a group of patients who rapidly desaturate on exercise). The third study showed that the iO_2Ts reduced intermittent hypoxia during ADL in patients on LTOT compared to usual LTOT. In a fourth pilot study, the iO_2Ts maintained oxygenation as well as usual LTOT and did not change transcutaneous carbon dioxide levels compared to LTOT during sleep.

In summary, this thesis has shown that the iO_2Ts can reduced intermittent hypoxia in patients on LTOT during various activities which typically take place over 24 hours. The reduction in intermittent hypoxia could optimise domiciliary and ambulatory oxygen for patients on LTOT.

Table of Contents

Declaration of originality

I declare that the contents of this thesis are my work unless where otherwise acknowledged. The smartphone based intelligent oxygen therapy system used in this thesis was developed in collaboration with the bioengineering department of Imperial College London, Dr Robert Dickinson and Mr Rishi Goburdhun (development described in chapter 2).

The studies in this thesis were designed with the assistance of my supervisors Professor Anita Simonds and Professor Mary Morrell. I wrote all the protocols, the patients information sheets and made all the submissions to the research ethics committees. Once the studies were approved, I recruited all the patients, carried out all assessments including history taking, examinations, anthropometric measurements, spirometry and ear lobe blood gases. For chapters 4 and 5, I conducted all the 6-minute walk tests. For chapter 7, I conducted all the activities of daily living. Chapter 6 involved conducting domiciliary polysomnography. I visited all the patients at home to set-up polysomnography with the assistance of Yousef Al-Qurashi. I analysed all the data presented in chapters 4, 5 and 7. The polysomnography data presented in chapter 6 was analysed by Yousef Al-Qurashi. No parts of this thesis have been submitted to any other institution for a higher degree. Abstracts published from this thesis are listed on page 12.

Copyright declaration

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Abstracts arising from this thesis

Mohammad Moghal, Rishi Goburdhun, Nicholas Hopkinson, William Man, Mary Morrell, Robert Dickinson, Anita Simonds

An auto-titrating intelligent oxygen therapy (iO2T) system in COPD patients: A randomised cross-over trial. European Respiratory Journal Sep 2015, 46 (suppl 59) OA3281; DOI: 10.1183/13993003.congress-2015.OA3281

Mohammad Moghal, Rishi Goburdhun, Mary Morrell, Robert Dickinson, Anita Simonds

A Novel Smartphone Based Auto-Titrating Oxygen System Reduces Intermittent Hypoxia During Activities of Daily Living in Patients on Long-Term Oxygen Therapy. American Journal of Respiratory and Critical Care Medicine 2017;195:A7709

List of figures

List of tables

List of Appendices

List of Abbreviations

6MWT	6-minute walk test
A&E	Accident and emergency
ABG	Arterial blood gas
ADL	Activities of daily living
APP	Application software
ATS	American thoracic society
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body mass index
BRU	Biomedical Research Unit
BTS	British Thoracic Society
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRF	Case report form
ELBG	Ear lobe blood gas
ERS	European respiratory society
FEV_1	Forced expiratory volume in the first second
FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
IH	Intermittent hypoxia

ILD Interstitial lung disease

iO_2T Intelligent oxygen therapy

iO_2Ts intelligent oxygen therapy system

IPF Idiopathic Pulmonary Fibrosis

IQR Interquartile range

kPa Kilopascals

LTOT Long term oxygen therapy

LVRS Lung volume reduction surgery

MHRA Medicines and Healthcare products Regulatory Agency

mmHg millimetres of mercury

MRC Medical research council

N_2O Nitric Oxide

NIHR National Institute of Health Research

NIV Non-invasive ventilation

NOTT Nocturnal oxygen therapy trial

O_2 Oxygen

$PaCO_2$ Partial pressure of carbon dioxide

PaO_2 Partial pressure of oxygen

PID Proportional-integral-derivative

PSG Polysomnography

REC Research Ethics Committee

SD standard deviation

SpO_2 Saturation of peripheral oxygen

tcpCO_2 transcutaneous partial pressure of carbon dioxide

UK United Kingdom

USA United States of America

WHO World Health Organisation

1 Chapter 1 Introduction

1.1 A brief history of oxygen and its clinical relevance

Oxygen constitutes approximately 21% of the Earths' atmosphere and is essential for human survival. Joseph Priestley (1733 – 1804, England), Carl Scheele (1742 – 1786, Sweden) and Antoine Lavoisier (1743 – 1794, France) discovered oxygen almost simultaneously. However, Priestley is most credited with the discovery as he was the first to publish his work entitled "Observations on Different Kinds of Air" in the late 18th century (Priestley, 1772). Lavoisier not only isolated oxygen but also provided its' current name derived from the Greek words "*acidum*" meaning acid and "*gignor*" meaning to produce (Lavoisier, 1789). This is because Lavoisier believed that one of the main properties of this newly discovered gas was to form acids when combined with other substances. Lavoisier demonstrated that oxygen was 1) important for the survival of animals and plants 2) could be combined with carbon to make carbon dioxide and 3) could be utilised therapeutically for patients (Sackner, 1974). After the discovery of oxygen in England, Thomas Beddoes (who has studied under Lavoisier) and James Watt opened the Pneumatic institute in Clifton in 1798 and pioneered inhalational therapy not only for oxygen but also other gases (e.g. N_2O) for the treatment of asthma and heart failure amongst other conditions.

The therapeutic use of oxygen was intermittent at best during the 18th century and the early part of the 19th century. However, this changed with the advent of anaesthesia and the need for oxygen therapy during operations under anaesthesia. This led to the production of the first oxygen cylinder in 1868 (Leigh, 1974) and the use of oxygen during anaesthesia became widely practiced thereafter. Oxygen continued to receive favourable publication in the early 20th century and its therapeutic benefits became more renowned after its use during World War 1 for the treatment of Chlorine poisoning (Hill, 1915).

The use of oxygen for therapeutic benefit was further enhanced by the works of John Haldane and Alvan Barach. In their reviews, they described the scientific basis for the use of oxygen and the different method of oxygen administration including oxygen tents and masks (Barach, 1922, Haldane, 1917).

Oxygen tents and masks remained the mainstay of oxygen delivery before the use of the double pronged nasal cannulas gained popularity in the 1960s (Addis, 1963). Along with its useful benefits in patients with hypoxaemia, the deleterious effects of excessive oxygen were also appreciated in plants, animals and especially so in patients with acute exacerbations of chronic bronchitis and emphysema (Sackner, 1974). It became acknowledged that oxygen should be administered in a controlled manner and this led to the invention of the venturi mask by Moran Campbell in 1960 (Campbell, 1960).

The most extensive use of long-term oxygen therapy (LTOT) has been in patients with chronic obstructive pulmonary disease (COPD). Studies in the late 1960s demonstrated that patients with COPD and hypoxaemic respiratory failure had an excess mortality compared to patients who did not have hypoxaemic respiratory failure (Burrows and Earle, 1969, Jones et al., 1967). LTOT was trialled in patients with COPD and hypoxaemic respiratory failure with promising early results (Abraham et al., 1968, Neff and Petty, 1970, Stark et al., 1972, Stark et al., 1973). Subsequently the MRC and NOTT studies demonstrated that LTOT improved survival in patients with COPD and hypoxaemic respiratory failure (NOTT, 1980, MRC, 1981) (see section 1.10 and 1.11 for further details). However, further studies including the recently published long-term oxygen therapy treatment trial, have failed to demonstrate a survival advantage for patient with less severe hypoxaemia and COPD (Gorecka et al., 1997, Haidl et al., 2004, Chaouat et al., 1999, Albert et al., 2016). It has also been demonstrated that the administration of oxygen to non-hypoxaemic patients with acute medical problems provides no additional benefit and may be in fact be harmful (Stub et al., 2015, Roffe et al., 2014, Hofmann et al., 2017). The harm associated with administering high concentrations of oxygen to patients with acute hypercapnic respiratory failure especially those with COPD has also become clearer as have the benefits of judicious oxygen therapy (Plant et al., 2000, Austin et al., 2010, Hollier et al., 2014).

Over 300 years after the discovery of oxygen, we have arrived at the stage where we appreciate that oxygen is essential for life, that in its purist form, it is a drug, which like all others should be administered with clear indications. When administered, the lowest therapeutic dose should be delivered to achieve a given target oxygen saturation. The British Thoracic Society (BTS) Emergency Oxygen Audit Report demonstrated that despite patients having a prescribed oxygen saturation target, only 69% of patients had oxygen saturations actually within the prescribed range (9.5% of patients were below the target range and 21% above the target range)(O'Driscoll, 2016). In a domiciliary setting, several studies have demonstrated that despite LTOT, many patients continue to experience episodes of intermittent hypoxia (Śliwiński et al., 1994, Morrison et al., 1997, Abdulla et al., 2000). Even within the setting of an intensive care unit (with its greater nursing intensity), a recent study reported that patients' oxygen saturations were within a pre-specified range for only 64% of the recorded time (Jochmans et al., 2016). These studies demonstrate the need for better delivery systems to supply the ideal oxygen flow rate to match to a pre-set oxygen saturation target. **This thesis explores how an auto-titrating oxygen system could be utilised to deliver oxygen to match a pre-set oxygen saturation target and how this could be used for the optimisation and personalisation of oxygen therapy in self-ventilating patients on domiciliary oxygen.**

1.2 The physiological effects of oxygen

Air enters the lung alveoli through the process of ventilation. Thereafter oxygen diffuses into the pulmonary capillaries across a pressure gradient and is delivered to the body tissues bound to haemoglobin. As oxygen travels from the atmosphere to mitochondria there is a gradual reduction in its partial pressure known as the oxygen cascade (Figure 1-1) (Sjoberg and Singer, 2013).

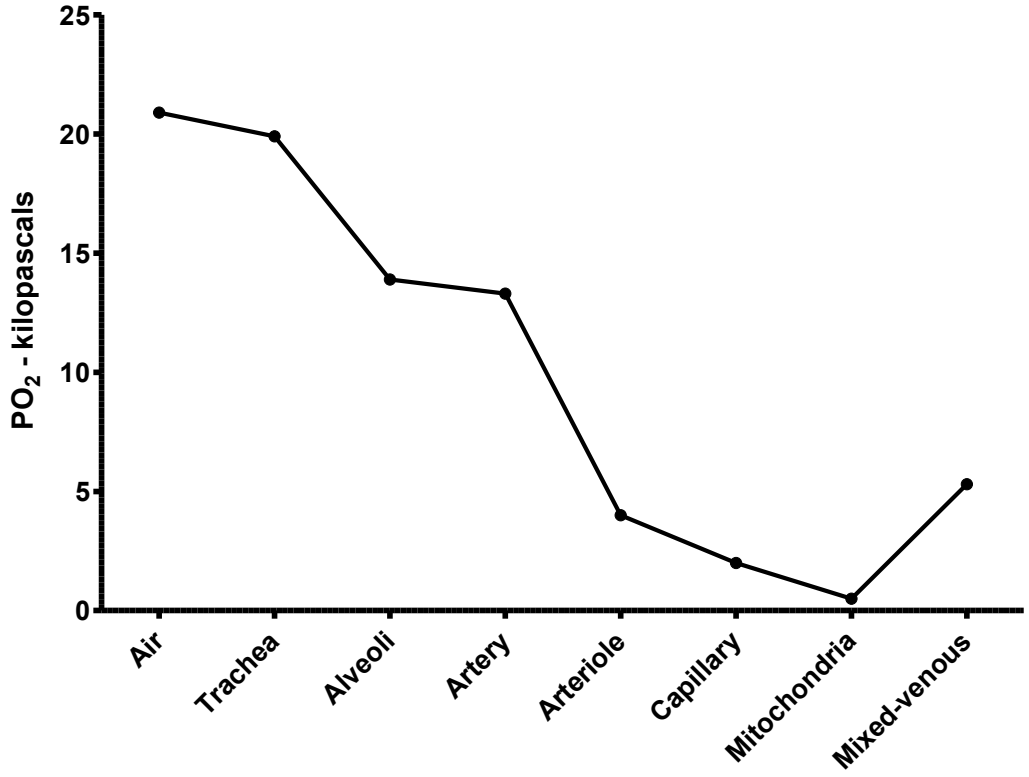


Figure 1-1 The oxygen cascade
From atmosphere to mitochondria whilst breathing room air. PO_2 = partial pressure of oxygen. Modified from Sjoberg and Singer 2013.

Oxygen is involved in multiple metabolic processes in the human body. The most important of these is oxidative phosphorylation – the process of producing the energy rich adenosine triphosphate (ATP) from adenosine diphosphate (ADP). There is no capacity for long term storage of either oxygen or ATP so therefore the human body needs a constant supply of oxygen and ATP. Oxidative phosphorylation is possible only if the partial pressure of oxygen in the mitochondria is above a minimal level of approximately 0.5 kilopascals (West, 2012b). In the absence of oxygen, the body switches to anaerobic metabolism which is far less efficient.

1.3 Control of breathing

The aim of ventilation is to maintain optimum levels of oxygen, carbon dioxide and hydrogen ions in the blood during any number of daily activities including sleep, rest and exercise. In common with many other processes in the body, the control of ventilation works as a negative feedback loop which contains three main components: sensor/s, a processing unit and effectors. Oxygen sensors are located in the carotid body and aortic arch and carbon dioxide sensors are located in the brainstem. The signals from these sensors are relayed to a central control unit in the brainstem, which has outputs to many effectors.

1.3.1 The control centre for ventilation

The control centre for ventilation is a group of nuclei located in the medulla and pons known as the "respiratory centre" (Figure 1-2). The respiratory centre receives input from three main sources: the peripheral and central chemoreceptors, the higher brain centres and receptors in muscles and the lungs. It is involved in generating the basic rhythm of respiration, processing signals from all its inputs and responding appropriately to maintain haemostasis. Its main output is via the phrenic nerve (West, 2012b).

1.3.2 The effects of oxygen on ventilation

The major chemoreceptors for oxygen are located at the bifurcation of the common carotid artery bilaterally and on the aortic arch with the carotid body chemoreceptors being the most important in humans. Both sets of chemoreceptors receive their own arterial blood supply via small arteries directly from the adjacent carotid artery and aorta. These chemoreceptors respond within seconds to hypoxaemia by increasing their firing rate (the receptors respond to changes in the partial pressure of oxygen [PaO_2] and not oxygen concentration) (West, 2008). The peripheral chemoreceptors have also been shown to respond to the partial pressure of carbon dioxide ($PaCO_2$), H+, glucose and changes in total blood flow (Dempsey and Smith, 2014). The carotid body chemoreceptors afferent fibres connect to the respiratory centre through the Glossopharyngeal nerve. The aortic body afferent fibres pass to both the respiratory and cardiovascular centres in the brainstem via the Vagus nerve. Reduction in PaO_2 lead to an increase in ventilation. However, this response to hypoxia is attenuated due to the sigmoid shape of the oxygen dissociation curve. There can be a significant reduction in the PaO_2 before there is a reduction in oxygen saturation. Figure 1-3a demonstrates that there is little change in ventilation until the PaO_2 has reduced to 60 mmHg. After this point, there is an exponential increase in ventilation with further reductions in the PaO_2. However as seen in Figure 1-3b, the response to ventilation is linear when plotted against oxygen saturation.

1.3.3 The effect of carbon dioxide on ventilation

In health, the changes in ventilation are influenced almost entirely influenced by changes in the $PaCO_2$. The $PaCO_2$ in the blood is very closely regulated to within 3mm of the mean value irrespective of any daytime activities (West, 2012b). During sleep, $PaCO_2$ is allowed to rise by between 2 and 6.5 mmHg above the daytime value. The chemoreceptor for carbon dioxide is located centrally in the ventral medulla and has direct connections with the neurones of the respiratory centre. This area responds to changes in H^+ concentration in the surrounding extracellular fluid (ECF). In turn the ECFs' composition in influenced by three main factors: the cerebrospinal fluid (CSF) (having the greatest influence), local metabolism and blood flow. CO_2 exerts it effects on ventilation indirectly through changes in H^+ concentration in the CSF (and therefore the ECF). CO_2 diffuses out of the blood, across the blood-brain barrier and into the CSF where it combines with water to produce H^+ and HCO_3. An increase in H^+ concentration leads to increased ventilation and a decrease in H^+ concentration leads to a reduction in ventilation.

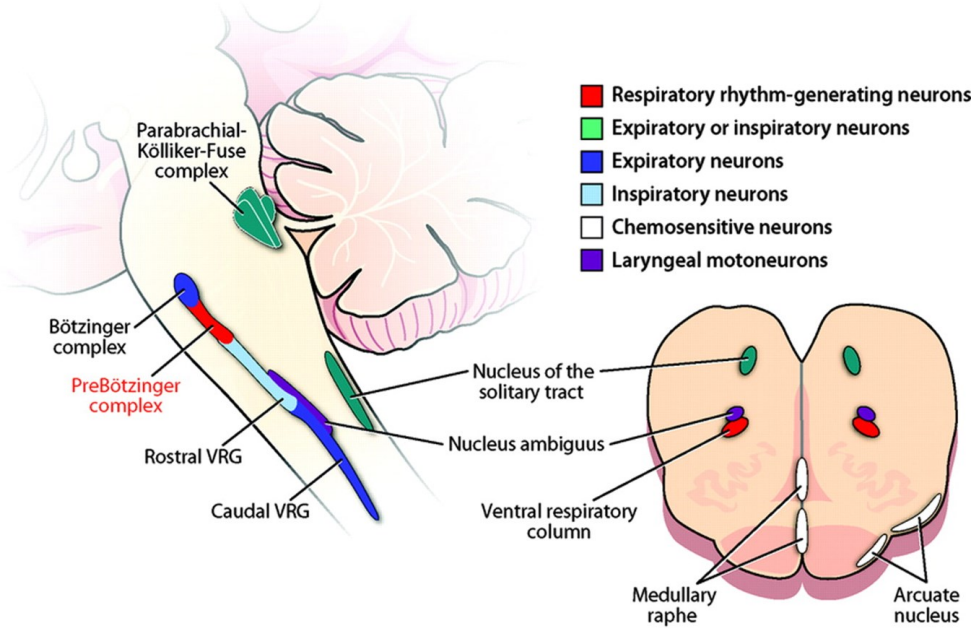


Figure 1-2 The respiratory control centre in the brainstem
A sagittal section on the left and a transverse section on the right through the brainstem demonstrating the respiratory control centre. The central pattern generator for automatic breathing is distributed in the nucleus of the solitary tract, the dorsolateral pons and ventrolateral medulla (ventral respiratory column). The pre-Bötzinger complex (in the ventral respiratory system) is believed to be involved in the basic rhythm generation of the respiratory system and the Bötzinger complex contains excitatory neurones. The parabrachial and Kölliker nuclei in the dorsolateral pontine tegmentum are involved in phase switching from inspiration to expiration. Reproduced with permission (Benarroch, 2007).

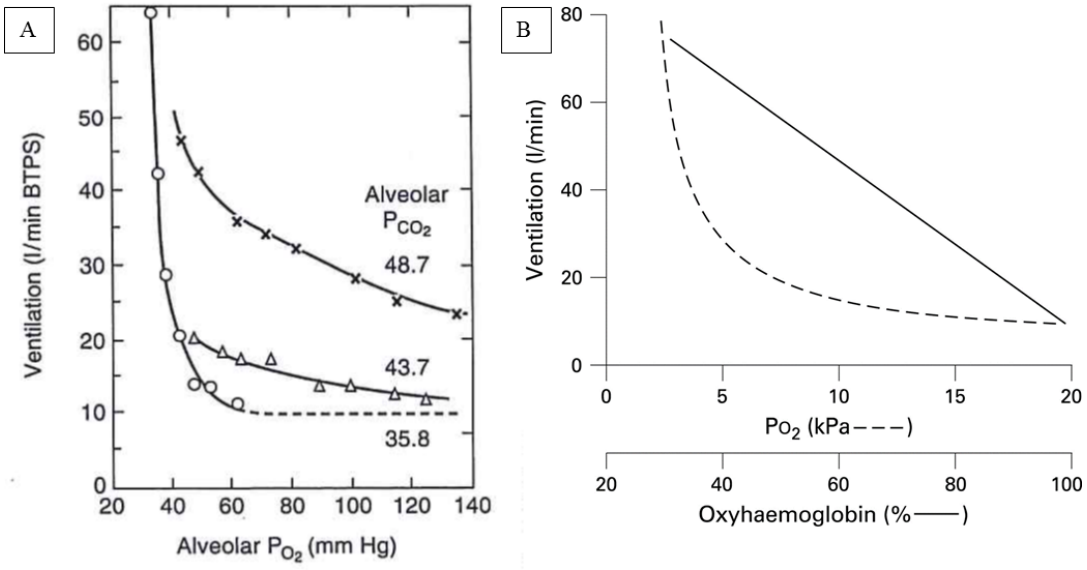


Figure 1-3 Ventilation and PO_2 curve
The change in ventilation plotted against changing PO_2 and at different levels of carbon dioxide (A) (West, 2008) and SpO_2 and PO_2 (B) (O'Driscoll et al., 2008) . Both figures reproduced with permission.

1.4 Pathophysiological changes in control of ventilation, response to carbon dioxide and oxygen in patients with chronic ventilatory failure

The causes of chronic ventilatory failure are obstructive lung diseases (such as COPD, bronchiectasis and cystic fibrosis), chest wall disorders (such as scoliosis), neuromuscular diseases (such as amyotrophic lateral sclerosis) and neurological conditions (such as a stroke). The most extensively studied condition causing chronic ventilatory failure is COPD in terms of the changes in ventilatory control, the response of patients to oxygen and carbon dioxide and compensatory mechanisms.

1.4.1 Ventilatory changes in COPD

The functional changes in COPD which consist predominantly of airflow limitation, emphysema and hyperinflation lead to several changes in ventilatory control. In general, there is increased neural drive to the respiratory muscles and diaphragm to compensate for advancing disease (Gorini et al., 1990, De Troyer et al., 1997). This mechanism can maintain gas exchange and prevent hypercapnia in early disease and the increase in work of breathing and neural drive may contribute to the onset of breathlessness. It also leads to the classical pattern of rapid

shallow breathing seen in most patients. The ventilatory response to oxygen in patients with chronic hypoxaemic respiratory failure is reduced compared to patients with the same severity of COPD but without chronic hypoxia. In general, patients with COPD have a blunted response to CO_2 and this is mediated by a combination of mechanical factors and insensitivity to carbon dioxide (Scano et al., 1995, Duranti et al., 1995, Van de Ven et al., 2001, Flenley et al., 1970, Altose et al., 1977). In many patients, this is a slow process which leads to daytime hypercapnia with subsequent renal compensation through increased bicarbonate retention to prevent a respiratory acidosis.

1.4.2 The change in CO_2 in response to oxygen during acute exacerbations of COPD

Hypercapnic respiratory failure is a frequently encountered problem during acute exacerbations of COPD. The clinical problem of hyperoxia worsening or causing hypercapnia during acute exacerbations of COPD has been well studies in the past 40 years. There is evidence to support several different mechanisms causing this problem including a reduction in ventilatory drive with the addition of oxygen, increase in ventilation perfusion mismatch caused by the release of hypoxic pulmonary vasoconstriction, the Haldane effect and absorption atelectasis (Feller-Kopman and Schwartzstein, 2001, Robinson et al., 2000, Pain et al., 1965, Aubier et al., 1980, Erbland et al., 1990, Dick et al., 1997, Berry et al., 1993, Tyuma, 1984, Downs, 2003, O'Driscoll et al., 2017).

1.4.3 The change in CO_2 in response to oxygen in patients with stable COPD and chronic hypoxaemic respiratory failure

Changes in $PaCO_2$ in response to LTOT in stable COPD patients have been documented in trials investigating the survival benefit of LTOT and change in pulmonary pressures in response to LTOT. Stark and colleagues investigated the effects of changes in pulmonary pressure in response to different durations of LTOT in patients with COPD (Stark et al., 1972). The addition of LTOT increased $PaCO_2$ by a mean of 6.2±9.9 mmHg, and this was borderline for statistical significance ($p = 0.053$). In the MRC oxygen study, there was an increase in the $PaCO_2$ in 3 out of the 4 randomised groups (MRC, 1981). However, no statistical analysis of the change in mentioned in the publication and individual data are not available for analysis. Cooper and colleagues followed 72 patients with hypoxic cor pulmonale who were give LTOT for a period of 12 years (Cooper et al., 1987). At rest, compared to air, LTOT increased the $PaCO_2$ by a mean of 0.39 kPa (from 6.9 to 7.3kPa) (no statistical analysis in the paper). There are no published arterial blood gas data available on the change in the $PaCO_2$ with LTOT from the

NOTT, the long-term oxygen therapy treatment trial (LOTT) or from four other important studies on oxygen therapy (NOTT, 1980, Albert et al., 2016, Strom, 1993, Haidl et al., 2004, Gorecka et al., 1997, Chaouat et al., 1999).

1.5 Physiological response to acute hypoxia

Acute severe total hypoxia is very poorly tolerated by the human body and very quickly leads to a reduction in ATP synthesis and if not corrected to cellular death especially brain death within minutes.

Less severe acute hypoxia such as that experienced by mountain climbers who transition from sea level to heights of above 4,000 feet without acclimatisation, leads to a several physiological compensatory mechanisms. Firstly there is an increase in the respiratory rate and tidal volumes leading to greater ventilation (West, 2004). There is also an increase in heart rate and cardiac output leading to greater oxygen delivery. The pulmonary vasculature vasoconstricts in response to hypoxia (Dunham-Snary et al., 2017, Hambraeus-Jonzon et al., 1997). This is in part a protective mechanism, which allows blood to flow from under oxygenated areas of the lung to others, which may be better oxygenated. However, in the context of global hypoxia this causes generalised pulmonary vasoconstriction and pulmonary hypertension. Hypoxia alone is sufficient to cause pulmonary hypertension in the absence of any underlying lung disease and this has been demonstrated in mountain climbers who usually dwell at sea level and climb to high altitudes and in healthy human volunteers (Hambraeus-Jonzon et al., 1997, West, 2004). In individuals who go onto live at high altitudes having been brought up at sea level, there is an acute rise in pulmonary pressure on first exposure to hypoxia. Thereafter the exposure to persistent hypoxia leads to a maintenance of pulmonary pressure and this can persist for up to 4 weeks after return to sea level (West, 2012a). In response to acute hypoxia, there is vasodilation of the peripheral circulation to enhance oxygen delivery to the tissues. Acute exposure to hypoxia without acclimatisation can lead to symptoms such as headaches, fatigue, dizziness and breathlessness, which in severe cases can progress to high altitude pulmonary oedema (HAPE) and/or high altitude cerebral oedema (HACE) (West, 2012a).

1.6 Consequences of chronic hypoxia

If exposure to hypoxia becomes chronic, it can lead to several consequences the most important of which are pulmonary hypertension, polycythaemia and cognitive deficits which are now discussed further. These chronic effects of hypoxia have been best studied in populations of lowlanders who have ventured and lived or worked at high altitudes and in patients with chronic

lung diseases, which can cause chronic hypoxic respiratory failure, and this has been best described in patients with COPD.

1.6.1 Pulmonary hypertension

Pulmonary hypertension is currently defined as a mean pulmonary pressure of ≥25mm Hg at rest after assessment with right heart catheterisation (Galie et al., 2015). The causes of pulmonary hypertension are grouped into five categories depending upon whether the cause in pre-capillary or post-capillary and chronic hypoxia from lung disease is in group 3 of the classification (Galie et al., 2015). Pulmonary hypertension due to chronic hypoxia has been most extensively studies in healthy subjects who have migrated to environments with low oxygen concentrations and in disease, it has been best studies in patients with COPD.

Pulmonary hypertension on exposure to hypoxia at high altitude

The concept of hypoxic pulmonary vasoconstriction was first demonstrated experimentally in cats in 1946 (Euler and Liljestrand, 1946). Pulmonary vasoconstriction can begin within as quickly as 15 minutes of exposure to hypoxia and develops further over the next 2 hours (Hambraeus-Jonzon et al., 1997). The severity of pulmonary vasoconstriction is dependent on the severity of the hypoxic insult (Dorrington et al., 1997, Hambraeus-Jonzon et al., 1997). It has been shown that lowlanders who ascend rapidly to high altitude can develop acute pulmonary hypertension and in severe cases acute pulmonary oedma (Dunham-Snary et al., 2017). If the exposure to hypoxia continues and becomes chronic so does the pulmonary hypertension. It has also been demonstrated that when individuals who have developed pulmonary hypertension at high altitude descend to normal altitude, it takes a number of weeks for the pulmonary pressures to return to normal (West, 2012b, Nunn, 2014).

Pulmonary hypertension from hypoxia due to lung disease

Pulmonary hypertension is a very well recognised complication of many chronic respiratory diseases. The commonest respiratory conditions associated with the development of pulmonary hypertension are COPD, interstitial lung disease, combined pulmonary fibrosis and emphysema and sleep disorders (Hurdman et al., 2013). The presence of pulmonary hypertension in combination with a primary respiratory disorder is very significant as it is associated with increased mortality and a greater risk of hospitalisation in patients with COPD (Oswald-Mammosser et al., 1995, Kessler et al., 1999, Weitzenblum et al., 1981) and greater mortality in patients with idiopathic pulmonary fibrosis and cystic fibrosis (Lettieri et al., 2006, Hayes et al., 2014). The two most important mechanisms leading to pulmonary hypertension as result of

respiratory disorders is a combination of 1) hypoxic pulmonary vasoconstriction and 2) loss of the pulmonary vasculature as a result of the underlying lung disease (Rowan et al., 2016).

The overall prevalence of pulmonary hypertension in patients with COPD remains unknown. However, in patients with advanced COPD it has been demonstrated to be as high as 90% in a cohort of patients in the National Emphysema Treatment Trial (Scharf et al., 2002) and 50% in a French cohort eligible for lung transplantation or lung volume reduction surgery (Thabut et al., 2005). Pulmonary hypertension associated with COPD is mild in most cases and is severe (pulmonary artery pressure >35mmHg) only in approximately 1 to 4% of patients (Chaouat et al., 2005, Thabut et al., 2005).

LTOT is recommended for the treatment of hypoxaemic respiratory failure in association with COPD and other respiratory diseases. Early studies of LTOT in patients with COPD demonstrated that supplemental oxygen could reduce pulmonary artery pressures if utilised for 15 or 18 hours per day but not when utilised for 12 hours per day (Stark et al., 1972). However, various studies have demonstrated contrasting results of the effects of supplementary oxygen on pulmonary hypertension secondary to lung disease. In the MRC oxygen study, participants underwent right heart catheterisation at baseline and at the end of the study. The study demonstrated that men on LTOT who survived over 500 days, had a very minimal reduction in the pulmonary artery pressure compared to baseline (-0.06 mmHg per year) whereas men not on LTOT who had survived over 500 days had a small rise in pulmonary artery pressure compared to baseline (+2.79 mmHg per year) (MRC, 1981).

In the NOTT, participants underwent right heart catheterisation at baseline and at 6-month follow-up. This study showed that nocturnal oxygen therapy was associated with a small reduction in pulmonary artery pressure during exercise but not at rest. Continuous long-term oxygen therapy was associated with a significant reduction in pulmonary artery pressure during both exercise (-6 ± 14 mmHg) and rest (-3 ± 11 mmHg). Survival analysis demonstrated that for patients surviving at least 6 months, changes in mean pulmonary artery pressure during the first 6 months were associated with subsequent survival for both the nocturnal oxygen therapy group and the continuous oxygen therapy group (Timms et al., 1985). Therefore, the MRC study showed a stabilisation of pulmonary artery pressures and no survival advantage whereas the NOTT study showed a reduction in pulmonary artery pressures and a subsequent survival advantage if there was a reduction.

Fletcher *et al*., conducted a three-year randomised trial of nocturnal oxygen therapy against placebo in patients with COPD who had nocturnal oxygen desaturations but without daytime hypoxaemia (daytime PaO_2 >60mm Hg) (Fletcher et al., 1992b). They demonstrated a

significant reduction in the pulmonary artery pressure of patients on nocturnal oxygen therapy of 3.9 mmHg compared to a rise of 3.9 mmHg in patients treated with room air. The study also showed a non-significant reduction in mortality for patients treated with oxygen. Zielinski *et al*., investigated the pulmonary haemodynamic of a cohort of 95 patients with COPD who had started LTOT (Zielinski et al., 1998). The study demonstrated an initial fall in pulmonary artery pressures in the first 2 years, a subsequent rise in the next 2 years and stabilisation compared to baseline values at 6 years.

Taken together the above studies demonstrate that LTOT may improve or stabilise pulmonary haemodynamic variables in patients with COPD, chronic hypoxia and pulmonary hypertension. However, supplementary oxygen does not completely reverse or normalise pulmonary pressures. There are several potential explanations for these observations. Firstly, there are other mechanisms aside from hypoxic pulmonary vasoconstriction which have led to pulmonary hypertension which have not been treated or addressed (such as the loss of lung tissue from the underlying respiratory disorder). Secondly, if chronic hypoxia has been present for a sufficient time period, it may produce remodelling of the pulmonary vasculature which is not fully reversible upon removal of the initial hypoxia. Thirdly, the delivery of LTOT may not be as adequate as one would hope and therefore despite LTOT patients are experiencing episodic intermittent hypoxia (see section 1.16).

1.6.2 Polycythaemia and hypoxia

Polycythaemia is defined as an abnormal increase in the total number of red blood cells causing an increase in haemoglobin concentration and haematocrit (Warrell et al., 2010). Chronic hypoxia with appropriate increase in erythropoietin production is a well-known cause of secondary polycythaemia and this has been described in healthy individual on exposure to chronic hypoxia and in patients with chronic lung diseases who develop chronic hypoxia.

Polycythaemia on acute exposure to hypoxia at high altitude

Polycythaemia is a well-known adaptive response to hypoxia for lowlanders who migrate to high altitudes. The response is mediated through increased production of erythropoietin that results in increased oxygen carrying capacity. It begins within 24 to 48 hours of exposure to hypoxia but can take months reach its peak effect (Nunn, 2014, Jelkmann, 1992).

Polycythaemia from chronic hypoxia due to lung disease

Chronic hypoxia from lung disease is a well-known cause of secondary polycythaemia and is a marker of severity of the underling lung disease. It is mediated through the increased secretion

of erythropoietin and this has been best described in patients with COPD (Vanier et al., 1963, Guidet et al., 1987). It has been demonstrated that withdrawal of oxygen (intermittent hypoxia) in patients established on LTOT can lead to an increase in the production of erythropoietin in as little as two hours (Balter et al., 1992). The prevalence of polycythaemia depends very much on the population that is studies and can vary from 6% in a general COPD population (Cote et al., 2007), to 8.7% in patients admitted with acute exacerbation of COPD (Toft-Petersen et al., 2016), 8.5% in COPD patients on LTOT, and up 18% in COPD patients starting LTOT and non-invasive ventilation (Kollert et al., 2013, Chambellan et al., 2005).

Polycythaemia in patients with COPD is associated with an increased incidence of gout, pulmonary embolism, increased pulmonary artery pressure, a reduction in cerebral blood flow and endothelial dysfunction (Kohkhar, 1980, Ryan, 1963, Nakamura et al., 2000, York et al., 1980). In a recent study, Guo *et al*., demonstrated that patients with COPD who have polycythaemia and have a subsequent pulmonary embolism have a greater mortality, longer hospital stay and higher requirement for mechanical ventilation than patients with pulmonary embolism without polycythaemia (Guo et al., 2016).

The best treatment for polycythaemia secondary to chronic hypoxia and COPD is supplemental oxygen and has this has been best studied in the NOTT and MRC studies. Supplemental LTOT in the MRC study reduced red cell mass and pulmonary hypertension as well as reducing mortality (MRC, 1981). In the NOTT, 18 months after oxygen therapy, patients in the continuous oxygen group had on average a 9.2% reduction in red cell mass whereas patients on nocturnal oxygen therapy had a reduction of only 2.0%. In another open label study, Block *et al*., demonstrated a reduction in haemoglobin, red cell mass and haematocrit in patients with severe hypoxaemia just one month after the initiation of continuous oxygen therapy (Block et al., 1974). Severe polycythaemia can cause symptoms of hyperviscosity syndrome, arterial and venous thromboses and cognitive effects. Although supplementary oxygen can reduce polycythaemia over weeks to months, if acute treatment is necessary for any indication in polycythaemia then venesection and erythrapheresis are the best available options (Kim and Oh, 2016, Wedzicha et al., 1983).

1.6.3 Cognitive effects of chronic hypoxia

Cognitive dysfunction is very common in patients with COPD and one review highlighted that ≥ 90% of patients with COPD demonstrated a deficit in at least one domain of cognitive function (Dodd et al., 2010). There are numerous factors which may contribute to cognitive dysfunction in patients with COPD and these can be classified as generic factors such as age and educational attainment and those specific to COPD such as lung function, smoking, hypercapnia, hypoxia,

physical inactivity, vascular co-morbidities and exacerbations. The mechanisms of cognitive deficits in patients with COPD are thought to result from a combination of hypoxia, direct damage from cigarette smoke and the systemic inflammatory effects of COPD. However, the exact relationship between the degree of chronic hypoxia and severity of cognitive function and the relative contributions of other factors remains unclear. Some studies have demonstrated that worsening hypoxia is associated with worsening cognitive function whereas other have failed any demonstrate any clear relationship (Dodd et al., 2010). Thakur and colleagues showed that COPD in associated with a substantial risk of cognitive dysfunction in comparison to healthy ag matched individuals (Thakur et al., 2010). Additionally, they demonstrated that low oxygen saturations were associated with an increased risk of cognitive dysfunction and that oxygen therapy reduced the risk of cognitive impairment. In a recent study, Karamanli and colleagues elucidated the effects of LTOT on cognitive function in patients with COPD. They showed that non-users of LTOT had significantly lower cognitive function than patients who regularly used LTOT (Karamanli et al., 2015). In the only interventional study of oxygen therapy to have tested cognitive function, the NOTT, patients receiving continuous oxygen therapy had a small improvement in cognitive functioning after compared to patients on nocturnal oxygen therapy after 12 months. However, this did not translate into any additional benefit in quality of life (Heaton et al., 1983).

1.7 Effects of hyperoxia

At the cellular level, hyperoxia leads to the development of reactive oxygen species (ROS) in the form of superoxide, hydrogen peroxide, hydroxyl radical all of which can damage the cellular membrane with subsequent cell death.

Healthy volunteers exposed to high concentration of oxygen develop symptoms such as cough, sore throat and substernal discomfort within 24 hours with associated changes in their vital capacity and tracheobronchitis (Sackner, 1974, Fisher, 1980). Other morphological changes in the lungs associated with hyperoxia include absorption atelectasis, bronchopulmonary dysplasia, pulmonary oedma and possible adult respiratory distress syndrome (ARDS) (Fisher, 1980).

Physiologically, hyperoxia leads to vasoconstriction of the peripheral circulation and this effect has been demonstrated in the vascular supply of the heart (Kenmure et al., 1971), brain (Watson et al., 2000, Sjoberg et al., 1999) and retina (Kiss et al., 2002). Hyperoxia leads to a reduction in the heart rate and subsequent reduction in cardiac output (Rousseau et al., 2005, Daly and Bondurant, 1962). The effect of hyperoxia on the pulmonary vasculature has been somewhat contradictory with some studies demonstrating vasodilation (Barer et al., 1970), some

demonstrating vasoconstriction and others demonstrating no discernible change (Hambraeus-Jonzon et al., 1997).

Several clinical studies have investigated directly or indirectly the effects of hyperoxia on morbidity and mortality in patients with low or normal oxygen saturations. The Oxygen-ICU trial was a prospective, randomised, parallel group study which randomised patients admitted to a single intensive care unit to receive either conservative oxygen therapy to maintain a PaO_2 between 70-100 mmHg (SpO_2 between 94-98%) or liberal oxygen administration to maintain PaO_2 up to 150 mmHg (SpO_2 97-98%) (Girardis et al., 2016). The study showed reduced in-hospital and overall mortality in favour of patients in the conservative oxygen therapy group. In a recently published study, the effects of inducing hyperoxia (by increasing FiO_2 to 1.0) and hypersaline solution for volume resuscitation were examined in patients with septic shock and requiring mechanical ventilation (Asfar et al., 2017). The study showed that hyperoxia may increase the risk of death, whereas hypersaline fluid did not improve survival.

Wang *et al*., performed a systematic review and meta-analysis of observational studies in humans looking at the effects of hyperoxia on mortality in patients who had a cardiac arrest and subsequent return of circulation (Wang et al., 2014). The analysis included approximately 3000 patients and demonstrated an increased risk of in-hospital mortality with hyperoxia (OR, 1.62; 95% CI, 0.87–3.02; I2, 55.61%; 2 studies).

Stub *et al*., investigated the effects of additional oxygen therapy given to non-hypoxic patients with an acute ST-elevation-myocardial infarction (Stub et al., 2015). This study showed that acutely there was increased rate of recurrent myocardial infarction and higher rate of arrhythmias in patients given oxygen. After 6-months follow-up, patients who had received additional oxygen had a greater infarct size on cardiac MRI than those who did not receive supplemental oxygen.

Roffe *et al*., conducted a three arm trial of continuous *versus* daytime *versus* no oxygen in non-hypoxic patients with acute stroke (Roffe et al., 2014). The study showed no difference in neurological outcome or overall mortality after 3-months follow-up.

Taken together, the above studies demonstrate that hyperoxia is harmful to cells, has harmful physiological effects, and increases morbidity and mortality in some patients. Therefore, it is essential that we treat oxygen as a drug and avoid both hypoxia and hyperoxia.

1.8 Current utilisation of oxygen therapy

Many respiratory diseases can lead to hypoxaemic respiratory failure. The morbidity and mortality associated with hypoxaemia along with the evidence for the therapeutic benefit of oxygen therapy has informed international guidelines for oxygen use and has led to an increase in oxygen prescription in England and worldwide over the past 20 years (Royal College Of Physicians, 1999, Hardinge et al., 2015, McDonald et al., 2016, Qaseem et al., 2011). Currently approximately 85,000 patients in England are prescribed home oxygen therapy. The most common condition for which home oxygen therapy is provided in COPD (Table 1-1).

Table 1-1 Data on home oxygen therapy use in England
Adapted from Department Of Health document (Health, 2010)

Type of Therapy	Proportion of home oxygen therapy users	All Patients	Estimated COPD Patients
Short-burst (SBOT)	25%	21,000	13,000
Ambulatory (AO)	4.5%	4,000	3,000
Long-term (LTOT)	22%	19,000	11,000
LTOT and AO	32%	27,000	16,000
Other (combination of LTOT, AO, SBOT)	16.5%	14,000	8,000
TOTAL	**100.0%**	**85,000**	**51,000**

Internationally the most common conditions for which LTOT are prescribed is COPD (most common), sequalae of tuberculosis and interstitial lung disease (Zielinski, 2000b, Zielinski, 2000a). In the UK, the most conditions are COPD and ILD and these deserve special attention are now discussed further.

1.9 Oxygen therapy and chronic obstructive pulmonary disease

COPD is the most common condition for which oxygen is prescribed in England. It is a respiratory disorder (with systemic effects) characterised by airway obstruction (which is not fully reversible) and chronic inflammation, most commonly caused by cigarette smoking (GOLD, 2014). It is a very common disorder and the world health organisation (WHO) estimates that there are 65 million people with moderate to severe COPD worldwide (WHO, 2015). It is the third most common cause of worldwide mortality after ischaemic heart disease and stroke (Lozano et al., 2012). In the United Kingdom (UK), there are an estimated 900,000

patients currently diagnosed with COPD and a further 1.1 million who are undiagnosed (NICE, 2010). The estimated COPD mortality in the UK is 25,000 per year (Health and Safety Executive, 2013).

The commonest cause of COPD is cigarette smoking (Vogelmeier et al., 2017). However, COPD can also be caused by inhalation of substances from occupational airborne exposure, outdoor and indoor pollution and genetic factors. The effect of the inhaled substances is to cause a chronic inflammatory reaction in the small airways (leading to chronic bronchiolitis) and damage to the respiratory alveolus (leading to emphysema). It is the combination of chronic bronchiolitis and emphysema that leads to airflow obstruction. The presentation of COPD in an individual patient depends upon the patients' age, coexisting comorbidities and the predominant pathology (emphysema vs chronic bronchiolitis).

The first step in confirming the diagnosis of COPD in patients presenting with typical symptoms and risk factors is the demonstration of airflow obstruction on spirometry, which is defined as a forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) ratio of less than 70%. The severity of COPD is most commonly classified according to the severity of the airflow obstruction (Table 1-2). The severity of COPD correlates poorly with symptoms but correlates well with mortality.

Table 1-2 The classification of COPD
The severity of COPD according to spirometry (post-bronchodilator FEV_1) and the associated 3 year mortality (GOLD, 2014)

GOLD staging	FEV_1/FVC ratio	Percentage predicted FEV_1	3-year mortality
1 – mild COPD	<70%	FEV_1 - ≥80% predicted	Unknown
2 – moderate COPD	<70%	FEV_1 ≥50 - <80% predicted	11
3 – severe COPD	<70%	FEV_1 ≥30 - <50% predicted	15
4 - very severe COPD	<70%	FEV_1 <30% predicted	24

The aims of treatment in patients with COPD are to 1) reduce mortality 2) improve symptoms and quality of life and 3) reduce exacerbation frequency. There are a number of interventions available for the treatment of COPD and oxygen is one of the few shown to reduce mortality (Table 1-3).

In some patients, the progression of COPD causes hypoxaemic respiratory failure with or without hypercapnia. Hypoxaemia is due to a combination of ventilation/perfusion mismatch, reduction in gas diffusion across the alveolar membrane and shunting. Hypercapnia in COPD is caused by a combination of ventilation/perfusion mismatch, reduced tidal volumes and hyperinflation (static and dynamic) all leading to alveolar hypoventilation.

Several studies have demonstrated the increased mortality of patients with hypoxaemic respiratory failure and COPD (Jones et al., 1967, Burrows and Earle, 1969). The recognition of this increased mortality lead to the design of two randomised, controlled trials, the nocturnal oxygen therapy trial (NOTT, 1980) and the Medical Research Council (MRC) oxygen study (MRC, 1981) both of which demonstrated that LTOT improves survival in patients with hypoxaemic respiratory failure (discussed further in sections 1.10 and 1.11). After the results of the NOTT and MRC studies, two uncontrolled, retrospective studies were published which confirmed that LTOT improves survival in patients with hypoxaemia and COPD compared to historical cohorts who had not received LTOT (Cooper et al., 1987, Strom, 1993).

Table 1-3 Important interventions in COPD and their main effects

Intervention	Main effects	References
Long-term oxygen therapy	Reduce mortality in severely hypoxaemic patients but not in moderately hypoxaemic patients	(MRC, 1981, NOTT, 1980, Albert et al., 2016)
Influenza vaccination	Reduce Influenza infection and reduce mortality	(Nichol et al., 1994, Wongsurakiat et al., 2004)
Lung transplant	In selected patients can improve quality of life and functional capacity	(Trulock, 1998)
Lung-volume reduction surgery	Reduce mortality in selected patients	(Fishman et al., 2003)
Pneumonia vaccination	Recommended for older individuals and reduces incidence on pneumonia is older patients and those with severe COPD	(Alfageme et al., 2006, Jackson et al., 2003)
Smoking cessation	Reduce mortality	(Anthonisen et al., 2005)
Inhalers	Improve symptoms, quality of life, reduce exacerbations and reduce lung function decline	(Calverley et al., 2007, Tashkin et al., 2008, Wedzicha et al., 2016)
Long-term antibiotics	Reduce exacerbation frequency	(Albert et al., 2011)
Pulmonary rehabilitation	Reduces exacerbation frequency and breathlessness in stable patients	(Puhan and Lareau, 2014)
Roflumilast	Reduces exacerbation frequency	(Martinez et al., 2015)
Non-invasive ventilation (NIV) for hypercapnic respiratory failure	Reduces mortality in acute exacerbations of COPD. Long term domiciliary NIV may reduce mortality (conflicting studies) and exacerbation frequency.	(Struik et al., 2014, Kohnlein et al., 2014, Murphy et al., 2017, Ram et al., 2004)

1.10 The nocturnal oxygen therapy trial (NOTT)

The NOTT, published in 1980, examined the effect of two different LTOT durations on overall mortality in patients with COPD. This was a prospective, multicentre study based in North America. Patients were eligible for the study if they were over 35 years-old, had COPD with hypoxaemic respiratory failure (partial pressure of oxygen [PaO_2] $\leq$ 55 mmHg or $PaO_2 \leq$ 59 mmHg with evidence of pulmonary hypertension, polycythaemia or oedema). The patients were randomised to oxygen therapy of two different duration; either 12 hours per day (nocturnal oxygen therapy) or 24 hours per day (continuous oxygen therapy).

The aim of oxygen therapy was to prescribe the lowest flow rate possible to increase the resting PaO_2 to between 60 and 80 mmHg. Participants were asked to increase the flow rate by 1 litres/minute above their resting flow rate whilst walking and during sleep.

A total of 203 patients were recruited and followed for an average of 19.3 months. The compliance data demonstrated that the nocturnal oxygen therapy group utilised oxygen for a mean±SD of 12 ± 2.5 hours /day and the continuous oxygen therapy group utilised oxygen for a mean±SD of 17.7 ± 4.8 hours/day. The 12-month mortality rate with continuous oxygen was 11.9% vs 20.9% for nocturnal oxygen therapy. The 24-month mortality rate with continuous oxygen was 22.4% vs 40.8% for nocturnal oxygen. Both of these results demonstrating a survival advantage in favour of continuous oxygen over nocturnal oxygen were highly statistically significant ($p < 0.01$).

1.11 The MRC study

The MRC oxygen study, published in 1981, examined the effects of LTOT (delivered for at least 15 hours per day including the night time period) on mortality in patients with COPD compared to no supplemental oxygen. This study was based in the UK. Patients under 70 years of age were recruited if they had COPD with a FEV_1 <1.2 litres with evidence of hypoxaemia (PaO_2 between 40 and 60 mmHg) with additional evidence of heart failure.

Patients were prescribed oxygen at a fixed flow rate of at least 2 litres/minute or higher if necessary in order to maintain a resting PaO_2 >60 mmHg (there was no upper limit of PaO_2 as compared to the NOTT). No formal compliance data was collected.

The results of the study demonstrated that over a follow-up period of 5 years, 30 of the 45 control patients died and 19 of the 42 LTOT patients died. There was a marked discrepancy in the male and female experience in MRC study. For men the survival benefit was not evident until 500 days into the study at which point the annual risk of death was 29% in the control

group and 12% in the LTOT group (p=0.04). For the female participants in the study (n=21), improvement in survival was noted shortly after oxygen therapy was started and continued throughout the study (p<0.05).

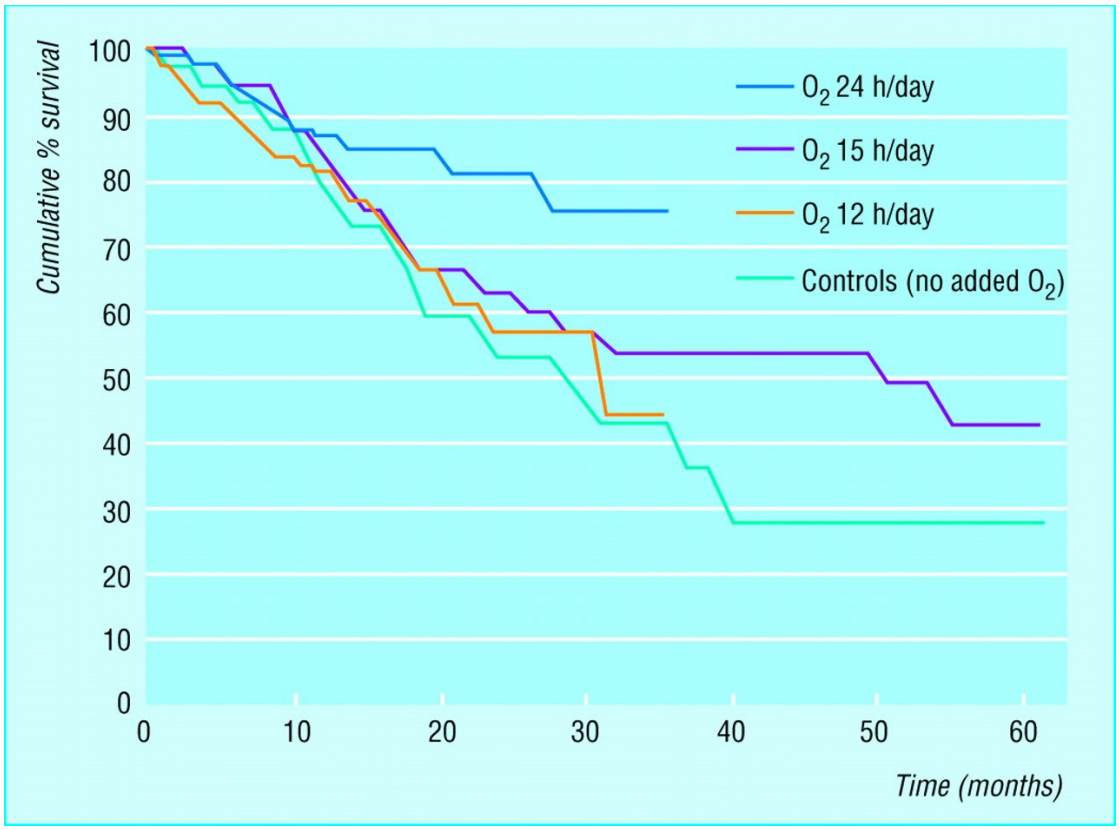


Figure 1-4 Survival curves from the MRC and NOTT studies
The cumulative survival of patients from the combined cohort of the NOTT study (O_2 24 hours/day and O_2 12 hours/day) and the MRC oxygen study (O_2 15 hours/day and controls [no added O_2]). Reproduced with permission from BMJ (Rees and Dudley, 1998).

Figure 1-4 shows the cumulative survival of patients in both the MRC and the NOTT study on one graph. What is clear from these two studies is that some form of LTOT is better than no LTOT and that the longer the duration of LTOT the greater the reduction in mortality compared to a shorter duration.

1.12 Long-term oxygen therapy for moderate hypoxaemia

The MRC and NOTT studies clearly demonstrated that LTOT improved survival in patients with severe hypoxaemic respiratory failure. The severity of hypoxaemia below which LTOT was prescribed in both the MRC and NOTT studies was chosen as a best guess and not with

any scientific rigour. Therefore, there has always remained the question of whether LTOT could improve survival in patients with moderate hypoxaemia. Several small studies have also demonstrated that COPD patients without resting hypoxaemia but with exercise induced desaturation have an increased risk of death compared to patients without exercise induced desaturation and therefore oxygen supplementation in this group may reduce mortality (Casanova et al., 2008, Vandenbergh et al., 1973, Takigawa et al., 2007).

Górecka and colleagues randomised 135 patients with COPD and moderate hypoxamia (PaO_2 between 7.4 – 8.7 kPa) to LTOT or non LTOT and followed them for a period of 3 years (Gorecka et al., 1997). The study did not demonstrate any survival benefit for patients with additional LTOT. Haidl and colleagues randomised 28 patients with COPD and moderate hypoxaemia (PaO_2 66.5 ± 6.3 mmHg) to 1 year of supplemental LTOT or no supplemental oxygen (Haidl et al., 2004). Once again, this study showed no benefit of additional oxygen on 1-year mortality. Chaouat and colleagues randomised 76 patients with COPD with mild to moderate daytime hypoxaemia (PaO_2 8.4 ± 0.4 kPa) with additional nocturnal hypoxaemia to nocturnal oxygen therapy or no additional oxygen and followed them up for two years (Chaouat et al., 1999). Additional nocturnal oxygen therapy did not improve mortality and additionally it did not reduce progression of patients meeting LTOT criteria nor did it have any effects on pulmonary haemodynamic. All the above studies were randomised studies but lacked the appropriate sample size to detect an effect on mortality.

In October 2016, the largest study of moderate hypoxaemia in patients with COPD, The Long-Term Oxygen Treatment Trial (LOTT), was published in the New England Journal of Medicine. In this study, which required a change in inclusion criteria and primary outcome due to poor initial recruitment, 738 patients with COPD with moderate hypoxamia (SpO_2 89-93%) or with normal resting SpO_2 and exercise associated desaturation were randomised to additional oxygen therapy or no additional oxygen. Patient with resting moderate hypoxaemia were prescribed LTOT and those with exercise induced desaturation were prescribed ambulatory and nocturnal oxygen. The study demonstrated no benefit of additional oxygen therapy on the combined primary outcome of time to death or first hospitalisation. There was also no effect of important secondary outcome such as exacerbation frequency, quality of life, lung function and distance walked during a 6MWT. Therefore, on the basis of this large randomised study, LTOT cannot be recommended for patients with COPD and moderate hypoxaemia.

1.13 Oxygen therapy in patients in patients with interstitial lung disease

Interstitial lung disease (ILD) is the name given to a group of heterogeneous disorders characterised by similar symptoms, signs and lung function abnormalities (Bradley et al., 2008). The prognosis and course of these diseases is very variable and is dependent on both patient and disease factors.

There are many subtypes of ILD and multiple guidelines over the years have used various classification systems based on clinical presentation, radiological features and histological subtypes. The most up-to-date classification system is the ATS/ERS update published in 2013 (Travis et al., 2013). The most common ILD is idiopathic pulmonary fibrosis (IPF). This is characterised by progressive pulmonary fibrosis and has a median survival of 2.9 years (Hubbard et al., 1998). Disease progression in IPF inevitably leads to hypoxaemic respiratory failure and the need for oxygen therapy. Oxygen may be given to relieve breathlessness after exercise without oxygen desaturation (short-burst oxygen therapy), to enable patients to walk for longer distances (ambulatory) or prescribed as LTOT for persistent hypoxaemic respiratory failure.

1.13.1 Evidence for long-term oxygen therapy in IPF and ILD

There are no published prospective, randomised trials which have investigated the impact on survival of long-term oxygen therapy in patients with IPF. One unpublished study quoted by Crockett *et al*. in their Cochrane review has been completed and it demonstrated no difference in survival for ILD patients with or without oxygen (Crockett et al., 2001).

Strom *et al*. published a retrospective survival analysis of 240 Swedish patients with parenchymal lung diseases including patients with pulmonary fibrosis on long-term oxygen therapy (Strom and Boman, 1993). Fifty-one patients with pulmonary fibrosis were followed for an average of 28 months. The mean age of patients was 72-years (SD ±1 year) with a mean FEV_1 of 1.6 litres (SD ± 0.6 litres). The median survival of patients on LTOT was 15 months. Survival was better for patients with a higher FEV_1 (>2.1 litres).

The British Thoracic Society (BTS) guidelines recommend the use of LTOT for IPF when the PaO_2 is below 7.3kPa or PaO_2 between 7.3 and 8kPa with evidence of pulmonary hypertension (Hardinge et al., 2015). This is extrapolated from COPD guidelines based on the NOTT and MRC studies (NOTT, 1980, MRC, 1981). Despite the lack of randomised evidence, there is

indirect evidence that oxygen may be helpful in the form of studies showing a worse prognosis for patients with ILD who have persistent hypoxaemia.

Flaherty *et al*., investigated the prognostic value of physiological measures and the 6MWT in patients with IPF (Flaherty et al., 2006). The authors showed that patients who desaturated to SpO_2 <88% during their initial 6MWT had a median survival of 3.21 years which was significantly lower than those patients who had SpO_2>88% during the initial 6MWT (6.83 years).

Hallstrand *et al*., prospectively followed 28 patients with IPF for ≥4 years to investigate for any association between survival and the results of an initial modified 6MWT (Hallstrand et al., 2005). The results showed that greater desaturation and lower end-exercise saturations during the initial modified 6MWT were both associated with lower survival in IPF patients.

A retrospective analysis of ILD patients with nocturnal desaturation (defined as SpO_2 <90% for >10% of sleep time) by Corte *et al*., showed increased mortality in patients with nocturnal hypoxia than those without nocturnal hypoxia independent of age, gender or BMI (Corte et al., 2012). Kolilekas *et al*., prospectively studies 31 patients with ILD to investigate for any association between sleep indices and mortality. The authors showed that a higher AHI and the lowest SpO_2 recorded during sleep were both linked to lower survival for patients with IPF (Kolilekas et al., 2013).

Although the current evidence for LTOT in patients with ILD is extrapolated from studies in patients with COPD, it is unlikely that there will be future trials of LTOT in patients with ILD. This is because patients with ILD can become profoundly hypoxic and therefore it would become ethically difficult to randomise such patients to placebo and in all likelihood the study maybe unacceptable to patients for the same reason.

1.13.2 Evidence for ambulatory oxygen therapy in patients with IPF and ILD

Ambulatory oxygen is prescribed to relieve exertional breathlessness, reduce exercise induced desaturation and improve walking distance. It is commonly prescribed for many conditions including ILD.

Two non-randomised studies have been published investigating the effect of ambulatory oxygen on patients with ILD. Visca *et al*., published a single centre retrospective analysis of 52 patients who desaturated to SpO_2 <88% during a 6MWT and were offered ambulatory oxygen. The authors showed that with ambulatory oxygen patients walked further (280.0 ± 14.9 meters v

255.1 ± 16.8 meters, $p < 0.001$), had lower Borg scores at the end a 6MWT with oxygen than without oxygen (3.75 [3 – 4.3] *versus* 4.75 [4 – 5], $p < 0.001$) and had a shorter heart rate recovery time (145.5 ± 10.4 seconds *versus* 218.5 ± 19.9 seconds, $p < 0.001$) than at baseline without oxygen. Frank *et al*., published another single centre retrospective analysis of the benefit of oxygen therapy in patients with ILD (Frank et al., 2012). Firstly, the authors optimised the ambulatory oxygen of patients on LTOT and those who required ambulatory oxygen due to oxygen desaturation during a 6MWT. Oxygen therapy was optimised by increasing the flow of oxygen until the SpO_2 was consistently above 90% during a 6MWT. Compared to the baseline 6MWT, optimal oxygen therapy increased the distance walked in patients on ambulatory oxygen only (216.2 ± 115.0 meters *versus* 135.0 ± 108.8 meters, $p < 0.01$) and for patients usually on LTOT and ambulatory oxygen (93.4 ± 66.6 meters *versus* 76.5 ± 66.5 meters, $p = 0.02$).

There have been only three randomised studies of oxygen therapy in patients with ILD. Nishiyama *at al*., randomised 20 patients without resting hypoxaemia who desaturated to <88% during a 6MWT to have a further two 6MWTs on oxygen and air with blinding of the therapy delivered and in a randomised order (Nishiyama et al., 2013). The results showed that there was no difference in the distance walked (oxygen = 400 ± 80 meters, air = 387 ± 80 meters, $p = 0.61$), no difference in the heart rate, no difference in the dyspnoea score immediately, 1 minute or 2 minutes after the 6MWT. Two other studies, both published as abstracts, have investigated the use of ambulatory oxygen in patients with IPF. Arizono and colleagues investigated the effects of oxygen (at 4 litres/minute) versus air during cycle ergometry in 106 patients with ILD in a randomised cross-over study (Arizono et al., 2015). The study showed that oxygen significantly increased exercise endurance time and increased the nadir SpO_2. Troy and colleagues, tested the effects of oxygen versus air during cardiopulmonary exercise tests (CPET) (cycle ergometry) and endurance shuttle walk tests in a double-blind cross-over study (TROY et al., 2014). The study showed a trend towards an increase in exercise capacity for patients on oxygen during both CPET and endurance shuttle walk tests.

The above mentioned studies and others were reviewed in the recently published Cochrane review of ambulatory oxygen therapy in patients with ILD (Sharp et al., 2016). The review concluded that there was insufficient evidence to support or refute the use of ambulatory or short burst oxygen in patients with ILD and recommended further research into this area. The review also noted that two of the three randomised studies identified did not give enough oxygen to prevent exercise induced desaturation. Therefore, an auto-titrating oxygen system which could potentially reduce exertional desaturations better than usual ambulatory oxygen and maybe of benefit in patients with IPF.

1.14 Current guidelines for the prescription of long-term oxygen therapy

The current BTS guidelines for LTOT are heavily based on the results of the MRC and NOTT studies.

Patients are eligible for LTOT if they have stable chronic respiratory failure and:

1) $PaO_2 < 7.3$ kPa
2) $PaO_2 \leq 8$ kPa with evidence of pulmonary hypertension, peripheral oedma or polycythaemia.

Patients should be assessed when stable (no exacerbations or infections in the last 4 weeks) and ideally twice, 3 weeks apart. The PaO_2 should be obtained by means of an arterial blood gas. Once prescribed, the prescription of LTOT should be considered life-long unless prescribed in acute setting in which case its need should be reassessed after a short period of time.

1.15 Mechanism of increased survival of long-term oxygen therapy

The exact mechanisms of how LTOT reduces mortality remain unclear. It is thought this could be a combination of various factors including reduction in pulmonary artery pressure, better oxygenation, improved haemodynamics and improved utilisation of oxygen by tissues during exercise. The original hypothesis and study designs for the MRC and NOTT were based on the results of a previous study which had demonstrated a reduction in pulmonary hypertension when oxygen therapy was utilised for 15 and 18 hours per day but not for 12 hours (Stark et al., 1972). The MRC study demonstrated little change in pulmonary artery pressure between the treated and control group over the follow-up period. In the NOTT, participants had cardiac catheterization at baseline and at 6 months' follow-up only. The results demonstrated a small reduction in the mean pulmonary artery pressure and pulmonary vascular resistance during exercise for patients on nocturnal oxygen and a much greater reduction in both parameters for patients on continuous oxygen therapy. Significantly, the reduction in the mean pulmonary artery pressure in the first 6 months of oxygen therapy was associated with longer subsequent survival (Timms et al., 1985).

1.16 The shortfalls in home long-term oxygen therapy use and its effects

After the NOTT and MRC study were published, LTOT became an integral part of the management of patient with COPD. Patients were prescribed LTOT after an appropriate assessment with the oxygen flow rate assessed at rest. Several studies have subsequently investigated the adequacy of LTOT by measuring oxygen saturations in a domiciliary setting in patients on LTOT. The main aim of these studies was to assess how oxygen saturations changed over different periods of time and with different everyday activities.

Sliwinski *et al*., monitored 34 patients with COPD on LTOT over a period of 24 hours with a patient diary completed concurrently to monitor activities of daily living (Śliwiński et al., 1994). One example of the changes in SpO_2 over 24 hours is shown in Figure 1-5. Every patient was given oxygen at a flow rate of least 2 litres/minute with the aim of increasing PaO_2 above 65mmHg at rest (this is higher than the recommended guidelines). All patients had a satisfactory SpO_2 of 94% at study commencement. The results revealed the mean SpO_2 over 24 hours to be 92% but the minimum SpO_2 was as low as 61%. The results also revealed that despite using LTOT, patients spent a total of 2.2hours/day with SpO_2 <90%. The activities causing greatest desaturation were sleep, naps, watching television and other activities of daily living despite a higher than guideline recommended PaO_2 at baseline.

Morrison *et al*., measured SpO_2 continuously over a period of 24 hours in 20 patients with COPD on LTOT (Morrison et al., 1997). 11 of the 20 patients had a resting PaO_2 >8kPa whilst on their usual LTOT flow rate (in accordance with recommended guidelines) whilst the remainder had a resting PaO_2<8kPa on LTOT. Patients with an adequate PaO_2 at baseline (PaO_2 >8kPa) spent 78% of the time with SpO_2 >90%. Patients with a PaO_2 <8kPa at rest whilst on oxygen spent 69% of the time with SpO_2 <90%.

Plywaczewski *et al*., continuously monitored SpO_2 overnight in 82 patients with COPD on LTOT (Plywaczewski et al., 2000). SpO_2 was measured over two nights; the first on air and the second on the patients' usual oxygen therapy. The results showed that whilst on air the mean SpO_2 was 82.7% and patients spent >90% of the night with SpO_2 <90%. On the second night with the use of their usual oxygen therapy, 52% of the patients remained well oxygenated with a mean SpO_2 94% and spent little time hypoxic (SpO_2 <90% for 7% of the time). The remaining 48% of patients remained hypoxic at night whilst on usual oxygen therapy with a mean SpO_2 of 87% and spending 66% of the time with SpO_2 <90%. The patients who continued to desaturate at night had a lower PaO_2 and a higher $PaCO_2$ during the daytime whilst on their usual LTOT than those patients who did not desaturate.

The evidence from these studies (summarised in Table 1-4), is that despite an adequate resting and mean SpO_2, many patients experience episodes of intermittent hypoxia (IH) and spend significant periods of time with SpO_2 <90%. Patients experience episodes of IH during various activities of daily living including watching television, doing housework, washing up and eating. These episodes of IH may be harmful as they may cause symptoms, affect cerebral blood flow (Higashimoto et al., 2015, Oliveira et al., 2012), cause ischaemic heart disease (Choudhury et al., 2014), arrhythmias (Tirlapur and Mir, 1982) and intermittent increases in pulmonary artery pressure (Selinger et al., 1987).

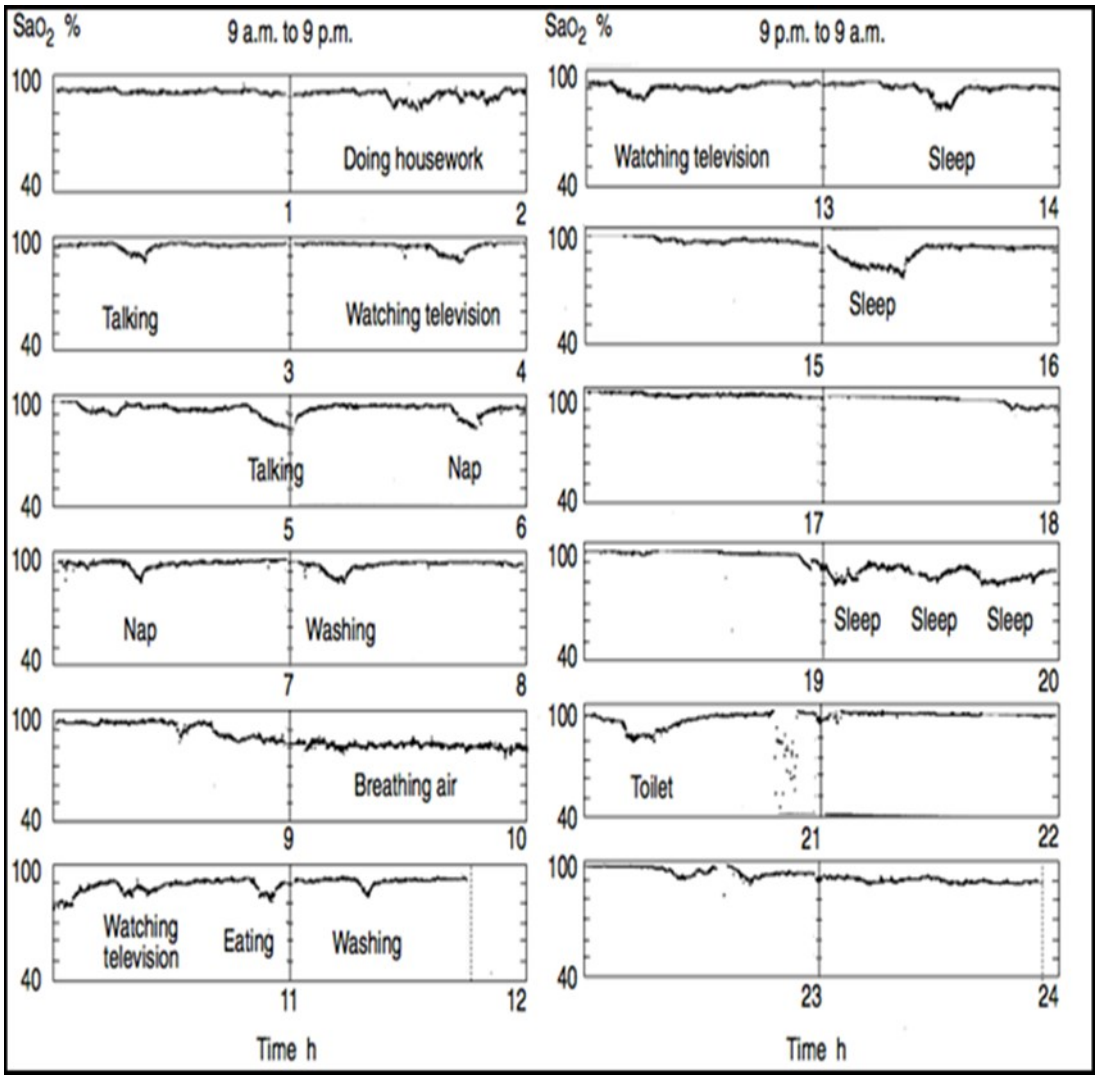


Figure 1-5 Variations in oxygen saturations over 24 hours

The variation in oxygen saturations for one patient over a period of 24 hours. Adapted from (Śliwiński et al., 1994).

Table 1-4 The adequacy of oxygen for patients on LTOT

A summary of the studies in which the SpO_2 of patients with COPD on LTOT was investigated in a domiciliary setting.

1st Author and year	Country	No. of patients	Diurnal or nocturnal study	Study recording period per patient (hours)	Mean SpO_2±SD (%)	Hypoxia index	Result	
Pilling, 1999	USA	27	Diurnal	18	92.0±0.5	% of time spent with SpO_2 <90%	24.6 ± 3.8	
Abdulla, 2000	Denmark	26	Diurnal	24	94±2	Number of hours spent with hypoxaemia*	2.5 hours out of 17 spent	
Sliwinski, 1994	Poland	34	Diurnal	24	92±3.2	% of time spent with SpO_2 <90%	09:00 – 21:00	21:00 – 09:00
							30±26.7	28±27.3
Morrison, 1997	UK	20	Diurnal	24	Not reported	% of time spent with SpO_2 ≤90%	09:00 – 21.00	21:00 – 09:00
							28±30	23±24
Plywaczewski, 2000	Poland	82	Nocturnal	12	90.9±5.0	% of time spent with SpO_2 <90%	35.1±34.7	

*not defined

1.17 Oxygen therapy during sleep

The onset of sleep induces several physiological changes in the respiratory system including reductions in hypoxic and hypercapnic ventilatory responses, increased resistance in both the upper and lower airways, changes in ventilation/perfusion and a reduction in minute ventilation (Sowho et al., 2014). These changes are particularly pronounced during rapid eye movement (REM) sleep. In healthy individuals, these changes lead to mild hypoventilation but the effects are not significant. However, for patients with pre-existing chronic hypoxia such as those with COPD, these changes can lead to significant nocturnal hypoxaemia (McNicholas, 2000).

The flow rate for LTOT is assessed during the daytime with the patient at rest. Oxygen is prescribed at a fixed-flow rate to maintain daytime $PaO_2 \geq 8$kpa or $SpO_2 > 90\%$. In recognition of the increased hypoxia during sleep, participants in the NOTT were advised to increase oxygen flow rates by 1 litres/minute from their baseline as a compensatory mechanism. However, no such recommendation was made for patients in the MRC oxygen study and yet both studies demonstrated increased survival with LTOT. Current clinical practice also reflects the different approaches taken in both studies with some clinicians increasing nocturnal oxygen flow rates 1 - 2 litres/minute, whilst others opt to prescribe the resting daytime oxygen flow rate and some preferring to individualise the flow rate by investigating nocturnal oxygen saturations in individual patients and tailoring oxygen therapy (Wijkstra et al., 2001).

Several studies have demonstrated that some patients despite LTOT continue to experience episodes of intermittent hypoxia at night and spend significant periods of time with $SpO_2 < 90\%$ (Śliwiński et al., 1994, Plywaczewski et al., 2000, Tarrega et al., 2002). The simplest solution would be to increase oxygen flow rates by 1 litres/minute for all patients on LTOT as this was the approach taken by the NOTT. Samolski and colleague investigated this approach in thirty-eight patients with COPD who were on LTOT and had hypercapnic respiratory failure (Samolski et al., 2010). In a randomised cross-over study, patients were evaluated over two nights: on one night, they were given their usual LTOT flow rate during sleep and on the second night they were given flow rates 1 litre/minute greater than their usual LTOT flow rate. The authors showed that although increasing the oxygen flow rate by an additional 1 litre/minute reduced nocturnal hypoxia, this increased nocturnal hypercapnia and caused respiratory acidosis. In the context of nocturnal oxygen therapy in patients on LTOT, an auto-titrating oxygen system which could supply oxygen to maintain a pre-set SpO_2 target could be one solution to reduce nocturnal hypoxia in patients on LTOT without the potential risk of oversupplying oxygen and exposing the patient to hyperoxia and respiratory acidosis.

1.18 The consequences of intermittent hypoxia

Intermittent hypoxia can cause pulmonary hypertension. Selinger *et al*., (Selinger et al., 1987) investigated the acute effects on pulmonary haemodynamics of removing oxygen therapy in 20 patients with COPD who were on LTOT. This study demonstrated that removing oxygen increased pulmonary arterial pressure, reduced the stroke volume index during rest and exercise, and reduced oxygen delivery during rest and exercise.

Oxygen desaturations reduce cerebral oxygenation. Oliveira *et al*., (Oliveira et al., 2012) demonstrated impairment in the change in cerebral oxygenation (as measured by near infrared spectroscopy) in COPD patients who desaturate whilst exercising compared to COPD patients who did not desaturate during exercise. This impairment in cerebral oxygenation was corrected with supplementary oxygen. Higashimoto *et al*., (Higashimoto et al., 2015) demonstrated that cortical oxygenation (as measured by multichannel near-infrared spectroscopy) was impaired in patients with COPD who desaturated on exercise compared to COPD patients did not desaturate and age matched controls. The impairment in cerebral oxygenation was corrected by supplementary oxygen.

COPD is a recognised risk factor for the development of ischaemic heart disease and its related complications. The potential mechanisms for this could be systemic inflammation, lung inflammation, vascular dysfunction, polycythaemia and hypoxia which, may either be sustained or intermittent. Hypoxia can induce atherosclerosis through oxidative stress, haemodynamic stress, activation of the sympathetic nervous system and through systematic inflammation (Choudhury et al., 2014).

Intermittent and persistent hypoxia can cause arrhythmias and ECG changes. Tirlapur and Mir demonstrated that sleep leads to worsening of hypoxaemia in patients with COPD and that this associated with multiple atrial and ventricular premature contractions, a higher heart rate and ST-T wave changes which were all abolished with oxygen therapy and higher SpO_2 levels (Tirlapur and Mir, 1982).

1.19 The consequences of hyperoxia in patients with COPD

One simple way of overcoming intermittent and persistent hypoxia is by increasing the LTOT flow rate by 1 or 2 litres/minute. However, the difficulty with this approach is that it could lead to hyperoxia at rest with its detrimental effect of hypercapnia.

The problem of hyperoxia causing hypercapnia for patients with COPD has been known for a number of years. Westlake *et al*., (Westlake et al., 1955) described 14 cases of hypercapnia worsening as a result of oxygen administration to patients presenting with acute exacerbations of underlying chronic bronchitis and emphysema. In some of the patients there was a clear worsening of $PaCO_2$ with the administration of oxygen and subsequent improvement with its withdrawal in terms of both $PaCO_2$ and clinical condition. Lopez-Majano *et al*., (Lopez-Majano and Dutton, 1973) assessed the change in $PaCO_2$ in stable COPD patients after administering 100% oxygen for 20 minutes. They showed a significant rise in $PaCO_2$ in the first five minutes in all groups with a more significant effect in those patients with an initial $PaCO_2$ >60mmHg. Plant *et al*., (Plant et al., 2000) observed that 20% of COPD patients admitted to accident and emergency (A&E) with type two respiratory failure had their pH normalised with controlled oxygen therapy. The implication being these patients had received high flow supplementary oxygen (most likely in a pre-hospital setting) which provoked hypercapnia which subsequently resolved with controlled oxygen therapy. On the basis of this, the British Thoracic Society recommends that all patients who are at risk of hypercapnic respiratory failure and who require oxygen, should be given the lowest oxygen flow rate with the aim of maintain a target SpO_2 of 88-92% (O'Driscoll et al., 2008). This target has been set as a compromise to prevent hypercapnia from hyperoxia and to prevent the detrimental effects of hypoxia particularly on the cardiovascular and neurological systems.

The SpO_2 target range of 88-92% was tested in a randomised trial in 2010 (Austin et al., 2010). Austin *et al*., randomised patients with an exacerbation of COPD to either high flow oxygen (8-10 litres/minute via non-rebreathe mask) or controlled oxygen therapy (via nasal prongs aiming to maintain SpO_2 88-92%) in a prehospital setting. Adjusting oxygen flow rate to maintain a target SpO_2 led to a 78% reduction in mortality for patients with an acute exacerbation of COPD.

Increasing LTOT by 1 litre/min could also have a detrimental effect on nocturnal hypercapnia. Samolski *et al*., (Samolski et al., 2010) demonstrated that increasing the LTOT flow rate by 1 litre/min in patients with COPD who are on LTOT with nocturnal hypoxia increased the mean nocturnal SpO_2, reduced the percentage of time spent with SpO_2 <90% but also increased the $PaCO_2$ and reduce the pH.

In summary, patients with COPD on LTOT experience episodes of intermittent hypoxia which may be harmful. Therefore, the delivery of LTOT needs to optimised to reduce or prevent potential harm. LTOT is currently prescribed at a fixed-flow rate which is determined with the patients at rest aiming to maintain a resting PO_2 >60mm Hg. Simply increasing the flow rate by 1 or 2 litres/min may lead to hyperoxia which may be harmful. The concept of titrating oxygen therapy to maintain a particular SpO_2 target or SpO_2 target range has worked very well in

patients with acute hypercapnic respiratory failure. The same concept should be applied to optimisation on LTOT – oxygen therapy should be delivered to maintain a constant SpO_2 rather than prescribed at a fixed-flow level. One method of achieving this aim is to deliver oxygen using an auto-titrating oxygen system. These systems work as a closed-loop system, by constantly monitoring the oxygen saturations of a patient and automatically changing the flow rate to match a pre-programmed target SpO_2. Auto-titrating oxygen systems have been reported most commonly in paediatric medicine where they are used to tightly control oxygen saturations in premature babies. They have also been utilised in ventilated adults, tested in healthy individuals and in self-ventilating patients with COPD.

1.20 Auto-titrating oxygen systems

Auto-titrating oxygen systems are closed loop systems which are designed to maintain constant pre-defined oxygen saturations in the face of continually changing patient factors. As with all closed loop systems, there is a sensor to detect oxygen saturations (a pulse oximeter in the modern era), a control unit which process the oxygen saturation signal and an effector which adjusts oxygen flow rates. Auto-titrating oxygen systems were first utilised in preterm neonates and thereafter, they have been used in ventilated and self-ventilating adult patients.

1.20.1 Auto-titrating oxygen system in paediatrics

In paediatrics, preterm neonates are at high risk from the effects of both hypoxia and hyperoxia. Hypoxia can lead to significant brain injury, damage to the pulmonary vasculature and death (Bolton and Cross, 1974, Skinner et al., 1999, Support Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al., 2010). Hyperoxia can lead to an increased risk of developing retinopathy of prematurity, bronchopulmonary dysplasia and cerebral palsy (Jobe and Bancalari, 2001, Davis, 2002, Saugstad, 1997, Collins et al., 2001). The first report of an auto-titrating system for use in pre-term neonates was in 1979 (Beddis et al., 1979). Since then further studies have been published looking at the control of oxygen levels in pre-term neonates (Dugdale et al., 1988, Bhutani et al., 1992, Morozoff and Smyth, 2009, Morozoff and Evans, 1992, Morozoff et al., 1993, Claure et al., 2001, Claure et al., 2009, Claure et al., 2011, Urschitz et al., 2004, Hallenberger et al., 2014). The primary end-point of all the studies has been the percentage of time spent within a predefined SpO_2 or PaO_2 range. Overall, most of the studies have demonstrated that auto-titrating oxygen systems are better at maintaining oxygen levels at pre-defined levels than usual oxygen therapy or manual control (Table 1-5).

Table 1-5 Summary table of auto-titrating oxygen studies in children

First author	Year	Location	Gestational age range (weeks)	Birth weight (grams)	N	Input	Target PO_2/SpO_2	Testing time period- each mode	Ventilation mode	Results - % of time spent in the target range				Result - % of time spent above the target range				Result - % of time spent below the target range			
										Manuel			AUTO	Manuel			AUTO	Manuel			AUTO
Beddis	1979	London, UK	26 – 34 (mean 31.3)	760 – 2260 (mean 1640)	12	PO_2	7.3 – 10.7kPa	18 – 76.5 hours	Headbox/ Face mask/ CPAP/IPPV	72.4			87.8	9.3			4.7	18.3			7.5
Dugdale	1988	Leeds, UK	27 – 35 (mean 31.8)	1100 – 2500 (mean 1940)	7	PO_2	10 kPa target (range for results 9-11)	48 hours	Headbox	45.2			74.9	13			11.3	41.8			13.9
Bhutani	1992	Pennsylvania - USA	25-27 (mean 25)	860	14	SpO_2	95% target (results 94 – 96%)	40 minutes	Hood	Set	Physician		81	ND			ND	ND			ND
										54	70										
Morozoff	1992	Vancouver, Canada	26 – 30 (mean 27.3)	810 – 2025 (mean - 1170)	6	SpO_2	92%	3hours	IPPV	ND			ND	ND			ND	ND			ND
Morozoff	1993	Vancouver, Canada	26-31 (mean 27.8)	800-2470 (mean 1671)	8	SpO_2	92% for automatic. Results 90-95% range	3hours	IPPV	39			50	39			23	22			27
Claure	2001	Miami, USA	25±1.6 (mean ±SD)	714±142 (mean±SD)	14	SpO_2	88 – 96%	2 hours	IPPV	66.3			74.9	13.2			10.2	15.0			16.1
Urschitz	2004	Tuebingen, Germany	24 – 33 (mean 25.5)	600 – 2490 (mean 800)	12	SpO_2	87 – 96%	90 minutes	Nasal CPAP	Routine	Optimal		90.5	Routine	Optimal		1.3*	Routine	Optimal		3.2*
										81.7	91.0			5.0*	1.8*			6.7*	4.0*		
Morozoff	2009	Vancouver, Canada	25 – 31 (mean 28)	885-1500 (mean 1227)	7	SpO_2	90-96%	18-42hours	IPPV	57			X	Y	Z		ND	ND			ND
													71	71	73						
Claure	2009	Miami, USA	23.5 – 26.3 (mean 24.9)	534 – 822 (mean 678)	16	SpO_2	88 – 95%	4 hours	IPPV	42			58	31			9	27			33
Claure	2011	Miami, USA	Mean 25	Mean 622	32	SpO_2	87 – 93%	24 hours	IPPV	32			40	37			21	23			32
Hallenberg	2014	Mainz, Germany	Mean 26.4 (range 23.0 – 35.3)	Median 840 (range 410 – 2460)	34	SpO_2	Variable between centres	24 hours	IPPV, CPAP	61**			72.1**	16**			15.9**	15**			9.1**

AUTO – automated SpO_2 – Oxygen saturation PO_2 – Partial pressure of oxygen CPAP – continuous positive airway pressure

IPPV – intermittent positive pressure ventilation UK – United Kingdom USA – United States of America ND – no data

*- calculated from given data ** - median percentage values X = State machine controller Y=Proportional integral derivative (PID) controller Z=Adaptive model controller

1.20.2 Auto-titrating oxygen system in intubated adult patients

Auto-titrating ventilation systems have been utilised in patients who are fully intubated and ventilated (Anderson and East, 2002, Johannigman et al., 2009, Arnal et al., 2012, Lellouche et al., 2013a, Saihi et al., 2014).

Anderson and East described the use of an auto-titrating oxygen system in two patients with adult respiratory distress syndrome (ARDS) over a period of 184 hours (Anderson and East, 2002). The system was designed to adjust FiO_2 and positive end-expiratory pressure (PEEP) and the input signal was direct PaO_2 measurements from an arterial catheter. Their data demonstrated that the auto-titrating oxygen system changed FiO_2 and PEEP appropriately in response to desaturations.

Johannigman *et al*., testing an auto-titrating oxygen system in fifteen military trauma patients requiring intubation and ventilation (Johannigman et al., 2009). They demonstrated that autonomous control of oxygenation maintained oxygen saturation in the desired oxygen saturation range of 92-96% for 83±21% of the time versus 33±36% for clinician control. They also demonstrated a 44% reduction in oxygen utilisation.

Arnal *et al*., described the utilisation of fully closed ventilator (IntelliVent-ASV) in 50 intubated and ventilated patients (Arnal et al., 2012). They demonstrated that the IntelliVent-ASV system was safe and able to ventilate patients with less pressure, less oxygen, lower tidal volumes whilst producing the same results for oxygenation and CO_2.

Lellouche *et al*., conducted a randomised controlled trial comparing protocolised ventilation against automated ventilation in 60 patients immediately post cardiac surgery (Lellouche et al., 2013a). They demonstrated that the automated ventilation system increased the percentage of time spent within a pre-defined optimal ventilation zone from 12% to 89.5%. The automated system also reduced the percentage of time spent with unacceptable ventilation from 7% to 0.5%.

From the above described studies, it can be appreciated that the potential advantages of automated systems in ventilated patients are reductions in:

- oxygen use without loss of clinical benefit
- staff numbers
- time spent with inappropriately high or low oxygen saturations

1.20.3 Auto-titrating oxygen system in self-ventilating adults

Three studies had been published investigating automatic control of oxygen in self-ventilating patients before I started my research in October 2013. A further two publications and two important abstracts have been published during my research period and these studies are summarised in Table 1-6.

Lellouche and L'Her (Lellouche and L'Her, 2012a) have published the only paper in which an auto-titrating oxygen system ($FreeO_2$) has been tested to control SpO_2 in healthy adult subjects with induced hypoxia. Hypoxia was induced in 10 healthy volunteers with the use of an air/nitrogen mixture. Each subject underwent three hypoxic challenge tests (one on air, one with supplemental oxygen at a fixed rate of 1.5L/min and one with an auto-titrating system). The target SpO_2 of 92–96% was achieved for a median of 26% and 36.8% with air and constant oxygen flow respectively. The $FreeO_2$ system increased the median time within the target SpO_2 range to 66.5%. There was also a reduction in the heart rate for patients on automated oxygen compared to fixed flow and air.

Cirio and Nava (Cirio and Nava, 2011) tested an auto-titrating system in patients with COPD on LTOT whilst patients were undergoing a cycling exercise tests. One test was conducted by a respiratory therapist titrating oxygen during exercise to keep SpO_2 at 94% and the second test was conducted with an auto-titrating oxygen system programmed to keep the SpO_2 at 94%. The use of the auto-titrating system resulted in a significantly higher SpO_2 during exercise (95±2% vs 93±3% P=0.04) and less time spent below the target SpO_2.

Rice et al., (Rice et al., 2011) tested the ability of a portable, closed-loop oxygen delivery system ($AccuO_2$) to keep SpO_2 ≥90% in patients with COPD on LTOT for 8 hours a day for 2 consecutive days. This system was compared to a continuous oxygen flow device and a standard conserving device which were also tested for 8 hours a day for 2 consecutive days. The target SpO_2 set for the $AccuO_2$ system was 90%. The results showed that the mean SpO_2 was somewhat unsurprisingly higher with the continuous flow and the standard conserving device as compared to $AccuO_2$. $AccuO_2$ reduced the amount of time spent with SpO_2 <90% but this difference was not statistically different. However, with the $AccuO_2$, there was reduced variability of SpO_2 and less oxygen consumption than with the other two devices. This study also measured activity in the form of actigraphy but found no difference between the three systems.

Recently two articles and two abstracts have been published on another auto-titrating oxygen system, the Free O_2 system. Lellouche and colleagues reported feasibility of the use of the Free

O_2 system in patients admitted with exacerbation of COPD in the setting of a hospital ward (Lellouche et al., 2016a). The study showed that the Free O_2 system significantly reduced hypoxia, hyerpoxia, and maintained SpO_2 within a target SpO_2 range for greater periods of time than fixed-flow oxygen and the system was deemed appropriate for oxygen administration by both nurses and doctors. Lellouche and colleagues tested the FreeO_2 system against air and fixed-flow oxygen in patients with COPD who had oxygen induced exercise desaturation during endurance shuttle walk tests (ESWT) (Lellouche et al., 2016b). The study showed that the FreeO_2 system significantly reduced the percentage of time spent with SpO_2 <88% compared to air and fixed-flow oxygen. There were no differences in the distance walked or the end of test Borg scores between the Free O_2 system and fixed-flow oxygen.

L'Her and colleagues reported the use of the FreeO_2 system in patients with acute respiratory failure attending the A&E department (L'Her et al., 2015). The study showed that the FreeO_2 system increased the percentage of time spent with SpO_2 in the optimal range for patients with type 1 and type 2 respiratory failure. Vivodtzed and colleagues reported the use of the FreeO_2 system in patients with hypercapnic respiratory and COPD who were on LTOT during an ESWT (Vivodtzev et al., 2016). The FreeO_2 system significantly increased end of test SpO_2 compared to fixed-flow oxygen. There was no significant increase in walking distance. Additionally, higher oxygen flow rates during the ESWT on the FreeO_2 system were not associated with any increase in transcutaneous carbon dioxide.

Taken together, the above studies demonstrate that auto-titrating oxygen systems increase the percentage of time spent with oxygen saturations in the optimal SpO_2 range, reduce intermittent hypoxia and reduce the percentage of time spent with high oxygen saturations. The primary end-point for these studies was the percentage of time spent within a specified SpO_2 range to demonstrate that the systems are functional and that this is an achievable target.

Table 1-6 Summary table of auto-titrating studies in self-ventilating adults

First author	Year	Country	Type of subjects	Age of patients Mean±SD	N	Input	Target SpO_2	Testing time period- each mode	Results - % of time spent in the target range			Result - % of time spent above the target range			Result - % of time spent below the target range		
									Manuel		AUTO	Manuel		AUTO	Manuel		AUTO
Cirio	2011	Italy	COPD on LTOT	68±8	18	SpO_2	94%	15min cycle test	ND		ND	ND		ND	38±24		19±20
Rice	2011	USA	COPD on LTOT	72.3	22	SpO_2	90% (<88%is below target)	2 consecutive days at home	ND		ND	Constant flow	O_2 conserver	10	Constant flow	O_2 conserver	10
												39	41		15	19	
Lellouche	2012	Canada	Health volunteers	25±5.5	10	SpO_2	92-96%	3 hypoxic challenges	Air	Constant flow	66.5	Air	Constant flow	14.5	Air	Constant flow	0.4
									26	36.8		4.1	39.1		33.7	12.7	
Lellouche	2016	Canada	COPD – acute exacerbation	71±8*	25	SpO_2	90±2%	4.0±2.1days*	51.3±19.7		81.2±15.9	10.4±10.3		1.5±1.9	2.3±2.7		0.2±0.2
				73±8**	25			5.8±9.9days**									
L'Her+	2015	Canada	Acute respiratory failure	75±13*	93	SpO_2	Type 1 RF: 92-96% Type II RF: 88-92%	3 hours	51±30		81±21	~20%		~7	5.5±19.3		1.9±6.3
				77±12**	94												
Lellouche	2016	Canada	COPD	69±9	16	SpO_2	94%	ESWT	43.9±34.3		60.3±26.7	Not reported		Not reported	23.9±32.7		0.6±1.1
Vivodtzev#	2016	France	COPD on LTOT	69±9	8	SpO_2	94%	ESWT	Not reported		Not reported	Not reported		Not reported	Not reported		Not reported

** Control * $FreeO_2$ +=Abstract ERS 2015 # = Abstract ERS 2016 ESWT = endurance shuttle walk test

1.21 Auto-titrating oxygen system at the Royal Brompton Hospital

The intelligent oxygen therapy system (iO_2Ts) is an auto-titrating oxygen system which was initially developed between 2004 and 2007 from collaborative work between the Royal Brompton Hospital NHS Foundation Trust (Professor Anita Simonds) and the Bioengineering department at Imperial College London (Dr Gabriel Iobbi and Dr Robert Dickinson). The iO_2Ts is based on a proportional-integral-derivative (PID) controller and is designed to maintain constant oxygen saturations in the face of continually changing patient requirements.

The components of the 2005 system included a laptop computer as the control unit, a stationary oxygen supply, a flow regulator and a pulse oximeter (Figure 1-6). Given the large size of the equipment, the system was not ambulatory. In 2014, the system was completely redesigned and developed into an ambulatory smartphone system (see chapter 2 for details of the development of the smartphone iO_2Ts).

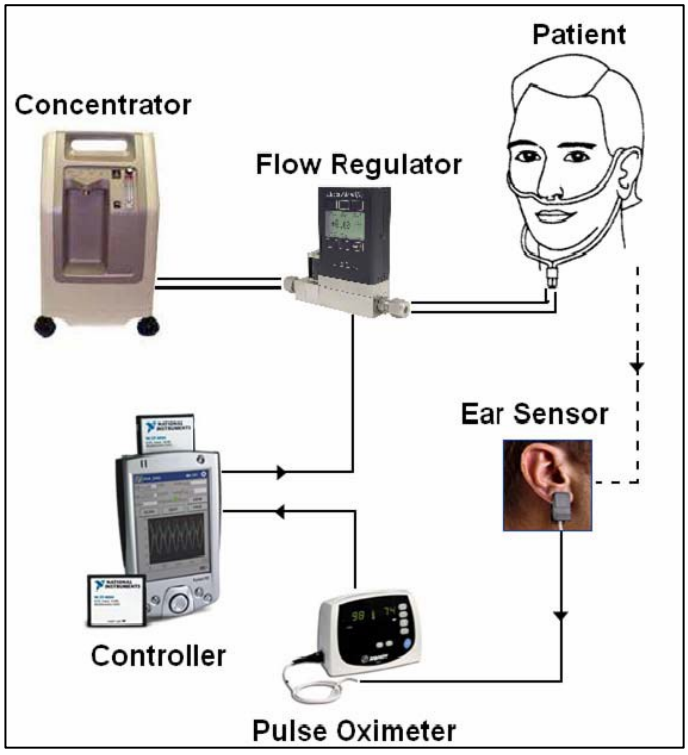


Figure 1-6 The components of the intelligent oxygen therapy system in 2005

The system was first tested in a computer simulation on Simulink™ in 2005. It was designed to maintain a target SpO_2 of 91% by artificially simulating hypoxic events and using real life data from pulse oximetry of patients with COPD undergoing nocturnal oximetry to look for nocturnal hypoxia. In the simulation setting, the system reduced the amount of time spent below the set threshold by 76% (Iobbi et al., 2007).

Following the success of the simulation, a small proof of principle study was conducted on seven patients with chronic respiratory failure on LTOT (five with COPD and two with interstitial lung disease [ILD]). Each patient undertook a 6-minute walk test (6MWT) with their standard oxygen therapy and the iO_2Ts in a random order. The results showed that the iO_2Ts reduced the percentage of time spent with $SpO_2 < 90\%$ from 45.6 ± 32.1% to 20.2 ± 22.9% (mean difference 25.4 ± 17.9%), $p = 0.018$ (t-test) (Iobbi, 2007). An analysis of the volume of oxygen delivered revealed less oxygen delivery by the iO_2Ts compared to fixed-flow oxygen which could result in cost savings as well as better clinical outcome (Iobbi, 2007).

The system was also tested in six patients with COPD during an incremental shuttle walk test. The iO_2Ts reduced the percentage of time spent with SpO_2 <90% by 17±13% ($p<0.05$) compared to fixed-flow oxygen (Iobbi MG, 2007). Additionally, the iO_2Ts improved the recovery time to baseline SpO_2 by 39±17% ($p<0.01$) and decreased the trough SpO_2 from 77.5±7.6% to 83.8±2.8% ($p<0.05$). There were no changes in the total distance walked or the end of test Borg score.

1.22 Aims of the thesis

At the start of my research in October 2013, no studies had yet been published which had tested auto-titrating oxygen systems in patients with COPD during any field walking tests (other than the iO_2Ts in a small pilot study). There were also no studies investigating the use of auto-titrating systems in patients with diseases other than COPD. There were also no studies which had investigated the effects of auto-titrating oxygen systems on $PaCO_2$ in patients with hypercapnic respiratory failure on LTOT during sleep.

Therefore, the overall aims of this research were to:

- Develop an auto-titrating oxygen system which could be utilised for the delivery of both LTOT and ambulatory oxygen
- Investigate the ability of the iO_2Ts to maintain a constant SpO_2 over a range of activities (including field walking tests) in patients with COPD and interstitial lung disease who are on oxygen therapy
- Assess the utility of the iO_2Ts as an oxygen assessment tool for ambulatory oxygen and during activities of daily living
- Investigate the effects of maintaining a constant SpO_2 on transcutaneous carbon dioxide during sleep in patients with hypercapnic respiratory failure who are on LTOT

2 Chapter 2 – The development of the intelligent oxygen therapy system

2.1 The development of the intelligent oxygen therapy system

The intelligent oxygen therapy system (iO_2Ts) was first developed between 2005 and 2008 as a collaboration between the Bioengineering department at Imperial College London (Dr Gabriel Iobbi and Dr Robert Dickinson) and the department of Sleep and Ventilation at the Royal Brompton Hospital (Professor Anita Simonds). It is an auto-titrating oxygen system designed to maintain constant oxygen saturations (SpO_2) in response to constantly changing patient requirements. The initial system was laptop based, consisted of an oxygen concentrator to deliver oxygen and a pulse oximeter. There were physical links between all the components and therefore the system was not portable (chapter 1, Figure 1-6). Consequently, the initial studies were conducted over a short test distance of 10 meters and the original system could not be used for domiciliary oxygen delivery due to its immobility.

At the outset of my research, the vision we had for the iO_2Ts was one in which the system could be utilised to: 1) optimise home LTOT, 2) optimise ambulatory oxygen 3) act as assessment tool for ambulatory oxygen. For all of these situations, the system needed to be portable and user friendly.

The first part of my research involved the development of a fully portable and user-friendly iO_2Ts, which could be utilised for both ambulatory and home oxygen. This task was undertaken together with the Bioengineering department at Imperial College London (Mr Rishi Goburdhen and Dr Robert Dickinson). My roles were:

- To identify the functional requirements for the mobile system which could be utilised in the home and for ambulatory oxygen (functional specification)
- To identify the safety aspects of utilising the device in different environments (in hospital and home use)
- To design a user-friendly app interface
- To validate the device prior to patient utilisation

2.1.1 Functional specification

The full functional specification is given in appendix 1. The most important functions which were desirable in the portable iO_2Ts and their rationale are outlined in Table 2-1.

Table 2-1 The important functional specifications of the iO_2Ts and their rationale

Function	Rationale
The control unit must be based on a smartphone or Arduino	The control unit must be portable and a smartphone or Arduino (an open-source low cost microcontroller) are the best methods of achieving this aim.
The system must accept a dual oxygen supply	It must be compatible with an oxygen concentrator to allow domiciliary LTOT delivery and oxygen cylinders for ambulatory oxygen.
There must be no physical link from the patient to system	The patients must be able to walk freely and conduct any daily activities
The system must deliver both fixed-flow oxygen and variable flow oxygen (intelligent oxygen therapy)	This allows blinded studies to be conducted as either mode of oxygen will be delivered from the system. It also acts as a safety mechanism so that fixed-flow oxygen can be delivered in case of system failure.
The system must contain security measures	To stop unwanted or unintended changes to settings
The system must record SpO_2 and heart rate continuously	Data for each experiment with any individual must be saved in individually created accounts and this allows data analysis.
The system must have a telemetry capability	This allows real time data to be observed without being at the patients' bedside and accessing the control centre. For example, the data can been be observed from a nurses station as is currently available with ECG monitoring.

2.2 The portable intelligent oxygen therapy system (iO_2Ts)

The iO_2Ts developed from the initial functional specification is a portable, lightweight and can be used to deliver oxygen for LTOT and ambulatory oxygen, see Figure 2-1. The system we devised consists of the following commercially available components:

1) A smartphone: Samsung Galaxy S3 (Samsung, Seoul, South Korea). 136.5mm X 70.6mm X 8.6 mm, weight 133 grams, 4.69 ounces

2) A mass flow controller, MC-5SLPM-O/5M (Alicat Scientific, Tuscon, USA). 10.3cm X9.5cm X 2.7cm, weight 544 grams, 1.2 lbs

3) A portable battery, Anker Astro Pro 2 (Anker Technology Company Limited, California, USA). 124mm X 284mm X 15mm, weight 544 grams, 1.2 pounds (lbs)

4) A pulse oximeter, Nonin 4100 Bluetooth® Enabled Digital Pulse Oximeter with ear lobe attachment (Nonin® Medical, Minnesota, USA)

All the above components are controlled by a complex algorithm in form of an app on the smartphone. The total weight of the iO_2Ts is 1.2 kilograms or 2.6 lbs.

An android based smartphone (Samsung Galaxy S3, Gt 19300) was chosen as the control centre for the portable iO_2Ts. This was because it contains both the basic software to allow easy programming to enable creation of an application (app) and Bluetooth technology to allow wireless communication with other devices. Both of these properties are crucial for the iO_2Ts to be portable. Another advantage of an android phone is that it can be connected to the internet (either through Wi-Fi or Sim card) and this allows encrypted data transfer for tele-monitoring from patients' homes. An android system was chosen as these systems in 2013 were, and still are, the most commonly utilised smartphones worldwide (compared to the iPhone). When fully charged, the Galaxy S3 can provide power for the iO_2Ts for approximately 12 hours.

We used a Nonin-4100 wireless Bluetooth pulse oximeter for monitoring of SpO_2 and heart rate. This is powered by 2 AA-sized batteries and can provide continuous power for up to 120 hours.

We used an Alicat mass flow controller to control oxygen output. These flow meters provide very accurate output of air and gases. The Alicat flow meter is powered by an external portable battery (Anker). When fully charged, the external battery can provide power for the Alicat flow meter for up to 56 hours.

The system can receive oxygen from an oxygen cylinder or an oxygen concentrator. We have not tested the system with liquid oxygen. Additionally, as the system continually changes oxygen flow rates, it is not suitable to be utilised with conserving devices. If the oxygen supply is from a cylinder, the connection from the cylinder and the connection to the Alicat flow meter must both be securely fastened to prevent disconnection of the oxygen tubing resulting from high pressure. When used with an oxygen cylinder, the system can be placed conveniently inside an ambulatory oxygen bag or trolley as shown in Figure 2-2. This is the system which was used for studies described in chapters 4, 5 and 7.

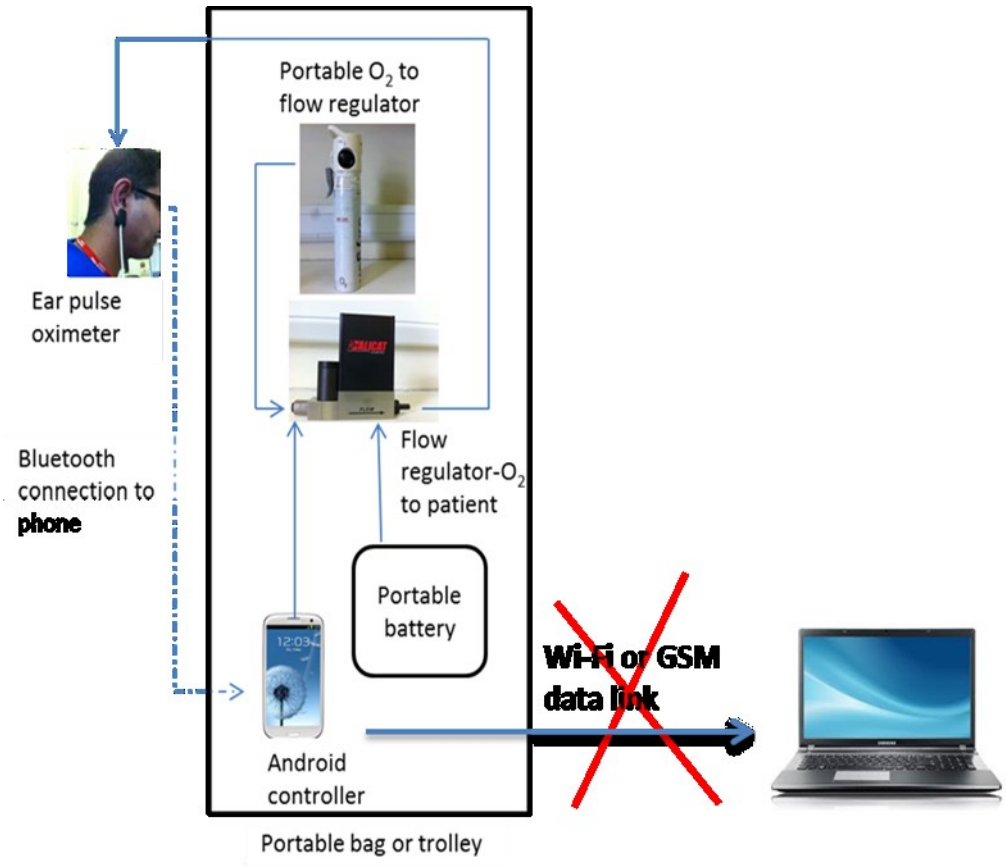


Figure 2-1 The intelligent oxygen therapy system
The system consists of various commercially available components are working together and controlled by an application on a smartphone. Unfortunately, telemetry capability could not be added to the system.

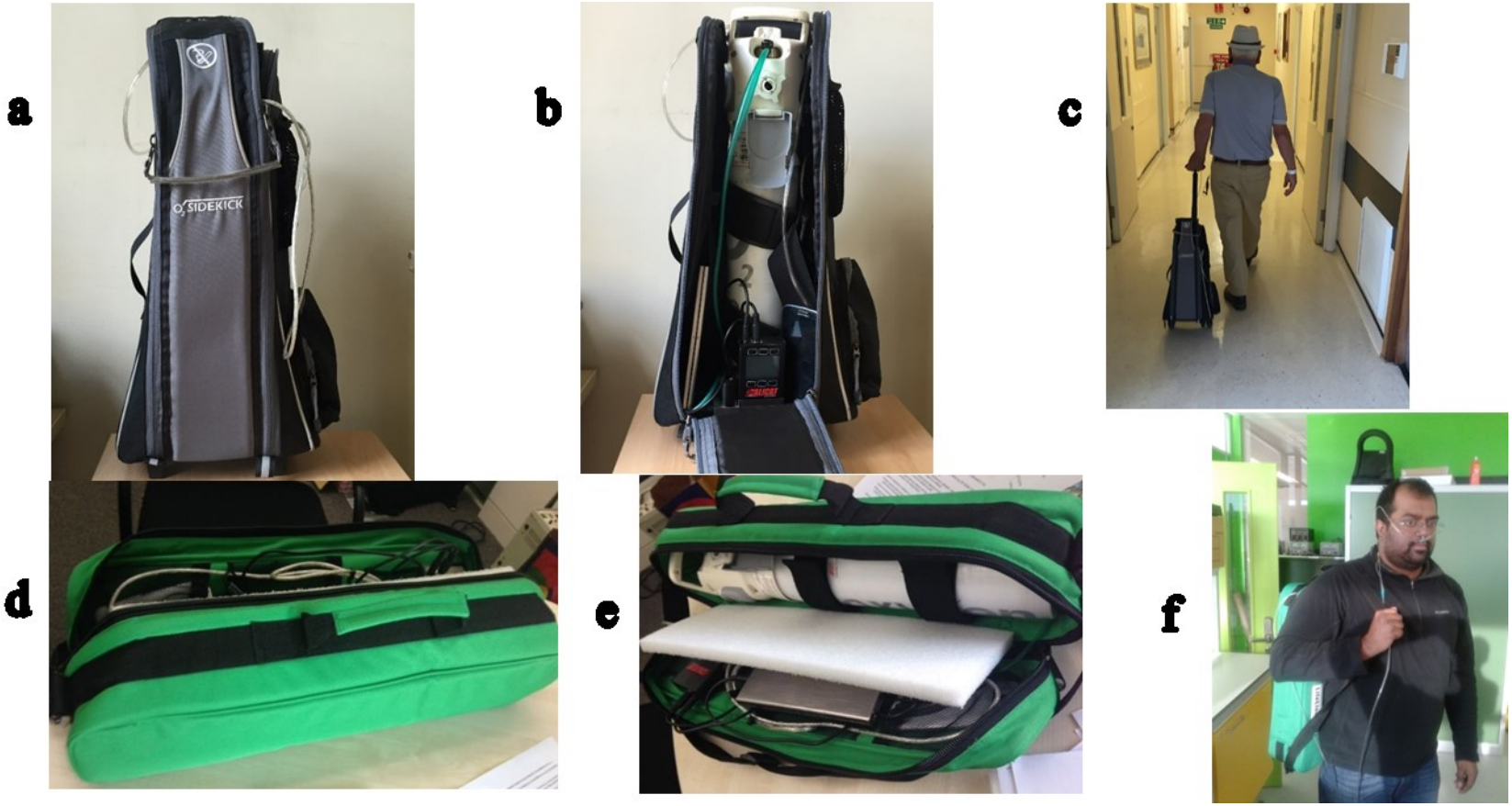


Figure 2-2 Portability of the intelligent oxygen therapy system
The iO_2Ts can be placed alongside oxygen, inside an ambulatory oxygen trolley (figures a, b and c) or an ambulatory oxygen shoulder bag (figures d, e and f).

2.3 Functionality of the iO_2Ts application

The iO_2Ts app resides on the home screen of the Samsung Galaxy S3 smartphone (1st screenshot Figure 2-3). The app can be activated in one of two ways: by touching the application on the home screen or by inserting a micro-USB cable which relays signals to the Alicat mass flow controller. The process of activating the iO_2Ts app and the steps to take to deliver oxygen are outlined in Figure 2-3.

The first screen which appears on the app allows the user to determine which type of oxygen flow to administer to the patient and this is step 1(fixed-flow oxygen or variable flow oxygen). Steps 2 and 3 are identical for both oxygen delivery types and require the entry of a unique experiment ID and the entry of a password. This allows only the researcher (me) to programme to system.

2.3.1 Delivering fixed-flow oxygen

To deliver oxygen at a fixed-flow rate, the next step is to enter the desired flow rate (between 0.0 to 5.0 litres per minute), step 4a. The maximum output of the mass flow controller meter we are using in the iO_2Ts is 5 litres per minute. This allows the use of a small flow meter to reduce the overall weight of the system. A bigger flow meter could be used; however, this would come at the cost of greater weight and may well become unattractive as an ambulatory oxygen option.

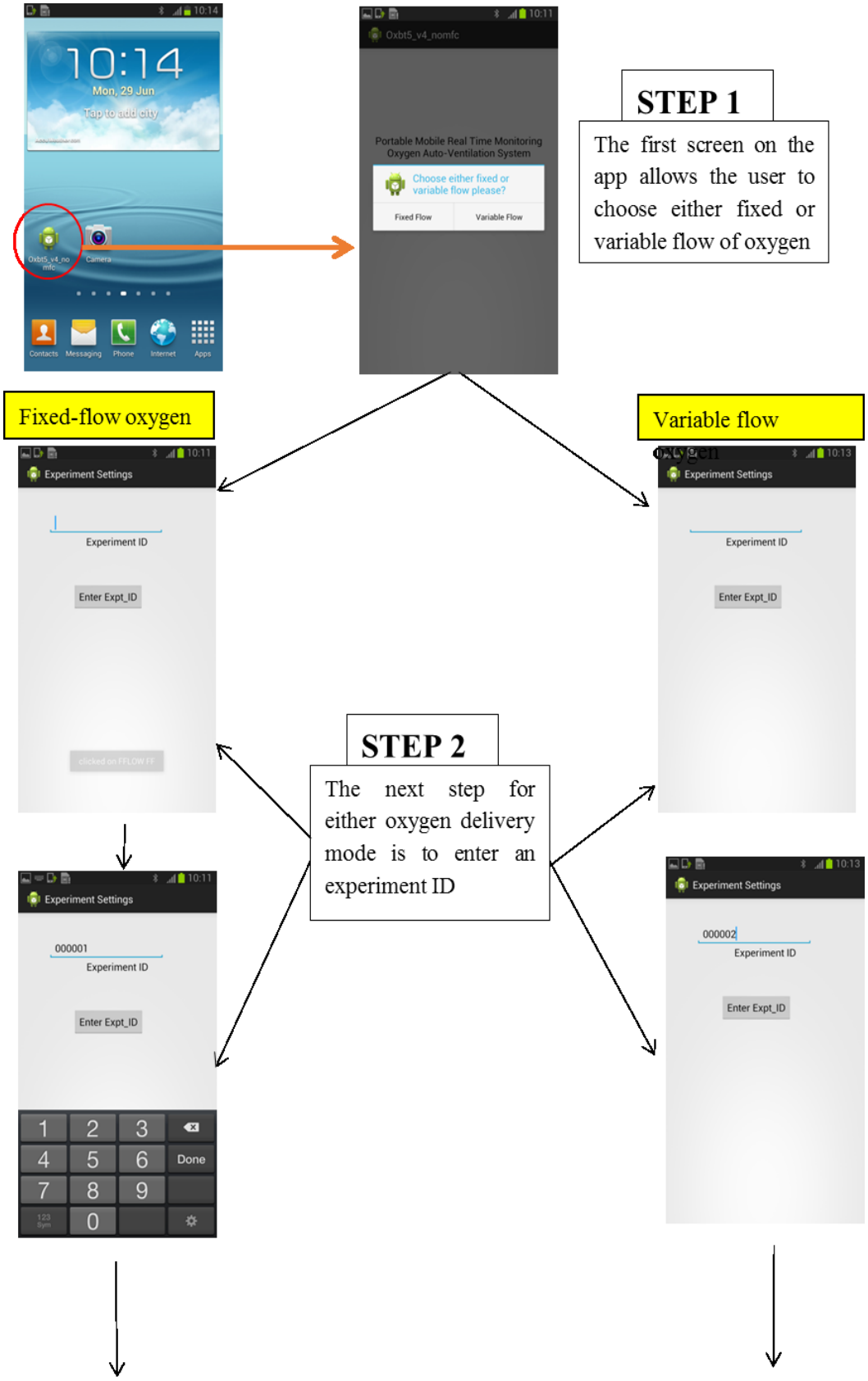
Once the required flow rate has been entered, the next screen allows the user to connect wirelessly to the pulse oximeter, step 5. As soon a valid SpO_2 and heart rate are displayed, the user can then press the 'Launch application" button to begin the delivery of fixed flow oxygen (remembering of course to ensure that all the remaining equipment is appropriately connected and the oxygen supply is turned on). The system starts to record SpO_2 and heart rate data once the "Launch application" button is activated. The experiment stops when the user presses the "Close application" button.

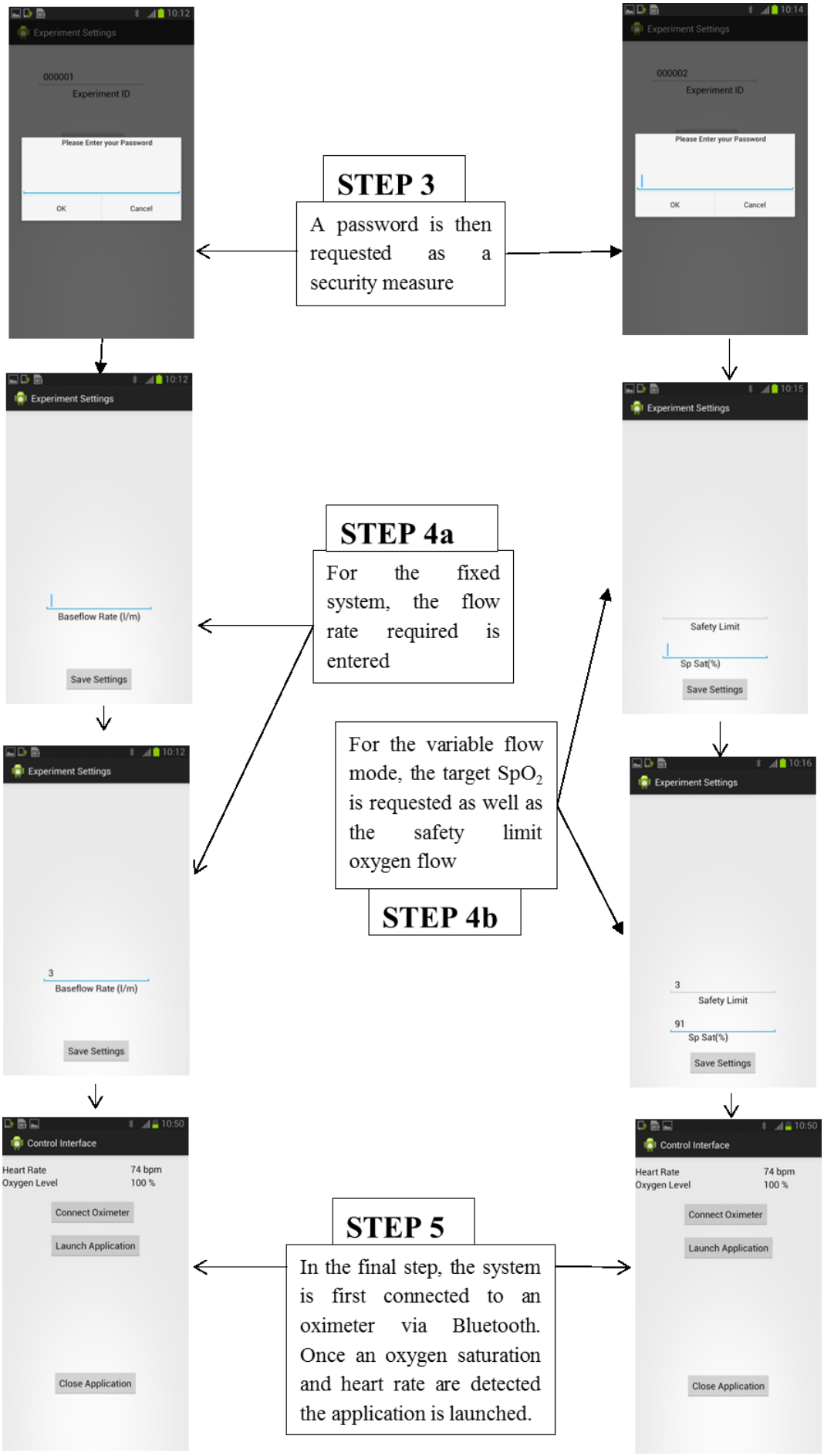
2.3.2 Delivering auto-titrating oxygen

To deliver auto-titrating oxygen/variable flow oxygen, the user chooses this option after activation of the app. The next few steps of entering the experiment ID and passwords are the same as for fixed-flow oxygen. At the next screen, step 4b, the user must enter the SpO_2 target for the individual patient for that individual experiment. The chosen SpO_2 can be any numerical value and this allows individualisation of oxygen therapy for every patient. A baseline flow rate, which acts as a back-up safety flow rate must also be entered. This is a fixed-flow rate of oxygen which, the system will revert to delivering if there are any failures in the system such as loss of SpO_2 signal. At the next screen the user connects to the pulse oximeter and press the

“Launch application” button to begin the experiment, step 5. The experiment stops when the user presses the “Close application” button.

Figure 2-3 Screenshots of the intelligent oxygen therapy system app
This shows the steps which should be followed to activate the iO_2T to deliver fixed-flow and variable oxygen




Experiment Settings
000001
Experiment ID
Please Enter your Password
OK
Cancel
000002
Baseflow Rate (l/m)
Save Settings
Safety Limit
Sp Sat(%)
3
91
Control Interface
Heart Rate
74 bpm
Oxygen Level
100 %
Connect Oximeter
Launch Application
Close Application
STEP 3
A password is then requested as a security measure
STEP 4a
For the fixed system, the flow rate required is entered
For the variable flow mode, the target SpO_2 is requested as well as the safety limit oxygen flow
STEP 4b
STEP 5
In the final step, the system is first connected to an oximeter via Bluetooth. Once an oxygen saturation and heart rate are detected the application is launched.

2.4 The external assessment of the iO_2Ts

Three of my studies involving the iO_2Ts were conducted within a hospital setting (chapter 4, chapter 5 and chapter 7) and used the iO_2Ts shown in Figure 2-1. I conducted all these studies and was present throughout the entirety of the experimental phase. This ensured safety in case of any problems with the system. I subsequently designed the study entitled "The assessment of intelligent oxygen therapy (iO_2T) in patients with respiratory failure on long-term oxygen therapy during sleep" (chapter 6). In this study, I recruited participants with respiratory failure on LTOT and conducted sleep studies in the participants' homes on their usual oxygen therapy and with the iO_2Ts. This study was presented for ethical approval to the West-Midlands South-Birmingham Ethics committee in April 2015. The committee raised a concern as to the safety of the device in the home and recommended that we seek an external review of device safety as it was to be utilised on a standalone basis in patients' homes.

Dr Rob Dickinson led the process of the external assessment, which involved demonstrating all the processes which had led to the development of the iO_2Ts and developing further safety mechanism in case of system failure. The engineering department of the Royal Brompton Hospital (Mr Stephen Squire) was commissioned to carry out the external assessment. The external assessment was carried out in two parts. In the first part of the assessment we met with Mr Squire and I gave a demonstration of the iO_2Ts and allow him to inspect the equipment. The second part involved submitting all necessary documents demonstrating the development and functioning of the iO_2Ts for critical review. The documents which were presented for external review were:

- System risk analysis
- Risk management file checklist
- Functional specification
- Technical specifications
- Instructions for use
- Usability check list
- System validation
- Hardware design document
- Software design document
- Software specification
- Software validation
- Software code walkthrough

I was involved in writing the following documents:

- System risk analysis
- Risk management file checklist
- Technical specifications
- Functional specifications
- Instructions for use

Stephen Squire reviewed the presented documents and issued a favourable safety assessment of the system (appendix 2).

"The design process and testing of the Auto-Titrating (Intelligent) Oxygen Therapy (iO2T) system has been independently reviewed by Clinical Engineering at the Royal Brampton through the inspection of the design and test documentation and is considered safe to use by participants when used according to the supplied instructions for use.

The risk assessments have been carried out in a manner consistent with EN ISO 14971:2012, Medical devices - Application of risk management to medical devices, which is the applicable standard for the safe development of medical equipment. Risks have been appropriately identified, evaluated and, where required, reduced by design or operational mitigations. The residual risks are considered low and are outweighed by the benefits.

The design and development of the iO2T system has been carried out at a standard considered sufficient for submission to a CE mark testing house, as is appropriate for all medical devices intended to be used on patients."

Based on the results of the external assessment, the Ethics committee gave a favourable opinion for our study. The iO_2Ts utilised for home studies is shown in Figure 2-4.

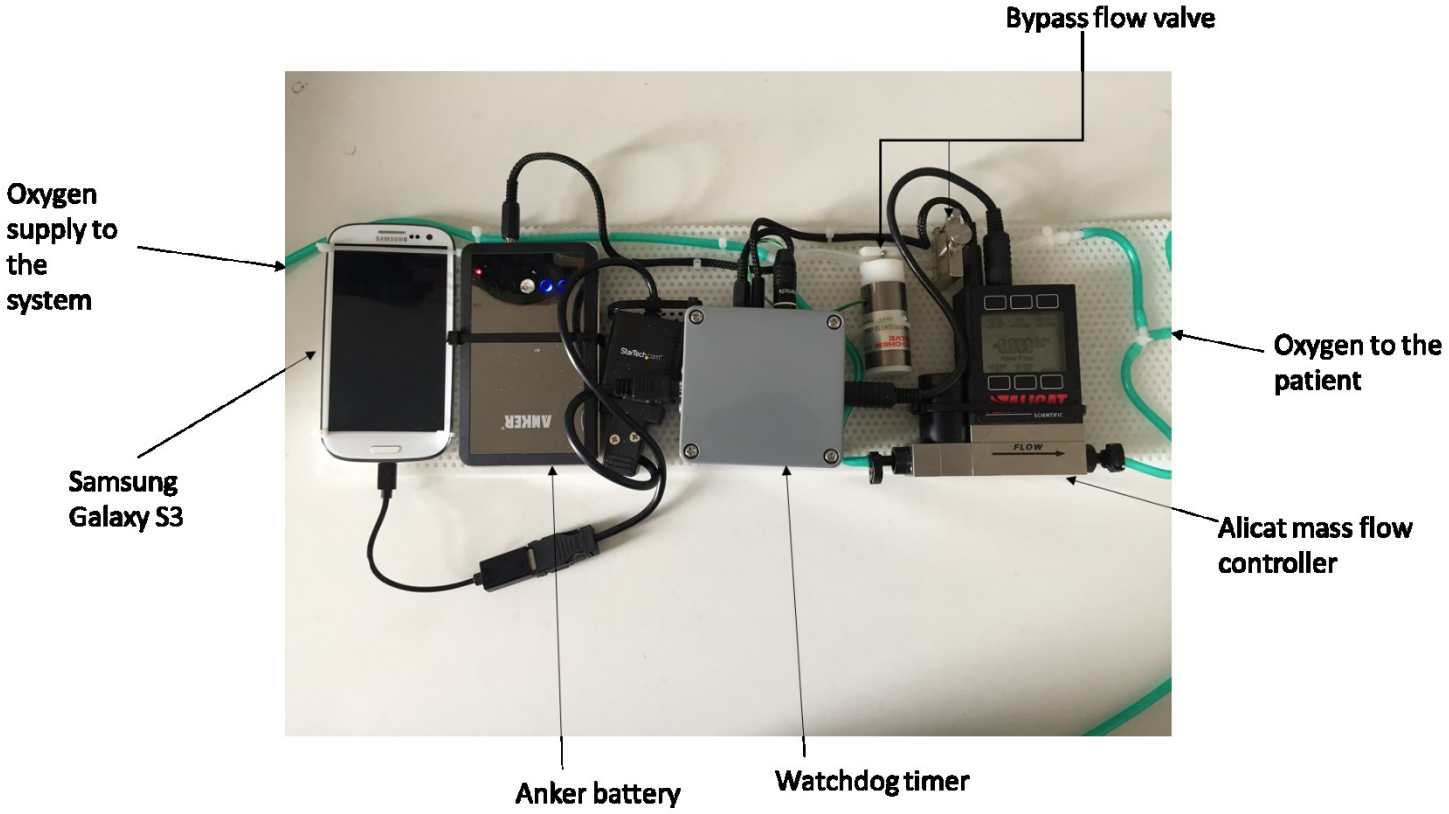


Figure 2-4 The iO_2T developed for home sleep studies
This system has the same basic equipment as that shown in Figure 2-1. But in addition, this system contains a "watchdog timer". This is a failsafe mechanism which allows oxygen to bypass the Alicat flow meter in case the portable battery or phone fail completely.

2.5 The safety feature of the iO_2Ts

We introduced a number of safety features into the design of the upgraded iO_2Ts after a rigorous safety assessment. This was necessary as it was envisaged that the system would eventually be utilised by patients in their own home. Having conducted the full safety assessment there were a number of minor and two major adverse events identified which could be harmful to the patients. Solutions to the two major adverse events are outlined below.

ADVERSE EVENT 1

Loss of Bluetooth pulse oximeter signal to smartphone (either from disconnection or battery failure)

Solution: The system would wait for 20 seconds for a return of Bluetooth signal. If after this time there is no signal, the iO_2Ts would revert to supplying the pre-programmed fixed-flow rate if in fixed-flow mode or the back-up flow rate in variable flow mode. As there is no Bluetooth signal the system would record an error for the pulse rate and SpO_2 data.

ADVERSE EVENT 2

Software crash

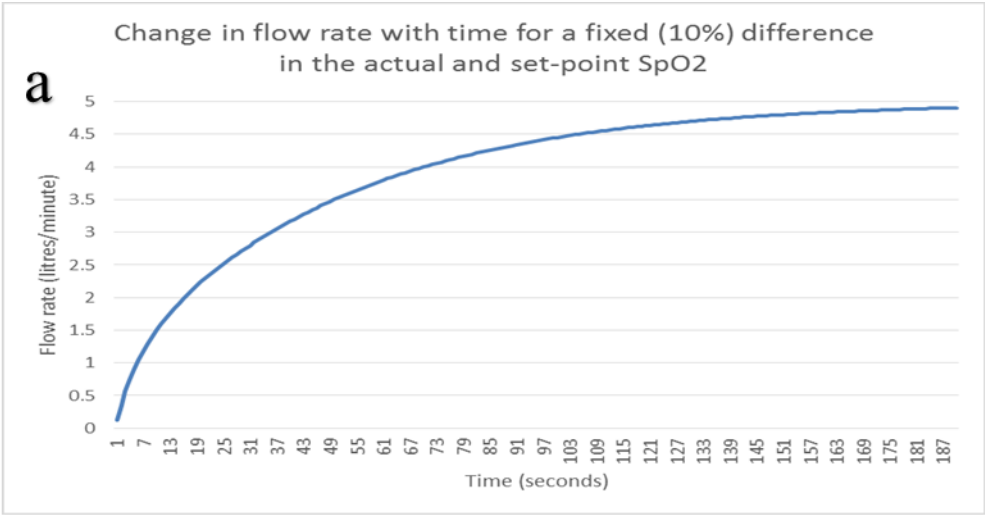
Solution: The system was tested multiple times to reduce the risk of failure. In the event of a software failure, an external watchdog timer was added which is activated in the event of a system failure. The activation of the watchdog timer activates a bypass valve which delivers oxygen directly to the patients independent of the iO_2Ts (Figure 2-4).

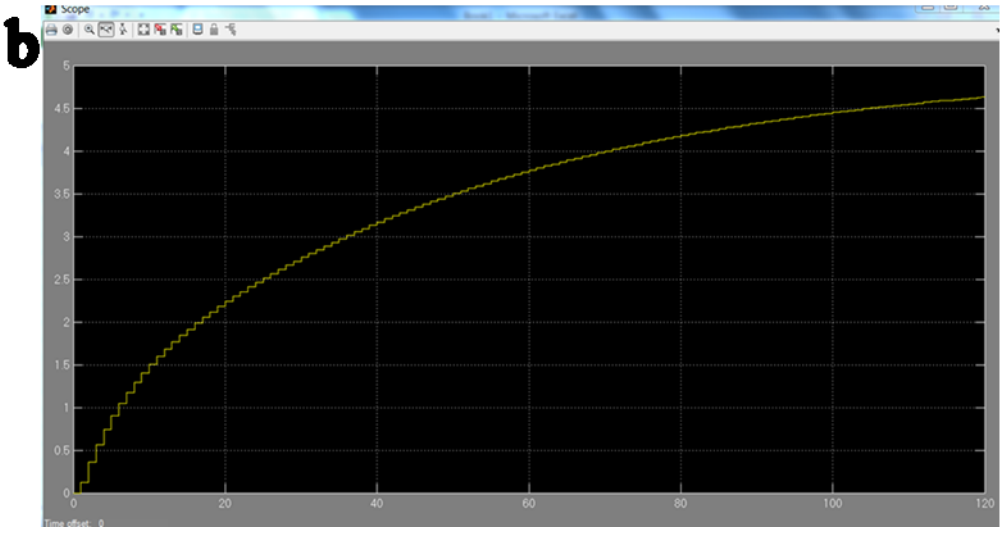
2.6 Validation of the smartphone algorithm

The auto-titrating oxygen system algorithm is based on a proportional–integral–derivative controller. The initial system was designed and tested in Simulink® and MATLAB® (MathWorks®, Cambridge, United Kingdom). Unfortunately, these programmes are very large and not operational on mobile devices. Therefore, the iO_2Ts algorithm was encoded in JAVA and an app created on a smartphone.

The transfer of the algorithm from the laptop onto the smartphone in the form of an application was undertaken by the Bioengineering department of Imperial College London (Rishi Goburdhun). Once the app was completed, it was validated against the original algorithm to ensure correct, accurate and complete transfer. Validation was conducted by investigating the

output flow-rate from the laptop algorithm and the app in a series of simulated scenarios and the results are shown in Figure 2-5a and Figure 2-5b. The actual output (in litres per minute) from the fixed-flow algorithm using the app was validated by checking the displayed output on the Alicat mass flow controller and externally validated to a flow meter and this data is shown in the table in Figure 2-5.





Output requested from iO_2Ts (litres/minute) fixed-flow	Output displayed on Alicat mass flow meter (litres/minute)	Output on analogue external flow meter
1.0	1.0	1.1
2.0	2.0	2.0
3.0	3.0	3.0
4.0	4.0	4.1
5.0	5.0	5.1

Figure 2-5 Algorithm validation of the iO_2Ts
Figure a shows the output in litres/minute from the smartphone application for a 10% difference between set-point and actual SpO_2. Figure b shows the output from the laptop based system for the same difference in set-point and actual $_{SpO2}$. The table shows the validation of the output of the iO_2Ts referenced to an external flow meter. iO_2Ts = intelligent oxygen therapy system, SpO_2 = oxygen saturation

2.7 Data collection and storage for experimental studies

Each time a new experiment was started on the iO_2Ts, a unique ID was entered for the study. The data during the subsequent experiment was stored under the unique ID code. The ID was a numerical 1-15 digits in length. The application created eight files and the data recorded in each file is shown in Table 2-2.

Table 2-2 The eight experimental files created by the iO_2Ts and the data recorded by each file.

File Name	Function
ExptSettings	Date and time the experiment was started and the type of oxygen delivered (fixed or variable flow). If delivering fixed-flow the flow rate requested in recorded. If delivering variable flow, the set-point SpO_2 safety flow rate is recorded.
TimeMeasurement	The time throughout the experiment
OxygenLevelMeasurement	The SpO_2
HeartRateMeasurement	The heart rate
Spsat_hr_Measurement	SpO_2 and heart rate measurements together
FlowCalculation	The flow calculated for delivery (In variable flow mode only)
ErrorInput	The error between the set-point SpO_2 and the actual SpO_2
Error_In vs flow	The error between the set-point SpO_2 and actual SpO_2 and the flow calculated (in variable flow mode only)

2.8 Setting the ideal target (SpO_2 or PO_2) for the correction of hypoxaemia in patients on long-term oxygen therapy

Ideally, oxygen should be prescribed to match a given SpO_2 target whenever possible. In the acute setting, the British Thoracic Society guideline for emergency oxygen use in adult patients recommend that oxygen should be prescribed to maintain a SpO_2 target of 88-92% for those at risk of hypercapnia and 94 – 98% for those not at risk of hypercapnia (O'Driscoll et al., 2008). *However, there is currently no consensus as to the ideal target SpO_2 or PO_2 in patients prescribed home LTOT*. When considering what the ideal target SpO_2 or PO_2 for LTOT, one must consider the following:

- the chosen target must correct hypoxia
- the chosen target must minimise the risk of hypercapnia
- the SpO_2 of patients in studies which have demonstrated an improvement in mortality in patients with COPD on LTOT
- the SpO_2 of patients with moderate hypoxaemia in negative LTOT studies

In the NOTT, the aim was to provide supplementary oxygen in increments of 1 litre/minute to increase the PO_2 at rest to between 60 mmHg and 80 mmHg (approximate SpO_2 range 90.6 – 95.7%). Unfortunately, there is no published data on the actual resting PO_2 of the patients in the NOTT. In the MRC study, supplementary oxygen was prescribed at a flow rate of at least 2 litres/minute or greater to maintain a PO_2 >60 mmHg. There was no upper limit for the PO_2 in this study. The actual resting mean PO_2 was 76.6 mmHg (approximate SpO_2 95.2%). In an earlier open label study, thirty-three patients with COPD received LTOT for 24 hours and were followed over a period of 2.5 years (Neff and Petty, 1970). Compared to historical cohorts, these patients showed a reduction in mortality and their mean PO_2 on oxygen was 71.3 mmHg (approximate SpO_2 94.1%). In a registry study by Kerstin Ström which demonstrated increased survival in patients with COPD on LTOT compared to historical cohorts, the resting SpO_2 of patients was between 93.0±2.6% to 93.8±2.7% (Strom, 1993).

There have been three negative studies in patients with COPD and moderate hypoxaemia given supplemental LTOT. In the LOTT study the resting SpO_2 of patients in the interventional group was 93.3±2.1% and in the control arm it was 93.5±1.9% (Albert et al., 2016). In the study was GÓrecka *et al*., the resting SpO_2 was 90.7%±1.9% (Gorecka et al., 1997). In the study by Chaouat *et al*., in which patients with nocturnal hypoxaemia were given nocturnal oxygen therapy, the resting SpO_2 of patients was 91.6±2.0% (Chaouat et al., 1999).

Most experts agree that a PO_2 between 60-65mmHg (SpO_2 between of 90-94%) would represent a clinically adequate correction of hypoxaemia without the risk of hypercapnia for patients on LTOT (Odonohue, 1997, Hanania and Sharafkhaneh, 2007). Given the above data from both positive and negative studies of LTOT, we have selected a SpO_2 target of 93% for our studies. This is a target which both correct hypoxia and does not overtly increase the risk of hypercapnia.

3 Chapter 3 - General Methods

3.1 Participant and hospital information

All participants were recruited between July 2014 and January 2017 from the Royal Brompton & Harefield NHS Foundation Trust. Participants were identified from selected clinics at the Royal Brompton Hospital, from a database of patients on ambulatory oxygen, those attending pulmonary rehabilitation and sleep studies, and a specialist oxygen clinic at Harefield hospital. Participants were potentially eligible if they met the inclusion criteria and lived within travelling distance of the Royal Brompton Hospital. The participants were screened and assessed for eligibility at the National Institute for Health Research (NIHR) Biomedical Research Unit (BRU) at the Royal Brompton Hospital or Harefield Hospital. The 6-minute walk tests (6MWTs) were conducted on the 4th floor of the Royal Brompton Hospital (Lind ward) or on the 2nd floor of Harefield Hospital along flat corridors of 30 meters. The activities of daily living were conducted in a sleep research laboratory of the Academic Department of Sleep and Ventilation on the 2nd floor of the Royal Brompton Hospital. Overnight sleep studies were conducted in the patients' homes.

3.2 Ethical approval and the conduct of research

"The assessment of intelligent oxygen therapy (iO_2T) in patients with chronic obstructive pulmonary disease on long term oxygen therapy" (chapter 4) (REC reference: 14/WM/0130), "The assessment of intelligent oxygen therapy (iO_2T) in patients with idiopathic pulmonary fibrosis on oxygen therapy" (chapter 5) (REC reference: 14/WM/0130) and "The assessment of intelligent oxygen therapy (iO_2T) in patients with hypercapnic respiratory failure on long-term oxygen therapy during sleep" (chapter 6) (REC reference: 15/WM/0137), were all approved by the West Midlands – South Birmingham Research Ethics committee (see appendices 3,4 and 5 for approval letters). The "The assessment of intelligent oxygen therapy (iO_2T) in patients on long-term oxygen therapy during activities of daily living" (chapter 7) (REC reference: 15/LO/1435), was approved by the London – Stanmore Research Ethics committee (see appendix 6 for approval letter). All participants gave written informed consent. All studies were conducted in accordance with the principals set out in the Good Clinical Practice (GCP) guidelines and the Helsinki declaration on the principles of research conduct involving human participants. The studies were registered on ClinicalTrials.gov.

3.3 Regulatory clearance from the Medicines and Healthcare products Regulatory Agency

At the planning stage of the first experimental study for the iO_2Ts (chapter 4), the Medicines and Healthcare products Regulatory Agency (MHRA) were contacted by Professor Anita Simonds to discuss the iO_2Ts and regulatory approval. The MHRA confirmed that no further regulatory approval was required as the study was being performed within the trust without current intent to commercialise (see appendix 7 for confirmation email).

3.4 Clinical and physiological assessment

All participants underwent a medical review including a review of their medical history, their drug history and oxygen history. A case report form (CRF) was completed to collect medical and physiological data. Anthropometric measurement of height and weight were recorded. Blood pressure was measured in the office and shortly before the 6MWTs. I conducted all the medical reviews, completion of the CRF and measurements of physiological data.

3.4.1 Spirometry

Spiromety was conducted using a Carefusion MicroLab^{TM} handheld spirometer in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al., 2005). The spirometer was calibrated on the day of assessment using a 3-litre syringe (following the manufacturer's instructions). Participants were asked to take a deep inspiration and perform a sharp expiration for as long as possible with standard encouragement. The FEV_1 and FVC were considered acceptable if the difference between the two largest volumes was ≤150mls (having conducted a minimum of three attempts and a maximum of eight). The Carefusion MicroLab spirometer has built in software to allow interpretation of spirometry in accordance with the ATS/ERS guidelines. In patients with a diagnosis of COPD, the results were interpreted according to the GOLD classification (chapter 1, Table 1-2).

3.4.2 Arterialised ear lobe blood gases

Arterial blood gases (ABG) are used in routine clinical practice and are the gold standard to assess the pH, PaO_2, $PaCO_2$, bicarbonate and base excess of arterial blood. The sample is most commonly collected from the radial artery. However, the procedure requires skilled staff and can result in injury and morbidity for the patient. Arterialised ear lobe blood gas or ear lobe blood gas (ELBG) is a technique for collecting arterialised capillary blood sample which is less invasive, requires less skill and the results of which show a close correlation with ABG results

in stable patients (Pitkin et al., 1994, Zavorsky et al., 2007). In general, patients find ear lobe blood gases less painful and more acceptable than arterial blood gases. Therefore, for my research studies, data was collected from an ELBG.

Conduct of ear lobe blood gases

The ear was cleaned with an alcohol swab and prepared with deep heat cream (Mentholatum Company Ltd, Scotland) to arterialise the capillaries in the ear. The patient was asked to stay seated for at least 30 minutes either on their usual LTOT flow rate or on air depending upon the conditions that are required before the ear lobe blood gas was taken. The ear was disinfected using an alcohol swap again. A lancet was used to make a small incision of 2-4mm in depth in the ear lobe. Blood was collected in a capillary tube and analysed immediately. The ELBGs were analysed on a SIEMENS RAPIDLAB® 1265 (SIEMENS, Germany) at the Royal Brompton Hospital and RADIOMETER ABL90 (Radiometer, United Kingdom) at Harefield Hospital.

3.4.3 The MRC Breathlessness scale

All participants were asked to complete the MRC breathlessness scale shown in Table 3-1. This is a five-point scale utilised by patients to indicate the effects of breathlessness on their everyday lives. The result from the breathlessness scale correlate well with FEV_1 and distance achieved during a 6MWT (Mahler and Wells, 1988, Stenton, 2008).

Table 3-1 The MRC Breathlessness Scale
From (Stenton, 2008)

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 metres or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

3.5 The principles of oxygen saturation monitoring

Oxygen saturations were monitored throughout all studies and the primary outcome was the percentage of time spent below 90% for all studies and therefore an understanding on how oxygen saturation is measured is important. Arterial oxygen saturation in blood was measured non-invasively using pulse oximetery. This is based on the principle of spectral analysis of light of different wavelengths as it passes through body tissues. Oxygenated haemoglobin and reduced haemoglobin absorb light of different wavelengths as shown in Figure 3-1. Most pulse oximeters contain two light emitting diodes: one for red light and one for infrared light (as these wavelengths penetrates tissues readily whereas light of other wavelengths are absorbed significantly). The light emitting diodes shine light of different wavelengths which travel through tissues surfaces and is measured on the other side by a detector. By measuring the relative amounts of red and infrared light that are absorbed, oxygen saturation can be calculated.

For all studies in this thesis, a Nonin-4100 pulse oximeter (Nonin, Plymouth, Minnesota, USA) containing Bluetooth technology was used to measure oxygen saturation and it is these measurements which were input into the iO_2Ts algorithm to drive changes in oxygen flow rates. In chapters 4, 5 and 7 an ear clip attachment was used to allow the patients to be hands free and simulate how the pulse oximeter could be worn in a domiciliary setting. For the study in chapter 6, a soft finger sensor was utilised during sleep. The oximeter has a SpO_2 range of 0 – 100% and a heart rate range of 18 – 300 beats per minute. The measurement wavelength for red light is 660 nanometres and for Infrared is 910 nanometres. It has an accuracy of ±2 digits for finger soft sensor and ±4 digits for the ear clip over the range of SpO_2 of 70-100%. The Bluetooth technology has an operating radius of 10 meters. The SpO_2 is averaged over 4 beats.

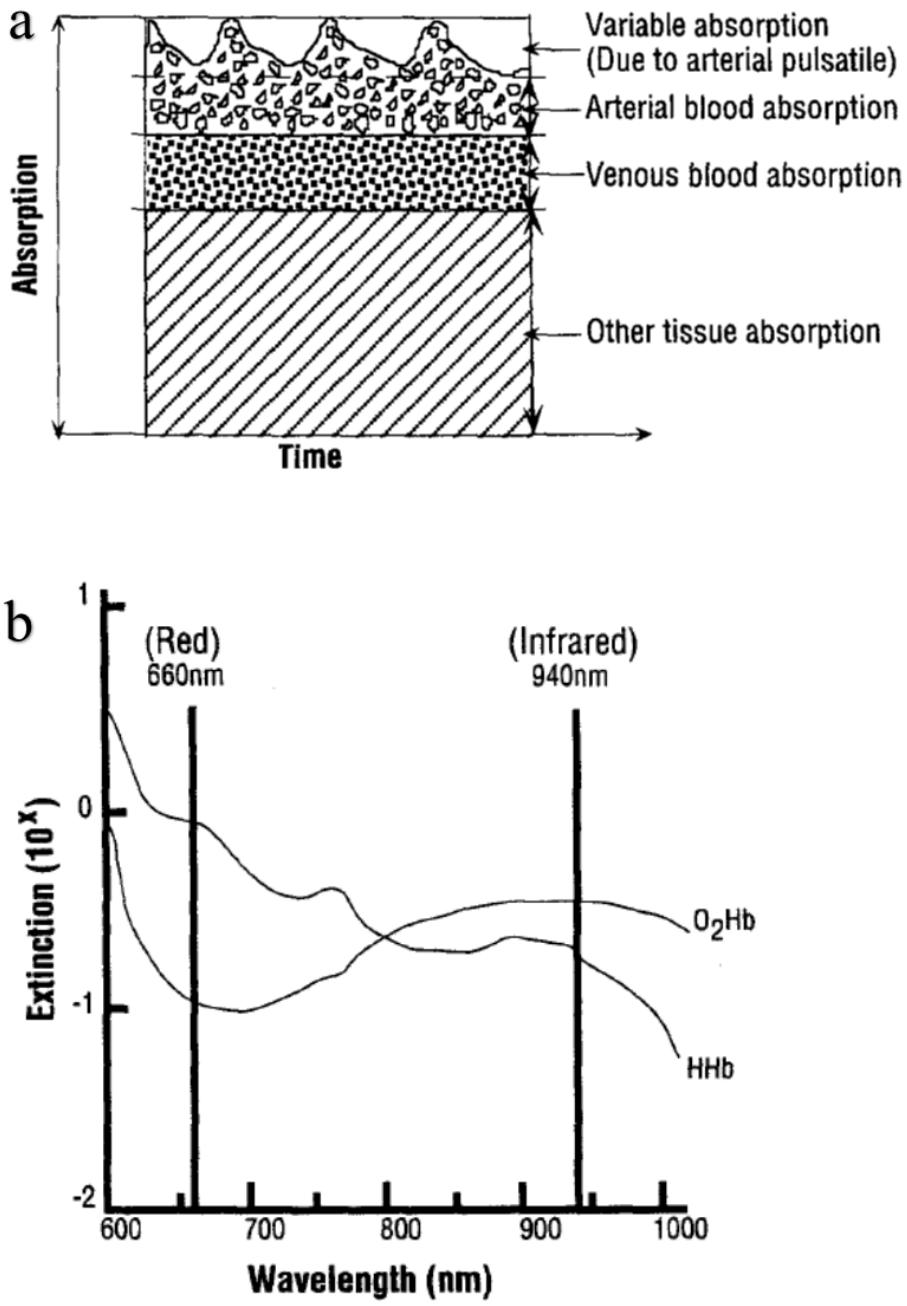


Figure 3-1 The absorption of light by tissues and wavelengths for oximetry
Figure a shows the tissues that light must pass through and where it comes into contact with haemoglobin. Figure b shows the wavelengths of lights most commonly used for pulse oximetry and the relative absorption of oxygenated and reduced haemoglobin. O_2 Hb = oxyhaemoglobin, HHb = deoxyhaemoglobin. Reproduced with permission. (Sinex, 1999).

3.6 The principles of transcutaneous carbon dioxide monitoring

The transcutaneous partial pressure of carbon dioxide (tc*p*CO_2) was recorded for the study in chapter 6, and therefore an understanding of how tc*p*CO_2 is measured, its benefits and limitations are discussed. The optimum sites for the measurement of tc*p*CO_2 should have good skin perfusion, contain no large veins, contain no hair and no skin defects. Therefore, the most commonly utilised site for tc*p*CO_2 is the ear lobe and this was the site utilised for the study in chapter 6. tc*p*CO2 was measured continuously all night using a TOSCA 500 (Radiometer, Copenhagen, Denmark).

A Stow-Severinghaus sensor was utilised to measure tc*p*CO_2. The sensor works by heating the skin and thereby dilating the underlying capillaries. This increases gas diffusion through the skin and allows CO_2 and oxygen to diffuse up to 20 times quicker from the capillaries to the skin. Once it reaches the skin, the CO_2 diffuses into the membrane where it reacts with the electrolyte solution and is converted in to HCO_3- and H+. As the HCO_3- is kept at a constant level, the change in H+ concentration will lead to a change in pH and these changes in pH lead to changes in voltage between the glass sensor and the reference sensor. The pH is then converted back to CO_2 and displayed in kPa or mmHg. The TOSCA was calibrated before each use in a known gas mixture of 12.0% oxygen, 7.0% CO_2, balance nitrogen.

3.6.1 Advantage of using transcutaneous carbon dioxide monitoring

The most accurate method of CO_2 measurement is arterial blood gas analysis. If continuous measurement of CO_2 is required, an arterial line can be inserted into the radial or brachial artery which allows sampling of arterial blood at the required frequency. However, this is invasive and in the UK, is normally conducted in a level 2 care facility and is associated with potentially multiple complications. A less invasive method is the measurement of CO_2 in exhaled breath (capnography). However, capnography is difficult to interpret in patients with mixed ventilatory, metabolic and perfusion problems. It can also be inaccurate in patients with nasal obstruction, in those with severe lung disease and more difficult to interpret in self-ventilating patients and in those who mouth breathe.

The TOSCA reliably provides continuous, almost instantaneous, non-invasive measurement of CO_2. It has minimal local effects and one site can be utilised continuously for >8 hours. It combines the advantages of accurate and reliable CO_2 measurement that comes from an arterial line with the non-invasive technique of capnography. TOSCA has been utilised to diagnose hypoventilation during sleep, to guide changes to NIV during acute exacerbations of COPD, during conscious sedation during bronchoscopy and to guide changes in nocturnal NIV for the set-up of long-term domiciliary NIV.

3.6.2 Limitations of transcutaneous carbon dioxide monitoring

tc*P*CO_2 does not provide CO_2 results equivalent to arterial blood gas sampling but rather shows how the trend in CO_2 varies overnight. It takes time for the sensor to be placed on the skin and up to 20 minutes for the sensor to stabilise and obtain values for tc*P*CO_2. There is a response time of approximately 16 seconds and a lag time of approximately 2 minutes and therefore tc*P*CO_2 is not useful in the analysis of short respiratory events such as apnoeas and hypopneas. Additionally, there is a drift of -0.5mmHg/hr in tc*p*CO_2 overnight (this can be corrected by knowing the exact values of $PaCO_2$ at the beginning and at the end of the recording). tc*p*CO_2 can also be affected by skin vasoconstriction (from shock or drugs), hypothermia and cardiac failure.

3.7 The 6-minute walk test (6-MWT)

In the early stages when clinical studies were being planned to test the iO_2Ts during an exercise test, we had the choice of either a 6MWT or a shuttle walk test. We opted to use the 6MWT as there is comprehensive prognostic information available for most chronic respiratory diseases, it is responsive to oxygen therapy and has been used extensively in clinical trials in the USA especially in patients with ILD (Puente-Maestu et al., 2016).

The 6MWT is a simple and very well validated test of exercise capacity in patients with COPD, ILD and many other cardiorespiratory diseases (Singh et al., 2014, Puente-Maestu et al., 2016). It is a relatively simple test to perform both for healthcare professionals (requires no specialist equipment) and for patients (the instructions are easy to understand). The 6MWT is an especially useful tool to assess change in exercise capacity in response to specific medical interventions and is therefore a good test to perform to look at the effects of the iO_2Ts in patients with COPD and ILD.

The 6MWTs were conducted along a long 30-meter corridor at either the Royal Brompton Hospital or Harefield Hospital. The tests were conducted in accordance with the American Thoracic Society (ATS) guidelines (American Thoracic Society, 2002). For the studies in chapter 4 and 5, participants were asked to perform three 6MWTs. The first 6MWT was a practice walk to account for the learning effect of the 6MWT (unless the participants had undergone a 6MWT in the last 3 months). The next two 6MWTs were conducted either on the patient's usual fixed-flow oxygen or variable flow oxygen therapy (intelligent oxygen therapy – iO_2Ts) in a randomised order. Between each of the 6MWTs, the participants were given a break of up to 30 minutes or longer if necessary in order to fully recover from their previous exertion. Before the 6MWT all participants were given standard instructions in accordance with ATS guidelines:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself.

You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready." (American Thoracic Society, 2002)

During the 6MWT, a portable oxygen cylinder (BOC, Surrey, UK) was utilised to supply oxygen. The cylinder and the iO_2Ts were all placed inside a "Side-Kick Oxygen Cylinder Carrier" (HH System, Sheffield, UK) as shown in Figure 3-2. The patients had to pull the lightweight trolley for the duration of the 6MWT and during all three 6MWTs (including the practice 6MWT on air). The patients wore a Nonin 4100 pulse oximeter on their earlobe.

Before the start of the 6MWT, all participants were asked to complete the Borg score (shown in Table 3-2) for breathlessness and fatigue (American Thoracic Society, 2002). Participants were asked to complete the Borg score again immediately after the completion of the test and again at 1-minute intervals (to document recovery times after the 6MWT).

Figure 3-2 An example of one patient undertaking a 6MWT.
The iO_2Ts and the portable oxygen cylinder are all place in the ambulatory oxygen bag which is pulled by the patient.

Table 3-2 The Borg scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
3	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

3.7.1 Data collection during the 6-minute walk test

Once the iO_2Ts is activated by pressing the "Launch Button" on the smartphone, data on SpO_2 and heart rate is recorded once per second in individually created accounts. This data is time stamped and can be downloaded later for analysis.

3.7.2 Blinding for studies in chapters 4 and 5

The iO_2Ts app was designed in such a way as to allow blinding for clinical studies. The most important feature which permits blinding is that the same app is used to deliver both iO_2T and fixed-flow oxygen. Once a mode of oxygen delivery is chosen, it is programmed into the app as shown in Figure 2-3. After the "Launch application" button is pressed, the mobile phone is then place on standby mode. Once the mobile is in stand-by mode, it is not possible to tell which mode of oxygen is being delivered and any observer looking at the phone would be blinded as to the oxygen delivery type and the participant of in the experiment equally so.

In the double-blind studies described in chapters 4 and 5, I conducted the all the 6MWTs. For me and the patient to be blinded during the 6MWT, I asked an individual familiar with the iO_2Ts to programme the mode of oxygen delivery for all the blinded 6MWTs. Once the oxygen delivery type had been programmed, the mobile phone was placed in standby mode and placed into the ambulatory oxygen bag so that neither the patient nor I were aware of the type of oxygen being delivered. For the single blind studies described in chapters 6 and 7, I programmed the iO_2Ts with the oxygen delivery type and placed the mobile phone in stand-by mode so that the patient was blinded to the type of oxygen delivered

3.7.3 Randomisation for the 6MWTs

Randomisation of the order of the 6MWTs was achieved by using opaque envelopes. The patient was asked to choose one of four envelopes which would determine the order of the 6WMT. This process was carried out by the same independent individual who subsequently programmed the mobile phone for the 6MWT.

3.7.4 The minimally important distance for the 6MWT

The minimally important change in walking distance for patients with COPD in response to an intervention which is considered to be clinically meaningful is a subject of debate and depends upon the methodology utilised to research the subject. In the study by Redelmeier *et al*., participants with COPD undergoing a pulmonary rehabilitation programme were asked to compare their breathlessness against other patients on the same programme. The 6-minute walking distance had to change by 54 meters for a patient to start rating themselves either "a little bit better" or a "little bit worse" than other participants (Redelmeier et al., 1997). Puhan *et al*., using a distribution based method, demonstrated that a change of 35 meters (10% of the baseline) in the 6-minute walking distance would represent an important effect for patients with moderate or severe COPD (Puhan et al., 2008). Furthermore, Puhan *et al*., investigated the minimally important distance for the 6MWT in patients with COPD who had enrolled in the National Emphysema Treatment Trial (Puhan et al., 2011). Using both anchor based and distribution based methods, they determined the minimally important difference to be 26 meters. Polkey *et al*., investigated the minimally important distance for the 6MWT by utilising data from the observational ECLIPSE cohort. They determined that a reduction in walking distance of 30 metres over 1 year was associated with an increased mortality in the ECLIPSE cohort. Guidelines from the ERS and ATS have reviewed the subject of the clinically meaningful difference in the 6MWT and concluded that irrespective of the disease, the difference lies between 25-33 meters (Singh et al., 2014, Puente-Maestu et al., 2016).

3.8 Activities of daily living

As previously described in chapter 1, section 1.16, many patients experience episodes of intermittent hypoxia especially during activities of daily living (ADL) despite domiciliary LTOT. Three studies have investigated which ADL patients find the most difficult at home. Lahaije and colleagues investigated the physiological limitation of patients with COPD during ADL (Lahaije et al., 2010). The most common ADL which patients found most difficult were vacuum cleaning, carrying weights during walking, showering, putting on socks and shoes, getting dressed, climbing stairs, and dish washing. Annegarn and colleagues investigated the correlation between problematic ADL and clinical correlation in patients with COPD (Annegarn et al., 2012). The most common problematic activities which identified by patients were walking, stair climbing, cycling, showering, gardening, cleaning the floor, dressing and undressing and sports. Nakken and colleagues investigated which ADL patients found most difficult and which ADL their carers thought the patients found most difficult (Nakken et al., 2017). The study concluded that carers were not good at identifying which ADL patients found difficult. The most common ADL which patients found most difficult were walking, stair climbing, washing and bathing, dressing and undressing, transfers and self-care.

There have also been several studies which have assessed oxygen uptake during ADL in patients with COPD. Vaes and colleagues investigated oxygen uptake and breathlessness perception during six ADL: putting on shoes, putting away shopping onto shelves at various heights, folding and putting away towels, washing up 4 dishes, 4 cups and 4 saucers and sweeping the floor for four minutes (Vaes et al., 2011). The results showed that patients with COPD had higher task related oxygen uptake than healthy volunteers and they experienced greater breathlessness during ADL. Castro and colleagues investigated the metabolic demands of 18 different ADL in patients with COPD (Castro et al., 2013). The study showed that the ADL with the greatest oxygen consumption were those that involves movement of both arms and legs such as bathing movement, carrying weight and putting on and taking off clothes.

Taking all the above studies into consideration a protocol was designed to investigate if the iO_2Ts could reduce intermittent hypoxia during ADL in patients on LTOT (chapter 7). The activities chosen are shown in Table 3-3.

Table 3-3 Activities of daily living undertaken by participants

Activity categories	Activity	Time (minutes)
Resting	Resting in a dorsal position	5*
	Resting in a lateral position	5*
	Sitting in a chair	5*
	Standing	5*
Personal care	Brushing teeth	2*
	Washing face	Approximately 2
	Combing hair	1*
	Bathing: simulated bathing movement as if washing the head, chest, abdomen and limbs	Approximately 5
	Dressing and undressing	Approximately 5
	Putting on and taking off shoes	Approximately 1-5
Labour activities	Sweeping the floor	2*
	Storing cans on shelves of various heights	Approximately 1
	Washing dishes	Approximately 2
	Writing on paper	2*
	Talking on the phone without any arm support	1*
	Opening and closing draws	1*
	Moving paper sheets from one side of the desk to the other side	1*
Total time		Approximately 50

*Denotes activities in which the time for the activity was strictly adhered to the time stated in the table above.
The nature of some of the other activities did not allow strict timing. During these activities, the aim for the patients was to finish the activity rather than stop mid-activity after a pre-specified time.

3.8.1 The conduct of the activities of daily living

The protocol began with a period of rest of 20 minutes. This was to ensure that all patients were completely rested before ADL started and allowed assessment of the iO_2Ts as an oxygen assessment tool at rest.

The ADL which the patients were asked to perform were divided into two categories: personal care and labour activities. The protocol began with the patient brushing their teeth for 2 minutes, washing their face for approximately 2 minutes and combing hair for one minute. Next the patients simulated having a bath or a shower as they would in normal life. The patients were instructed to make all the movements as if they were having a shower or bath. There was not a strict time limit on how long the patients could take and the activity was complete when the patients stated they had finished.

Next the patients were asked to dress and undress. The patients were required to bring with them an extra top and bottoms to wear over the top of the clothes they were already wearing for the day. The patients were then asked to put the additional clothes on and take them off. Again, there was not strict time limit for this activity as patients usually carried out this activity at their own pace at home. Next patients were asked to put and take off shoes. To try and standardise this activity, patients were not asked to do up their laces as many patients do not own shoes with laces or avoid them due to difficulty putting them on.

Next the patients were asked to sweep the floor for two minutes. A previous study described asking patients to sweep the floor for four minutes but due to the severity of the lung disease in our patients and the fact that all were on LTOT, this was shortened to two minutes and strictly time monitored (Vaes et al., 2011). Patients were then asked to carry six cans of beans (total weight 2.5kgs) in a tray for 2 meters and place them into shelves of different heights (1 one can at 29cms, 1 can at 133cms, 1 can at 140cms and 3 cans at 155cms). Next the patients were asked to wash 4 cups, 4 saucers and 4 plates in warm water in any order. Both activities were not strictly time monitored.

The patients were asked to write on paper for two minutes. They could write from memory or copy a text. In the next activity, they were asked to speak on a landline telephone for 2 minutes without resting their elbow on the table. They could call a friend or a relative to have a conversation or they could choose to read out a passage from a magazine.

In the next activity patients were asked to open and close draws of a small cabinet which had seven draws. This was to simulate the patients looking for an object in their draws at home. In

the last activity patients were asked to move 2 packets of plain paper of 500 grams each from one side on the desk to another to simulate office activities of moving stationary.

As shown in Table 3-3, the nature of some of the activities meant that they could not be time constricted. The aim during these activities was to allow the patients to complete the task rather than to suddenly stop after a certain time even if the task had not been completed. In between the activities, patients could stop and take a rest and recover completely before continuing onto the next activity and this was a condition of the ethical approval for the study.

3.9 Overnight monitoring of sleep

Overnight monitoring of sleep was conducted for the study in chapter 6. Nocturnal unattended home Polysomnography (PSG) (type II sleep study) was performed using portable equipment (SOMOscreen^{TM} Plus, SOMNOmedics GmbH,Germany) as shown in Figure 3-3. In addition, transcutaneous carbon dioxide levels were also monitored using a TOSCA monitor (Radiometer, Denmark).

3.9.1 Validity of home versus sleep laboratory polysomnography

In the planning stage of the study in chapter 6, a decision was made to conduct all polysomnographies in the patients' home. This was in part due to the design of the study (a cross-over study) which necessitated two studies for every patient and results from a previous survey in which when asked, approximately three quarters of patients preferred to home rather than attended hospital PSG (Ward, 2011). However, this does raise the question of: "How valid is unattended home polysomnography against attended sleep laboratory PSG?"

When investigating the question of validity, there are two important questions to answers; firstly, what is the difference in measured physiological variables between home and laboratory setting? And secondly, what is the rate of study failure in the home and laboratory setting?

Campbell and Neill investigated the utility of home unattended PSG versus laboratory PSG for 30 patients suspected of having OSA (Campbell and Neill, 2011). They found that there was a higher loss of signal for home sleep studies but that home PSG is technically feasible and achieves excellent diagnostic utility which was identical that of laboratory attended PSG. Mykytyn and colleagues compared validity of a new portable polysomnographic recorder against a laboratory-based PSG system in 20 patients (Mykytyn et al., 1999). They found greater signal loss from SpO_2 and a slight decrease in respiratory signal quality during home PSG. They found good agreement (r=0.99) in the apnoea-hypopnea index and sleep variables. For both home PSG and in-laboratory PSG, 10% of patients had poor signal quality which would have required a second study if the study had been conducted for clinical practice. In contrast Portier and colleagues found very different results when they compared home PSG against laboratory PSG in patients suspected of having sleep apnoea (Portier et al., 2000). Twenty percent of home PSG studies had to excluded due to poor signal quality as compared to 5% for laboratory PSG. Their study did not find any evidence of better sleep quality at home and their results suggested that home PSG was not suitable for one-third of their patients.

Iber and colleagues investigated the difference in sleep parameters in home unattended PSG versus in laboratory attended PSG in 67 patients not participating in the sleep heart health study

(SHHS) but using the SHHS methodology (Iber et al., 2004). The study showed that home unattended PSG was associated with a longer sleep time, a better sleep efficiency and a small but statistically significant reduction in stage 1 and REM sleep. The variability of the respiratory disturbance index (RDI) was similar to the normal biological variability as measured by night to night comparisons seen in previous studies.

The largest use of home unattended PSG has been for the diagnosis of OSA in patients participating the SHHS. Kapur and colleagues investigated the senor loss of unattended PSG for patients taking part in the SHHS (Kapur et al., 2000). They analysed a total of 6802 patients and 7151 studies and found that 90.6% of the initial studies were acceptable and this number increased to 94.7% after a further study.

Overall, there is good validity of home unattended PSG when compared to attended in laboratory PSG if the correct methodology is utilised and especially when additional equipment such as on-site laptop is available to look at electrode signal strength. From the evidence available, there are minor but definite differences in some physiological variables between home PSG and attended in laboratory PSG and the rate of study failure is between 5% to 20%.

3.9.2 Polysomnography channels

The portable polysomnography had the following channels:

- Ten electroencephalography (EEG) channels
- Three submental electromyogram (EMG) channels and two additional EMG channels placed on the tibialis anterior muscle of the left and right lower leg
- Two electrooculogram (EOG) channels
- Electrocardiography (ECG) channel
- Respiratory signals (measurement of airflow, chest and abdominal movement, oxygen saturation, snore)

3.9.3 Measurement of sleep

Sleep was measured from the electrical activity from the brain (EEG), movements of the eyes (EOG) and measurement of muscle activity from EMG. EEG was measured by a combination of 10 mm gold cup electrodes (Grass Technology, Rhode Island, USA) and pre-gelled self-adhesive electrodes (Neuroline 720, Ambu Ltd, Cambridgeshire) placed on the scalp according the ten-twenty system as shown in Figure 3-4. Gold cup electrodes were placed on the scalp at position C3, C4, Cz, F3, F4, O1 and O2. Neuroline electrodes were placed at A1, A2, EOG left and right, ground electrode and chin EMG (x 3). Before each electrode was positioned, the scalp

or skin were prepared by cleaning with an abrasive paste (Neuprep, Weaver and Company, Colorado, USA) and subsequent wiping with an alcohol swab. The gold cup electrodes were filled with a conductive paste (Ten20 conductive paste, Weaver and Company, Colorado, USA) and held in position on the scalp with an adhesive (Collodion, SLE Ltd., South Croydon, UK). The self-adhesive Neuroline electrodes were help in position by micropore tape. Once the electrodes were attached biological checks were conducted.

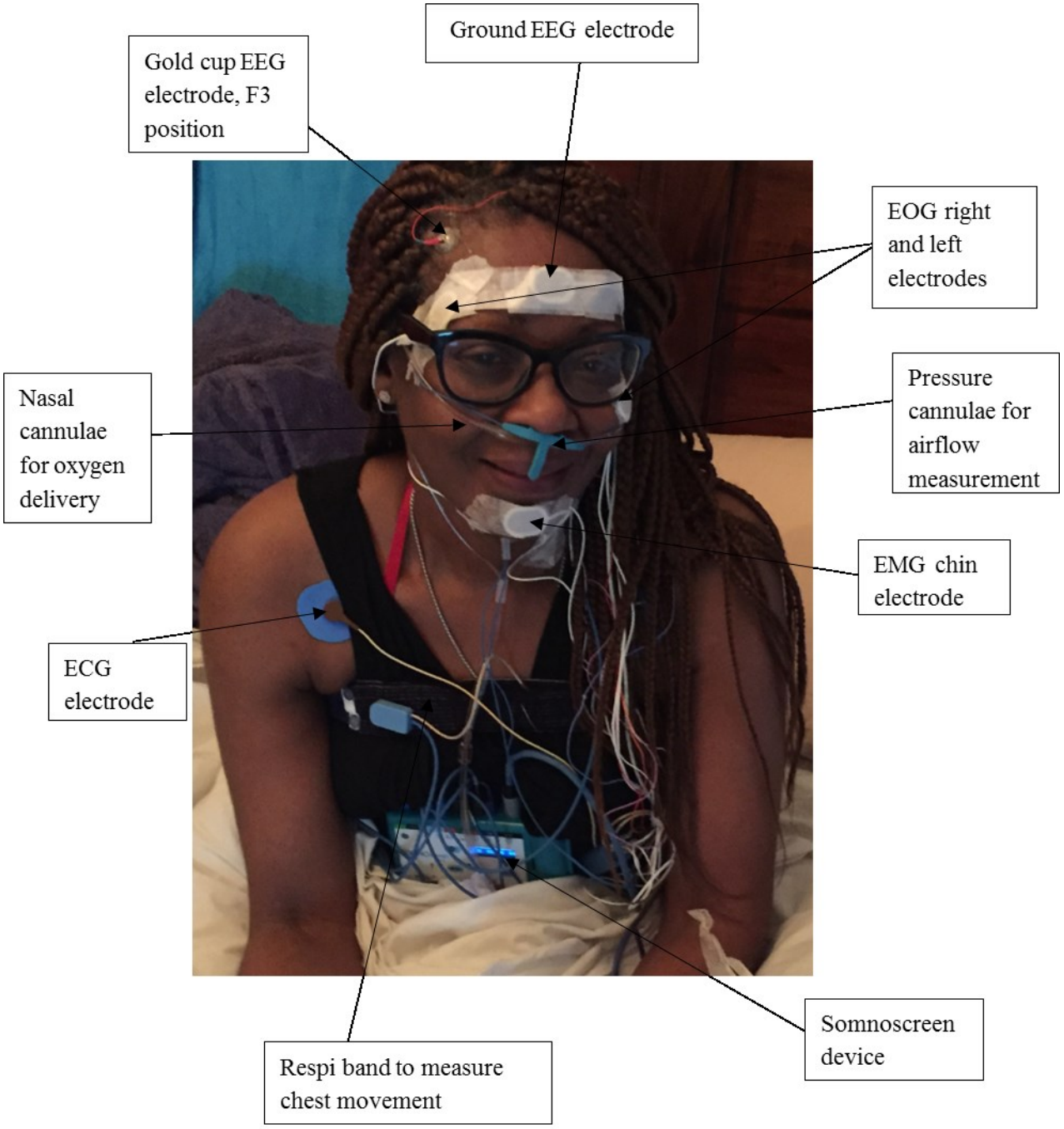


Figure 3-3 An example of one patient with portable full polysomnography equipment attached.
EEG = electroencephalogram, ECG = electrocardiogram, EMG = electromyogram, EOG = electrooculogram. Photograph included with the written consent of the patient.

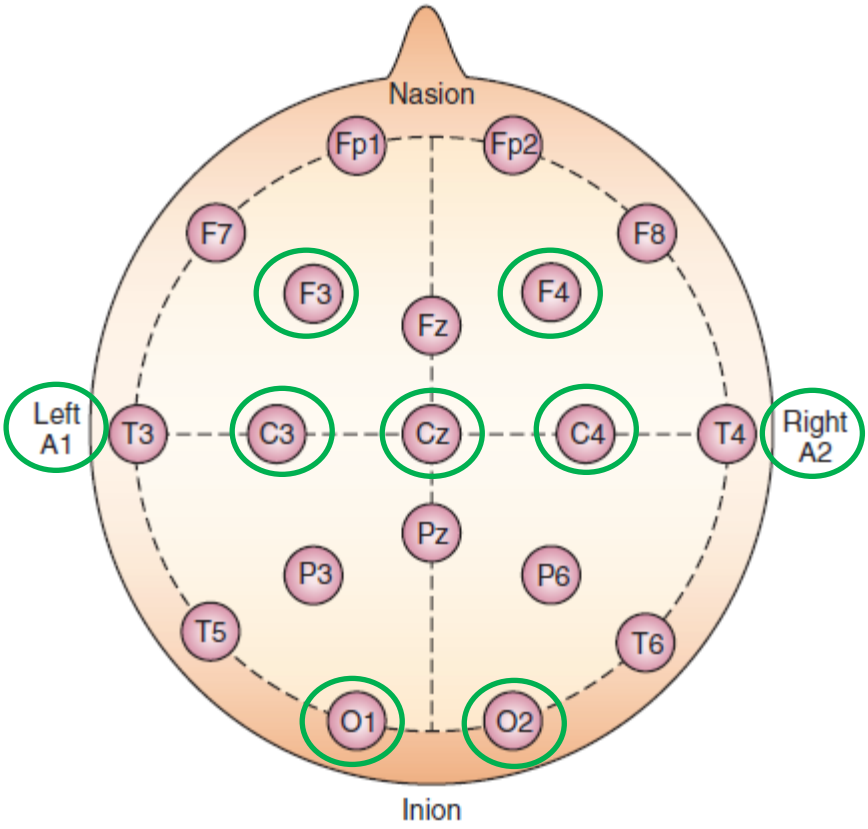


Figure 3-4 The Ten-Twenty system for the placement of EEG electrodes for PSG. The electrodes are placed are at 10% and 20% of the distance from nasion to inion and from the left and right preauricular points. For my sleep studies the electrodes were places at F3 (left frontal), F4 (right frontal), C3 (left central), C4 (right central), Cz (central), A1 (left mastoid), A2 (right mastoid), O1 (left occipital) and O2 (right occipital) all in green ellipses. An additional ground electrode was placed on the forehead 10% of the distance from the nasion to Inion (not shown in this diagram). Figure modified from Principle and Practice of Sleep medicine, 5th edition.

Raw data signals

Electrical potential between each pair of EEG, EOG and EMG electrodes was measured in voltage in AC mode. Electrode impedance was tested to ensure it was <10kOhms. Raw signals were sampled at rates shown in Table 3-4 then passed through predetermined filters to remove external noise prior to digitisation (Domino v250 Software).

Table 3-4 Signal sampling rates and filter settings for polysomnography

	Sampling rate, (Hertz)	Frequency, range (Hertz)	Highpass filter, (Hertz)	Lowpass filter, (Hertz)
EEG	256	Delta (0.5 – 3) Alpha and beta (8 – 32	0.3	30
EOG	128	0.2 – 35	0.3	10
EMG	256	1 – 128	10	75
ECG	256	1 – 128	1	75
SpO_2	4	n/a		
RIP	32	0 – 10	0	1

3.9.4 Respiratory measurements

The respiratory parameters measured were airflow, chest and abdominal movements and oxygen saturations.

Measurement of airflow

Airflow during sleep can be measured by several techniques including pneumotachography, thermistor, capnography, a body box or nasal pressure cannuale. The body box is an unsuitable approach for sleep studies and especially home sleep studies. Pneumotachography provides very accurate quantitative measures of airflow but requires the patients to wear a face mask, requires bulk equipment and is uncomfortable for the patients and again this makes this method unsuitable for most sleep studies.

Thermistors monitor changes in air temperature and as exhaled is usually warmer than ambient air, this creates a temperature difference between inhaled and exhaled air which can be converted into airflow measurements. Nasal pressure cannuale are placed directly into the nares to detect changes in pressure; with inspiration, there is negative pressure inside the thoracic cavity with respect to the atmosphere and with expiration there is positive pressure inside the thoracic cavity with respect to the atmosphere. These changes in pressure can provide a surrogate for airflow. The American Academy of Sleep Medicine (AASM) manual recommends a thermal sensor to document apnoeas and a nasal pressure sensor to detect hyponeas.

In the sleep studies described in chapter 6, airflow was measured using a thermistor. This is because all patients were already on LTOT delivered through nasal cannulae. Therefore, the

placement of another set of nasal cannulae into the nares would be difficult and uncomfortable. Additionally, the use of nasal pressure cannuale to measure flow would have produced confounding results given the continuous flow of oxygen through the existing nasal cannulae.

Measurement of oxygen saturation, chest and abdominal movements

Oxygen saturation was measured by Nonin OEM III Module (Nonin, Plymouth, Minnesota, USA). It has a SpO_2 range of 0 – 100% with an accuracy of ±2 digits for SpO_2 between 70 – 100%. Respiratory inductance plethysmography (RIP) was used to evaluate chest and abdominal movements during sleep. This is based on the principle of electromagnetism. The respiratory bands utilised (RIP, Respitrace, USA), contain a coiled wire which generates a magnetic field when an electric current is passed through it. Respiratory effort changes the cross-sectional area of the patients' chest and abdomen and consequently the shape of the electric field generated by the belt which can be measured as a change in the frequency of the applied current. Two bands were placed: one to measure chest movement at the level of the axilla and the second to measure abdominal movement placed at the level of the umbilicus.

Additional measurements recorded during polysomnography

ECG was recorded continuously using two electrodes (Blue sensor, Ambu Ltd., Cambridgeshire, UK) placed under the right and left clavicles. Leg movements were monitored using EMG electrodes (Blue sensor, Ambu Ltd., Cambridgeshire, UK) placed on the right and left tibialis anterior muscles. The preparation of the skin for both ECG and EMG electrodes was prepared by the same method as that used to prepare skin for the placement of EEG electrodes. Snoring was recorded using a microphone place in the middle of the neck and to right side of the trachea.

3.9.5 Measurement of transcutaneous carbon dioxide

Oxygen saturation, heart rate and the tcpCO_2 were measured during sleep using a TOSCA 500 (Radiometer, Copenhagen, Denmark). The data from the TOSCA 500 was integrated into the SOMOmedics software by an analogue opto coupler (S-med, UK).

3.9.6 Data collection

The data from the polysomnography was recorded on an integral memory card on the SOMNOscreen plus device (1GB Compact Flash card SOMNOmedics). The data was also simultaneously recorded on a laptop computer (Dell LATITUDE E6510) via telemetry. SOMOscreen software (DOMINO, Version 2.7.2) was used for signal processing and analysis.

3.10 Data analysis

3.10.1 6-minute walk tests and activities of daily living

Data for SpO_2 and heart rate was collected continuously once per second before, during and after the 6MWTs and ADL. The data was stored on the Samsung Galaxy smartphone and downloaded after completion of the 6MWTs and ADL. The data was subsequently organised into 3 periods; the period before, during and after the 6MWT and ADL.

6-minute walk test

The data during the 6MWT was used to calculate the percentage of time spent with SpO_2 below 90%, the percentage of time spent with SpO_2 below 88%, the mean and nadir SpO_2 and heart rate calculations. To calculate the SpO_2 and heart rate recovery time, the baseline SpO_2 and heart rate were taken as those just before the start of the 6MWT.

Activities of daily living

During the ADL, a careful record was kept of how long each patient spent during each activity and when every activity started and when it stopped. This data was used to organise the time spent by each patient into periods of time when they were at rest and periods of time they were conducting activities. The time spent conducting activities was used to calculate the primary and secondary outcomes.

3.10.2 Polysomnography

All polysomnography studies were blindly scored score by the same experienced polysomnographer and clinical research fellow Mr Yousef Al-Qureshi (RPSGT). The studies were all scored according to the American Academy of Sleep Medicine (AASM) standards manual 2012.

Scoring of sleep stage

Sleep stages were initially scored according to the manual produced by an ad-hoc committee chaired by Rechtshaffen and Kales in 1968. Subsequently the AASM have revised these criteria and the current sleep staging was updated in 2007 (Table 3-5).

Table 3-5 Characteristics of sleep stages according to EEG, EMG and EOG criteria

Sleep stage	EEG	EMG	EOG
Wake	Fast beta activity >13Hz, high amplitude. With eyes closed there is alpha activity 8 – 13Hz.	High tone	Rapid eye movements, Blinks
N1	Theta activity 4 – 7Hz	Reduced tone compared to wake	Eye rolling and no rapid eye movements
N2	Spindles (fast bursts [0.5 – 2 seconds] of 12 – 15Hz activity) K-complexes (negative EEG deflections followed by positive) Both K-complexes and spindles occur on a background of low voltage mixed frequency EEG	Lower tone than in N1 and wake.	Occasional slow eye movements
N3	Slow (delta) waves (0-3Hz, ≥75μV in amplitude) in more than 20% of the epoch.	Low tone	No eye movement
REM	Low voltage, mixed frequency EEG	Atonia	Burst of rapid eye movement
EEG = Electroencephalogram EMG = Electromyogram EOG = Electrooculogram REM = Rapid eye movement			

The standardised technique for sleep scoring requires a single mono-polar central lobe scalp EEG electrode referenced to a single contralateral mastoid electrode. This single channel brainwave recording when seen together with EOG and EMG data reveals brain, eye and muscle activity and this is sufficient to classify sleep staging.

Sleep studies were scored in 30 second epochs. To score a stage, at least half of the epoch (15 seconds) must have been classifiable as one particular stage. Arousals were scored according to the AASM definition of an abrupt change in frequency lasting ≥ 3 seconds, preceded by a stable sleep stage of ≥10 seconds (arousals scored in REM additionally required the presence of an increase in EEG activity). Arousal were classified as either respiratory or due to periodic limb movements of there was a clear temporal relationship between a respiratory or limb event to an arousal.

Scoring of respiratory events

Apnoeas were scored when there was a ≥90% reduction in airflow (thermistor signal) for ≥10 seconds. The apnoeas were classified as obstructive apnoeas if there was continued respiratory effort and central apnoeas in the absence of continued respiratory effort. The apnoea was scored as mixed if there was absence of respiratory effort at the beginning of the event but resumed in the second portion of the event.

Hypopneas were scored if there was a ≥30% reduction in airflow from baseline for ≥10seconds associated with either a 3% desaturation or an arousal. The hypopneas were classified as obstructive if there was continued respiratory effort or central in the absence of continued respiratory effort.

Hypoventilation was scored during sleep if:

- There was an increase in tcpCO_2 to a value >55mmHg for greater than 10 minutes or
- A >10 mmHg increase in tcpCO_2 above the baseline value during sleep to a value exceeding 55mmHg for ≥10 minutes (baseline taken as awake and supine).

Analysis of pulse oximetry data

Once the sleep study had been staged, the SpO_2 data during sleep was analysed by the Domino software to give the percentage of time spent at SpO_2 < 90% and 88%, the mean and trough SpO_2 and mean and peak heart rate. This data was further analysed according to sleep stage (REM versus non-REM).

Analysis of transcutaneous carbon dioxide data

Once sleep had been staged, a baseline level for tcpCO_2 was established (from when the patient was awake and supine). The Domino software analysed the $tcCO_2$ data to produce mean, peak and trough SpO2. This data was further analysed according to sleep stage (REM versus non-REM).

Scoring of periodic limb movements

A leg movement was defined according to the AASM manual as an increase in leg EMG of ≥8μV above the resting EMG for a duration of between 0.5 and 10 seconds. No leg movements were scored 0.5 seconds before or after a respiratory event. A PLM series was defined as a group of ≥4 leg movements with a gap of 0.5 – 90 seconds between each movement. Leg movements occurring from different legs <5seconds apart were considered one movement.

3.11 Statistical analysis and data presentation

All statistical analyses were performed by myself in SPSS version 21, 22 or 23 (IBM, Illinois, USA). Additional diagrams and graphs were produced in GraphPad Prism (GraphPad Software, Inc. California, USA) and Adobe illustrator (Adobe Systems Incorporated, California, USA). Full details of the statistical methods used are given in each chapter.

4 Chapter 4 – Intelligent oxygen therapy during a 6-minute walk test in patients with COPD on long-term oxygen therapy

4.1 Introduction

4.1.1 Background

Two seminal studies published in the early 1980s, demonstrated that LTOT improved survival in patients with COPD and severe resting hypoxaemia (MRC, 1981, NOTT, 1980). Further observational studies have confirmed those finding (Cooper et al., 1987, Strom, 1993, Gulbas et al., 2012), and LTOT is recommended by many international guidelines for respiratory failure and persistent hypoxaemia (Hardinge et al., 2015, Qaseem et al., 2011, Vogelmeier et al., 2017, McDonald et al., 2016, O'Reilly and Bailey, 2007).

The criteria for prescribing LTOT in patients with COPD are:

1. Partial pressure of oxygen (PaO_2) ≤7.3 kilopascals (kPa) while breathing room air

2. PaO_2 between 7.3kPa – 8kPa while breathing room air with evidence of pulmonary hypertension (p-pulmonale on an electrocardiogram, pulmonary hypertension on echocardiography), peripheral oedema or secondary polycythaemia [haematocrit ≥55%]) (Hardinge et al., 2015).

The assessment of LTOT is conducted with the patient at rest, when they are stable (no exacerbation in the last 4 weeks) and on two separate occasions three weeks apart. If required, LTOT is prescribed at a fixed-flow rate with the aim of maintain a PaO_2 ≥8 kPa SpO_2 >90% at rest. LTOT is recommended for at least fifteen hours per day including during sleep and continuously for 24 hours if possible, and is usually prescribed indefinitely (Hardinge et al., 2015).

However, several studies have demonstrated that some patients once established on fixed-flow domiciliary LTOT, experience episodes of intermittent hypoxia (SpO_2 <90%) whilst at rest, walking, during activities of daily living and during sleep (Śliwiński et al., 1994, Morrison et al., 1997, Pilling and Cutaia, 1999, Abdulla et al., 2000, Plywaczewski et al., 2000). These episodes may be harmful as they could lead to symptoms, transient increases in pulmonary pressures (Selinger et al., 1987), reduction in cerebral oxygenation (Oliveira et al., 2012, Higashimoto et al., 2015), ischaemic heart disease (Choudhury et al., 2014) and arrhythmias (Tirlapur and Mir, 1982). Although increasing the LTOT flow rate may reduce intermittent hypoxia, it may also cause hyperoxia and in vulnerable patients risks hypercapnia especially during sleep.

To mitigate episodes of intermittent hypoxia, a novel auto-titrating oxygen system, the iO_2Ts, has been developed. This provides oxygen at variable flow rates to maintain a pre-set SpO_2 with

the aim of reducing episodes of intermittent hypoxia compared to fixed-flow oxygen and thereby optimise domiciliary and ambulatory LTOT.

4.1.2 Aims and hypothesis

The primary aim of this study was to assess if the iO_2Ts could reduce intermittent hypoxia (time spent with SpO_2 <90%) in patients with COPD on LTOT during a field walking test. The secondary aim was to assess the utility of the iO_2Ts to act as an oxygen assessment tool for ambulatory oxygen. We tested the hypothesis that the iO_2Ts, by providing variable flow oxygen to maintain a pre-set SpO_2 target, could reduce intermittent hypoxia during a 6MWT compared to fixed-flow ambulatory oxygen.

4.2 Methods

4.2.1 Study design

This was a prospective, single centre, randomised, double blind, crossover study. Patients with COPD on LTOT were recruited and asked to complete three 6MWTs. The first 6MWT was an open label, non-randomised practice walk on air to account for the learning effect of the 6MWT and offered to all participants who had not undertaken a 6MWT in the previous 3 months. Subsequent to the practice walk, participants undertook two further 6MWTs: one 6MWT on the patients' usual fixed-flow ambulatory oxygen therapy and another on the iO_2Ts (crossover design). The order of the tests would be randomised and the patient and the assessor would both be blinded to the test order.

The 6MWT was chosen for this study as it is a well validated test in patients with COPD and correlates well with daily activities in patients with COPD.

Ethical approval was given by the West-Midlands South Birmingham research ethics committee (14/WM/0130) (appendix 3 for ethical approval letter). All patients gave informed and written consent for the study. The study was registered on Clinicaltrials.gov, NCT02248064. Regulatory clearance was received from the MHRA (see chapter 2 for details of the regulatory approval and appendix 7 for email correspondence from the MHRA).

4.2.2 Study participants

This was a single centre study based at the Royal Brompton and Harefield NHS Foundation Trust. Patients were identified from outpatient clinics, those attending a specialist oxygen clinic, those attending pulmonary rehabilitation, from a database containing patients on LTOT and those attending for an assessment of ambulatory oxygen.

4.2.3 Inclusion criteria

1. Age >18

2. Patients with COPD on or eligible for LTOT

4.2.4 Exclusion criteria

1. Inability to mobilise for a 6MWT

2. Inability to consent for the study

3. PaO_2 <6.0 kPa or $PaCO_2$ > 8 kPa on air

4. Patients with unstable cardiovascular disease (e.g. arrhythmias, severe valvular disease, unstable hypertension or ischaemic heart disease).

5. Pregnancy

6. Exacerbation of COPD in the previous 4 weeks

7. High ambulatory oxygen flow rate (≥5 litres per minute)

4.2.5 Protocol

Patients were asked to complete three 6MWTs in total. It is known that there is a learning effect for the 6MWT and in order to address this factor in this study, all participants were asked to complete a practice open label 6MWT before the blinded 6MWTs unless they had undergone a 6MWT within the previous three months. The patients were given standard instructions for all the 6MWTs in accordance with the ATS guidelines (American Thoracic Society, 2002). In between each 6MWT, there was at least a 30-minute rest period. After the practice walk, the patients were randomised to undertake a 6MWT on their usual fixed-flow ambulatory oxygen first or the intelligent oxygen therapy system. The ambulatory oxygen flow rate chosen was individualised for each patient. If a patient had undergone an ambulatory oxygen assessment, the oxygen flow rate from that assessment was utilised for this study. If the patients had not undergone such an assessment, the ambulatory flow rate set was 1 litre/minute higher than their usual LTOT flow (NOTT, 1980).

Blinding of the patients was achieved by utilising the same system to deliver both iO_2T and fixed-flow oxygen. Blinding of the assessor was achieved by asking an individual familiar with the working of the intelligent oxygen therapy system to enter detail of the blinded 6MWTs. Randomization was achieved with opaque envelopes.

4.2.6 Data collection

Anthropometric data was collected on all patients. Data was collected on the patients past medical history, their drug history and oxygen therapy utilisation. Spirometry was performed

by all patients on a Carefusion® portable spirometer in accordance with the ATS/ERS guidelines (Miller et al., 2005). Arterialised ear lobe blood gases were carried out on all patients on air (patients were asked to sit comfortably for 30 minutes off their usual LTOT). The blood gases were analysed on a SIEMENS RAPIDLAB® SIEMENS RAPIDLAB® 1265 (SIEMENS, Germany) at the Royal Brompton Hospital and RADIOMETER ABL90 (Radiometer, United Kingdom) at Harefield Hospital.

Before the start of the 6MWT, patients were asked to complete a Borg scale for breathlessness and fatigue (American Thoracic Society, 2002)(chapter 3 Table 3-2). During the 6MWT, data was collected continuously on the patients' heart rate and SpO_2 and recorded on the mobile phone app. Then after the 6MWT, patients were asked to complete the Borg scale again. Patients were asked to complete the Borg scale every minute after the 6MWT was completed until they had reached their pre-6MWT Borg score. Once this point has been reached the 6MWT was considered complete. Once all three 6MWTs had been completed, the patients' participation in the study was complete.

4.2.7 Study outcomes

Primary outcome

The primary outcome was the difference in the percentage of time spent with SpO_2 <90% during the 6MWT whilst on iO_2T system compared to fixed-flow oxygen. This was selected as the primary outcome as the aim of the system is maintain a constant SpO_2 and hence reduce intermittent hypoxia (defined as SpO_2 <90%).

Secondary outcomes

1. The change in the following parameters between the iO_2Ts and fixed-flow ambulatory oxygen during the 6MWT:

- Percentage of time with SpO_2 <88%
- Mean and nadir SpO_2
- Mean and peak heart rate
- Total distance walked
- Volume of oxygen delivered during the 6MWT and recovery period

2. The potential change in ambulatory oxygen flow rate as assessed by flow-time data from the iO_2Ts.

4.2.8 Sample size estimation

The sample size was estimated by taking into account data from a pilot study of the iO_2T system in patients with respiratory failure (Iobbi, 2007) (see chapter 1 section 1.21 for preliminary data). An a priori decision was made to design the study to investigate for a large (20%) reduction in the percentage of time spent with SpO_2 <90% by the intelligent oxygen therapy system against usual fixed flow oxygen. Using a standard deviation of 18% (derived from the pilot data), with an α of 0.05 and β of 0.8, the estimated sample size was 9 patients – 12 patients were recruited to allow for a dropout rate of 25%.

4.2.9 Statistical analysis

The continuous variables in the baseline characteristics are presented with means and their standard deviation or median with interquartile range. The categorical variables are presented as the number and percentage is in each category.

For the primary and secondary outcomes, the differences in each outcome parameter between fixed-flow oxygen and the iO_2Ts were tested for normality (visually with a histogram and boxplot, skewness and kurtosis and the Shapiro-Wilks test). The differences between the groups for each outcome parameter were analysed using a Wilcoxon-signed rank test as the differences were not normally distributed. Analysis of variance (ANOVA) was used to analyse the difference in group mean SpO_2 at 30 second time intervals during the 6MWT between room air, fixed-flow oxygen and the iO_2Ts.

The flow-time data from the iO_2Ts was analysed to produce percentiles of time spent at a given flow rate. The 90^{th} percentile data was compared to the patients' usual ambulatory oxygen flow rate. All statistical analyses were performed in SPSS version 21 (IBM, New York, USA). Additional figures were produced in GraphPad Prism (California, USA) version 6.0 and Adobe Illustrator (Adobe Systems Incorporated, California, USA).

4.3 Results

4.3.1 Patient recruitment

Fifty-five patients meeting the inclusion criteria for age, having COPD by GOLD criteria and requiring LTOT were identified between October 2014 and February 2015 (consort diagram for the study is shown in Figure 4-1). Of the fifty-five eligible patients, twenty-one were excluded as their ambulatory oxygen demand was at or above the maximal output from the intelligent oxygen therapy system (≥5 litres/minute). Thirty-four patients were approached to participate in the study. Eighteen declined to participate and one patients was excluded after further assessment as he longer met the criteria for LTOT.

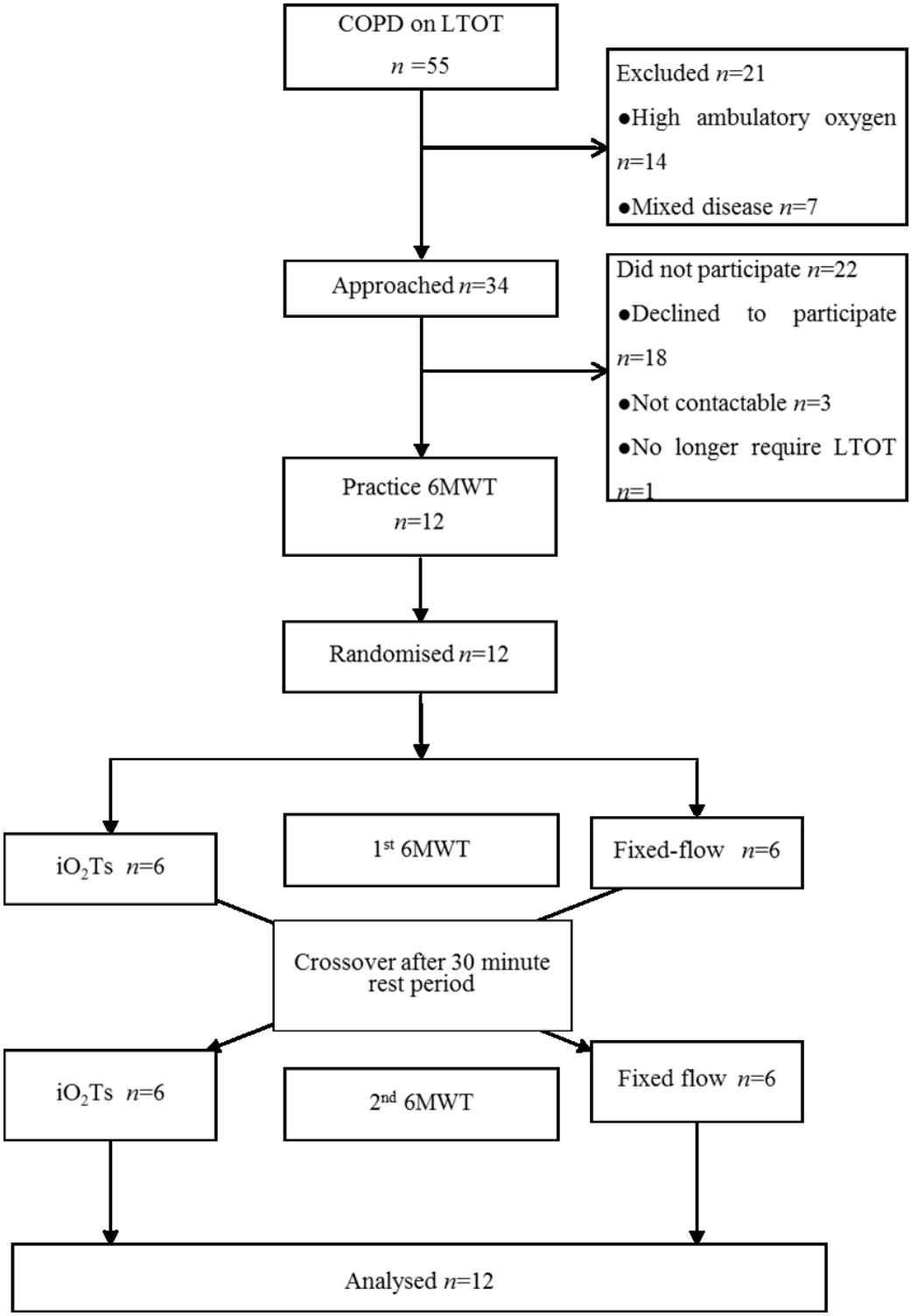


Figure 4-1 Consort diagram for patient recruitment
COPD = chronic obstructive pulmonary disease 6MWT = 6-minute walk test
LTOT = long-term oxygen therapy iO2Ts = intelligent oxygen therapy system

4.3.2 Baseline characteristics

Table 4-1shows the baseline characteristics for the study population. A total of twelve patients competed the protocol (9 males; 3 females). The mean ± SD age was 69.9 ± 6.4 years. The population was lean with a BMI of 25.4 ± 3.5 kg/m2. The population had severe COPD with a mean FEV_1 of 0.88 ± 0.44 litres with a percentage predicted FEV_1 of 31.9 ± 14.0%. Seven patients were currently utilising nocturnal non-invasive ventilation with eight patients having pulmonary hypertension which reflects the severe nature of COPD patients treated at the Royal Brompton and Harefield NHS Foundation Trust. The median LTOT flow rate was 2 litres/minutes (IQR: 1 – 2) with a median ambulatory flow rate of 3 litres/minute (IQR: 2.0 – 3.5). All patients were on the triple therapy of inhalers consisting of a long-acting muscarinic antagonist (LAMA) and a combination of a long-acting beta agonist (LABA) and inhaled corticosteroid (ICS) combination.

Table 4-1 Baseline characteristics of the study patients, *n* = 12

Parameter		Value
Gender (male), n (%)		9 (75)
Age, years		69.6 ± 6.4
BMI, kg/m^2		25.4 ± 3.5
FEV_1, Litres		0.88 ± 0.44
Percentage predicted FEV_1, %		31.9 ± 14.0
FVC, Litres		2.17 ± 1.06
Percentage predicted FVC, %		64.6 ± 23.0
LTOT duration, years		2.5 [1.0 - 7.0]
Baseline PaO_2 on air, kPa		7.28 ± 0.93
Baseline $PaCO_2$ on air, kPa		6.12 ± 1.07
Baseline $PaCO_2$ >6.0 kpa, n (%)		7 (58)
GOLD stage (II/III/IV), n (%)		2 (17) / 3 (25) / 7 (58)
Nocturnal NIV use, n (%)		7 (58)
Pulmonary Hypertension, n (%)		8(67)
LTOT flow rate, Litres/minute		2 [1-2]
Ambulatory flow rate, Litres/min		3 [2.0 – 3.5]
MRC breathlessness score (2/3/4/5), n (%)		1 (8) / 4 (33) / 6 (50) / 1(8)
Smoking history, pack years		46.0 [47.7 – 56.6]
Medications	LABA/ICS, n (%)	12 (100)
	LAMA, n (%)	12 (100)
	Theophylline, n (%)	5 (42)

Data shown as n (%), mean ± SD or median [interquartile range]. BMI = Body mass index, FEV_1 = Forced expiratory volume in the first second, FVC = Forced vital capacity, LTOT = Long-term oxygen therapy, PaO_2 = Partial pressure of oxygen, kPa = kilopascal, $PaCO_2$ = Partial pressure of carbon dioxide, GOLD = Global initiative for chronic obstructive lung disease, NIV = Non-invasive ventilation, MRC = medical research council, LABA = long-acting beta agonist, ICS = inhaled corticosteroid, LAMA = Long-acting muscarinic antagonist

4.3.3 The effect of the iO_2Ts on SpO_2 during 6MWT

Twelve patients completed the study as per the study protocol. Figure 4-2 shows the mean SpO_2 (with 95% CI) at 13 different time-points at 30 second intervals, for all patients during the 6MWT for the three oxygen delivery modalities (air, fixed-flow oxygen and intelligent oxygen therapy). The 6MWT on air was unblinded and undertaken by ten participants (the other two participants did not feel confident in undertaking a 6MWT without their oxygen and therefore they conducted the practice walk on their usual ambulatory oxygen).

There was no difference in the baseline starting SpO_2 between the iO_2Ts compared to fixed-flow oxygen therapy, 95.0 % (IQR: 93.0 – 95.8) vs. 93.0% (IQR: 91.0 – 95.8), respectively, p=0.111.

During the early stages of the 6MWT, there is rapid desaturation when patients are on air. However, there is little difference in SpO_2 between fixed-flow oxygen and the iO_2Ts. As the duration of the 6MWT increases there is an increasing difference in the mean SpO_2 between the fixed-flow oxygen and the iO_2Ts. The explanation as to why this happens can be appreciated by studying the oxygen saturations and oxygen flow rates over the course of the 6MWT for one patient as demonstrated in Figure 4-3. In the example shown, at the beginning of the 6MWT, the patients' ambulatory oxygen flow rate is higher than with the iO_2Ts flow rate. Therefore, during the first part of the 6MWT, this higher flow rate protects the patients from oxygen desaturations and it takes some time for the iO_2Ts to reach the same flow rate as the fixed-flow system. As the 6MWT progresses, there is oxygen desaturation with fixed-flow oxygen. There is also desaturation with the iO_2Ts but the system reacts to increase the delivered flow rate and therefore maintain a higher SpO_2. Therefore, during the second half of the 6MWT, there is a greater difference in the mean SpO_2 between fixed-flow oxygen and the iO_2Ts.

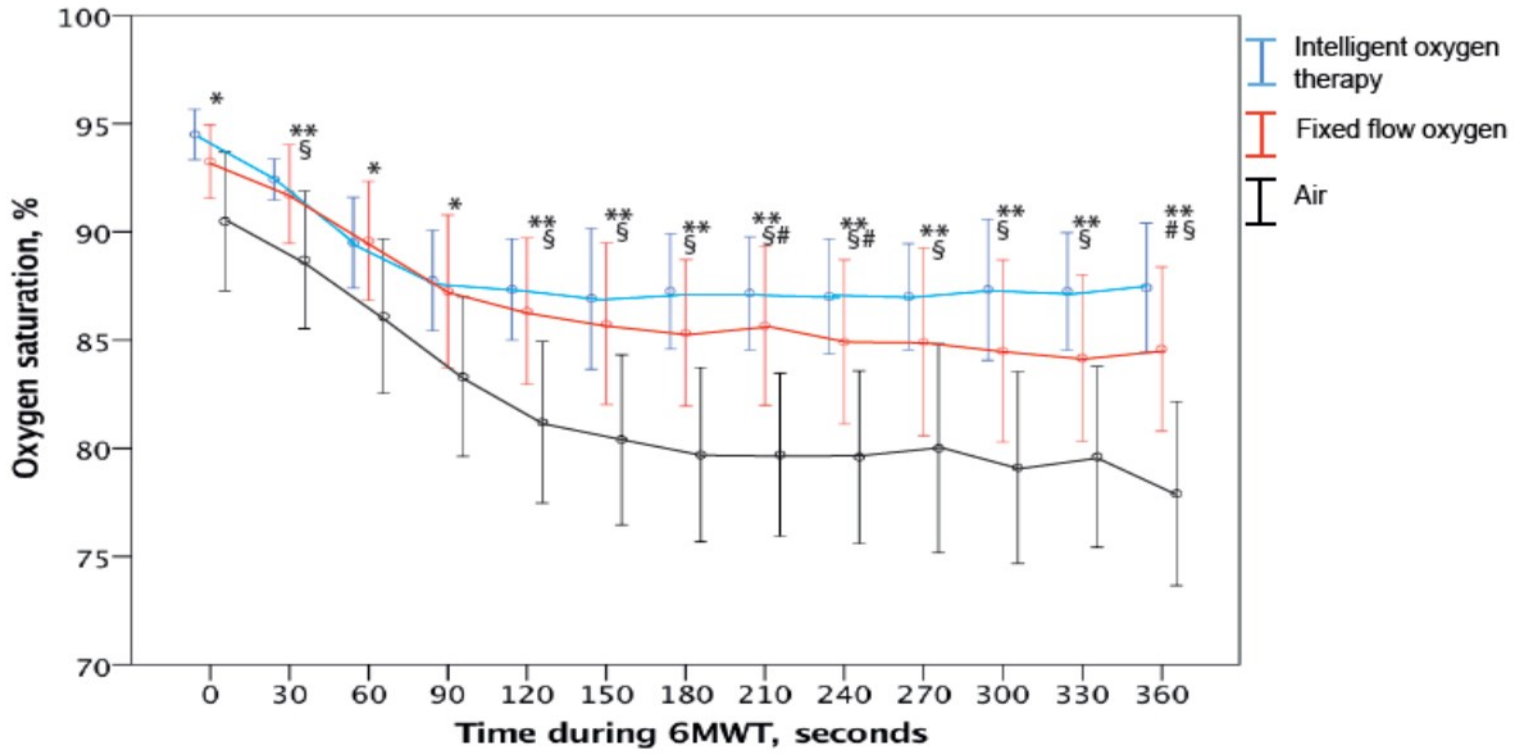


Figure 4-2 Oxygen saturations during the 6MWT

The group mean oxygen saturations (with 95% confidence intervals) at 30 second intervals during the 6MWT on three different oxygen flow rates. Between group analysis using ANOVA. * = p ≥0.05, ** p = <0.05 for ANOVA

Significant results were further analysed using paired-T test with Bonferroni correction for multiple comparisons. § = p <0.05 iO_2Ts v air # = p <0.05 fixed-flow v air. 12 patients undertook 6MWTs on fixed-flow oxygen and the iO_2Ts and 10 on air.

iO_2Ts = intelligent oxygen therapy system 6MWT = 6-minute walk test

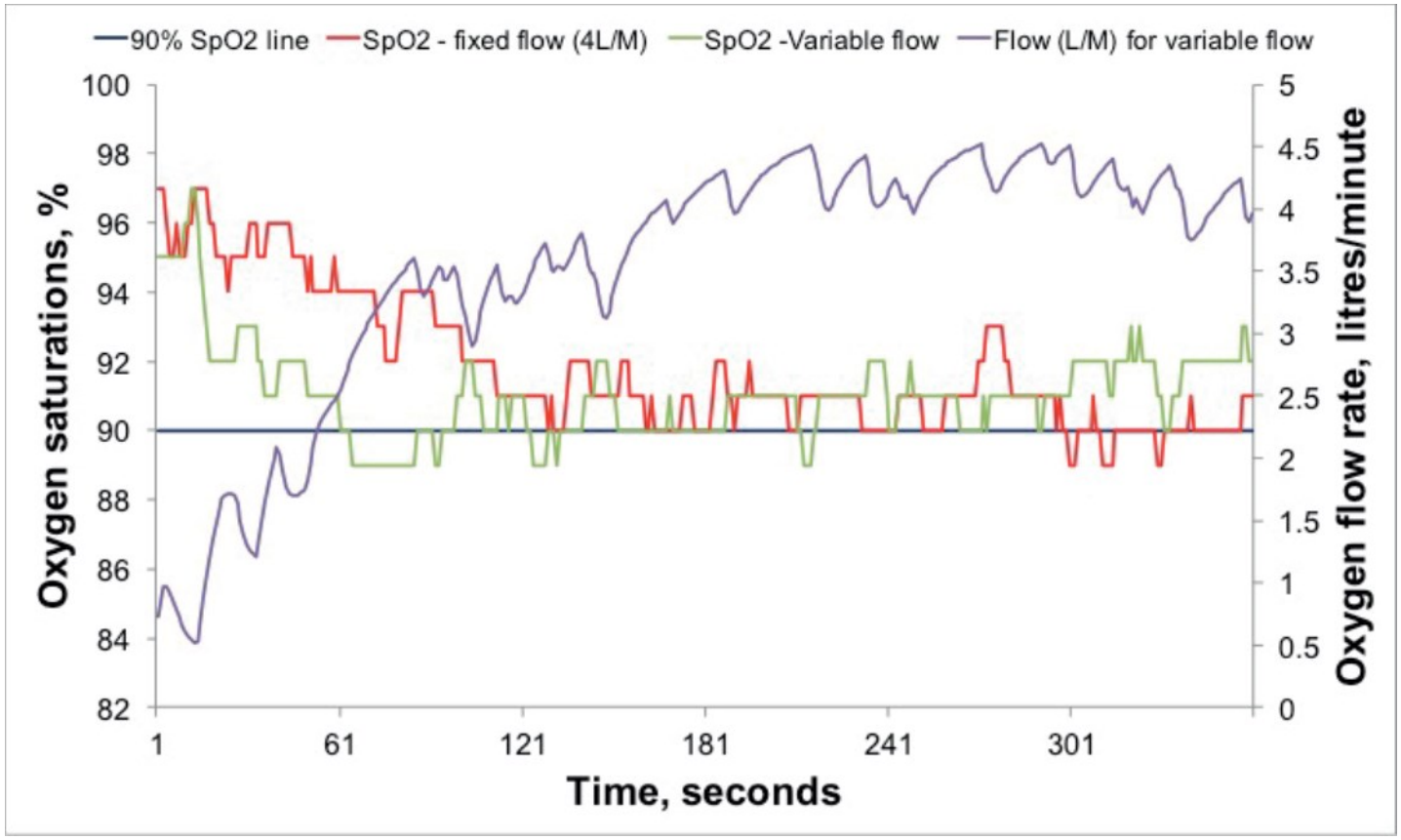


Figure 4-3 Change in oxygen saturation and flow with fixed-flow ambulatory oxygen and the iO_2Ts
This is an example of one patients' change in oxygen saturations and oxygen flow rate during a 6-minute walk tests on fixed-flow oxygen and the intelligent oxygen therapy system. The change in oxygen flow rate with the intelligent oxygen therapy system is also shown in blue.
iO_2Ts = intelligent oxygen therapy system

4.3.4 Primary outcome: percentage of time spent with SpO_2 <90%

Figure 4-4 shows that the iO_2Ts statistically significantly reduced the median percentage of time spent with SpO_2 <90% compared to fixed-flow oxygen from 84.6% [IQR: 42.3-90.0] to 62.1% [IQR: 22.6-83.7], p=0.033. For nine patients, there was reduction in the percentage of time spent with SpO_2 <90% with the iO_2T system, no difference for one patients and two patients were less hypoxic with fixed-flow oxygen therapy than with the iO_2T system.

Figure 4-5 shows that the reduction in the percentage of time spent with SpO_2 <90% was predominantly in the second half of the 6MWT (181 - 360 seconds) rather than the first half (1 - 180 seconds). Associated with this, there is a trend towards an increase in the distance walked in the second half of the 6MWT.

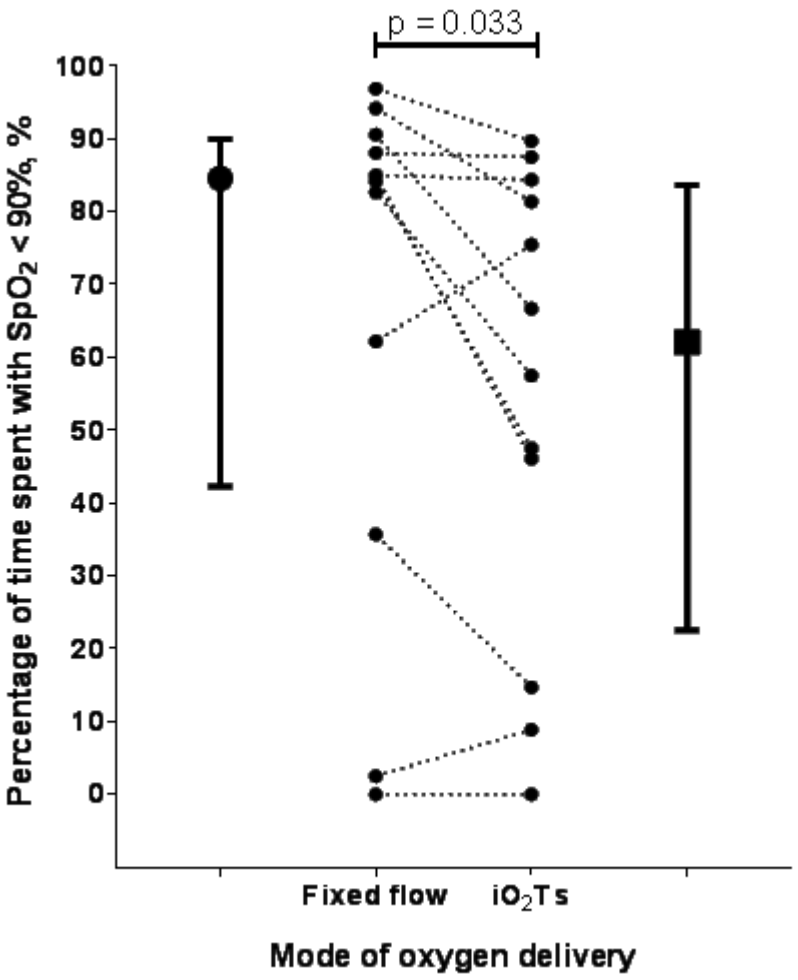


Figure 4-4 Percentage of time spent with SpO_2 <90% with fixed-flow oxygen and the iO_2Ts

Plot showing the primary outcome of percentage of time spent with SpO_2 <90% by 12 patients whilst on fixed-flow oxygen and intelligent oxygen therapy. Each dashed line represents one patient. The error bars represent the 95% confidence interval of the median. Overall, there was a statistically significant reduction in the median time spent whilst on the intelligent oxygen therapy system compared to fixed-flow therapy, p=0.033, Wilcoxon-Sign ranked test.

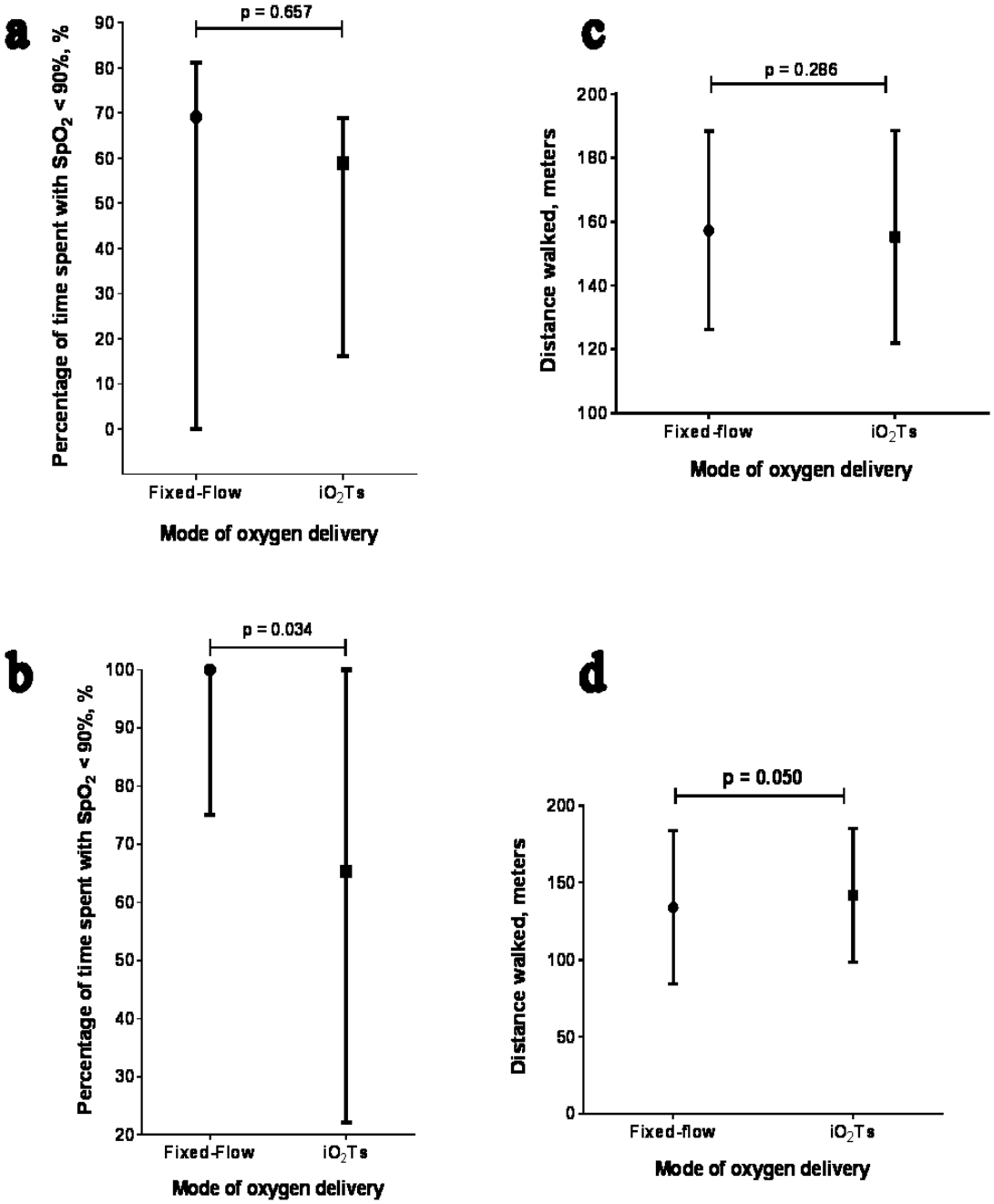


Figure 4-5 Percentage of time spent with SpO_2 <90% and the total distance walked during the two halves of the 6MWT

The median percentage of time spent with SpO_2 <90% during the first half of the 6MWT (a) versus the second half (b) and the effect on the median walking distance during the first half of the 6MWT (c) versus the second half (d). The error bars represent the 95% confidence interval of the median. p-values are for Wilcoxon-Signed rank test

6MWT = 6-minute walk test, SpO_2 = oxygen saturation, iO_2Ts = intelligent oxygen therapy system

4.3.5 Secondary outcomes

The mean SpO_2 was statistically significantly higher with the iO_2Ts compared to fixed-flow oxygen therapy; 89.5% (IQR: 85.1-90.8) vs. 86.5% (IQR: 84.4-90.5), respectively, p=0.038 (Figure 4-6a). The trough SpO_2 was also statistically significantly higher with the iO_2Ts compared to fixed-flow oxygen therapy; 87.0% (IQR: 82.3 – 88.0) vs. 83.5% (IQR: 79.0 – 87.5), respectively, p=0.009 (Figure 4-6a).

There was no statistically significant difference in median percentage of time spent with SpO_2 <88% between the iO_2Ts and fixed-flow oxygen 0.956% (IQR: 0 – 81.1) and 68.1% (IQR: 8.4-80.1) respectively, p=0.110. There is considerable difference in the medians but due to the very large range of values, there is no statistically significant difference.

There was no difference in the mean heart rate between the iO_2Ts and fixed-flow oxygen, 111.0 beats/minute (IQR: 104.9 – 118.3) vs. 110.0 beats/minute (IQR: 106.5 – 118.4), respectively, p=0.953. There was also no difference in the peak heart difference between the iO_2Ts and fixed-flow oxygen, 115.5 beats/minute (IQR: 113.5 – 124.8) vs. 117.0 beats/minute (IQR: 113.0 – 125.5), respectively, p=0.574 (Figure 4-6b).

There was no difference in the total distance walked, the end of 6MWT Borg score, Borg score recovery time or the total volume of oxygen delivered between the iO_2Ts and fixed-flow oxygen (Table 4-2).

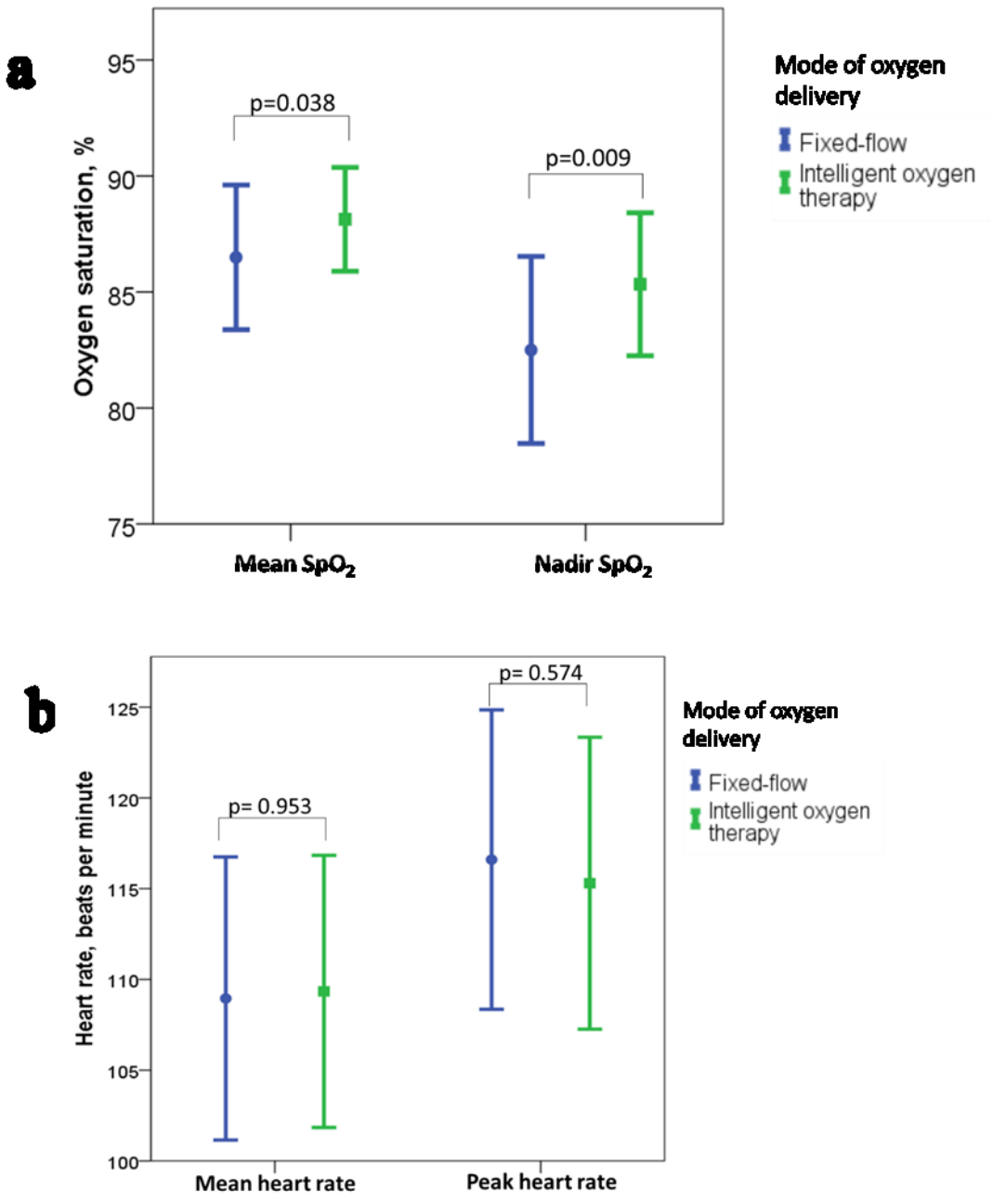


Figure 4-6 Change in SpO_2 and heart rate during the 6MWT
Panel a shows the change in median of the mean SpO_2 and median trough SpO_2 and panel b shows the change in median of the mean heart rate and median peak heart rate during the 6MWT on fixed-flow oxygen and the iO_2Ts. The error bars represent the 95% confidence interval of the median. p-values are for Wilcoxon-Sign ranked test. SpO_2 = oxygen saturation, iO_2Ts = intelligent oxygen saturation system.

Table 4-2 Selected secondary outcomes

Outcome parameter	Mode of oxygen delivery		p-value
	Fixed-flow oxygen	iO_2Ts	
Total distance walked, meters#	298 [222 – 355]	309 [240 – 340]	0.386
End of test Borg sore, dyspnoea§	5.0 [4.0 – 6.0]	4 [3.3 – 5.0]	0.336
End of test Borg score, leg fatigue§	4.0 [2.0 – 6.0]	3.0 [1.3 – 4.8]	0.172
Borg score recovery time, seconds§	198 [120 – 270]	180 [120 – 260]	0.646
Volume of oxygen delivered (walk and recovery), litres§	27.9 [16·3 – 35·5]	35.1 [27·8 – 35·5]	0.248

Data are all median [interquartile range]. The p-values are all for Wilcoxon signed rank test. iO_2Ts = intelligent oxygen therapy system, SpO_2 = oxygen saturations; # = 12 patients, § = 11 patients

4.3.6 The iO_2Ts as an oxygen assessment tool

Table 4-3 shows the percentage of time spent with SpO_2 <90% for each patient and the 90th percentile flow rate for each patient. Utilising the 90th percentile flow rate as the optimal for the 6MWT, ten patients would require an increase in their ambulatory flow prescription, one patient a reduction and there would be no change for one patient.

Table 4-3 Individual patient data on the primary outcome and oxygen flow rates

Individual patient data showing the percentage of time spent with SpO_2 <90% by each patient on the fixed-flow and iO_2T system, their usual ambulatory oxygen flow rate and 90th percentile flow rate on the iO_2T system.

Patient ID	Percentage of time spent with SpO_2 <90%		Ambulatory flow rate, Litres/minute	90th percentile flow rate – iO_2T data, litres/minute	Change in fixed-flow required
	Fixed-flow	iO_2T			
1	85	84.4	4	>5	↑
2	82.7	57.5	2	5	↑
3	35.7	14.7	3	4	↑
4	84.2	47.5	2	4	↑
5	90.6	66.7	3	5	↑
6	88.1	87.5	4	>5	↑
7	85	46.1	0.75	5	↑
8	62.2	75.5	3	>5	↑
9	94.2	81.4	3	>5	↑
10	96.9	89.7	2	>5	↑
11	0	0	3	2	↓
12	2.5	8.9	4	4	↔

4.4 Discussion

The main finding of this study was that the iO_2Ts significantly reduced the median percentage of time spent with SpO_2 <90% compared to fixed-flow oxygen in patients with COPD on LTOT during a 6MWT. The overall median SpO_2 on the iO_2Ts was close to 90% and significantly higher than on fixed-flow oxygen. The trough SpO_2 was also significantly higher on the iO_2Ts compared to fixed-flow oxygen. Therefore, patients not only spent less time with SpO_2 <90% whilst on the iO_2Ts, the severity of the hypoxia they did experience was also reduced by the iO_2Ts. These improvements in oxygenation and the reduction in intermittent hypoxia may improve oxygen supply to the brain, reduce episodic pulmonary hypertension associated with desaturations and reduce the risk of hypoxia associated arrhythmias (Selinger et al., 1987, Oliveira et al., 2012, Higashimoto et al., 2015, Tirlapur and Mir, 1982).

Despite the improvement in oxygenation there was no difference in the total distance walked nor breathlessness with the iO_2Ts. The improvement in oxygenation was more significant in the second half of the 6MWT rather than the first and this was associated with a trend towards a small increase in the distance walked with improved oxygenation ($p=0.05$). In a previous systematic review, ambulatory oxygen was shown to increase exercise capacity and reduce breathlessness in the short term in patients with COPD and therefore these results are not consistent with data from this study (Bradley et al., 2007). However, it is imperative to note that most of the studies in the systematic review have compared supplementary oxygen with either placebo or air. This study specifically investigated if optimised oxygen therapy delivered via the iO_2Ts could reduce intermittent hypoxia compared to fixed-flow oxygen and thereby improve exercise capacity and breathlessness. Davidson and colleagues and Somfay and colleagues both investigated the effects of different oxygen concentration on exercise capacity and breathlessness (Davidson et al., 1988, Somfay et al., 2001). Bradley and O'Neill performed a meta-analysis of data from these two studies for their Cochrane review and demonstrated that higher concentrations of oxygen improved neither exercise capacity nor breathlessness compared to lower oxygen concentration and this is consistent with the findings of this study (Bradley and O'Neill, 2005).

Despite improvements in oxygenation, there was no effect on the patients' sensation of breathlessness or fatigue as measured on the Borg scale. However, this may not be very surprising as breathlessness and fatigue during exercise are influenced by physical (hyperinflation, airflow obstruction), psychological as well as environmental factors and the optimisation of oxygen therapy alone may not contribute significantly to changes in the overall sensation of breathlessness (O'Donnell et al., 2007). Despite the improvement in oxygenation,

there was no difference in the stress response on the cardiovascular system as measured by the mean or peak heart rate during the 6MWT.

Several previous studies have investigated the use of auto-titrating oxygen systems in self-ventilating adults. In an open label study, Rice et al., investigated the use of an auto-titrating oxygen system in patients with COPD on LTOT in a domiciliary setting comparing their own auto-titrating oxygen system ($AccuO_2$) to fixed-flow LTOT and an oxygen conserving system (Rice et al., 2011). The $AccuO_2$ system maintained SpO_2 close to 90% (in accordance with its design) and reduced the percentage of time spent with SpO_2 <90% compared to the other two systems (although statistically not significant). There was no difference in activity levels on the different oxygen systems. Circio and Nava tested an auto-titrating system in patients with COPD during a cycling test (Cirio and Nava, 2011). The auto-titrating system maintained a higher SpO_2, reduced the amount of time spent with SpO_2 below the set target and required less operator input than usual fixed-flow oxygen. There was no change in breathlessness scores or heart rate between fixed-flow oxygen and the auto-titrating oxygen system.

Two recent studies involving the $FreeO_2$ system, which have comparable methodology with this study have been published. Lellouche and colleagues tested the $FreeO_2$ system in patients with COPD (not on LTOT) during an endurance shuttle walk test (ESWT) (Lellouche et al., 2016b). Participants undertook tests on air, fixed-flow oxygen and the $FreeO_2$ system in a randomised and blinded study. They demonstrated that the $FreeO_2$ system maintained SpO_2 in optimal range of 92-96% for a greater time than air or fixed-flow oxygen and significantly reduced the percentage of time spent with SpO_2 <88%. There was no statistically difference in walking distance between fixed-flow oxygen and the $FreeO_2$ system and most patients required >5 litres/minutes when utilising the $FreeO_2$ system. Vivodtzev and colleagues also tested the $FreeO_2$ system against fixed-flow oxygen in 8 patients with COPD on LTOT during an ESWT (Vivodtzev et al., 2016). They demonstrated that the $FreeO_2$ system significantly improved oxygenation ($p=0.03$) with a trend towards an improvement in walking distance during the ESWT ($p=0.07$). The mean flow rate whilst the patients were utilising the $FreeO_2$ system was 5.9±3.1 litres/minute.

Both studies involving the $FreeO_2$ system have demonstrated a greater reduction in intermittent hypoxia than the iO_2Ts. This is almost certainly because the $FreeO_2$ system can supply greater flow rates (up to 20 litres/minute) than the iO_2Ts which is flow limited at 5 litres/minute. The iO_2Ts is flow limited at 5 litres/minute as this is maximum flow rate provided by most oxygen concentrators in the UK and our intention with developing the iO_2Ts is to optimise domiciliary LTOT. Therefore, we have developed a novel smartphone based portable system that can be utilised in patients' homes and for ambulatory oxygen but is not intended for hospital utilisation.

Although the iO_2Ts does not reduce intermittent hypoxia to the same degree as the $FreeO_2$ system, it does reduce intermittent hypoxia significantly (%Δ27%), and could potentially be used in patients' home whereas the $FreeO_2$ system is suitable for hospital use but due its size not suitable for domiciliary or ambulatory oxygen.

In this study, the iO_2Ts reduced intermittent hypoxia compared to fixed-flow oxygen consistent with published studies utilising other auto-titrating oxygen systems. Consistent with other auto-titrating oxygen systems, the improvements in oxygenation were not associated with any reduction in breathlessness, increase in exercise tolerance nor reduction in the mean or the peak heart rate.

4.4.1 The iO_2Ts as an oxygen assessment tool

Currently there is no gold standard as to the best method of determining the oxygen flow rate required for ambulatory oxygen. The oxygen flow data from the iO_2Ts was analysed to determine the flow rate required for 90% of the time during the 6MWT (i.e. the flow rate above which patients spent little time). This revealed that most of the patients would require an increase in their ambulatory oxygen flow rate to >5 litres/minute. Given that most of the patients spent a significant amount of time with SpO_2 <90% whilst of the iO_2Ts, the flow-time data is of little value in determining the ideal ambulatory oxygen flow rate in this study.

4.4.2 Strengths and limitations of the study

There were three main strengths to this study. Firstly, it was a randomised and double-blind so that neither the investigator nor the participant were aware of the oxygen delivery method during the 6MWT. Secondly all patients underwent a practice 6MWT to negate the learning effect of the 6MWT. Thirdly the primary endpoint was based on objective data.

There are also several limitations in this study which need further discussion. Despite the clinically significant 21% improvement in the percentage of time spent with SpO_2 <90%, patients still spent a significant 62% of the time with SpO_2 <90%. This is almost certainly due to the flow limitation of the iO_2Ts as already discussed. This is confirmed by analysing the flow data from the iO_2Ts which reveals that most participants would require flow rate of >5 litres/minute for ambulatory oxygen and this is greater than the maximum output of the iO_2Ts. In the exclusion criteria of the study, the aim was to exclude patients who required ambulatory oxygen flow rates of ≥5litres/minute due to the limitation of the device. Despite this, most of the participants recruited have been found to require flow rates >5litres/minute and one reason

for this may be the limitation of how ambulatory oxygen flow rates were assessed for the individual patients.

The sample size of this study was calculated using pilot data and investigating for a large difference between the iO_2Ts and fixed-flow oxygen. Given the small sample size, it is difficult to extrapolate from this small number to every patient who is on LTOT.

This study compared fixed-flow oxygen to variable flow oxygen (iO_2Ts). As oxygen was delivered by nasal cannulae, most patients are aware of the sensation of how their usual oxygen flow rate feels. Thus, some patients may have been able to make an educated guess as what type of oxygen was being delivered which could have inadvertently lead to unblinding of some participants. As a result, this could have affected some of the secondary outcomes such as the Borg score. However, as the primary outcome was objective, this was unlikely to have been affected.

4.4.3 Conclusion

In this prospective, randomised, double-blind study, the iO_2Ts reduced intermittent hypoxia in patients with COPD on LTOT compared to fixed-flow during a 6MWT. Due to the flow limitation of the device, the iO_2Ts is best suited for patients with ambulatory flow rates ≤ 4 litres/minute. Its value as an oxygen assessment tool could not be assessed in this study as most of the patients had residual intermittent hypoxia despite the iO_2Ts.

5 Chapter 5 – Intelligent oxygen therapy during a 6-minute walk test in patients with idiopathic pulmonary fibrosis

5.1 Introduction

5.1.1 Background

Interstitial lung disease (ILD) is a term used to describe a heterogenous group of disorders characterised by varying degrees of pulmonary inflammation and fibrosis, similar clinical presentations and changes in lung function that can all lead to progressive respiratory failure (Travis et al., 2013). The most common ILD is idiopathic pulmonary fibrosis (IPF) (Travis et al., 2013). IPF is characterised by a usual interstitial pneumonia histological pattern with honeycombing on CT imaging and its incidence in increasing worldwide (Gribbin et al., 2006, Raghu et al., 2014). It has a median survival of just 2.9 years and effective therapies to reduce disease progression are only just becoming available (Hubbard et al., 1998, King et al., 2014, Richeldi et al., 2011, Richeldi et al., 2014).

Many patients with IPF have normal oxygen saturations at rest but desaturate rapidly during exercise and this desaturation is more rapid than that seen in patients with COPD (Nishiyama et al., 2007). The aim of ambulatory oxygen in patients with IPF who desaturate on exercise is to reduce intermittent hypoxia, reduce breathlessness, improve exercise capacity and improve quality of life (Hardinge et al., 2015). Ambulatory oxygen is recommended for patients with normal resting SpO_2 who have a reduction in SpO_2 of greater than 4% to an SpO_2 <90% during an exercise test with an associated improvement is symptoms or improvement in exercise capacity (Hardinge et al., 2015). Ambulatory oxygen is also recommended for patients already on LTOT to allow patients to leave their home and to enable LTOT use for the minimum recommended period of 16 hours per day.

A retrospective study by Visca *et al*., showed that ambulatory oxygen significantly increased oxygen saturations, improved exercise capacity and reduced breathlessness in patients with ILD during a 6MWT (Visca et al., 2011). Another retrospective study from Field *et al*., showed that optimised ambulatory oxygen significantly improved exercise capacity in patients with IPF during a 6MWT (Frank et al., 2012). However, both studies were retrospective analyses with all the associated limitations of this study design and in both studies patients continued to experienced oxygen desaturations and therefore there is a need to optimise oxygen therapy further.

In a recent Cochrane review of ambulatory oxygen in patients with ILD, only three blinded and randomised studies of oxygen therapy in patients with ILD were identified (two conference abstracts and one publication) (Sharp et al., 2016). In two of these studies, intermittent hypoxia could not be completely reduced (Arizono et al., 2015, Nishiyama et al., 2013). In two studies,

there was no change in breathlessness or exercise capacity during exercise tests with supplementary oxygen in comparison to air (Nishiyama et al., 2013, TROY et al., 2014). The third study showed an increase in endurance time during constant load ergometry tests (Arizono et al., 2015). Overall, the Cochrane review found no evidence to support or refute the use of ambulatory oxygen in patients with ILD and recommended further research into this area.

5.1.2 Aims and hypothesis

The aim of this study was to investigate if the iO_2Ts, by delivering variable flow oxygen to maintain a pre-set SpO_2 target, could reduce intermittent hypoxia in patients with IPF compared to fixed-flow ambulatory oxygen during a 6MWT. This study was important for two reasons: firstly, due to the lack of evidence for ambulatory oxygen in patients with ILD and secondly because patients with ILD desaturate faster than patients with COPD and therefore this is a more rigorous test of the iO_2Ts in terms of delivering targeted oxygen therapy. We tested the hypothesis that optimised oxygen therapy with the iO_2Ts could reduce intermittent hypoxia compared to usual fixed-flow ambulatory oxygen.

5.2 Methods

5.2.1 Study design and participants

This was a prospective, single centre, randomised, double-blind, crossover study. Participants with a diagnosis of IPF who were on or eligible for ambulatory oxygen (either ambulatory oxygen only or ambulatory oxygen with LTOT) were invited to participate. Patients were identified from sources previously described in chapters 3 and 4. Participants were asked to complete three 6MWT. The first was an unblinded open label 6MWT on air to account for the learning effect of the 6MWT. The next two 6MWTs were carried out in a randomised order with blinding of both the patient and the assessor in a manner identical to that described in chapter 4.

Ethical approval was given by the West-Midlands South Birmingham research ethics committee as an amendment to the ethical application in chapter 4 (14/WM/0130) (appendix 4 for REC approval letter). All patients gave informed and written consent for the study. The study was registered on Clinicaltrials.gov, NCT02248064. Regulatory clearance was already in place as described in chapter 4.

5.2.2 Inclusion criteria

1. Age > 18
2. Patients with IPF currently on or eligible for ambulatory oxygen therapy (ambulatory oxygen only or ambulatory oxygen with LTOT)

5.2.3 Exclusion criteria

1. Unable to mobilise for a 6MWT
2. Unable to consent to study,
3. PaO_2 < 6.0 kPa or $PaCO_2$ > 8 kPa on air,
4. Exacerbation of the underlying lung disease in the previous 4 weeks
5. Unstable cardiovascular disease (e.g. arrhythmia, hypertension/hypotension or angina)
6. Pregnancy

5.2.4 The intelligent oxygen therapy system

The iO_2Ts is a novel smartphone auto-titrating oxygen system which continuously monitors a patients' SpO_2 and automatically adjusts oxygen flow rates to maintain a pre-set SpO_2 target in the face of continually changing patient requirements (for further details see Chapter 2). During the 6MWT the participants wore a Nonin-4100 Bluetooth pulse oximeter on the ear-lobe. The iO_2Ts was set to maintain a SpO_2 of 93%.

5.2.5 Protocol and data collection

The protocol and data collection followed the same methodology as described in the methods section of chapter 4.

5.2.6 Study outcomes

Primary outcome

The primary outcome was the difference in the percentage of time spent with SpO_2 <90% between fixed-flow oxygen and the iO_2Ts during the 6MWT.

Secondary outcomes

1. The differences in the following variables between the iO_2Ts and fixed-flow oxygen during the 6MWT:

- Percentage of time spent with SpO_2 < 88%
- Mean SpO_2
- Trough SpO_2
- Mean heart rate
- Peak heart rate
- Volume of oxygen delivered
- Borg score
- Borg score recovery time

2. The assessment of the iO_2Ts as an oxygen assessment tool.

5.2.7 Sample size estimation

There have been no previous studies describing the use of any auto-titrating oxygen system in patients with IPF. The preliminary work by Dr.Iobbi with the iO_2Ts included only one patients with IPF. Therefore, there is very little data to guide a sample size calculation. Therefore, the sample size calculation is extrapolated from the preliminary data described in chapter 1 and is the same as that used to calculate the sample size in chapter 4. An a priori decision was made

to investigate for a significant difference of 20% in the percentage of time spent with SpO_2 <90% between the iO_2Ts and fixed-flow oxygen. Using a standard deviation of 18% (derived from the pilot data), with an α of 0.05 and β of 0.8, the estimated sample size was 9 patients. Given the lack of data in patients with ILD, a decision was made to recruit 14 patients as this would allow greater experience to be gained with the use of the iO_2Ts in patients with ILD and additionally allow meaningful statistical analysis.

5.2.8 Statistical analysis

The continuous baseline characteristics are presented as mean ± SD or median [interquartile range]. The categorical variables are presented as numbers and percentage in that category. The primary outcome variable of the difference in the percentage of time spent with SpO_2 <90% between fixed-flow oxygen and the iO_2Ts was check for normality visually, with a histogram and boxplot, skewness and kurtosis and the Shapiro-Wilks test. The difference was not normally distributed and therefore the differences were analysed using a Wilcoxon-Signe ranked test. All continuous secondary outcome variables were analysed for normality using the above methods and as the differences were not normally distributed, the outcomes were analysed using the Wilcoxon-Sign ranked test.

Between group differences between patients who desaturated during the 6MWT and those who did not desaturate were analysed using either an Independent Samples T-Test or Mann-Whitney U test for continuous variables and Fishers exact test for categorical variables.

All statistical analyses were conducted in SPSS version 22.0 (IBM, New York, USA). Additional figures were created in GraphPad Prism version 7.0 (California, USA).

5.3 Results

5.3.1 Patient recruitment

Between November 2014 and September 2015, 68 patients meeting the inclusion criteria of having a diagnosis of IPF and prescribed ambulatory oxygen were identified (consort diagram Figure 5-1). Of these 68 patients, 36 were excluded as they were prescribed ambulatory oxygen at high flow rates (≥5 litres/minute). Of the 32 patients who were eligible, 18 declined to participate and 14 were randomised.

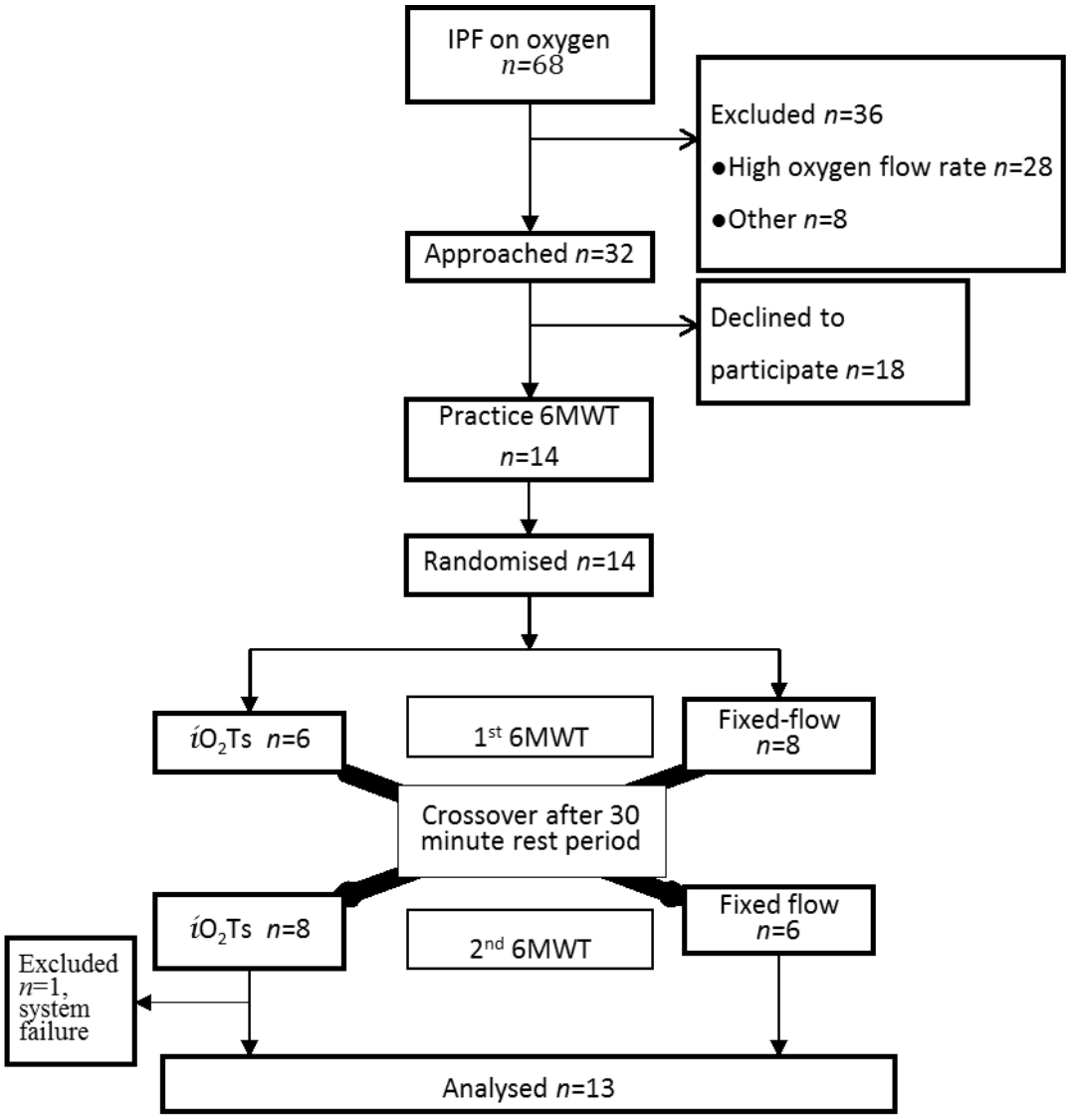


Figure 5-1 Consort diagram for patient recruitment
IPF = idiopathic pulmonary fibrosis, 6MWT = 6-minute walk test, iO_2Ts = intelligent oxygen therapy system.

5.3.2 Baseline Characteristics

Fourteen patients were randomised in line with the sample size calculation and the baseline characteristics of the patients are shown in Table 5-1. There were 8 males (57%), the mean ±SD age of 66.9 ± 9.2 years. The mean FEV_1 was 1.93 ± 0.60 litres and the percentage predicted FEV_1 was 72.0 ± 18.6%. The baseline PaO_2 was 9.22 ± 1.62 kPa and the baseline $PaCO_2$ was 4.83 ± 0.69 kPa. Of the randomised patients 12 (86%) were on ambulatory oxygen only and 2 (14%) were on LTOT with additional ambulatory oxygen. The median ambulatory oxygen flow rate was 3.0 litres/minute [IQR, 2.0 – 4.0]. Pirfenidone was prescribed for 8 (57%) patients.

Table 5-1 Baseline characteristics of the study population, n=14

Parameter	Value	
Gender (male), n (%)	8 (57)	
Age, years	66.9 ± 9.2	
BMI, kg/m^2	28.7 ± 3.6	
FEV_1, Litres	1.93 ± 0.60	
Percentage predicted FEV_1, %	72.0 ± 18.6	
FVC, Litres	2.35 ± 0.77	
Percentage predicted FVC, %	69.1 ± 17.0	
Duration of IPF	2.0 [1.4 – 2.5]	
Baseline PaO_2, kPa	9.22 ± 1.62	
Baseline $PaCO_2$, kPa	4.83 ± 0.69	
Pulmonary Hypertension, n (%)	4 (29)	
Ambulatory flow rate, Litres/min	3.0 [2.0 – 4.0]	
MRC breathlessness score (2/3/4/), n (%)	3 (21)/ 6 (43) / 5 (36)	
Smoking history, pack years	24.7 ± 11.9	
Oxygen history, n (%)	Ambulatory only	12 (86)
	LTOT and ambulatory	2 (14)
Medication		
Pirfenidone, n (%)	8 (57)	
Prednisolone	5 (36)	
N-acetylcysteine	5 (36)	

Data shown as n (%), mean ± SD or median [interquartile range]. BMI = Body mass index, FEV_1 = Forced expiratory volume in the first second, FVC = Forced vital capacity, LTOT = Long-term oxygen therapy, PaO_2 = Partial pressure of oxygen, kPa = kilopascal, $PaCO_2$ = Partial pressure of carbon dioxide, MRC = medical research council, IPF = idiopathic pulmonary fibrosis

5.3.3 The effects of the iO_2Ts on SpO_2 during 6MWT in patients with IPF

Figure 5-2 shows the change in SpO_2 with fixed-flow oxygen and the iO_2Ts during 6MWTs for three patients. These three patients have been selected as they demonstrate different aspects of the effects of fixed-flow oxygen and the iO_2Ts on oxygen saturations during the 6MWT.

From figures a and b it can be appreciated that in the early part of the 6MWT, patients on fixed-flow oxygen at a high flow rate are somewhat protected from oxygen desaturation. In contrast, with the iO_2Ts, patients desaturate quickly as they are on lower oxygen flow rates initially (as the system is providing oxygen to target SpO_2). However, this quickly changes as the iO_2Ts increases oxygen flow rates to reduce the severity of the desaturation. It can also be appreciated that although the system is targeting a SpO_2 of 93%, neither the patients in figure a or figure b reach a consistent SpO_2 of 93% even though the system could potentially increase the oxygen flow rate by an additional 0.5 – 1 litre/minute. This is probably related to the rate of change in flow rate as the actual SpO_2 reached the set-point SpO_2.

The patient in figure c will require very high oxygen flow rates as there is no discernible change in SpO_2 even with oxygen flow rates of 5 litres/minute. One interesting observation is that as the iO_2Ts reaches its flow limitation of 5 litres/minute, the rate of oxygen increase slows down markedly.

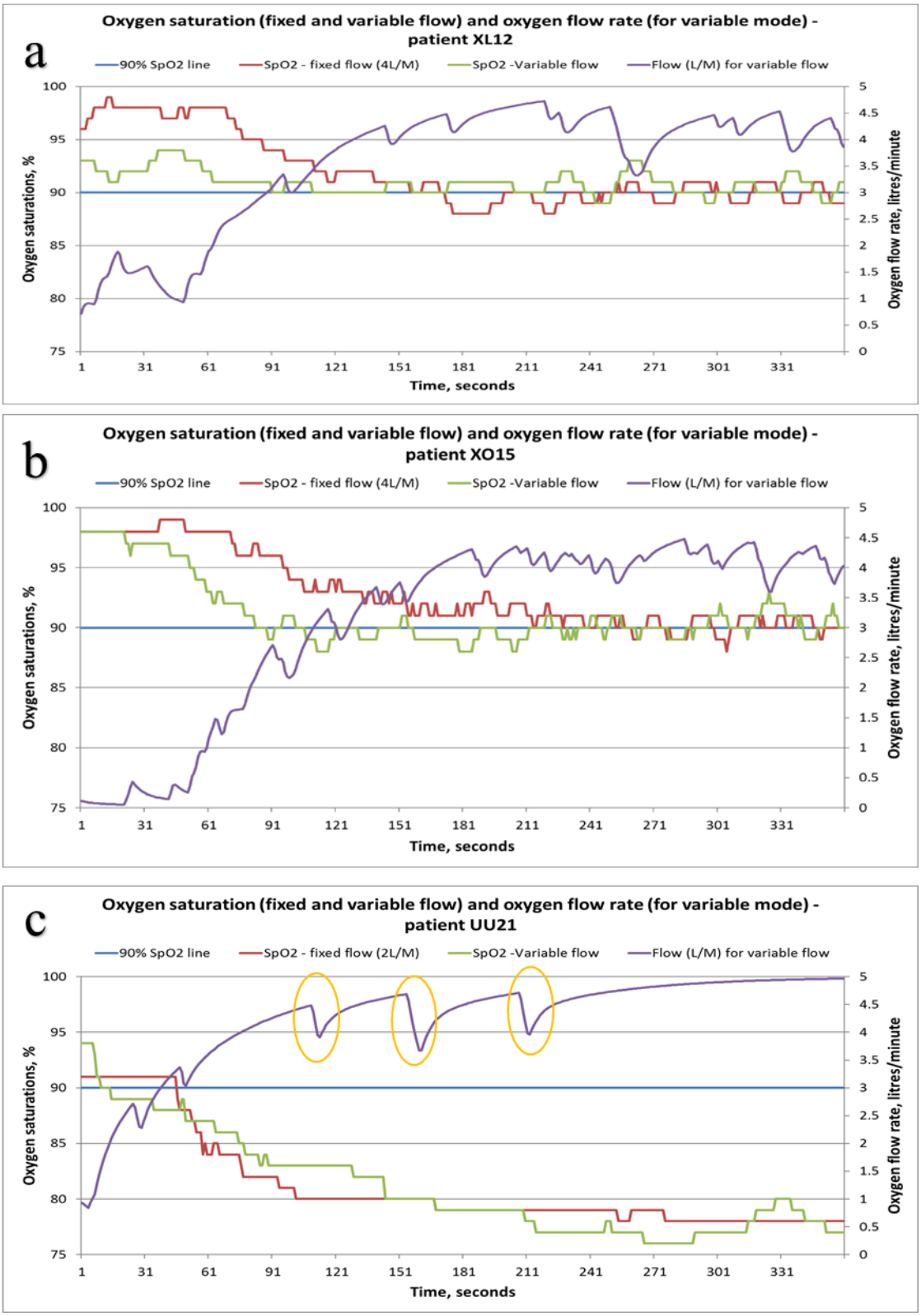


Figure 5-2 The change in SpO_2 with fixed-flow oxygen and the iO_2Ts during 6MWTs for three patients
In figures a and b, the high fixed-flow ambulatory oxygen flow rate protects the patients from desaturation during the first half of the 6MWT and it time for the iO_2Ts to increase the flow rate up to the level of ambulatory oxygen. For patient a, the oxygen flow rate with the iO_2Ts is high enough to stop desaturations below 90% but not so for patients b. Patient c is very hypoxic on their usual fixed-flow oxygen and on the iO_2Ts. For this patient, additional oxygen makes no difference at all to the patients SpO_2 as he continues to desaturate despite higher flows. There are sudden decreases in oxygen flow rate with the iO_2Ts system (circled in figure c) and this correspond to loss of SpO_2 signal from the pulse oximeter.

5.3.4 Primary outcome of percentage of time spent with SpO_2 <90%

Data from thirteen patients was analysed for the primary outcome. There was no difference in the median percentage of time spent with SpO_2 <90% between the iO_2Ts and fixed-flow ambulatory oxygen during a 6MWT: 0.0% [IQR, 0.0 – 80.5] and 14.9% [IQR, 0.0 – 80.6], respectively, p=0.866, shown in Figure 5-3.

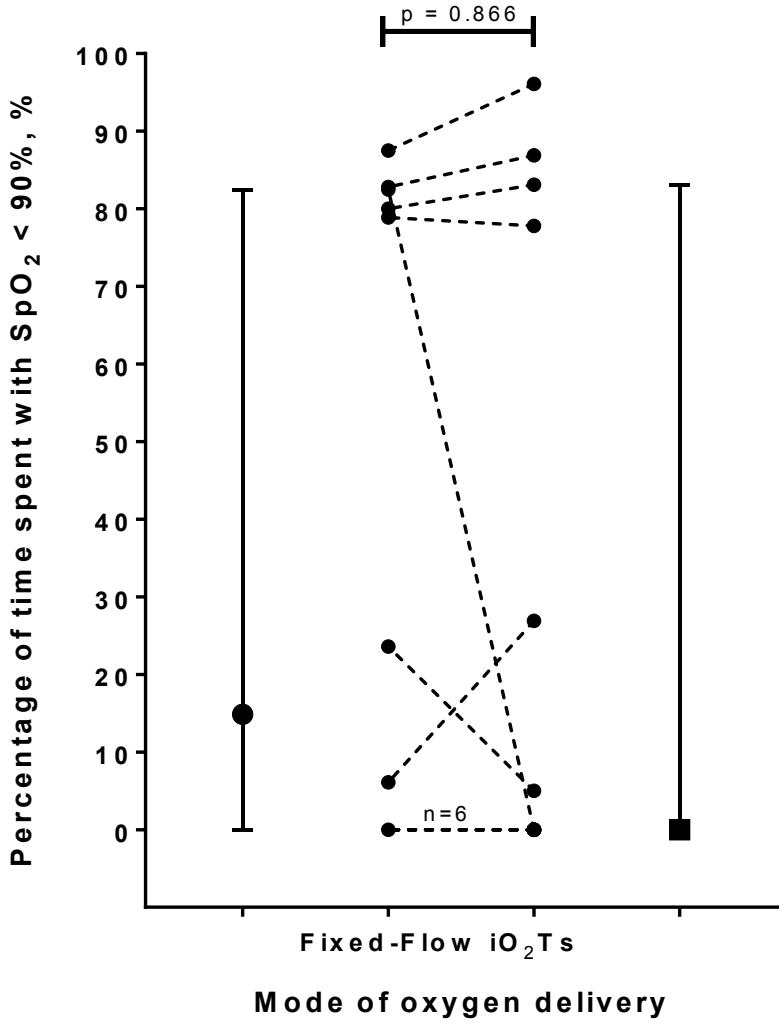


Figure 5-3 The primary outcome of percentage of time spent with SpO_2 <90% during the 6MWT
The was no difference in the percentage of time spent with SpO_2 <90% between fixed-flow oxygen and the iO_2Ts. Six participants had no intermittent hypoxia on their usual ambulatory oxygen and with the iO_2Ts. The error bars represent the 95% confidence interval of the median. p-value for Wilcoxon-Sign ranked test. SpO_2 = oxygen saturation, iO_2Ts = intelligent oxygen therapy system.

There were six patients who did not desaturate during the 6MWT with their usual fixed-flow oxygen. Of these six patients, two also did not desaturate during their practice walk on air which could suggest that they do not require ambulatory oxygen. Removing these two patients from the primary outcome analysis did not change the overall result with the median percentage of time spent with SpO_2 <90% with the iO_2Ts now 5.0% [IQR,0.0 – 83.1] and 23.6% [IQR, 0.0 – 82.5] with fixed-flow oxygen, p = 0.866 (Wilcoxon-Sign ranked test).

5.3.5 Secondary outcomes

There were no statistically significant differences for any secondary outcome variable between the iO_2Ts and fixed-flow oxygen. The median (of means) SpO_2 was 91.6% [IQR, 87.5 – 94.2] with the iO_2Ts versus 91.7% [IQR, 85.9 – 96.2] with fixed-flow oxygen, p = 0.625, Figure 5-4a. The trough SpO_2 was 89.0% [IQR, 82.5 – 91.0] with the iO_2Ts versus 88.0% [IQR, 80.8 – 93.8] with fixed-flow oxygen, p = 0.765, Figure 5-4c. The total distance walked was 361.0 meters [IQR, 317.0 – 380.5] with the iO_2Ts versus 370.0 meters [IQR, 336.0 – 383.3] with fixed-flow oxygen, p = 0.249, Figure 5-4b. The end of the 6MWT borg score for breathlessness was 3.0 [IQR, 1.3 – 4.5] with the iO_2Ts and 3.0 [IQR, 1.6 – 4.0] with fixed-flow oxygen, p = 0.450, Figure 5-4d. The other secondary outcome variables are summarised in Table 5-2.

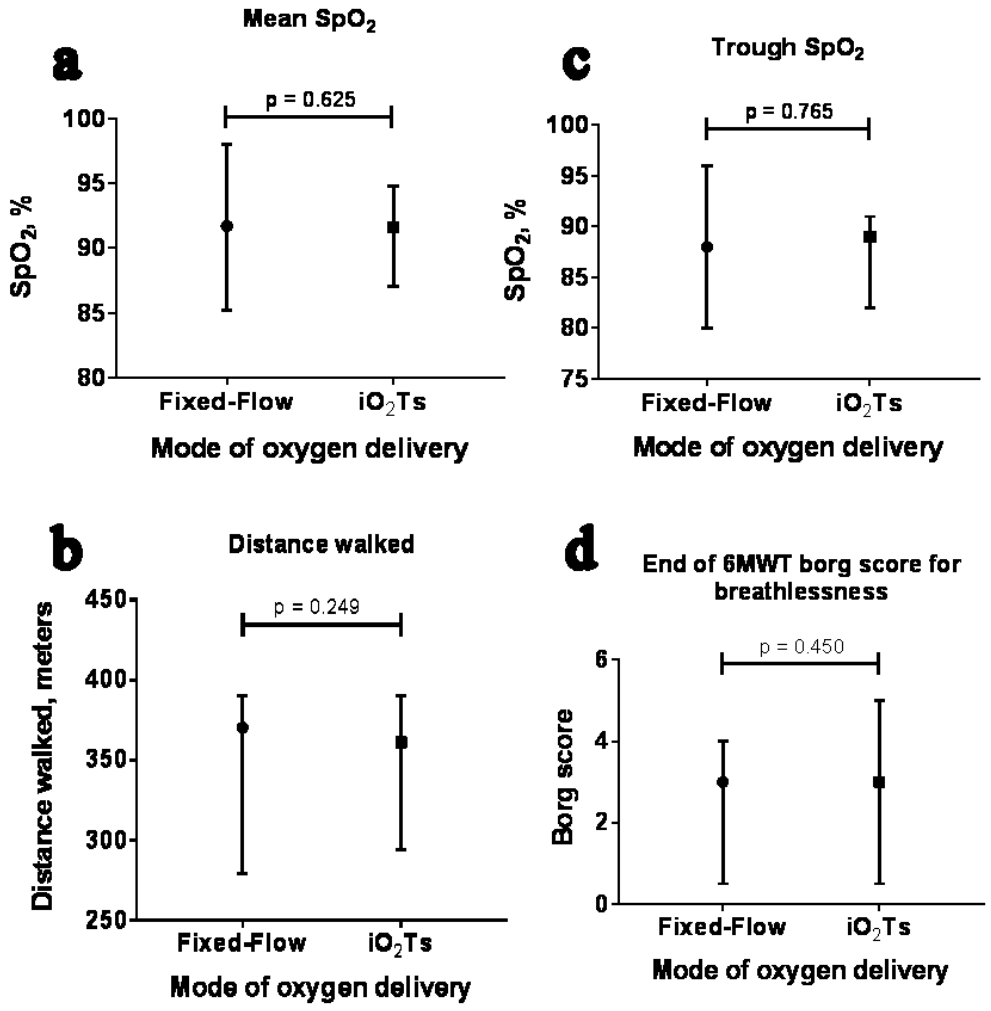


Figure 5-4 Selected secondary outcomes
N=13 for all outcome variables. All p-values are for Wilcoxon-Sign ranked test.
SpO_2 = oxygen saturation, iO_2Ts = intelligent oxygen therapy system, 6MWT = 6-minute

Table 5-2 Secondary outcomes

Outcome variable	Oxygen delivery type		p-value
	Fixe-flow oxygen	iO_2Ts	
#Percentage of time spent with SpO_2 <88%, %	0.0 [0.0 - 75.2]	0.0 [0.0 – 59.3]	0.080
§Mean heart rate, beats per minute	100.2 [94.7 – 115.0]	99.9 [90.8 – 116.2]	0.937
§Peak heart rate, beats per minute	112.0 [100.0 – 123.0]	110.5 [103.0 – 122.8]	0.858
§Borg score recovery time, seconds	166.0 [117.5 – 217.5]	180.0 [110.0 – 300.0]	0.374
#End of tests Borg score for fatigue,	2.0 [0.4 – 3.0]	2.0 [0.3 – 3.0]	0.336
#Volume of oxygen delivered during 6MWT and recovery phase, litres	26.0 [16.9 – 32.0]	23.4 [11.1 – 34.5]	0.583
All p-values are for Wilcoxon-Sign rank test. iO_2Ts = intelligent oxygen therapy system, 6MWT = 6-minute walk test, SpO_2 = oxygen saturation, # n=13, § n=12.			

5.3.6 Analysis of patients who did and did not desaturate during the 6MWT

During the 6MWT, six patients did not desaturate to SpO_2 <90% on their usual ambulatory fixed-flow oxygen. Analysis of the continuous baseline characteristics of patients who did not desaturate and those that did desaturate is shown in Table 5-3 and a comparison of the categorical variable are shown in Table 5-4.

Table 5-3 Continuous baseline characteristics of patients who did and did not desaturate during the 6-minute walk test

Variable	Non-desaturators (n = 6)	Desaturators (n = 8)	P-value
Age, years	68.0±7.0	66.3±11.8	0.753[#]
BMI, Kg/m^2	28.2±2.4	28.6±4.6	0.867[#]
PaO_2, kPa	10.10±1.46	8.25±1.30	0.037[#]
$PaCO_2$, kPa	5.05±0.61	4.74±0.77	0.439[#]
FEV_1, litres	2.23±0.60	1.75±0.56	0.160[#]
FEV_1 percentage predicted, %	76.4±17.6	69.4±21.3	0.534[#]
FVC, litres	2.79±0.77	2.06±0.68	0.098[#]
FVC percentage predicted, %	74.2±16.4	64.8±18.9	0.357[#]
Ambulatory oxygen flow rate, litres/minute	2.5 [2.0 – 4.0]	4.0 [2.0 – 4.0]	0.756[##]

BMI = body mass index, PaO_2 = partial pressure of oxygen, $PaCO_2$ = partial pressure of carbon dioxide, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity. [#] p-values for independent samples T-test without assuming equal variances. [##] p-value for Mann-Whitney U test

Table 5-4 Baseline categorical variables of patients who did and did not desaturate during the 6-minute walk test

Variable	Categories	Non-desaturators, n=6	Desaturators, n=8	p-value
Gender	Male	6	2	0.249
	Female	2	3	
Pirfenidone use	Yes	6	1	0.086
	No	2	4	
Pulmonary Hypertension	Present	2	2	0.510
	Absent	6	3	
All p-values are for Fisher's Exact Test				

The results show that PaO_2 was significantly higher in patients who did not desaturate compared to patients who did desaturate. No other baseline characteristics were different between patients who did and those that did not desaturate.

5.3.7 The iO_2Ts as an oxygen assessment tool

Table 5-5 shows the individual data for the primary outcome of percentage of time with SpO_2 <90% for every patient and their ambulatory oxygen flow rate. In addition, the 90th and 95th percentiles of flow rate calculated from the flow-time data on the iO_2Ts are also shown. The two patients who did not desaturate during the 6MWT on air are shaded in grey.

The flow time data produced from the iO_2Ts is very different to the ambulatory oxygen flow rates prescribed. The system is overestimating flow rates for some patients (patient numbers 3, 4 and 8 and 9) and not providing enough oxygen due to flow-limitations to other patients (patients numbers 1,5,11 and 13).

Table 5-5 Individual patient data for the primary outcome with ambulatory flow rates and percentiles of flow data from the iO_2Ts

Patient number	Percentage of time spent with SpO_2 <90% Fixed-flow oxygen, %	Ambulatory oxygen flow rate, litres/minute	Percentage of time spent with SpO_2 <90% on the iO_2Ts, %	90^{th} percentile flow rate on iO_2Ts	95^{th} percentile flow rate on iO_2Ts
1	82.8	4	86.9	4.9	4.9
2	0.0	2	0.0	1.6	1.8
3	0.0	2	0.0	0.7	0.8
4	0.0	2	0.0	3.6	3.7
5	78.9	4	77.8	4.8	4.8
6	82.5	1	0.0	4.0	4.1
7	0.0	4	0.0	2.7	3.0
8	0.0	4	0.0	0.9	1.1
9	0.0	3	0.0	4.5	4.5
10	23.6	4	5.0	4.5	4.6
11	80.0	2	83.1	5.0	5.0
12	6.1	4	26.9	4.3	4.4
13	87.5	2	96.1	4.9	5.0

5.4 Discussion

The main finding from this study was that the iO_2Ts did not reduce intermittent hypoxia to any greater degree than usual fixed-flow ambulatory oxygen in patients in IPF during a 6MWT. Additionally, there were no differences for the important secondary outcome of breathlessness, exercise capacity or the volume of oxygen delivered between the iO_2Ts and fixed-flow ambulatory oxygen.

This is the first study to investigate the use of an auto-titrating oxygen system in patients with IPF therefore there are no studies which can be directly compared. Published studies to date have concentrated on using auto-titrating oxygen system in patients with COPD (Lellouche et al., 2016b, Lellouche et al., 2013b, Vivodtzev et al., 2016, Cirio and Nava, 2011, Rice et al., 2011) with some systems demonstrating reduction in intermittent hypoxia but without any change in breathlessness or exercise capacity.

There are very few randomised studies of ambulatory oxygen in patients with ILD. A recently published Cochrane review identified only three studies with the review concluding that there was insufficient evidence to support or refute the use of ambulatory oxygen in patients with ILD. Two studies in the Cochrane review failed to completely correct oxygen desaturations during the 6MWT. With respect to this, the iO_2Ts also failed to completely reverse oxygen desaturations as this may be one factor which accounts for its lack of efficacy in reducing breathlessness or increasing exercise capacity.

The iO_2Ts was not able to completely reverse oxygen desaturations during exercise in five patients with IPF and this difficulty was also encountered in chapter 4. The causes of this are twofold: firstly, the device is flow limited at 5 litres/minute and examining the oxygen flow data, five patients in this study required >5 litres/minute for ambulatory oxygen and it not surprising that is these patients the iO_2Ts was not more efficacious. Secondly, the rate of increase in oxygen flow decreases as the system reaches its flow limitation point of 5 litres/minute. In practice this means that it quicker to go from 1 litre/minute to 2 litres/minute than to go from 4 litres/minute to 5 litres/minute even if the difference between the actual SpO_2 and the set-point SpO_2 is the same. Consequently, in patients requiring oxygen flow rates between 4-5 litres/minute, the increase in oxygen flow is slow and intermittent hypoxia is resolved slowly. This is a part of the algorithm which needs to be optimised.

Another interesting discovery is how the algorithm behaves when SpO_2 signal is lost from the pulse oximeter. As soon as SpO_2 signal is lost, the iO_2Ts starts to reduce the oxygen flow rate which it is supplying and this is an unexpected observation. The system is designed to revert to

supplying at back up flow rate if there is no signal after 20 seconds, but the reduction of oxygen flow when SpO_2 signal is lost is unexpected. This part of the algorithm also needs to be optimised to ensure that when signal is lost the oxygen flow rate remains the same as the last output rather than gradually decreasing.

5.4.1 Limitation of the study

The first limitation of the study is that of potential unblinding as discussed previously in chapter 4. Participants are aware of how their usual oxygen flow rate feels and therefore could make an educated guess as to the type of oxygen being delivered (their usual or the new system). This has the potential to change secondary outcome such as breathlessness but would not have affected the primary outcome.

The study included two patients who potentially did not require ambulatory oxygen as neither desaturated to a SpO_2 <90% during the practice 6MWT on air and this is a weakness of the study design. One patient had a 6MWT eight months prior to participation in this study where he had desaturated on air therefore ambulatory oxygen was appropriately prescribed. He was subsequently started Pirfenidone and it is conceivable that his exercise desaturation could have resolved with Pirfenidone. The improvement in oxygen desaturation with Pirfenidone has previously been described (Azuma et al., 2005). For the second patient, there is no record of a 6MWT before his participation in this study and he may have been prescribed ambulatory oxygen for breathlessness. To account for these events, the study design should have specified oxygen desaturation on air as an inclusion criteria. However, removal of these patients' data did not result in any changes to the primary outcome.

The flow limitation of the device is another limitation of this study. Over half of potentially eligible patients were excluded as they required oxygen flow rates >5 litres/minute. This has a significant impact on the generalisability of the results and could have a potential impact on the number of the patients that the device might be suitable for in the future.

5.4.2 Conclusion

The iO_2Ts did not improve intermittent hypoxia to a greater extent than fixed-flow ambulatory oxygen in patients with IPF during a 6MWT. The flow limitation of the device is a concern as many potentially eligible patients on ambulatory oxygen were excluded from the study.

6 Chapter 6 – The intelligent oxygen therapy system during sleep for patients with chronic respiratory on long-term oxygen therapy

6.1 Introduction

6.1.1 Background

LTOT improves survival in patients with hypoxaemic respiratory failure and COPD (MRC, 1981, NOTT, 1980). The current guidelines recommend LTOT for clinically stable patients with a resting daytime $PaO_2 \leq 7.3$kPa or a PaO_2 between 7.3kPa - 8kPa if there is evidence of pulmonary hypertension or secondary polycythaemia with an underlying respiratory disease (Hardinge et al., 2015, McDonald et al., 2016). LTOT is recommended for at least 15 hours per day which should include the night time period. The flow rate for LTOT is assessed during the day with the patient awake and at rest with the recommendation that patients are prescribed the minimum flow rate that increases the resting PaO_2 to >8kPa (Hardinge et al., 2015).

Several studies have investigated the adequacy of LTOT in a domiciliary setting. These studies have shown that many patients (despite having adequate resting oxygen levels) experience episodes of intermittent hypoxia during walking, activities of daily living and sleep (Śliwiński et al., 1994, Plywaczewski et al., 2000, Morrison et al., 1997, Pilling and Cutaia, 1999). These episodes of intermittent hypoxia may be harmful as they could lead to arrhythmias, transient increases in pulmonary pressure, reduced oxygen supply to the brain and potentially cause ischaemic heart disease (Selinger et al., 1987, Higashimoto et al., 2015, Oliveira et al., 2012, Choudhury et al., 2014, Tirlapur and Mir, 1982). One previous study demonstrated that patients who spend >30% of the night time period with SpO_2 <90% have a greater mortality than patient who do not (Fletcher et al., 1992a). Increasing oxygen flow rates by 1 litre/minute during sleep mitigates the effects of nocturnal hypoxia. However, increasing oxygen flow rates during sleep may be harmful to some patients, especially those with daytime hypercapnia. One previous study has demonstrated that increasing nocturnal oxygen flow rates by 1 litre/minute certainly reduces nocturnal hypoxia but the increased oxygen flow rate led to hyperoxia which in turn increased nocturnal $PaCO_2$ and caused respiratory acidosis in some patients (Samolski et al., 2010).

In addition to episodes of intermittent hypoxia, some patients also experience higher levels of carbon dioxide during sleep whilst on LTOT. This is due to a combination of sleep hypoventilation (as a consequence of reduced ventilatory drive and respiratory mechanics) and hyperoxia from LTOT (Sowho et al., 2014, Samolski et al., 2010). There is therefore a need to optimise oxygen therapy during sleep to reduce episodes of intermittent hypoxia, reduce hyperoxia and its most serious consequence of hypercapnia.

6.1.2 Aims, hypothesis and ethics amendment

Aim

The original aim of this study was to investigate the effects of an auto-titrating oxygen system – the iO_2Ts – on the transcutaneous pressure of carbon dioxide levels ($tcpCO_2$) of patients with hypercapnic respiratory failure who were on LTOT during sleep.

Hypothesis

It was hypothesised that the automated delivery of LTOT via the iO_2Ts during sleep to patients already on LTOT could reduce $tcpCO_2$ levels during sleep.

Ethics amendment and change in primary outcome

This study received Ethical approval in October 2015 and NHS approval in March 2016. The initial inclusion criteria for the study were:

1. Age >18 years
2. On or eligible for long-term oxygen therapy
3. Daytime $PaCO_2$ > 6.0 kPa

The initial primary outcome for the study was the change in $tcpCO_2$ during sleep.

However, there were difficulties in recruiting patients for this study and therefore, in July 2016, a decision was made to broaden the inclusion criteria to include any patients on LTOT but without the requirement of having daytime hypercapnia thus allowing more patients to become eligible for the study. Given that hypercapnia was no longer an inclusion criterion, the primary outcome was changed to the percentage of time spent with SpO_2 < 90% during sleep.

Revised aim

The revised aim of this study was to investigate the effects of an auto-titrating oxygen system – the iO_2Ts – on the oxygen saturation and $tcpCO_2$ of patients with respiratory failure who were on LTOT during sleep.

Revised hypothesis

It was hypothesised that the automated delivery of LTOT via the iO_2Ts during sleep to patients already on LTOT could reduce intermittent hypoxia (percentage of time spent with SpO_2 <90%) during sleep.

6.2 Methods

6.2.1 Study design and ethical approval

This was a prospective, randomised, single centre, single blind cross over study. Patients with respiratory failure who were LTOT were recruited and asked to complete two home PSGs: one on their usual LTOT flow rate and one on the iO_2Ts. This study was first presented to the West-Midlands South Birmingham research ethics committee in April 2015. The committee requested an external assessment of the iO_2Ts to attest to its safety as the system would be utilised in patients' homes without the presence of healthcare professionals on site. This external assessment was obtained from the Royal Brompton Hospital engineering department and on the basis of this the committee approved the study (15/WM/0137) (appendix 5 for REC approval letter) in October 2015. Due to poor recruitment, an ethical amendment for the study was submitted in August 2016 and granted in September 2016. All patients gave informed and written consent for the study. The study was registered on Clinicaltrials.gov, NCT02983565.

6.2.2 Study participants

This was a single centre study based at the Royal Brompton and Harefield NHS Foundation Trust. Consecutive patients were identified and recruited from outpatient clinics, those attending a specialist oxygen clinic, those attending pulmonary rehabilitation, and patients having overnight sleep studies.

6.2.3 Inclusion criteria

1. Age >18 years
2. On or eligible for long-term oxygen therapy

6.2.4 Exclusion criteria

1. Nocturnal use of non-invasive ventilation (NIV) or continuous positive airways pressure (CPAP)
2. A diagnosis of obstructive sleep apnoea
3. A diagnosis of a neuromuscular disease
4. Daytime $PaCO_2$ >8.0kPa
5. Inability to consent for the study
6. Exacerbation of the underlying lung disease or chest infection in the previous 4 weeks
7. Pregnancy
8. Severe co-morbidities
9. Patients with a tracheostomy
10. Long-term oxygen therapy flow rate ≥ 4 litre per minute
11. Inability to understand the English language

6.2.5 Data collection, protocol and measurements

Once a patient had consented to be in the study, they were assessed at the NIHR BRU at the Royal Brompton Hospital or at Harefield Hospital. A complete history and examination were undertaken as well as anthropometric measurements. All patients performed spirometry on a Carefusion® portable spirometer in accordance with the ATS/ERS guidelines (Miller et al., 2005). Ear lobe blood gases taken on the patients' usual LTOT flow rate (after being at rest on their usual LTOT flow rate for at least 30 minutes) and analysed on a SIEMENS RAPIDLAB® SIEMENS RAPIDLAB® 1265 (SIEMENS, Germany) at the Royal Brompton Hospital and RADIOMETER ABL90 (Radiometer, United Kingdom) at Harefield Hospital.

All patients underwent two home PSGs: one on their usual LTOT oxygen flow rate and the second on the iO_2Ts in a random order. Randomisation of patients was achieved using a random number generator. A maximum of 2 weeks was allowed between the first and second PSG. The iO_2Ts was programmed to maintain a SpO_2 of 93%. Full PSG was performed with simultaneous monitoring of tcpCO_2. During both PSGs, oxygen was delivered through the iO_2Ts to ensure blinding of the patient (single blind study). Two members of the research team conducted a home visit on the evening of the sleep study and set-up all the equipment necessary for a full PSG and tcpCO_2 monitoring:

- Electroencephalograms (EEG) electrodes on the head
- Electrooculogram (EOG) to monitor eye movements
- Electromyogram (EMG) to monitor chin muscle activity
- Thermistor to monitor changes in air flow
- Chest and abdominal effort monitored by inductance plethysmography
- Oxygen saturation measurement
- Electrocardiogram (ECG) to monitor heart rate
- Electromyogram (EMG) on the leg to identify any periodic limb movement disorder
- Additional TOSCA to monitor tcpCO_2

6.2.6 Study outcomes

Primary outcome

The difference in the percentage of time spent with SpO_2 <90% between the iO_2Ts and usual LTOT during sleep.

Secondary outcomes

The change in the following parameters between the iO_2Ts and usual LTOT during sleep:

- The peak $tcpCO_2$
- The mean $tcpCO_2$
- Mean SpO_2
- Trough SpO_2
- Total sleep time
- Sleep efficiency

6.2.7 Sample size estimation

Table 6-1 outlines studies which have investigated the adequacy of LTOT by using continuous pulse oximetry (either overnight or for 24 hours).

Table 6-1 Results of studies showing the percentage of time spent with SpO_2 <90% during the night

Study	% ± SD of time spent with SpO_2 <90% at night
Sliwinski et al, ERJ, 1994	28 ± 27.3
Plywaczewski et al, Chest, 2000	35.1 ± 34.7
Samolski, Respirology, 2010	12.7 ± 18.6
Tarrega et al, Respiratory care, 2002	21.5 ± 28
Morrison et al, Respiratory Medicine, 1997	23 ± 24

The above studies demonstrate that patients can spend anywhere between 13 - 35% of the night with oxygen saturations <90%. We believed that any intervention that could reduce the percentage of time spent with SpO_2<90% by 15% would be significant. With an alpha of 0.05, a power of 80%, a minimally important difference of 15% between the iO_2Ts and usual LTOT and a standard deviation of 20% (derived from recent studies with the iO_2Ts), our sample size was estimated to 16 patients. To allow for a dropout rate of 15% we aimed to recruit 19 patients.

6.2.8 Data analysis

All PSGs were blindly analysed by a single experienced physiologist. The studies were all scored according to the American Academy of Sleep Medicine (AASM) standards manual

2012. In addition, data from the overnight TOSCA (SpO_2 data and tcpCO_2) was blindly analysed.

6.2.9 Statistical analysis

For the combined baselines characteristics, the continuous variables are presented as the means with their standard deviation or median with the interquartile range. Categorical variables are presented as number and percentage in each category.

To allow comparison with published data and as this is a cross-over study, the primary outcome is presented as mean with its standard deviation and analysed using a paired t-test.

The sleep data from PSG is presented for each individual patient. Most secondary outcomes are presented as mean with standard deviation and analysed using a paired t-test where appropriate. Data from the overnight TOSCA (percentage of time spent with SpO_2 less than 90%, mean and trough SpO_2, mean and peak tcpCO_2) is presented as mean with standard deviation and analysed using a paired t-test. All statistical analysis was done in SPSS version 23 (IBM).

6.3 Results

6.3.1 Patient recruitment and baseline characteristics

Despite the change in inclusion criteria, only six patients completed two PSGs (consort diagram Figure 6-1). The combined baseline characteristics of the six patients are shown in Table 6-2 and the individual baseline characteristics are shown in Table 6-3. None of these patients had taken part in any other studies involving the iO_2Ts. Three (50%) were male, with a mean age of 64.3±5.0 years. The indications for LTOT were COPD (50%) and ILD (50%). The patients had severe respiratory failure with a mean FEV_1 of 0.94±0.60 litres and a mean percentage predicted FEV_1 of 33.5±17.2%. The median LTOT flow rate was 2.0 [1.0 – 2.3]. The mean baseline PaO_2 and $PaCO_2$ on the patients' usual LTOT flow rates were 10.03±2.27 kPa and 5.90±1.14 kPa respectively. Only one patient had a PO_2 <8kPa on their usual LTOT flow rate.

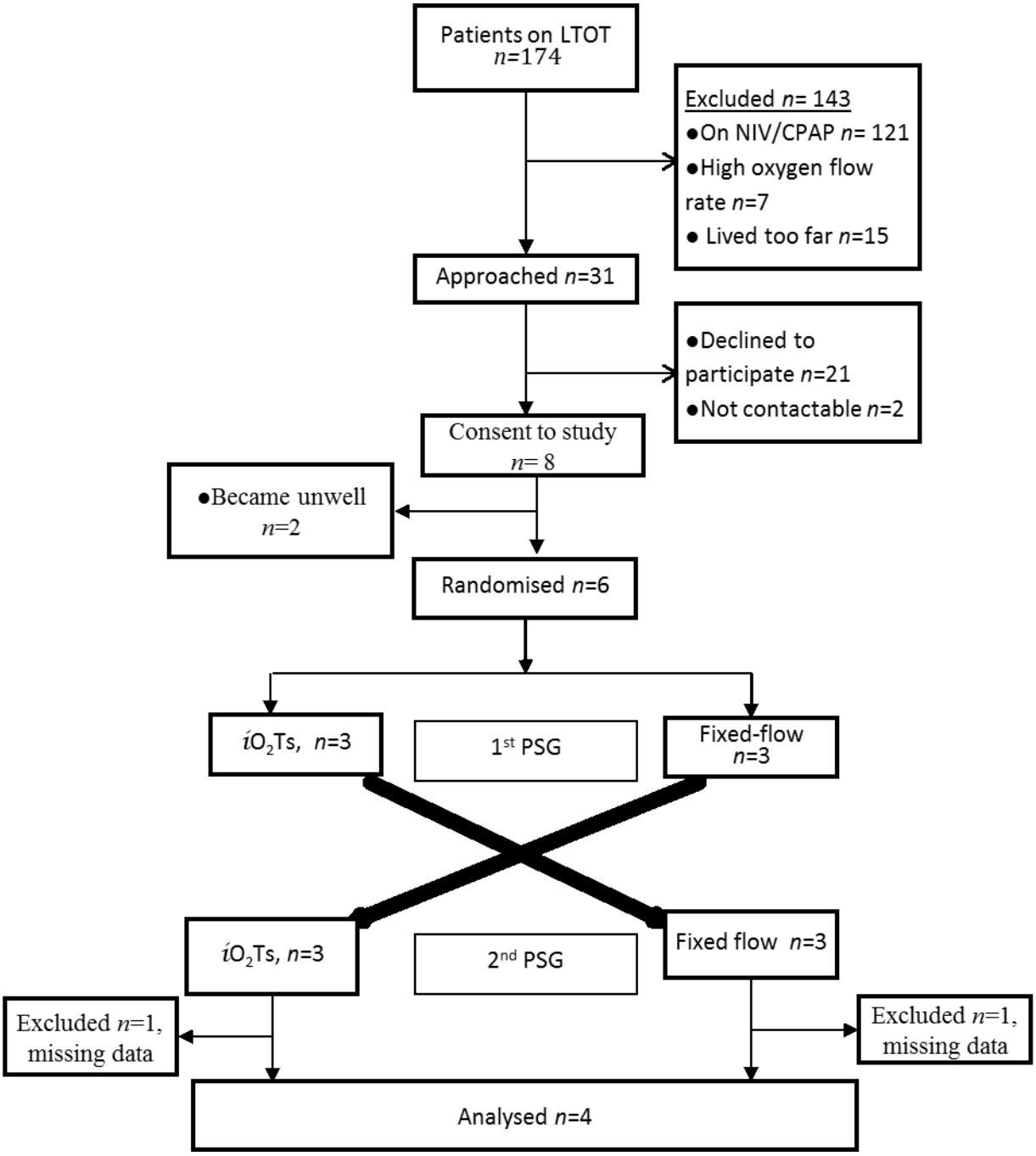


Figure 6-1 Consort diagram for the assessment of iO₂Ts during sleep
LTOT = Long-term oxygen therapy, NIV = non-invasive ventilation, CPAP = continuous positive airway pressure, $\acute{i}O_2Ts$ = intelligent oxygen therapy system, PSG = polysomnography

Table 6-2 Combined baseline characteristics of study patients

Parameter	Value	
	Randomised patients, n=6	
Gender (female), n (%)	3 (50)	
Age, years	64.3±5.0	
BMI, kg/m^2	23.0±8.6	
FEV_1, Litres	0.94±0.60	
Percentage predicted FEV_1, %	33.5±17.2	
FVC, Litres	2.19±1.10	
Percentage predicted FVC, %	63.7±22.5	
LTOT duration, years	1.25 [0.88 – 2.65]	
Baseline PaO_2 on oxygen, kPa	10.03±2.27	
Baseline $PaCO_2$ on oxygen, kPa	5.90±1.14	
Pulmonary Hypertension, n (%)	3 (50)	
LTOT flow rate, Litres/minute	2.0 [1.0 – 2.3]	
Ambulatory flow rate, Litres/min	3.0 [2.0 – 5.0]	
Smoking history, pack years	23.5±14.9	
Bicarbonate	28.2±5.7	
Indication for LTOT, n (%)	COPD, 3 (50)	ILD, 3 (50)

Data shown as n (%), mean ± SD or median [interquartile range]. BMI = Body mass index, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity, LTOT = long-term oxygen therapy, PaO_2 = partial pressure of oxygen, $PaCO_2$ = partial pressure of carbon dioxide, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease

Table 6-3 Individual baseline characteristics of study patients

Patient ID	Age, years	Gender	BMI, kg/M^2	MRC Scale	FEV_1, litres	FEV_1 (%predicted)	FVC, litres	FVC (%predicted)	FEV_1/FVC ratio (%)	Pack year smoking	PaO_2, Kpa	$PaCO_2$, kPa	Bicarboante, mmol/L	LTOT duration, years	LTOT flow rate, litres/minute	Ambulatory flow rate, litres/minute	Pulmonary hypertension	Days in between 2 PSGs	Diagnosis
SL00	71	M	39.7	4	2.04	66	2.56	63	77	Never smoker	10.8	6.72	30.5	1.4	2	2	NO	1	ILD
SL05	64	M	20.0	5	0.56	17	1.8	42	31	35	9.79	6.03	28.2	0.5	2	2	NO	8	COPD
SL08	62	M	21.0	5	1.10	32	4.25	98	25	20	8.24	3.76	17.9	4	3	8	YES	3	copd
SL13	69	F	16.4	3	0.53	28	1.68	72	32	35.1	14.1	6.38	29.1	1	1	2	NO	1	copd
SL16	63	F	17.3	3	0.45	23	1.67	71	27	3.75	9.5	6.88	35.4	1.1	1	4	YES	7	ILD
SL25	57	F	23.5	4	0.98	35	1.17	36	84	Never smoker	7.77	5.63	28.1	2.2	2	4	YES	2	ILD

BMI = Body mass index, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity, LTOT = long-term oxygen therapy, PaO_2 = partial pressure of oxygen, $PaCO_2$ = partial pressure of carbon dioxide, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease

6.3.2 Data analysis of PSG

All six randomised patients had two PSGs. The maximum number of days between two PSG was eight with most patient having the second PSG between 1-3 days after the first. Of the 12 completed PSGs, three studies could not be scored for sleep staging. Two of these studies were from one patient. Therefore, complete staging of sleep was available for nine PSGs and four patients. For the three PSGs which could not be reported, this was because of unidentified interference with the EEG signal which could not be corrected post processing.

Monitoring of transcutaneous carbon dioxide from the TOSCA was well tolerated by all the patients. The data from the TOSCA was independently analysed. However, the integrated tcpCO_2 data from PSG was only available for five PSGs and two patients. The data for the tcpCO_2 was present on all PSG studies, however, when the final report was published for the PSG, the tcpCO_2 data was only present for five PSGs. This problem was discussed with a number of individuals including a representative of SOMNOMedics but unfortunately the problem could not be resolved.

6.3.3 Primary outcome: percentage of time spent with SpO_2 <90% during sleep

The primary outcome of percentage of time spent with SpO_2 <90% during sleep was available for four patients and is shown in Table 6-4. The summary statistics of mean and median are presented, however, given the small sample size there is no benefit in conducting any statistical comparisons.

Table 6-4 Percentage of time spent with SpO_2 <90% during sleep for each patient

Patient / Test	Percentage of time spent with SpO_2 <90% on Fixed-Flow oxygen, %	Percentage of time spent with SpO_2 <90% on the iO_2Ts, %
SL05	0.0	0.0
SL08	7.8	0.0
SL13	92.1	36.5
SL25	7.1	25.4
Mean ± SD	26.8±43.7	15.5±18.4
Paired sample T-test	p = 0.526	

One patient spent no time with any hypoxia either with the iO_2Ts or with fixed-flow oxygen. One patient had significant hypoxia whilst on fixed-flow oxygen and had a large reduction in

the percentage of time spent with SpO_2 <90% with the iO_2Ts but still spent a significant 36.5% of the time with SpO_2 <90%. A third patient had a small degree of hypoxia on fixed-flow oxygen which was eliminated by the iO_2Ts. The fourth patient was less hypoxic with fixed-flow oxygen than with the iO_2Ts (SL25) which is not consistent with the data from the other three patients. On further examining the PSG data from patient SL25, there is clear problem with the SpO_2 data from approximately 1:30am onwards (Figure 6-2). Before 1:30am the SpO_2 signal is relatively stable. However, at 1:30am there is a clear and sudden drop in the signal when the patient turns from the left side to the prone position and after this point the SpO_2 signal is inconsistent and there is also missing data. This is most likely because the SpO_2 probe position was no longer optimal leading to poor data recording and results which do not reflect the actual SpO_2. This is confirmed by analysing the SpO_2 data from the iO_2Ts smartphone data and the TOSCA SpO_2 data both of which were unaffected. These data show that on the iO_2Ts, patient SL25 spent 0.7% and 2.0% of the night with SpO_2 <90% on TOSCA data and smartphone SpO_2 data respectively.

Given the small sample size of the data and the fact there was a problem with the SpO_2 signal from one patient, it is not surprising that there is no statistically significant difference in the primary outcome between fixed-flow oxygen and the iO_2Ts.

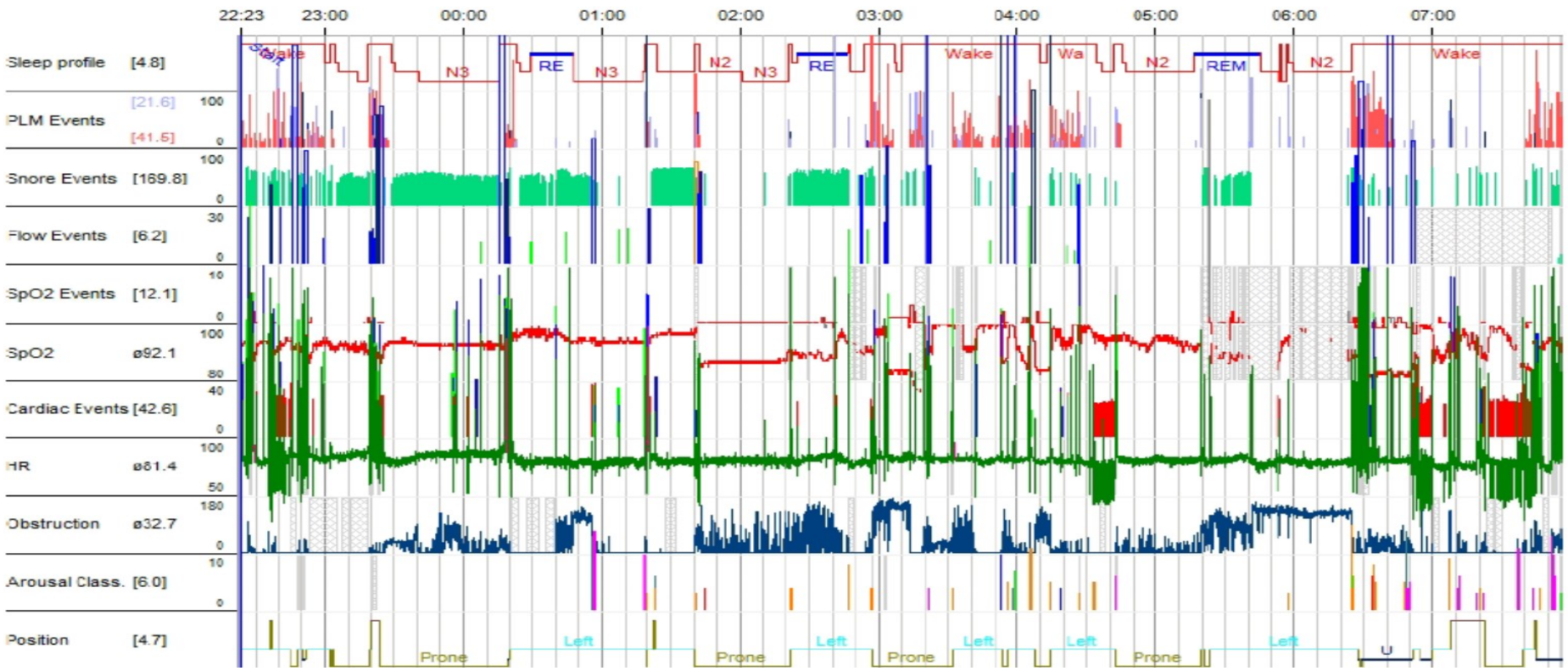


Figure 6-2 Sleep hypnogram for patient SL25 on the iO_2Ts

At approximately 1:30am there is a sudden change in SpO_2 signal when the patient moves from lying on the left side to the prone position. After this point the SpO_2 reading are lower, there is greater variability and loss of data all of which suggest that the SpO_2 probe position is suboptimal.

6.3.4 Secondary outcomes and changes in sleep study parameters

The secondary outcomes were available for only four patients and are shown in Table 6-5. There was very little difference in the mean or trough SpO_2 between fixed-flow oxygen or the iO_2Ts. It is very difficult to comment of the change in the $tcpCO_2$ as this data is only available for two patients. The sleep time and sleep efficiency were very similar between the two modes of oxygen delivery.

The changes in sleep parameters are shown in Table 6-6. The AHI was slightly increased in three patients with the iO_2Ts. The arousal index in similar in both groups apart from one patient who had a very arousal index with fixed-flow oxygen. The percentage of time spent in different sleep stages is very similar between fixed-flow oxygen and the iO_2Ts.

6.3.5 Changes in overnight SpO_2 and $tcpCO_2$ – TOSCA data

Transcutaneous monitoring of carbon dioxide was well tolerated by all the patients. Data from the TOSCA was independently analysed and these results are shown in Table 6-7. There was no difference in the percentage of time spent with SpO_2 <90% between the two modes of oxygen delivery overnight from the SpO_2 data. However, patients on fixed-flow oxygen did not have very much intermittent hypoxia spending only spent a mean of 6.2±11.6% of time with SpO_2 <90%, hence there is very little improvement to made in this group of patients. This is most likely because the baseline mean PaO_2 was 10.03±2.27kPa and it has been previously demonstrated that having a higher PaO_2 reduces intermittent hypoxia. The mean and trough SpO_2 were not different between the two modes of oxygen delivery nor were the mean or peak $tcpCO_2$.

The most interesting patient to be studies was SL13. She had a baseline PaO_2 of 14.1kPa and a baseline $PaCO_2$ of 6.38kPa. Despite her high baseline PO_2 she spent 29.5% of the night with SpO_2 <90% which reduced to 1.9% with the iO_2Ts. With this improved oxygenation, there was a very small increase in the mean $tcpCO_2$ (0.06 kPa) and a small reduction in the peak $tcpCO_2$ (0.26 kPa) with the iO_2Ts compared to fixed-flow oxygen. This improved oxygenation would have required higher oxygen flow rates than her usual fixed-flow oxygen. Unfortunately, the data from the iO_2Ts as to the flow rated delivered is missing as the mobile phone ran out of battery. This contrasts with patient SL00. This patient was mildly hypoxic with fixed-flow oxygen and this hypoxia was almost eliminated by the iO_2Ts. This required a slightly higher mean oxygen flow rate overnight of 2.2 litres/minute as compared to his usual fixed-flow rate of 2 litres/minute. This consequently lead to a greater volume of oxygen delivery overnight.

However, with the iO_2Ts, both the peak and mean tcpCO_2 were higher than with fixed-flow oxygen than with the iO_2Ts.

Patient SL16 who had a baseline $PaCO_2$ of 6.88kPa, spent a greater amount of time with SpO_2 < 90% on the iO_2Ts than with fixed-flow oxygen. Not only was her oxygenation worse with the iO_2Ts, but she also had a significantly higher mean and peak tcpCO_2 with the iO_2Ts.

Patient SL05 who had a baseline PaCO2 of 6.03kPa, was not hypoxic at all with his fixed-flow oxygen and his oxygenation was well maintained with the iO_2Ts. However, with the iO_2Ts his mean tcpCO_2 was significantly lower than with fixed-flow oxygen.

Table 6-5 Secondary outcomes of each patient with fixed-flow oxygen and the iO_2Ts

Patient	Mean SpO_2, %		Trough SpO_2, %		mean tcpCO_2, mmHg		peak tcpCO_2, mmHg		Total sleep time, min		Sleep efficiency, %	
	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts
SL00	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD
SL05	96	92	93	90	MD	54.0	MD	55.0	407	263	72.60	44.50
SL08	92	91	87	89	43.0	44.0	46.0	48.0	350	127	69.60	25.10
SL13	87	91	73	62	51.0	41.0	56.0	51.0	277	346	47.30	64.20
SL16	MD	91	MD	71	MD	MD	MD	MD	MD	261	MD	62.10
SL25	93	92	85	82	MD	MD	MD	MD	373	316	67.10	55.20

SpO_2 = Oxygen saturations, tcpCO_2 = transcutaneous pressure of carbon dioxide, iO_2Ts = intelligent oxygen therapy system, MD = missing data

Table 6-6 Change in PSG parameters for each patient with fixed-flow oxygen and the iO_2Ts

Patient	AHI, per hour		Arousal index, per hour		REM Sleep %, %		N1 Sleep %, %		N2 Sleep %, %		N3 Sleep %, %	
	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts
SL00	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD	MD
SL05	.2	5.0	.80	3.30	22.7	9.9	5.2	6.8	40.2	49.8	31.9	33.5
SL08	.8	9.6	30.20	3.30	17.7	31.0	8.1	2.7	41.3	20.0	32.9	46.3
SL13	1.3	11.1	2.00	4.40	20.2	9.7	1.6	3.8	39.7	51.2	38.4	35.4
SL16	MD	1.0	MD	9.70	MD	19.7	MD	2.1	MD	56.7	MD	21.5
SL25	2.5	1.5	1.50	1.00	18.8	21.8	2.1	5.4	50.1	43.2	29.0	29.6
AHI = Apnoea-Hypopnea index, REM = Rapid eye movement, iO_2Ts = intelligent oxygen therapy system, MD = missing data												

Table 6-7 Change in in SpO_2 and tcpCO_2 – TOSCA data

Patient/Test	Percentage of time spent with SpO_2 <90%, %		Mean SpO_2, %		Trough SpO_2, %		Mean tcpCO_2, mmHg		peak tcpCO_2, mmHg	
	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-flow	iO_2Ts	Fixed-Flow	iO_2Ts	Fixed-Flow	iO_2Ts
SL00	4.9	0.4	95.0	96.0	76	84	7.05	7.25	7.87	8.13
SL05	0.0	0.0	97.0	96.5	95	92	8.98	7.88	MD	8.53
SL08	0.7	0.0	94.9	95.9	85	90	5.93	5.75	6.40	6.13
SL13	29.5	1.9	90.0	95.5	62	82	7.09	7.15	8.13	7.87
SL16	1.4	9.8	98.4	95.6	83	66	8.94	9.04	9.87	9.65
SL25	0.56	0.7	97.9	95.5	80	85	8.08	8.05	9.33	9.16
mean±SD	6.2±11.6	2.1±3.8	95.5±3.1	95.8±0.4	80.2±10.9	83.2±9.2	7.68±1.20	7.52±1.10	8.32±1.36	8.19±1.36
Paired Sample T-Test	p = 0.456		p = 0.815		p = 0.577		p = 0.455		p = 0.256	
SpO_2 = oxygen saturation, tcpCO_2 = transcutaneous carbon dioxide, iO_2Ts = intelligent oxygen therapy system										

6.3.6 SpO_2 data from the iO_2Ts

As previously described, the data from each experiment is recorded on the smartphone for each experiment. For the twelve sleep studies, complete overnight data from the smartphone was available for eight sleep studies (four studies with no data or incomplete data). Unfortunately, only two patients had paired data available for comparison as shown in Table 6-8. The incomplete data collection for the studies resulted from two problems:

1. On two occasions the smartphone ran out of battery and no data on SpO_2 or heart rate was recorded on the smartphone for the entire night.
2. On the other two occasions whilst the iO_2Ts was in fixed-flow mode, the smartphone app failed to record data for the full length of the night. On the first occasion, data recording began but ceased after only 10 minutes and the cause of this remains unclear. On the second occasion, data recorded for three hours but after a prolonged period of approximately 15minutes where errors were recorded for both SpO_2 and heart rate measurements, the system ceased recording.

The mean SpO_2 for the iO_2Ts was 93.1% very close to the set-point SpO_2 of 93%. The mean percentage of time spent with SpO_2 <90% for the iO_2Ts was 7.7%. The mean SpO_2 recorded with the iO_2Ts using a Nonin finger probe pulse oximeter on the smartphone app was lower than that recorded on the TOSCA (95.8±0.4%). This is because the difference in the SpO_2 between the Nonin pulse oximeter used in the iO_2Ts and arterial SpO_2 is ±2%. However, the bias ± SDs for the TOSCA SpO_2 compared to arterial SpO_2 is 1±4% (Senn et al., 2005, RADIOMETER, 2012). This can lead to different SpO_2 measurements from the finger pulse oximeter and SpO_2 measured from the ear lobe TOSCA for the same arterial SpO_2.

Table 6-8 Oxygen saturation data from the iO_2Ts

Patient	Percentage of time spent with SpO_2 <90%, %		Mean SpO_2, %		Oxygen flow rates, litres/minute		Volume of oxygen delivered, litres	
	Fixed-flow oxygen	iO_2Ts	Fixed-flow oxygen	iO_2Ts	Flow rate of fixed-flow oxygen	Mean oxygen flow rate on the iO_2Ts	Fixed-flow rate	iO_2Ts
SL00	9.1	1.6	91.9	93.7	2	2.2	1139.0	1238.6
SL05	MD	0.4	MD	93.8	2	1.9	1416.0	1367.9
SL08	14.8	12.1	91.4	91.3	3	4.2	1035.6	1453.4
SL13	64.3	MD	88.5	MD	1	MD	MD	MD
SL16	MD	20.7	MD	92.8	1	2.6	438.8	1126.1
SL25	MD	2.0	MD	93.8	2	2.3	1172.4	1331.9
mean±SD	29.4±30.4	7.7±8.5	90.6±1.8	93.1±1.1			1040.4±364.1	1303.6±125.6

SpO_2 = oxygen saturations, iO_2Ts = intelligent oxygen therapy system, MD = missing data. The total volume of oxygen delivered in litres for fixed-flow rate is adjusted for the same period as that for the iO_2Ts.

6.4 Discussion

The main finding from this study was that the iO_2Ts did not significantly change the primary outcome of percentage of time spent with SpO_2 <90% compared to fixed-flow LTOT during sleep for a sample size of four patients. In addition, the results of the overnight TOSCA data also showed that there was no difference in the percentage of time spent with SpO_2 <90% and no difference in the mean or peak tc*p*CO_2 between fixed-flow oxygen and the iO_2Ts for a sample size of six patients. The type of oxygen delivery did not affect the mean or trough SpO_2. However, these results are pilot data given the small sample size and the fact that only one patient had any significant intermittent hypoxia with fixed-flow oxygen.

This is the first occasion when an auto-titrating oxygen system has been used to deliver variable flow oxygen during sleep. Unfortunately, the loss of data from three of PSGs, combined with the cross-over design of the study ultimately means that it is difficult to make any firm conclusions as to the impact of the iO_2Ts on sleep. There was also a failure of the smartphone based system to record data on three occasions which again impacts on data interpretation. The most reliable overnight SpO_2 data came from the TOSCA. Overall there was no difference in the primary outcome between the iO_2Ts and fixed-flow oxygen. There was also a very variable impact on overnight tc*p*CO_2 with one patient experiencing a reduction in tc*p*CO_2 with the iO_2Ts with improved oxygenation, whereas another patient experienced worse oxygenation with the iO_2Ts and worse tc*p*CO_2. Again, it is difficult to make any firm conclusions as to the impact of the iO_2Ts on overnight tc*p*CO_2, but from the overall results of six patients there is no significant difference in the mean or peak overnight tc*p*CO_2.

This is only the second time that an auto-titrating oxygen system has been tested in the home environment over an extended period of time. In the study by Rice and colleagues, the $AccuO_2$ system was tested in patients' homes for 8 hours during the day over consecutive days and the results showed there was no statistical difference in the percentage of time spent with SpO_2 <90% between the $AccuO_2$ system, usual LTOT and an oxygen conserver system (Rice et al., 2011). They did not report any problems or complications with their system.

Once this study commenced and on analysing the results, several shortcomings of the iO_2Ts were noticed. The most important shortcoming, which occurred on two occasions, was that the smartphone on which the iO_2Ts system is based ran out of battery. This was a failure which had been explored in safety assessments and been mitigated for by the addition of a watchdog timer and bypass circuit. On both occasions, the bypass circuit worked well and supplied patients with their backup oxygen flow rate in the absence of a control unit. It had originally been envisaged

that the smartphone battery would provide approximately 12 hours of power. However, it provided power for between 8-10 hours.

The second difficulty with the iO_2Ts was that the bypass circuit was very difficult to activate. Once the iO_2Ts had been programmed appropriately, the system was started. If the bypass circuit was appropriately activated, a red light would turn on and there would be an audible "click". However, this activation of the bypass system was intermittent and variable. Consequently, several attempts were needed to activate the bypass circuit and this was time consuming especially in a patient's home.

The third difficulty with the iO_2Ts was the lack of data recording. On both occasions that the smartphone ran out of battery, no data on SpO_2 or heart rate was recorded on the smartphone for the entire night. It subsequently became clear that data from each experiment was not recorded continuously on the smartphone but rather that once the "close application" button is pressed then data from the experiment is recorded. Consequently, if the "close application" button is not pressed no data is recorded for the experiment (as is the case when the smartphone runs out of battery).

In addition, on two further occasions whilst in fixed-flow oxygen delivery mode, the smartphone app failed to record data for the entirety of the night. On the first occasion, data recording began but ceased after only 10 minutes and the cause of this remains unclear. On the second occasion, data recorded for three hours but after a prolonged period of approximately 15minutes where errors were recorded for both SpO_2 and heart rate measurements, the system ceased recording. Why these issues occurred is not entirely clear but it may be related to a software issue which occurs when the system is used for longer periods of time.

Consistent with the findings of previous studies, there was a variable degree of intermittent hypoxia in the patients in this study. When the primary outcome was changed to the percentage of time spent with $SpO_2<90\%$, I could have included patients who had significant nocturnal hypoxia only and hence those who would most likely benefit from the iO_2Ts. However, this would have added an additional layer to the inclusion criteria and given that I struggled to recruit patient with a more open criterion, it would have been an even bigger challenge with a stricter inclusion criterion.

This study was designed as a patient blind (single blind) cross-over study. However, there were several occasions when the patients unblinded themselves and there were two main reasons why this occurred. Consistent with the previous discussion in chapters 3 and 4, most patients are aware of the feeling of their own LTOT flow rate and are keenly aware when too little oxygen

or too much oxygen is being delivered (especially patients who have high ambulatory oxygen flow rates). This led to some patients being able to deduce the type of oxygen flow rate that was being delivered. Secondly, when the iO_2Ts is programmed to deliver variable flow oxygen and attached to an oxygen concentrator, the flow meter on the oxygen concentrator changes as the oxygen flow rate delivered to the patient changes. This is contrast to when the iO_2Ts is attached to an oxygen cylinder, where once the flow rate on the cylinder is turned to 5 litres/minute the dial does not fluctuate. On several occasions, patients inspected the flow meter on their oxygen concentrator and deduced the type of oxygen therapy being delivered.

Difficulties with patient recruitment

The initial aim of the study was to recruit patients with hypercapnic respiratory failure who were on LTOT and the investigate the effects of the iO_2Ts on tc*p*CO_2. However, once the study started, I faced several challenges in recruiting patients to the study. Although many patients who had chronic respiratory failure on LTOT were identified, some of these patients had to be excluded as they were either of long-term nocturnal NIV, on nocturnal CPAP or had a diagnosis of OSA. This was a particular problem in patients who were attending the Royal Brompton Hospital as many of these patients attend for the management of respiratory failure requiring NIV. In addition, as we had intended to conduct home PSG, many patients attending the clinics with respiratory failure lived a long distance from the hospital and therefore it would not have been feasible for me to be able to travel out to their homes to set-up the PSG.

Another barrier to recruitment was that many patients declined to have home sleep studies. This contrasts with previous studies from this department which showed that when patients were asked as to whether they would like a home sleep study or a hospital sleep study, approximately 75% preferred a home sleep study to a hospital sleep study (Ward, 2011). This study may have been different as it was testing a new device and hence patients may have felt uncomfortable with using this in their homes. It may also reflect the severe nature of their underlying disease process and their inability to cope with any extra burden at home. In addition, some patients also declined to have two PSGs – some of these patients were happy to do one sleep study but felt that doing two was a major burden. The change in the inclusion criteria broadened the potential pool of patients but unfortunately not enough to recruit the numbers initially planned.

In addition to the issues faced with patient recruitment, there were also significant delays in setting up the study which reduced the time for completion. This study was first presented to the West-Midlands South Birmingham research ethics committee in April 2015. The committee raised safety concern with regards to the device being used outside of a hospital environment and therefore asked for an external review to attest to the safety of the device. This process is

described in detail in chapter two and took a further six months. The West-Midlands South Birmingham research ethics committee gave their favourable opinion in October 2015. However, it was further 6 months before NHS approval (March 2016) due to the contractual processes and agreements between the sponsor of the study (Imperial College London) and NHS organisation (Royal Brompton and Harefield NHS Foundation Trust).

6.4.1 Conclusion

In this pilot study, the delivery of oxygen with the iO_2Ts did not reduce intermittent hypoxia during sleep to any greater degree than fixed-flow oxygen for four patients. This study has shown that the iO_2Ts with its enhanced safety profile can be utilised in patient homes. However, given the number of technical issues which have been encountered, the system needs to be redesigned to have a greater battery capacity, wireless charging and more robust data collection, and improved software. The impact of the iO_2Ts on $tcpCO_2$ was very variable. As the study is incomplete, it should be completed in the first instance as it was designed if funding is available. Ideally, we should allow patients to have choice of location of the sleep study (hospital v home) as this may allow greater patients recruitment.

7 Chapter 7 - The intelligent oxygen therapy system during activities of daily living

7.1 Introduction

7.1.1 Background

LTOT improves survival in patients with COPD and chronic hypoxaemic respiratory failure (NOTT, 1980, MRC, 1981). Extrapolating from this, international oxygen guidelines recommend LTOT for patients with chronic hypoxaemic respiratory failure from several respiratory conditions (Hardinge et al., 2015, McDonald et al., 2016, Magnet et al., 2017). LTOT is prescribed at a fixed-flow rate with the aim of maintain $PaO_2 \geq 8$ kPa or SpO_2 >90%. In the MRC oxygen study, participants were prescribed oxygen flow rates of at least 2 litres/minute and more if necessary until the PaO_2 was ≥8kPa. Flow rates were not adjusted during sleep, activities or exercise. In the NOTT, flow rates were started at 1 litre/minute and increased until the PaO_2 was ≥8kPa. It was recommended that participants increase oxygen flow rates by 1 litre/minute during exercise and sleep but there were no specific recommendations for activities of daily living (ADL).

Several studies have demonstrated that some patients on domiciliary LTOT continue to experience episodes of intermittent hypoxia (SpO_2 <90%) during rest, sleep and activities of daily living despite having normal resting and mean SpO_2, (Śliwiński et al., 1994, Plywaczewski et al., 2000, Morrison et al., 1997, Pilling and Cutaia, 1999, Abdulla et al., 2000). Therefore, higher oxygen demands during some activities and changes in FiO_2 are not being met by fixed-flow oxygen (Bazuaye et al., 1992, O'Reilly Nugent et al., 2014). The episodes of intermittent hypoxia may be potentially harmful by causing transient increases in pulmonary pressure, reducing oxygen supply to the brain, causing arrhythmias and ischaemic heart disease (Selinger et al., 1987, Higashimoto et al., 2015, Oliveira et al., 2012, Choudhury et al., 2014, Tirlapur and Mir, 1982) (reviewed in chapter 1 section 1.18).

The British Thoracic Society Home oxygen guidelines recognise that having one fixed-flow oxygen prescription may not provide adequate oxygenation throughout the day and can lead to desaturation during everyday activities (Hardinge et al., 2015). The guidelines recommend tailoring of flow rates for different activities but how this should be achieved is not explored. The Thoracic Society of Australia and New Zealand guidelines recommend increasing oxygen flow rates by 1 litre/minute during ADL on the basis of consensus opinion only (McDonald et al., 2016).

The optimum method of tailoring oxygen is to assess patients during different activities and prescribe oxygen on the basis of such assessments. One study has demonstrated that using such an approach, the median LTOT flow rate could be reduced from 2.5 litres/minutes to 1.2

litres/minute without any significant increase in the percentage of time spent with SpO_2 <88% (Zhu et al., 2005). A survey in 2001 revealed great heterogeneity in how LTOT is prescribed and adjusted during rest, sleep and activities in different regions of the world (Wijkstra et al., 2001). This reflects the real-life approach of different clinicians to oxygen prescriptions and the uncertainty as there are no gold standards as to the best method of adjusting oxygen prescriptions.

Auto-titrating oxygen systems such as iO_2Ts could reduce intermittent hypoxia during ADL. The results in chapter 4 showed that the iO_2Ts reduced intermittent hypoxia by a significant 23% during a 6MWT compared to fixed-flow oxygen. The only study to date to test an auto-titrating oxygen system during ADL was by Rice and colleagues (Rice et al., 2011). The authors compared their auto-titrating oxygen system ($AccuO_2$) to continuous fixed-flow oxygen and an oxygen conserving device in a domiciliary setting in stable COPD patients on LTOT. The $AcuuO_2$ system was set to maintain SpO_2 at 90%. The authors found that the $AccuO_2$ system non-significantly reduced intermittent hypoxia (SpO_2 <88%) compared to fixed-flow oxygen whilst concurrently supplying significantly less oxygen than the conserving system and fixed-flow oxygen.

7.1.2 Aims and hypothesis

The primary aim of this study was to determine if the iO_2Ts could reduce intermittent hypoxia during ADL in patients with chronic hypoxemic respiratory on LTOT. The secondary aims of this study were to: 1) determine if the iO_2Ts could be utilised as an oxygen assessment tool during to determine optimal oxygen flow rates required during ADL and at rest 2) determine if the iO_2Ts by delivering targeted oxygen therapy could reduce breathlessness during ADL and 3) determine if by delivering targeted oxygen therapy, the iO_2Ts could reduce the volume of oxygen delivered during ADL. We tested the hypothesis that the iO_2Ts could reduce intermittent hypoxia during ADL compared to fixed-flow oxygen.

7.2 Methods

7.2.1 Study design and participants

This was a prospective, single centre, randomised, single blind, cross-over study. Participants with chronic hypoxaemic respiratory failure from any respiratory cause, who were on or eligible for LTOT were invited to participate. Participants were identified from respiratory outpatient clinics, those attending ambulatory oxygen assessments and from a specialist oxygen clinic. Participants undertook a series of ADL twice in a blinded and randomised order: once on their usual fixed-flow LTOT and once on the iO_2Ts. One patient who had participated in the study in chapter 4 and one patient who had participated in the study in chapter 5 also participated in this study. The ADL took place in a modified sleep laboratory at the Royal Brompton Hospital.

Ethical approval was given by the London - Stanmore Research Ethics Committee (15/LO/1435) (Appendix 6 for REC approval letter). All the participants gave informed and written consent. The study was registered on Clinicaltrials.gov, NCT02683486. Regulatory clearance from the MHRA was already in place prior to the study commencing.

7.2.2 Inclusion criteria

1. Age >18
2. Currently on or eligible for LTOT for chronic hypoxaemic respiratory failure

7.2.3 Exclusion criteria

1. LTOT flow rate ≥4L per minute
2. Exacerbation of underlying lung disease in the past 4 weeks
3. Inability to understand English
4. Significant co-morbidities
5. Patients who lack capacity to consent
6. Pregnancy

7.2.4 Protocol

Participants undertook a series of 13 different ADL twice in a cross-over design. The protocol started with a 20-minute rest period in different positions before the ADL. This allowed the participants to relax before starting the activities and the data could be utilised to assess the iO_2Ts as an oxygen assessment tool. The activities chosen for the protocol are shown in Table 7-1. These activities were chosen as they are known to be difficult for patients with respiratory failure, can cause oxygen desaturation and have previously been utilised in studies investigating oxygen uptake during ADL (Śliwiński et al., 1994, Annegarn et al., 2012, Van Remoortel et al., 2012, Vaes et al., 2011, Castro et al., 2013).

This was a single (patient) blind and randomised study. Blinding was achieved by utilising the same system to deliver both iO_2T and fixed-flow oxygen. Randomisation was achieved using a random number generator. As the participants were required to perform the ADL twice, they were given a choice of whether to carry out both in a single day (with a break of at least 15 minutes in between the two sets of activities) or they could elect to do this over 2 days. Twenty-eight of the twenty-nine participants elected to perform both sets of ADL on the same day with only one patient doing the ADL over two days.

7.2.5 The intelligent oxygen therapy system

The iO_2Ts is a novel smartphone auto-titrating oxygen system which continuously monitors a patients' SpO_2 and automatically adjusts oxygen flow rates to maintain a pre-set SpO_2 target in the face of continually changing patients' requirements (for further details see chapter 2). During ADL, the participants wore a Nonin-4100 Bluetooth pulse oximeter on the ear-lobe. This placement allowed the participants to be hands free to conduct the ADL easily. The iO_2Ts was set to maintain a SpO_2 of 93%.

Table 7-1 Activities of daily living performed by the participants

Activity categories	Activity	Duration (minutes)
Resting	Resting in a dorsal position	5*
	Resting in a lateral position	5*
	Sitting in a chair	5*
	Standing	5*
Personal care	Brushing teeth	2*
	Washing face	2
	Combing hair	1*
	Bathing: simulated bathing movement as if washing the head, chest, abdomen and limbs	5
	Dressing and undressing	5
	Putting on and taking off shoes	1-5
Labour activities	Sweeping the floor	2*
	Storing cans on shelves of various heights	1
	Washing dishes	2
	Writing on paper	2*
	Talking on the phone without any arm support	1*
	Opening and closing draws	1*
	Moving paper sheets from one side of the desk to the other side	1*
Total time		Approximately 50
*Denotes activities in which the time for the activity was strictly adhered to the time stated in the table above. The nature of some of the other activities did not allow strict timing. During these activities, the aim for the patients was to finish the activity rather than stop mid-activity after a pre-specified time.		

7.2.6 Data collection

Anthropometric data with additional information on patients past medical history, their drug history and oxygen therapy utilisation was recorded. Spirometry was performed by all patients on a Carefusion® portable spirometer in accordance with the ATS/ERS guidelines (Miller et al., 2005) unless already performed in the last 3 months. Arterialised ear lobe blood gases were measured on all participants on continuous flow oxygen on the participants usual LTOT flow rate.

The iO_2Ts recorded the SpO_2 and heart rate once every second whilst the participant was on fixed-flow or variable flow oxygen during the ADL. The system also recorded the flow rate of oxygen delivered every second. Before and after each activity participants were asked to rate their breathlessness and fatigue using the Borg score.

7.2.7 Study outcomes

Primary outcome

The primary outcome was the difference in the percentage of time spent with SpO_2<90% during activities of daily living with iO_2Ts *versus* the fixed-flow LTOT.

Secondary outcomes

1. The change in the following parameters between the iO_2Ts and fixed-flow LTOT during ADL:

- Mean SpO_2
- Percentage of time spent with SpO_2 ≥97%
- Percentage of time spent with SpO_2 range 90-96%
- Mean and peak heart rate
- Change in Borg score
- Volume of oxygen delivered

2. The assessment of the iO_2Ts as a tool to assess oxygen requirements during ADL and at rest
3. Mean SpO_2 at rest and volume of oxygen delivered at rest

7.2.8 Sample size estimation

Table 7-2 shows the results of four studies reporting the SpO_2 of patients with COPD on LTOT in a domiciliary setting including the percentage of time spent with SpO_2 <90%. The study by Rice *et al*., reported the percentage of time spent with SpO_2 <90% but did not report the standard deviation (Rice et al., 2011); the authors were contacted for further information but unfortunately did not provide any further data (personal communication). The average time spent with SpO_2 <90% was approximately 25% with a standard deviation of 25% in two studies with a low standard deviation in the study from Pilling *et al*. This may be because SpO_2 data was monitored and stored every 15 seconds rather than continuously in this study. Considering an absolute mean difference between the iO_2Ts and fixed-flow oxygen therapy of 15% to be clinically significant (from 25% with fixed-flow oxygen to 10% with the iO_2Ts – a relative decrease of 60%), with a standard deviation of 25% (derived from published studies), with an

α of 0.05 (2-tailed), power of 80%, the calculated sample size is 24. I therefore aimed to recruit 30 patients to allow for a dropout rate of 20%.

Table 7-2 The percentage of time spent by patients with SpO_2<90% from four studies

Study (First author and year)	Percentage of time spent with SpO_2<90% (± standard deviation)
Sliwinski *et al* (Śliwiński et al., 1994)	30 ± 26.7
Pilling *et al* (Pilling and Cutaia, 1999)	24.6 ± 3.8
Morrison *et al* (Morrison et al., 1997)	22 ± 24
Rice *et al* (Rice et al., 2011)	23 (no standard deviation reported)

7.2.9 Statistical analysis

For the baselines characteristics, the continuous variables are presented as the means with their standard deviation or median with the interquartile range. Categorical variables are presented as number and percentage in each category.

To allow comparison with published data and as this is a cross-over study, the primary outcome is presented as mean with its standard deviation and analysed using a paired t-test.

Most secondary outcomes are presented as mean with standard deviation and analysed using a paired t-test. Non-normally distributed variables are presented as median [interquartile range] analysed using Wilcoxon-Signed ranked test. Differences between groups were analysed using independent sample t-test and Mann-Whitney test. Differences in categorical variables were analysed using Fisher-Exact test.

The flow-time data from the iO_2Ts were analysed to produce percentiles of time spent at a particular flow rates and compared to the patients usual fixed-flow LTOT using Bland-Altman analysis. All statistical analyses were conducted in SPSS version 21. Bland-Altman analysis was carried out is GraphPad Prism version 7. Additional figures were produced in Adobe Illustrator.

7.3 Results

7.3.1 Patient recruitment

Between January 2016 and January 2017, 127 patients meeting the inclusion criteria of having chronic respiratory failure necessitating LTOT were identified; consort diagram shown in Figure 7-1. Of these, 18 were excluded as they required LTOT at a flow rate of ≥4 litres per minute. A further 16 were excluded as they had multiple co-morbidities or had very limited mobility and were identified as requiring help with ADL so therefore unable to participate in the study. A further six patients were excluded as they were unwell when first approached either with a current infection or with decompensated hypercapnic respiratory failure. A total of 35 patients consented for the study of whom 5 did not attend on study day, one patient after assessment no longer required LTOT and therefore 29 patients were randomised.

Of the 29 patients who were randomised, the primary outcome was analysed for 25 patients. Two patients (both randomised to the iO_2Ts first) stopped ADL during the first set of activities due to severe breathlessness. For a third patient, the battery failed to operate and did not supply oxygen to the patient during the ADL and therefore the patient's data was removed from the analysis[1]. The fourth patient had very small ear lobes and there was difficulty in both attaching and maintaining the pulse oximeter to the ear lobe. Consequently, there was a significant volume of missing data (40%) during the ADL including complete data loss during six of the thirteen activities. As a result, a decision was made to exclude this patients' data from primary outcome analysis.

[1] There were no other adverse reactions in this study.

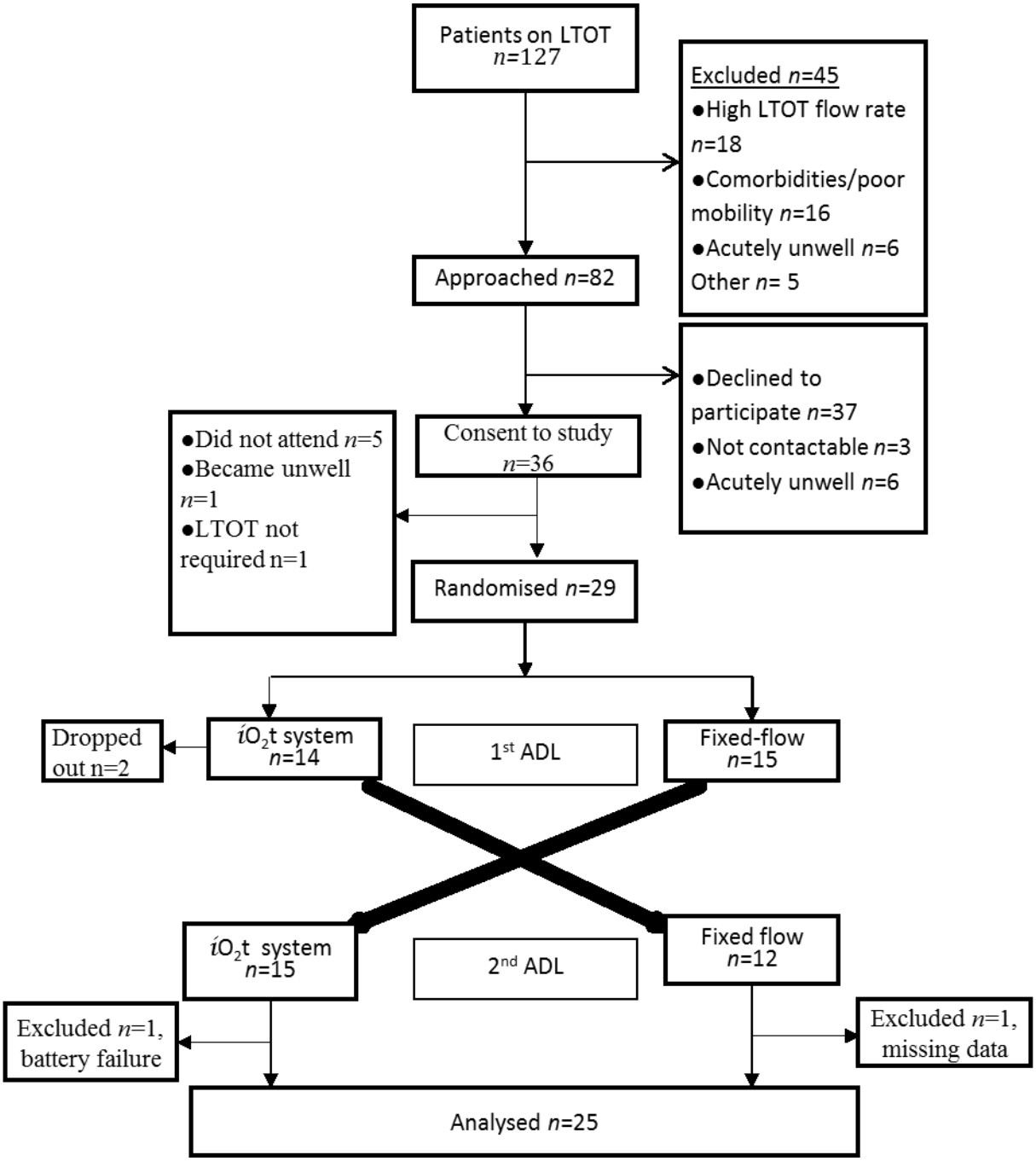


Figure 7-1 Consort diagram for activities of daily living study
iO_2Ts = intelligent oxygen therapy system, LTOT=long-term oxygen therapy, DNA=did not attend, ADL=activities of daily living

7.3.2 Baseline characteristics

The baseline characteristics of the 29 patients who participated and the 25 patients analysed for the primary outcome are shown in Table 7-3. For the randomised patients, the mean ± SD age was 69.7±9.7 years with more females (62%) than male participants. The most common diagnoses for respiratory failure were COPD 14 (48%), ILD 4 (14%), bronchiectasis 3 (10%) and kyphoscoliosis 3 (10%). For the patients with COPD, 5 (36%) had moderate disease, 4 (29%) had severe disease and 5 (36%) had very severe disease as defined by the GOLD classification.

The baseline PaO_2 and $PaCO_2$ of the participants on their usual LTOT flow rates were 9.40±1.63 kPa, and 6.15 ± 1.30 kPa respectively. Of the 25 participants included in the primary outcome analysis, only 4 had a PaO_2 < 8 kPa which would represent suboptimal correction of hypoxia with their usual LTOT flow rate.

The FEV_1 was 0.89 ± 0.4 reflecting the severe nature of the underlying diseases. Pulmonary hypertension was present in 20 (69%) patients and 16 (55%) were utilising nocturnal non-invasive ventilation. The median LTOT flow rate was 1 litre/minute with a median ambulatory flow rate of 3.5 litres/minute.

Table 7-3 Baseline characteristics of study patients

Parameter	Value		Value	
	Randomised patients, n=29		Patients included in the Primary outcome analysis n=25	
Gender (female), n (%)	18 (62)		15 (60)	
Age, years	69.7 ± 9.7		74.9 ± 4.5	
BMI, kg/m^2	25.6 ± 6.7		27.9 ± 5.3	
FEV_1, Litres	0.89 ± 0.41		0.98 ± 0.44	
Percentage predicted FEV_1, %	40.1 ± 17.0		43.6 ± 17.1	
FVC, Litres	1.71 ± 0.78		2.02 ± 0.81	
Percentage predicted FVC, %	60.0 ± 23.7		70.3 ± 24.7	
LTOT duration, years	1.6 [0.9-4.3]		2 [0.8 – 5.0]	
Baseline PaO_2 on oxygen, kPa	9.40 ± 1.63		9.52 ± 1.80	
Baseline $PaCO_2$ on oxygen, kPa	6.15 ± 1.30		6.01 ± 1.10	
Nocturnal NIV use, n (%)	16 (55)		13 (52)	
Pulmonary Hypertension, n (%)	20 (69)		17 (68)	
LTOT flow rate, Litres/minute	1 [1 - 2]		2 [1 – 2]	
Ambulatory flow rate, Litres/min	3.5 [2 - 6]		2 [2 – 6]	
Indication for LTOT, n (%)	COPD, 14 (48)	ILD, 4 (14)	COPD, 12 (48)	ILD, 4 (26)
	Bronchiectasis, 3 (10)	Kyphoscoliosis, 3 (10)	Bronchiectasis, 2 (8)	Kyphoscoliosis, 2 (8)
	Diaphragm weakness, 2 (7)	Sleep disordered breathing, 1 (3)	Diaphragm weakness, 2 (8)	Sleep disordered breathing, 1 (4)
	Asthma, 1 (3)	Obesity, 1 (3)	Asthma, 1 (4)	Obesity, 1 (4)

Data shown as n (%), mean ± SD or median [interquartile range]. BMI = Body mass index, FEV_1 = Forced expiratory volume in the first second, FVC = Forced vital capacity, LTOT = Long-term oxygen therapy, PaO_2 = Partial pressure of oxygen, kPa = kilopascal, $PaCO_2$ = Partial pressure of carbon dioxide, NIV = Non-invasive ventilation, COPD = chronic obstructive pulmonary disease, ILD = interstitial disease.

7.3.3 The effects of the iO_2Ts on SpO_2 during activities of daily living

Figure 7-2 shows an example of one patients' change in SpO_2 during the ADL over the test period for both the iO_2Ts and fixed-flow oxygen. Each patient had a rest period of 20 minutes before beginning the ADL, however, only 5 minutes is illustrated in Figure 7-2. Figure 7-2a shows the change in SpO_2 during ADL on fixed-flow oxygen at 1 litre/minute. There are intermittent desaturations during several ADL including when the patient is dressing and undressing and sweeping the floor. The SpO_2 recovers to the patients' normal baseline in between activities. Figure 7-2b shows the change in SpO_2 during ADL with the iO_2Ts. There are intermittent desaturations to which the iO_2Ts responds by increasing the oxygen flow rate and reducing the duration and severity of the desaturations.

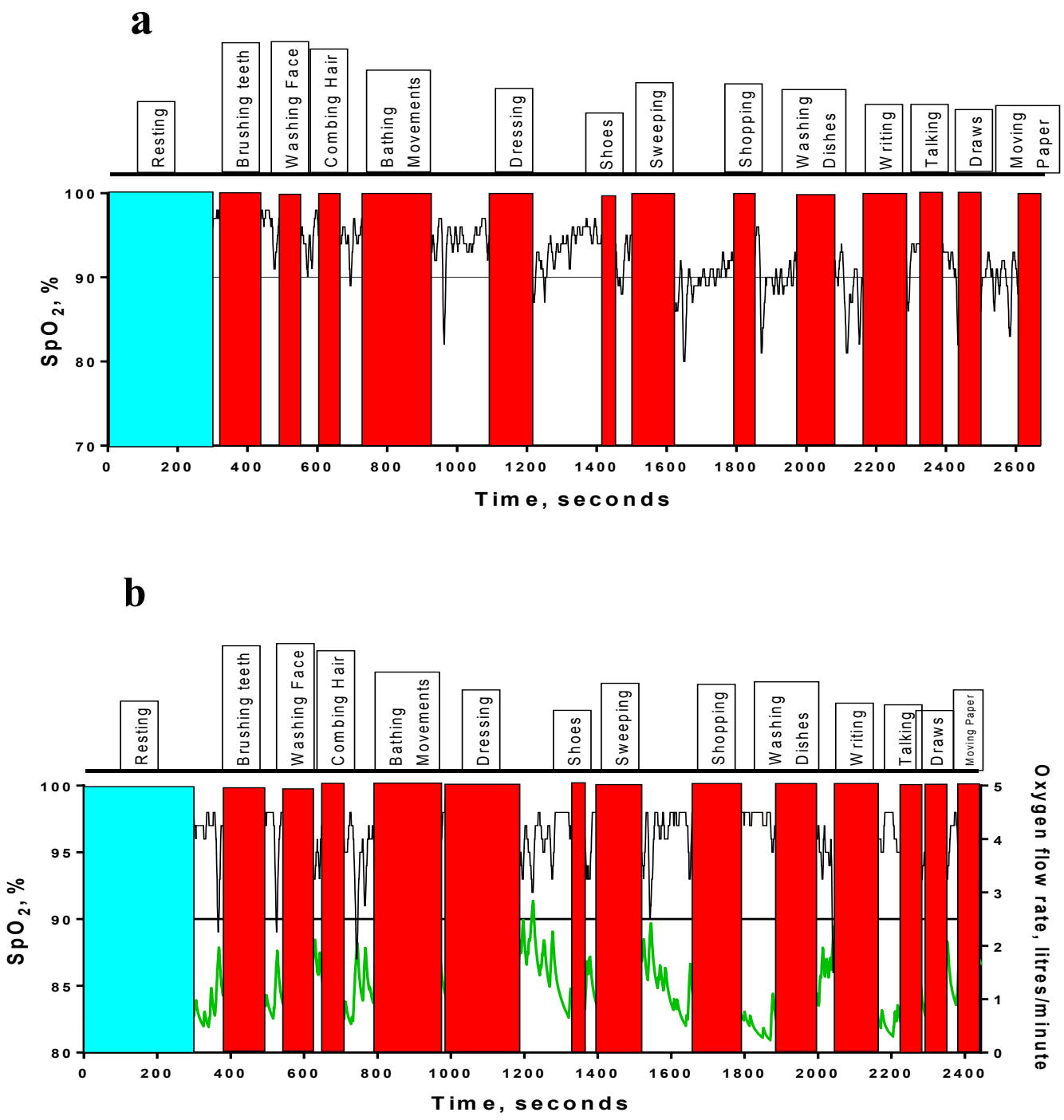


Figure 7-2 Change in oxygen saturation during activities of daily living
An example of one patients' change in oxygen saturation with 1 litre/minute fixed-flow oxygen (panel a) and the iO_2Ts in panel b. In panel b, the change in oxygen flow rate with different activities in shown in green. In both figures, a line drawn at a SpO_2 of 90% (as primary endpoint is the change in the percentage of time spent with SpO_2 <90%).

7.3.4 Primary outcome: percentage of time spent with SpO_2 <90%

Figure 7-3 shows that compared to fixed-flow LTOT, the iO_2Ts significantly reduced the mean percentage of time spent with SpO_2 <90% during ADL by 71% from 19.2 ± 26.1% to 5.5 ± 11.4%, p=0.002. The primary outcome was not affected by the order in which the participants performed the ADL (iO_2Ts first or fixed-flow oxygen first) as shown in Figure 7-4 a and b. There were 4 patients who had suboptimal correction of hypoxia with their usual LTOT flow rate at rest (resting PaO_2 <8 kPa). Analysis of the primary outcome after the removal of these 4 patients still showed a significant reduction in the percentage of time spent with SpO_2 <90% from 17.2±25.0% with fixed-flow LTOT to 3.6±5.7% with the iO_2Ts, p=0.006.

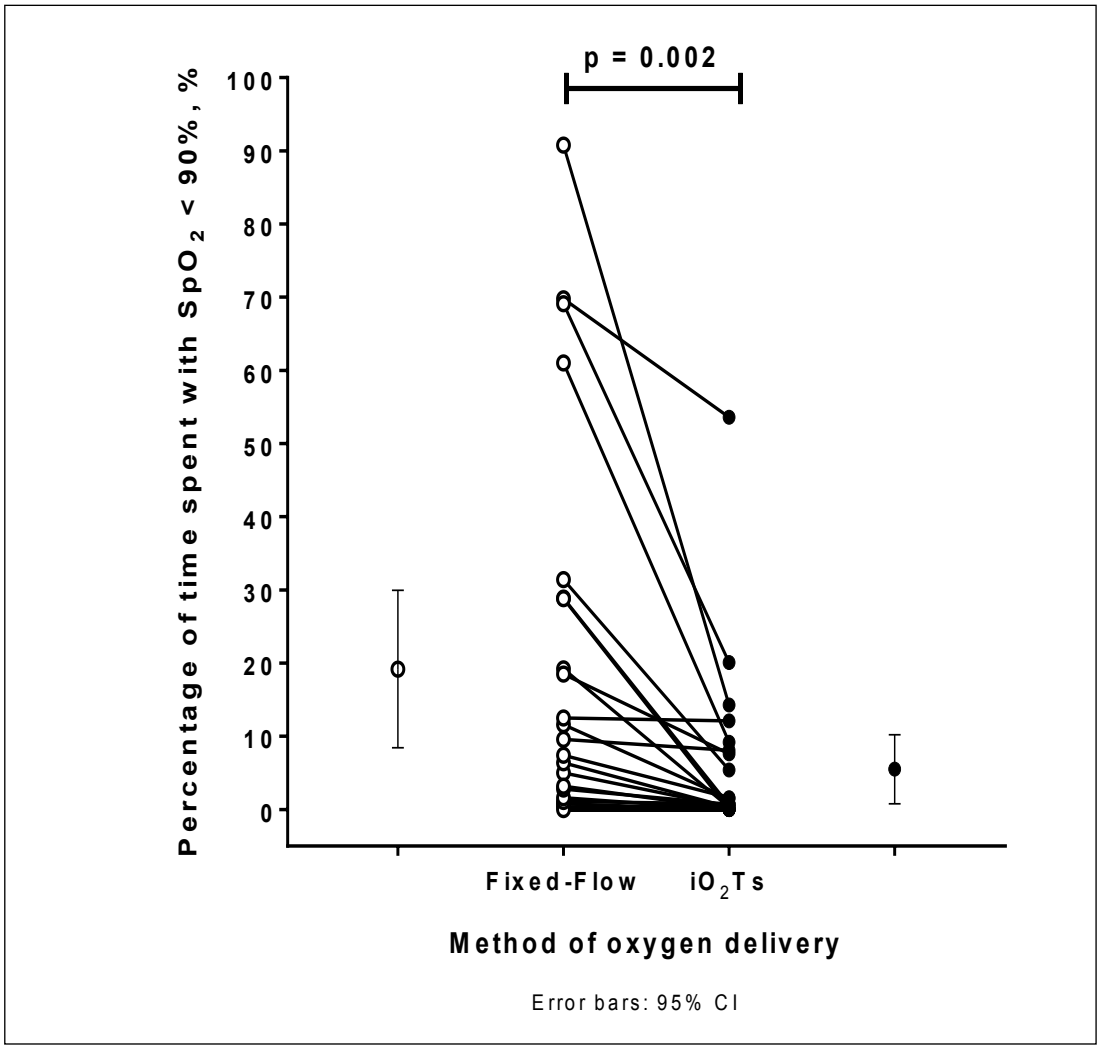


Figure 7-3 Primary outcome of change in the percentage of time spent with SpO_2 <90% with the iO_2Ts v fixed-flow oxygen during activities of daily living

SpO_2 – oxygen saturations, iO_2Ts=intelligent oxygen therapy system

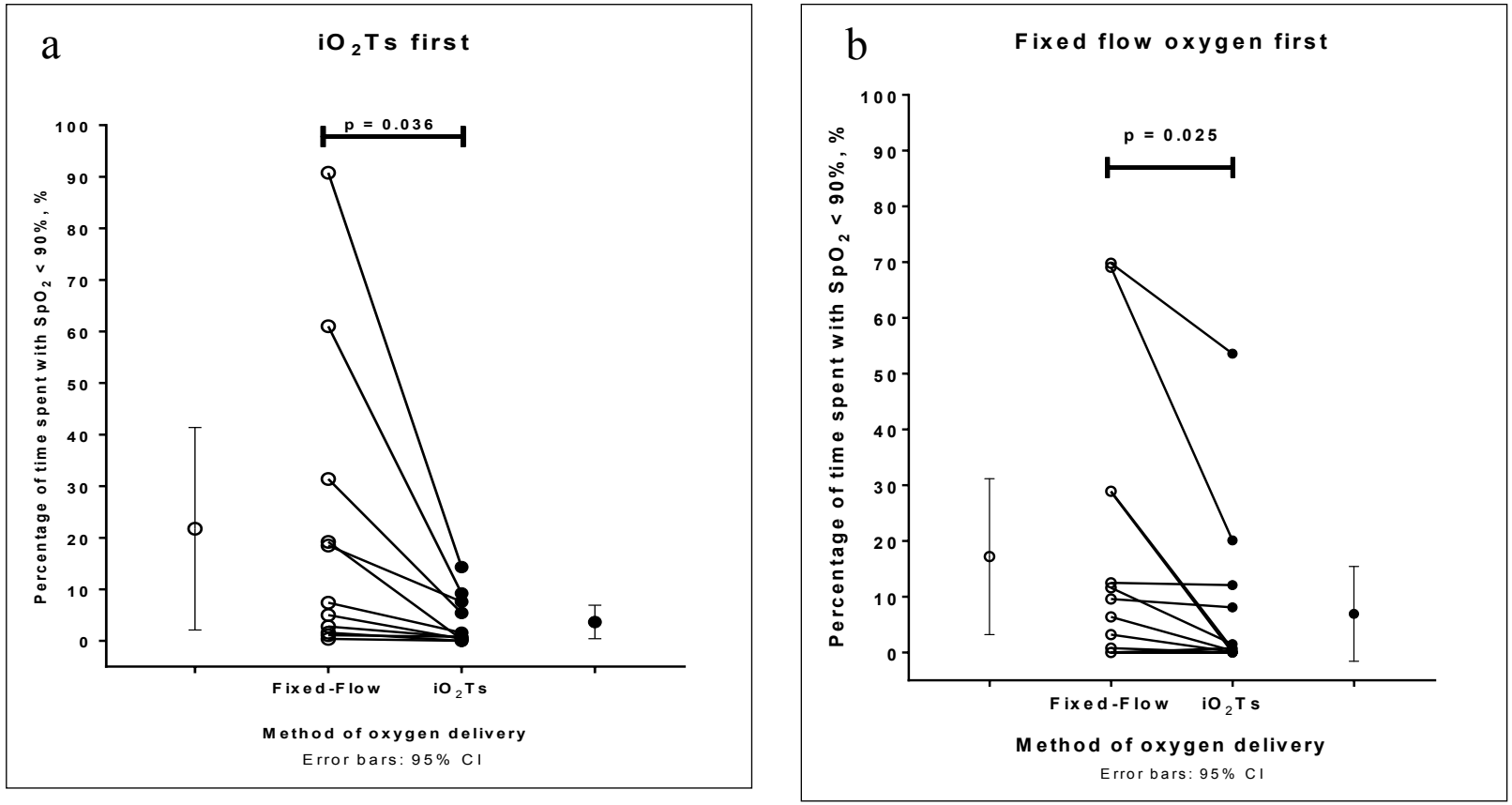


Figure 7-4 Analysis of order effect on the primary outcome

With the iO_2Ts first (figure a), the percentage of time spent with SpO_2 <90% is reduced from a mean of 21.7±29.2% with fixed-flow oxygen to 3.7±4.8% with the iO_2Ts, p=0.036. With fixed-flow oxygen first (figure b), the percentage spent with SpO_2 <90% is reduced from a mean of 17.2±24.2% with fixed-flow oxygen to 6.9±14.7% with the iO_2Ts, p=0.025.

7.3.5 Secondary outcomes

The iO_2Ts significantly increased the percentage of time spent in the optimum SpO_2 range of 90-96% to 81.4 ±18.6% from 51.6 ±24.7% with fixed-flow oxygen, $p<0.001$, Figure 7-5b and also significantly reduced the percentage of time that patients spent with hyperoxia ($SpO_2 \geq 97\%$) to 13.1±18.3% from 29.2 ±30.3%, p=0.002, Figure 7-5c.

The iO_2Ts significantly increased the trough SpO_2 from 84.5±6.9% to 87.7±3.2% p=0.001, Figure 7-6a. However, the mean SpO_2 was not different between the fixed-flow oxygen and the iO_2Ts during ADL, 93.2±4.1% *versus* 93.9±1.6% respectively, p=0.335, Figure 7-6b.

There was no difference in the mean heart rate between the iO_2Ts and fixed-flow oxygen, 91.2±16.9 beats/minute *versus* 93.2±4.1 beats/minute respectively, p=0.264 Figure 7-6c. There was no difference in the peak heart rate between the iO_2Ts and fixed-flow oxygen, 106±16 beats/minute v 107±16 beats/minute respectively, p=0.455, Figure 7-6d. There was also no difference in the volume of oxygen delivered during ADL between the iO_2Ts and fixed-flow oxygen, 28.4±14.1 litres v 26.6±9.5 litres respectively, p=0.568, Figure 7-6e.

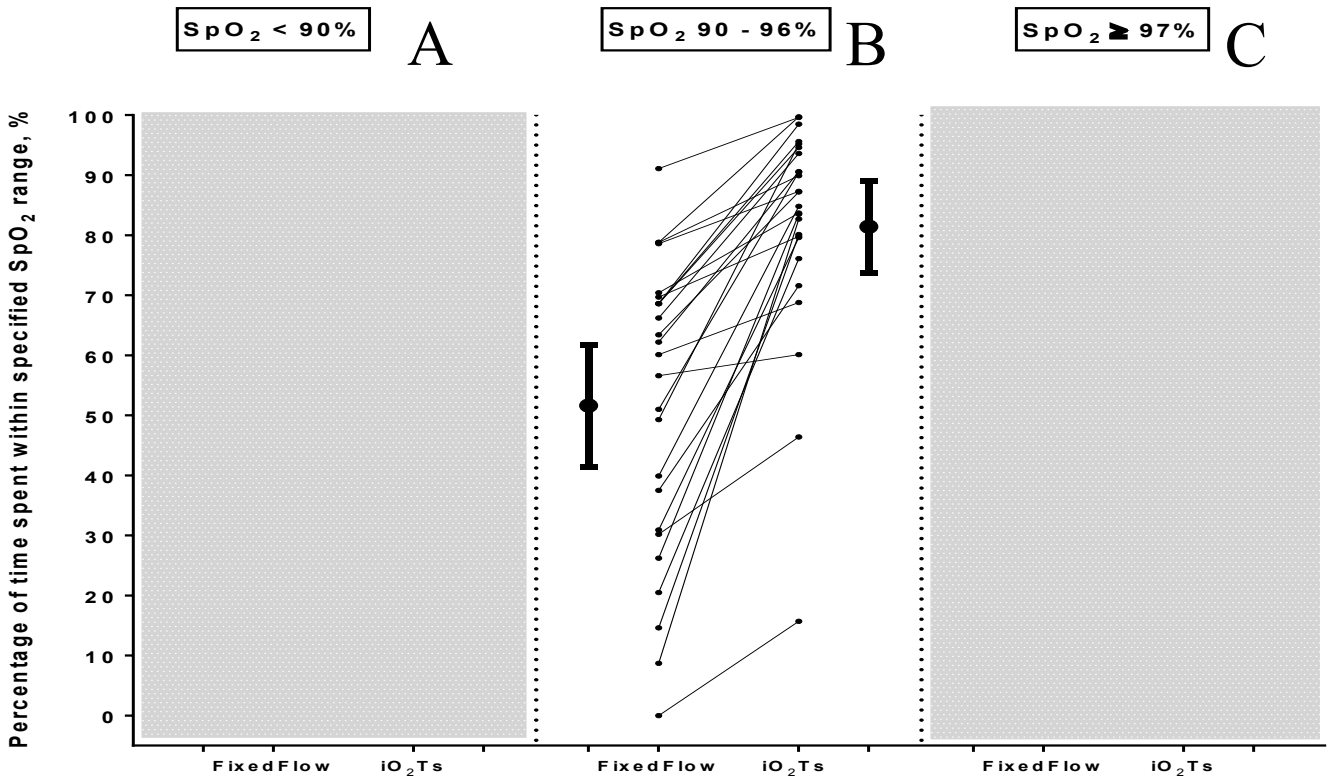


Figure 7-5 Change in the percentage of time spent at different SpO_2 ranges with fixed-flow oxygen and the iO_2Ts
The iO_2Ts reduced intermittent hypoxia (SpO_2 <90%, the primary outcome, panel A), increases the percentage of time spent in the optimal SpO_2 range of 90-96% (panel B) and reduced the percentage of time with hyperoxia (SpO_2 ≥97%, panel C).
iO_2Ts = intelligent oxygen therapy system, SpO_2 = oxygen saturation

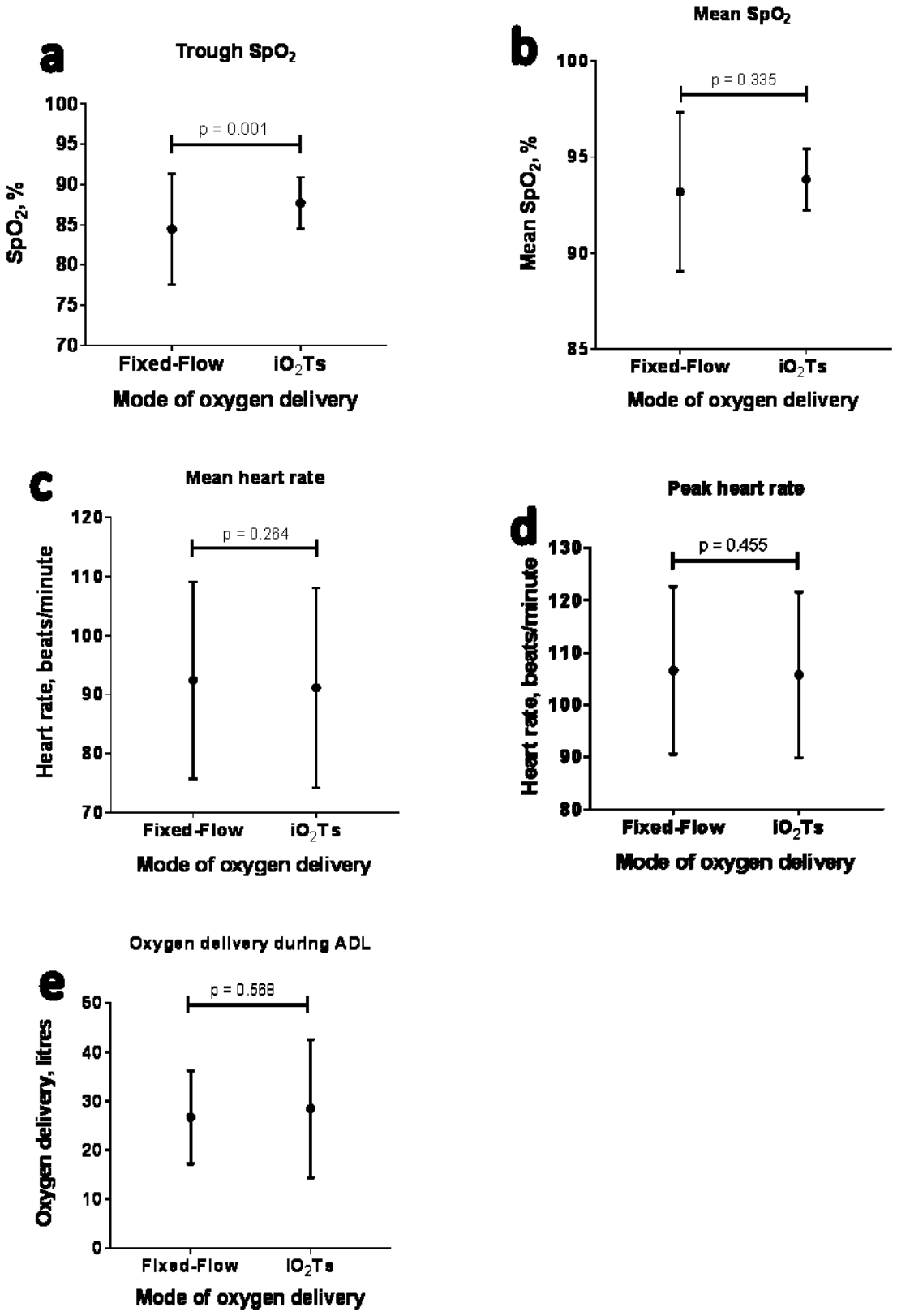


Figure 7-6 Changes in secondary outcome during activities of daily living between the iO_2Ts and fixed-flow oxygen

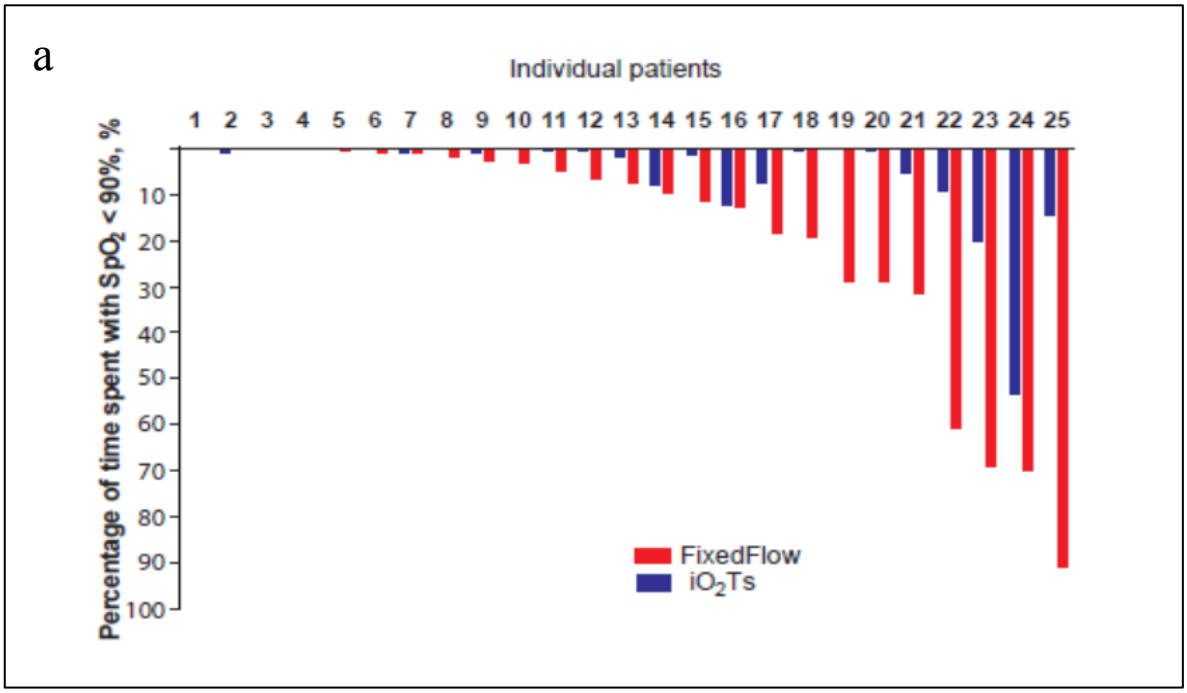
iO_2Ts = intelligent oxygen therapy system, SpO_2 = oxygen saturation

7.3.6 Analysis of patients who did and did not desaturate during ADL

As shown in the waterfall plot (Figure 7-7a), 11 of the 25 participants spent ≥10% of time with SpO_2 <90% during ADL (the desaturator group) and 14 participants spent <10% of time with SpO_2 <90% (the non-desaturator group). Analysis of the primary outcome of percentage of time spent with SpO_2 <90% only for the eleven participants who desaturated during ADL showed that the iO_2Ts still had a significant reduction of 28.9% in the percentage of time spent with SpO_2 <90% Figure 7-7b. Of the eleven participants who desaturated, nine had a very good response to the iO_2Ts with very significant reductions in the percentage of time spent with SpO_2 <90% and 2 had a poor response with the iO_2Ts. A further discussion of the patients who did not respond well to the iO_2Ts now follows.

The first patient was a 68-year-old female with COPD, had a body mass index (BMI) of 36.2 with pulmonary hypertension and requiring nocturnal NIV. She spent 69.8% of time with SpO_2 <90% during ADL with fixed-flow oxygen which only improved to 53.6% with the iO_2Ts. This participant was also very hypoxic at rest, spending 60.3% of time with SpO_2 <90% at rest with her usual LTOT flow rate of 3 litres/minute which improved to 16.8% with the iO_2Ts. Analysis of the flow time data with the participant at rest on the iO_2Ts reveals that the flow rate increased to as high as 4.7 litres/minute. Considering this, her LTOT flow rate requirement at rest is almost certainly 4 - 5 litres/minute rather than her current 3 litres/minute. Therefore, her usual LTOT flow rate requirement is almost at the maximum level of flow that can be provided by the iO_2Ts and this may well account for her poor response to the system.

The second participant with a poor response was a 77-year-old female with COPD, a BMI of 27.8 with pulmonary hypertension and an LTOT flow rate of 2 litres/minute. She spent 12.5% of time with SpO_2 <90% which improved to only 12.1% with the iO_2Ts during ADL. Analysis of the activity data when on fixed-flow oxygen reveals that she was only significantly hypoxic during one activity; sweeping the floor. During this activity on fixed-flow oxygen she desaturated from a baseline of 94% to 89% after 47 seconds and subsequently desaturated to a nadir of 79% after 2 minutes. With the iO_2Ts, the baseline SpO_2 was 94% with a flow-rate of 0.9 litres/minute at rest. The participant desaturated to 89% after 30 seconds with the flow rate reaching 2.4 litres/minute at this point. The flow rate increased steadily after this point but the rise was not able to arrest the fall in SpO_2 which continued to decline to a nadir of 83% with the flow rate reaching a peak of 4.5 litres/minute. In this case, the rate of change of the oxygen flow rate was not fast enough to prevent the decline in SpO_2.



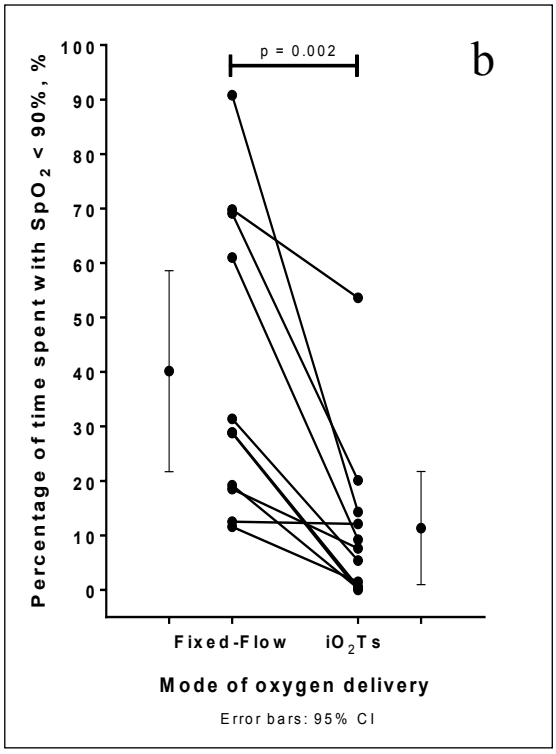


Figure 7-7 Change in the primary outcome in individual patients and oxygen desaturators

Figure a is a waterfall plot demonstrating the change in the percentage of time spent with SpO_2 <90%. 11 patients desaturated ≥10% during activities of daily living and figure b demonstrates that the iO_2Ts significantly reduced the percentage of time spent with SpO_2 <90% by 72% from 40.2±27.5% with fixed-flow oxygen to 11.3±15.5% in the desaturator group.

Analysis of the differences in continuous baseline characteristics between the participants who did and those that did not desaturate are shown in Table 7-4 and for categorical variable is shown in Table 7-5. This analysis shows that PaO_2 and FVC were statistically significantly greater in participants who did not desaturate compared to those who did desaturate.

Table 7-4 Comparison of baseline continuous variables of "desaturators" and "non-desaturators"

	Deasturators		Non-desaturators		
	N	Value	N	Value	p-values
Age, years	11	68.8 ± 8.9	14	74.1 ± 6.3	0.116#
BMI, kg/m^2	11	28.3 ± 6.9	14	27.4 ± 6.0	0.726#
FEV_1, litres	11	0.86 ± 0.40	14	1.0 ± 0.4	0.444#
FEV_1 % predicted, %	11	41.5 ± 13.8	14	43.7 ± 19.2	0.741#
FVC, litres	11	1.37 ± 0.73	14	2.1 ± 0.7	0.027#
FVC % predicted, %	11	53.0 ± 23.6	14	69.6 ± 20.9	0.08#
FEV_1/FVC ratio, %	11	68.9 ± 23.2	14	53.0 ± 18.5	0.079#
Pack year smoking	5	34.9 ± 26.9	11	30.0 ± 17.1	0.821#
PaO_2 on oxygen, Kpa	11	8.68 ± 1.16	14	9.91 ± 1.75	0.047#
$PaCO_2$ on oxygen, kPa	11	6.08 ± 1.35	14	6.00 ± 1.17	0.878#
LTOT duration, years	11	1.5 [0.8-4.5]	14	1.8 [0.8-1.3]	0.763##
LTOT flow rate, litres/minute	11	1.0 [1.0-2.0]	14	2.0 [1.0-2.0]	0.360##
Ambulatory flow rate, litres/minute	10	2.5 [2.0-6.0]	12	4.0 [2.0-6.0]	0.679##

Variables presented as with mean±SD or median (interquartile range). BMI=Body mass index FEV_1=Forced expiratory volume in the first second FVC=Forced vital capacity PaO_2=partial pressure of oxygen $PaCO_2$=partial pressure of oxygen LTOT=long-term oxygen therapy. #=Independent sample T-Test with equal variance not assumed ##=Mann-Whitney U Test

Table 7-5 Baseline categorical variables of patients who did and did not desaturate during ADL

Variable	Categories	Desaturators	Non-desaturators	p-value
Gender	Male	3	7	0.504
	Female	9	7	
Nocturnal NIV use	Yes	5	8	0.430
	No	6	6	
Pulmonary Hypertension	Present	7	10	0.231
	Absent	4	4	
NIV=non-invasive ventilation. All p-values for Fisher's Exact Test				

7.3.7 Change in borg score for individual activities

Table 7-6 shows the changes in Borg scores for breathlessness and fatigue resulting from all the ADL. For all almost all activities there was no significant change in either breathlessness or fatigue, except that the iO_2Ts significantly reduced fatigue after combing hair, although this difference is not clinically meaningful.

Table 7-6 Changes in Borg scores resulting from activities of daily living

Activity	Change in Borg scores for breathlessness, median (IQR)		p-value	Change in Borg scores for fatigue, median (IQR)		p-value
	Fixed-Flow Oxygen	iO_2Ts		Fixed-Flow Oxygen	iO_2Ts	
Brushing teeth	0.0 [0.0-1.25]	0.0 [0.0 – 1.0]	0.574	0.0 [0.0 – 0.63]	0.0 [0.0 – 1.0]	0.297
Washing Face	0.0 [0.0 – 0.75]	0.0 [0.0 – 1.0]	0.804	0.0 [0.0 – 0.5]	0.0 [0.0 – 0.5]	0.611
Combing Hair	0.0 [0.0 – 1.0]	0.0 [0.0 – 0.63]	0.297	0.0 [0.0 – 1.0]	0.0 [0.0 – 0.0]	0.043
Bathing Movements	1.0 [1.0 – 2.0]	1.0 [0.25 – 2.0]	0.118	1.0 [0.3 – 2.0]	1.0 [1.0 – 2.0]	0.527
Dressing and Undressing	2.0 [1.0 – 3.0]	2.0 [1.0 – 3.0]	0.641	1.0 [0.0 – 2.0]	1.0 [0.0 – 2.0]	0.223
Shoes	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.157	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.317
Sweeping Floor	3.0 [1.0 – 3.0]	2.0 [1.0 – 3.75]	0.298	1.5 [0.75 – 2.75]	2.0 [0.0 – 2.75]	0.489
Storing cans	0.0 [0.0 – 1.0]	0.0 [0.0 – 1.0]	0.860	0.0 [0.0 – 0.87]	0.0 [0.0 – 0.88]	0.865
Washing Dishes	0.5 [0.0 – 1.0]	0.0 [0.0 – 1.0]	0.353	0.0 [0.0 – 1.0]	0.0 [0.0 – 1.0]	0.829
Writing on paper	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.233	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.730
Talking on telephone	0.0 [0.0 – 0.25]	0.0 [0.0 – 0.0]	0.628	0.0 [0.0 – 0.0]	0.0 [0.0 – 0.0]	0.888
Opening and closing draws	0.0 [0.0 – 0.75]	0.0 [0.0 – 0.75]	1.000	0.0 [0.0 – 0.5]	0.0 [0.0 – 0.0]	0.084
Moving paper	0.5 [0.0 – 1.0]	0.0 [0.0 – 1.0]	0.787	0.0 [0.0 – 1.0]	0.0 [0.0 – 1.0]	0.351
iO_2Ts = intelligent oxygen therapy system. All p-values are for paired sample T test						

7.3.8 Analysis of oxygenation during individual activities

Table 7-7 show the mean SpO_2 and the percentage of time spent with SpO_2 <90% classified by individual activities. The mean SpO_2 was only statistically significantly different between fixed-flow oxygen and the iO_2Ts for two activities, taking off and putting on shoes and sweeping the floor. The activities to cause the greatest desaturation on fixed-flow oxygen were sweeping the floor, taking off and putting on shoes, dressing and undressing and combing hair. The iO_2Ts reduced the percentage of time spent with SpO_2 <90% to ≤5% for all but three activities. It also statistically significantly reduced the percentage of time spent with SpO_2 <90% compared to fixed-flow oxygen for eight activities (highlighted grey in Table 7-7).

Table 7-7 The mean SpO_2 and the percentage of time spent with SpO_2 <90% for individual activities

Activity	Number of participants	Mean SpO2, mean ± SD			Percentage of time spent with SpO_2 <90%, mean ± SD		
		Fixed-flow oxygen	iO_2Ts	p-value	Fixed-flow oxygen	iO_2Ts	P-value
Brushing teeth	22	94.6±3.9	94.2±1.3	0.569	12.5±31.3	0.1±0.5	0.076
Washing face	24	93.6±4.1	93.3±2.1	0.706	15.5±32.9	4.8±18.3	0.050
Combing hair	22	93.2±3.8	94.0±2.1	0.170	18.6±35.0	3.7±16.0	0.039
Bathing movements	25	93.6±3.5	93.8±1.8	0.814	14.0±26.5	5.7±15.3	0.079
Dressing and Undressing	23	91.6±5.3	92.9±1.6	0.209	22.3±27.8	7.0±10.8	0.004
Putting on taking off shoes	23	92.5±5.2	94.4±2.7	0.047	24.1±39.1	4.3±20.9	0.014
Sweeping floor	25	90.1±5.1	92.1±2.6	0.024	42.6±39.4	17.5±29.3	0.001
Storing cans at different heights	24	94.4±4.9	95.1±1.7	0.438	16.2±29.9	1.0±4.8	0.012
Washing up dishes	24	93.4±3.7	94.0±2.2	0.251	16.0±33.0	5.0±17.4	0.023
Writing	25	94.5±4.1	95.3±1.2	0.282	14.1±29.7	0.0±0.0	0.030
Talking on phone	25	95.7±3.8	95.0±1.5	0.351	4.7±20.1	0.0±0.0	0.257
Opening and closing draws	25	95.0±4.1	94.8±2.1	0.778	12.1±27.4	3.3±16.7	0.089
Moving paper	25	93.8±4.6	94.0±1.9	0.805	18.1±35.2	3.5±11.6	0.024
iO_2Ts = intelligent oxygen therapy system. All p-values are for paired sample T test							

7.3.9 The iO_2T as an oxygen assessment tool

The iO_2Ts continuously monitors SpO_2 and adjusts oxygen flow rates to maintain a pre-set SpO_2 target. The flow rates over time can be analysed to reveal the percentage of time spent at a particular flow rate. This data can identify maximum flow rate and flow rates that are rarely exceeded (90^{th} of 95^{th} percentile flow rates). This data can be used to assess the utility of the iO_2Ts as an oxygen assessment tool both for LTOT flow rates at rest and for oxygen flow rates during activities.

The oxygen flow rates over time produced from the iO_2Ts system with the participants at rest were analysed according to the 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 95^{th} percentiles of time spent a particular flow rate for each participant. Only participants who had spent little or no time with SpO_2 <90% at rest with their usual fixed-flow oxygen were chosen for this analysis n=23 (data for 26 patients was available for analysis; two patients were excluded as they spent a very significant amount of time with SpO_2 <90% at rest; one further patient with hyperoxia at rest was removed, PaO_2 = 14.5 kPa at rest). Figure 7-8 shows the Bland-Altman agreement between flow rate produced at 6 different percentiles compared to the usual LTOT flow rate for each patient. The best agreement with the shortest 95% limits of agreement and the smallest bias (0.187) is seen with the 90^{th} percentile of time.

The same analysis was conducted for oxygen flow rates during ADL and this is shown in Figure 7-9. For this analysis, only patients who had not significantly desaturated with their usual LTOT flow rate during activities of daily living was included in the analysis (the non-desaurators) n=13 (there were 14 patients who were non-desaturators but one was excluded from this analysis due to hyperoxia at rest). The smallest bias (-0.08) and second shortest 95% limits of agreement and the is seen with the 75^{th} percentile of time

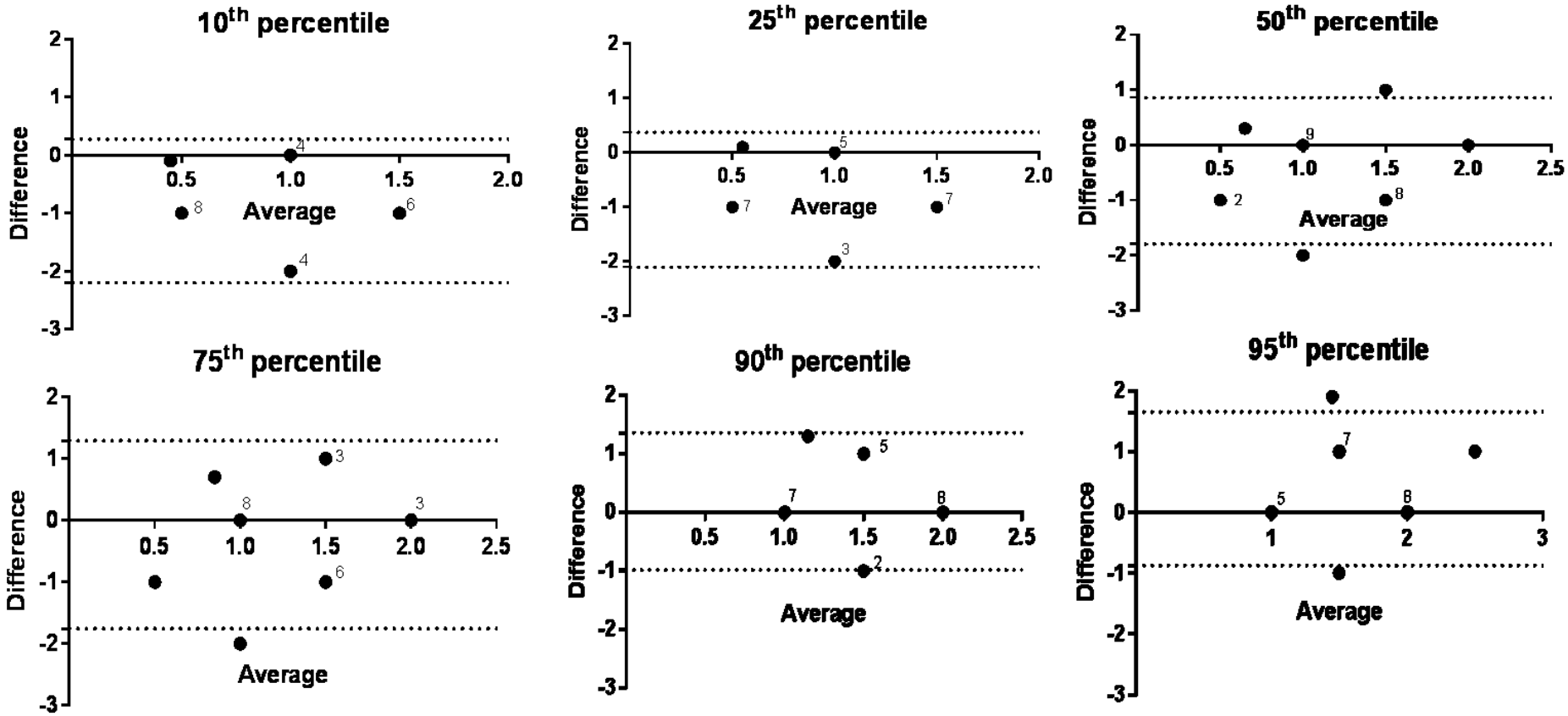


Figure 7-8 Difference vs average Bland-Altman plots for 6 percentiles of time at rest
Analysis for 23 patients' agreement between their long-term oxygen therapy flow rate and percentiles of time with the intelligent oxygen therapy system at rest (the number adjacent to the dots represents the number of patients at that point).

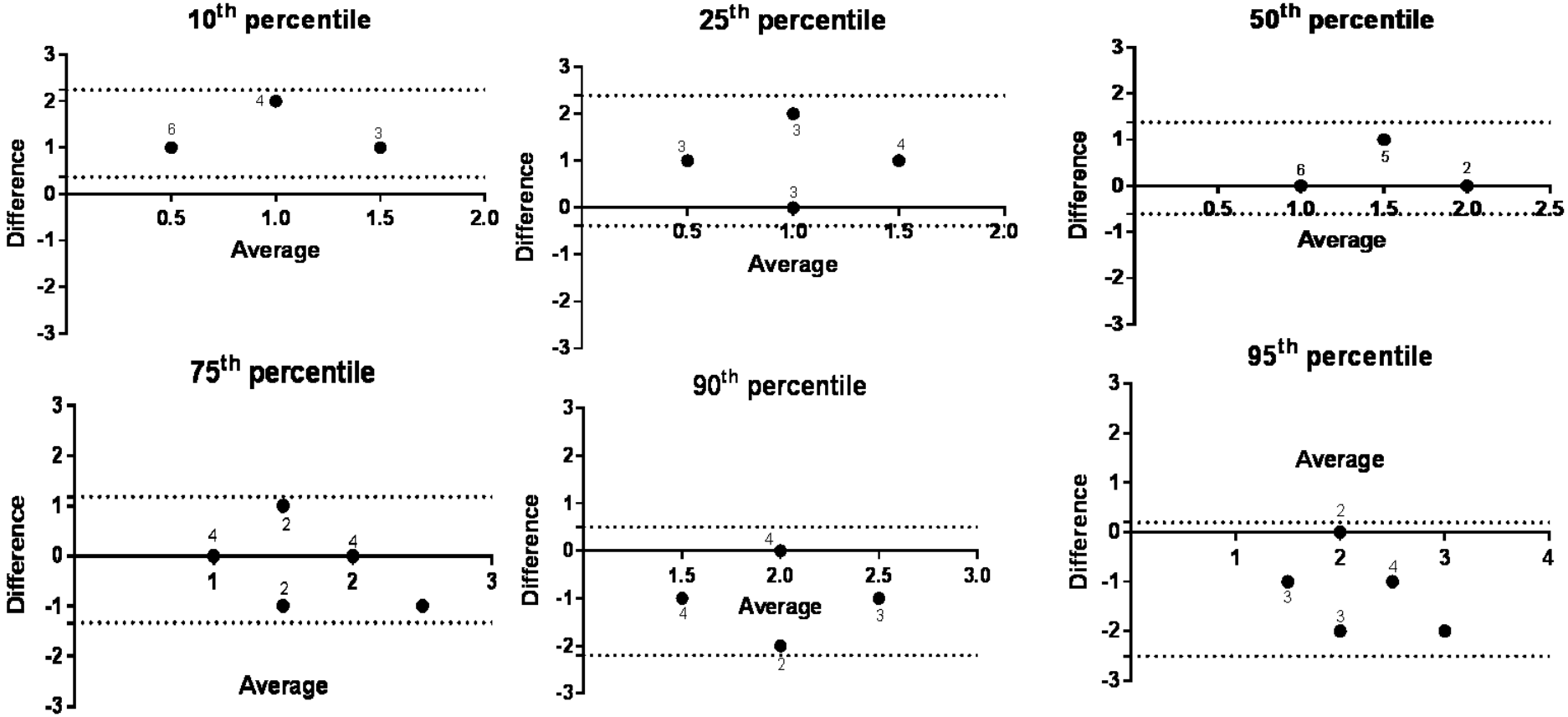


Figure 7-9 Difference vs average Bland-Altman plots for 6 percentiles of time during activities of daily living
Analysis for 13 patients' agreement between their long-term oxygen therapy flow rate and percentiles of time with the intelligent oxygen therapy system during activities of daily living (the number adjacent to the dots represents the number of patients at that point).

7.3.10 Analysis of the resting period before activities of daily living

All participants began their ADL protocol with a rest period of 20 minutes. The mean SpO_2 during the rest period was significantly higher with fixed-flow oxygen than with the iO_2Ts, 95.9±3.1% *versus* 94.7±1.1% respectively, p=0.023 shown in Figure 7-10a. The percentage of time spent with SpO_2 <90% during the rest period was not different with fixed-flow oxygen and the iO_2Ts; 4.7 ± 15.7% *versus* 0.8 ± 3.3%, respectively shown in Figure 7-10b. However, the volume of oxygen delivered at rest was significantly lower with the iO_2Ts than with fixed-flow oxygen, 21.0±13.1 litres *versus* 30.0±12.2 litres respectively, p=0.003, shown in Figure 7-10c.

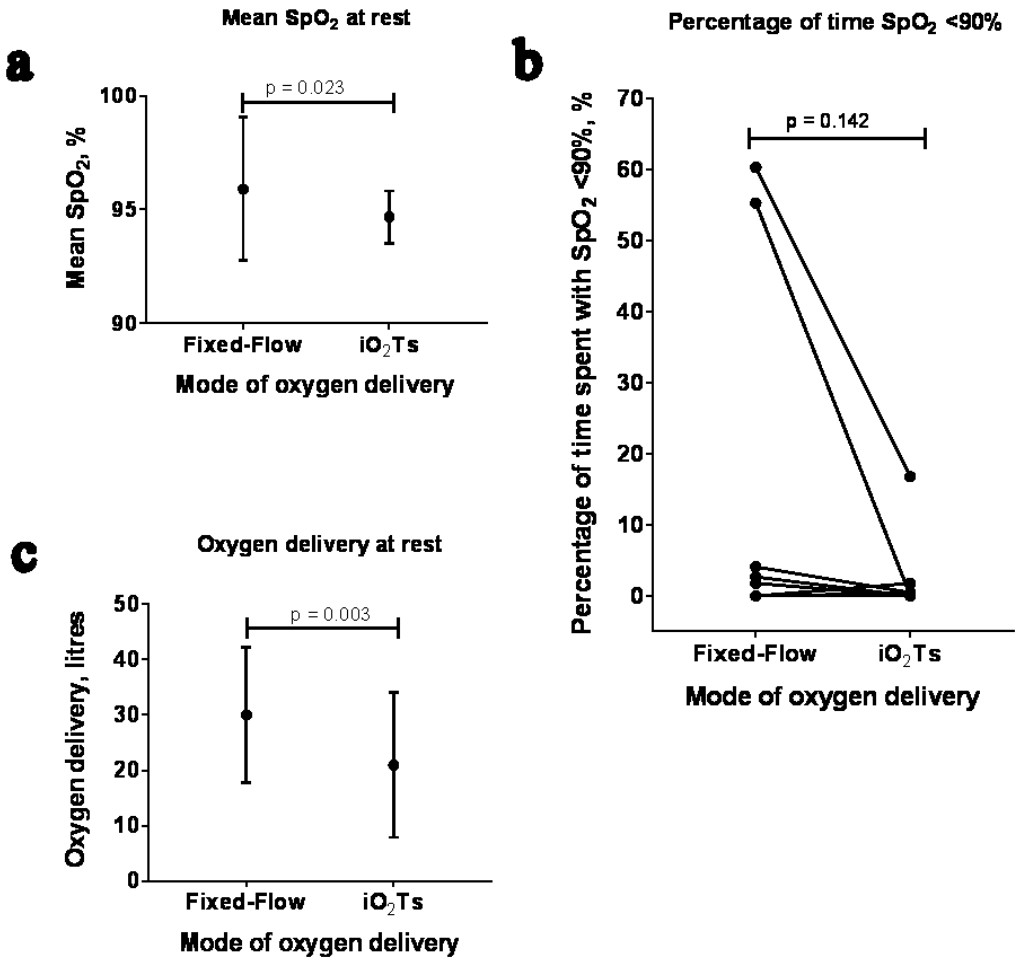


Figure 7-10 Change in three variables during the rest period between fixed-flow oxygen and the iO_2Ts.
iO_2Ts = intelligent oxygen therapy system, SpO_2 = oxygen saturation

7.4 Discussion

The main finding from this study was that the iO_2Ts significantly reduced intermittent hypoxia during ADL in patients with chronic hypoxamic respiratory on domiciliary LTOT. The iO_2Ts also significantly reduced the percentage if time spent with SpO_2 ≥97% (hyperoxia) and increased the percentage of time spent within the optimal SpO_2 range of 90-96%. In addition, the iO_2Ts also significantly increased the trough SpO_2. There was no difference in the mean SpO_2 between fixed-flow oxygen and the iO_2Ts.

The reduction in intermittent hypoxia during ADL could improve oxygen supply to the brain, reduce the risk of arrhythmias associated with hypoxia and reduce episodic pulmonary hypertension related to desaturation during ADL. As shown by Selinger and colleagues, withdrawal of oxygen therapy in patients on LTOT (akin to that patients experienced by patients having intermittent hypoxia), increases pulmonary artery pressures (Selinger et al., 1987). Additionally, two studies have demonstrated that the increases in pulmonary artery pressure induced by desaturations could well be underestimated. Christensen and colleagues investigated changes in pulmonary artery pressure in patients with COPD who had either normal SpO_2 at rest or only mild hypoxaemia at rest during exercise equivalents of ADL (no patients were on LTOT). The study showed that is most patients, ADL were associated with minor desaturations but that these were associated with significant rises in pulmonary pressure (Christensen et al., 2004). A study from Kjellstre and colleagues examined the change in pulmonary pressure in patients with pulmonary hypertension during ambulatory conditions using an indwelling pulmonary artery monitoring system (Kjellstrom et al., 2014). The study showed that the range of changes and peak pulmonary artery pressure were greater during home ambulation than during a 6MWT or exercise tests. The desaturations and associated increases in pulmonary pressure during ADL are very important as there is a suggestions that repeated episodes of intermittent hypoxia lead to pulmonary vasoconstriction and remodelling of the pulmonary vasculature and persistent pulmonary hypertension over longer periods of time (Weitzenblum, 1994).

The reduction in intermittent hypoxia with the iO_2Ts was not associated with any changes in either mean or peak heart rate. Additionally, there were no clinically meaningful changes in dyspnoea as measured by the Borg score after any activity with the iO_2Ts. In one previous study, hyperoxia during exercise was shown to reduce breathlessness in patients with COPD (O'Donnell et al., 2001). During my study, patients on fixed-flow oxygen spent a significant amount on time with hyperoxia but this did not result in a reduction in Borg score in favour of fixed-flow oxygen. The causes of exercise limitation and breathlessness in patients with COPD

are multifactorial including but not limited to hyperinflation, airflow obstruction, psychological as well as environmental factors and the optimisation of oxygen therapy alone may not be enough to relive breathlessness as all other mechanisms are not altered (Vogiatzis and Zakynthinos, 2012, O'Donnell et al., 2007).

In one previous study of an auto-titrating oxygen system during ADL by Rice and colleagues, the $AccuO_2$ system non-significantly reduced intermittent hypoxia when compared to fixed-flow oxygen and an oxygen conserver system (Rice et al., 2011). The $AccuO_2$ system also reduced oxygen utilisation in comparison to the other two systems. In comparison to the study by Rice and colleagues, there was no reduction in oxygen delivery during ADL in the present study. However, there was a significant reduction in oxygen delivery during the 20-minute rest period before ADL were started with the iO_2Ts. During this period, the mean SpO_2 was significantly higher with fixed-flow oxygen but this is expected given than the iO_2Ts is set to titrate oxygen delivery to meet a pre-specified SpO_2 and our data are consistent with the findings from study by Rice and colleagues. The percentage of time spent with SpO_2 <90% during the rest period was not different between the iO_2Ts and fixed-flow oxygen. Since most of the time during a day is spent at rest (Śliwiński et al., 1994), the reduction in oxygen delivery shown during the rest period could lead to reduced oxygen delivery over an entire day and therefore a reduction in the cost of using oxygen therapy.

Consistent with previous studies, not every patient on LTOT desaturated significantly (≥10% of time spent with SpO_2 <90%) during ADL (Annegarn et al., 2012, Van Remoortel et al., 2012, Vaes et al., 2011, Castro et al., 2013). However, somewhat surprisingly more patients did not desaturate (n=14) than those that did desaturated (n=11). The main physiological difference between these two groups was a higher baseline PaO_2 and FVC for patients who did not desaturate. These finding are in line with previously published data demonstrating that increasing oxygen flow rates to achieve higher baseline SpO_2 and PaO_2 reduces intermittent hypoxia. However, the same data also demonstrates that higher baseline PaO_2 can lead to hyperoxia and this is confirmed by data from this study with the non-desaturator group of patients spending a very significant 47.4% of time with SpO_2≥97% compared to only 6.0% for the desaturator group on fixed-flow oxygen during ADL (Samolski et al., 2010).

7.4.1 The iO_2Ts as an oxygen assessment tool

The assessment of flow rate required for LTOT is carried out with the patients at rest by manual titration of flow rate until the SpO_2 is consistently >90% followed by an ABG to confirm that the resting PaO_2 is ≥8kpa (Hardinge et al., 2015). As confirmed in this study and demonstrated in many others, patients on LTOT, can desaturate quite significantly during ADL. However,

there is very limited guidance as to how oxygen flow rates should be adjusted during ADL. Some guidelines recommend that the oxygen flow rate should be increased to that of ambulatory oxygen during ADL (British Thoracic Society (BTS) Working Group on Home Oxygen Services, 2006), others recommend that it should be 1 litre/minute higher than the LTOT flow rate (McDonald et al., 2016), whilst evidence shows that clinical practice of how oxygen flow rates are adjusted is very heterogenous across the world (Wijkstra et al., 2001). One previous study has investigated different methods of oxygen titration during a 6MWT and constant work rate exercise tests and showed that oxygen flow rates from constant rate exercise tests reduce time spent with SpO_2 <90% during ADL to a greater degree than flow rate titration from a 6MWT or by following the NOTT protocol (Galera et al., 2012). In the absence of a consensus, the best approach would be to either utilise the iO_2Ts all the time to optimise oxygenation or use SpO_2 data from domiciliary monitoring to investigate which patients desaturate on their usual LTOT flow rate and adjust flow rates according to data from a 6MWT or constant rate exercise tests. A third option is to utilise the flow-time data from the iO_2Ts to produce optimum flow rates for rest and ADL.

I utilised Bland-Altman analysis to investigate agreement between flow rates produced at different percentiles of time by the iO_2Ts against the actual LTOT flow rate in patients who had very little to no desaturation during rest and ADL. The percentile with the lowest bias and smallest 95% limits of agreement at rest was the 90^{th} percentile. The percentile with the lowest bias and second lowest 95% limits of agreement during ADL was the 75^{th} percentile. The bias for ADL was very low at -0.08 and at rest it was low at 0.187. The very small bias is supportive evidence that the iO_2Ts could be utilised as an oxygen assessment tool for LTOT flow rates at rest and during ADL. However, this clearly needs to be validated in another cohort of patients in a larger prospective study.

7.4.2 Limitations of the study

This study was designed to investigate if the iO_2Ts could reduce intermittent hypoxia during ADL in patients on LTOT. The iO_2Ts by delivering variable oxygen flow rates reduced intermittent hypoxia. However, many patients in the study had hypercapnia and transcutaneous CO_2 was not measured and therefore the impact of the iO_2Ts on CO_2 remains unknown. From published studies with auto-titrating oxygen systems, transcutaneous CO_2 did not change significantly with increased oxygen flow rates during an ESWT (Vivodtzev et al., 2016, Lellouche et al., 2016b).

This study was conducted in a modified sleep laboratory at the Royal Brompton Hospital and although this allowed standardisation of ADL, it may not reflect the behaviour of patients in

their usual home environment or the way which they do the activities requested which impacts on the generalisability of these results.

We made a decision to include only patients on LTOT with flow rates <4 litres/minute as the device is flow limited at 5 litres/minute. Although the results of this study as promising, almost 20% of potentially eligible patients on LTOT could not participate in this study and this impacts the generalisability of device use.

Consistent with the previous discussions in chapter 4 section 4.4.2, the participants in this study may have unblinded themselves as they are aware of how their usual LTOT flow rate feels and this may have had an impact on the patient reported outcome of borg score but is unlikely to affect the primary outcome as this was based on SpO_2 data.

7.4.3 Conclusion

In conclusion, the main finding from this study were that the iO_2Ts significantly reduces intermittent hypoxia, reduces hyperoxia and maintains SpO_2 in optimal range better than fixed-flow oxygen during ADL in patients on LTOT. Additionally, the iO_2Ts reduced oxygen delivery during the rest period and over a longer duration, this could lead to a reduction in oxygen use and a reduction in the associated costs of supplying oxygen.

8 Chapter 8 – General discussion

8.1 Summary of the aims

LTOT improves survival in patients with COPD and chronic hypoxaemic respiratory failure and is recommended by multiple international respiratory societies for the treatment of respiratory diseases with associated severe hypoxia (Hardinge et al., 2015, Magnet et al., 2017, McDonald et al., 2016). However, many patients on domiciliary LTOT experience episodes of intermittent hypoxia during rest, exercise, sleep and activities of daily living which may be harmful and there is therefore a need to optimise the delivery of LTOT (Śliwiński et al., 1994, Morrison et al., 1997, Plywaczewski et al., 2000, Pilling and Cutaia, 1999, Abdulla et al., 2000). Our group has previously developed an auto-titrating oxygen system – the iO_2Ts – which in a simulated setting followed by a pilot study reduced intermittent hypoxia (Iobbi et al., 2007, Iobbi MG, 2007).

The aims of my thesis were to develop an iO_2Ts which was capable of delivering both ambulatory and LTOT (a portable and lightweight oxygen delivery system), to investigate the ability of the iO_2Ts to maintain a constant SpO_2 during over a range of activities in patients with chronic respiratory failure, assess the utility of the iO_2Ts as an oxygen assessment tool and to investigate the effects of maintaining a constant SpO_2 on transcutaneous carbon dioxide during sleep in patients with hypercapnic respiratory failure who are on LTOT.

8.2 Summary of the main outcomes

Developing a portable and lightweight iO_2Ts

In conjunction with the bioengineering department at Imperial College London, we successfully miniaturised the iO_2Ts by creating an app on an android smartphone and created a portable system by incorporating Bluetooth technology. The app was designed to delivery both fixed-flow oxygen and auto-titrating oxygen (intelligent oxygen therapy). This has two main advantages: firstly, after the app has been programmed and the mobile phone placed on standby mode, type of oxygen therapy being delivered is concealed and this is important for blinding. Secondly, as the system can deliver fixed-flow oxygen, safety systems were built in to always allow a back-up fixed flow rate to be delivered in the event of a failure with the pulse oximeter, a loss of SpO_2 signal or a total system failure.

Clinical studies

From the clinical studies, the iO_2Ts was initially tested in patient with COPD and ILD during a 6WMT. For patients with COPD on LTOT, the iO_2Ts significantly reduced intermittent hypoxia compared to fixed-flow ambulatory oxygen. The mean SpO_2 was significantly greater with

iO_2Ts as was the trough SpO_2. However, despite the reduction in intermittent hypoxia, patients on the iO_2Ts still spent a median of 62% of the time with SpO_2 <90% during the 6MWT. For patients with ILD, there was no statistically significant difference in intermittent hypoxia between the iO_2Ts and fixed-flow ambulatory oxygen. In patients with COPD and ILD during the 6MWT, there was no change in Borg score nor the distance walked between the iO_2Ts and fixed-flow oxygen.

The iO_2Ts significantly reduced intermittent hypoxia in patients with respiratory failure on LTOT during ADL. Furthermore, the iO_2Ts reduced the percentage of time spent with hyperoxia and maintained SpO_2 in the optimal SpO_2 range for a greater period than fixed-flow oxygen. During the activities of daily living, there was no difference in the volume of oxygen delivered between the iO_2Ts and fixed-flow oxygen. However, during periods of rest, the iO_2Ts delivered significantly less oxygen to maintain the same optimum SpO_2 level compared to fixed-flow LTOT. This is significant as most patients on domiciliary LTOT spend significant periods of the day resting and the reduction in oxygen delivery during these rest periods could potentially lead to cost savings in oxygen delivery.

In a fourth pilot study which required a change in the inclusion criteria and primary outcome due to poor patient recruitment, the iO_2Ts did not have any significant effect on intermittent hypoxia during sleep in patients on LTOT for a small sample size of four patients. In addition, the iO_2Ts did not have a discernible effect on transcutaneous carbon dioxide levels overnight.

The iO_2Ts as an oxygen assessment tool

Flow-time data was analysed from the four clinical studies and the iO_2Ts assessed as an oxygen assessment tool. The iO_2Ts can be utilised as an oxygen assessment tool to assess the oxygen flow rate requirements for patients on LTOT during rest and during ADL with good degree of confidence. However, given the flow limitation of the device, it cannot be utilised as an oxygen assessment tool for patients undergoing assessment for ambulatory oxygen. There was insufficient data from the sleep studies in chapter 6 to allow any meaningful assessment of the iO_2Ts as an oxygen assessment tool during sleep.

8.3 The thesis in context of existing studies

Auto-titrating oxygen systems have been developed and tested in preterm neonates, ventilated patients and in self-ventilating adults. In self-ventilating adults, the three other systems published to date have been the $AccuO_2$ system, the $FreeO_2$ system and the O_2 flow regulator. The $AccuO_2$ system was tested in a domiciliary setting and set to maintain a SpO_2 of 90% and

compared to usual LTOT and a conserver device (Rice et al., 2011). The main outcomes studied from the study were the mean SpO_2, intermittent hypoxia and volume of oxygen delivered. The $AccO_2$ system maintained SpO_2 at a mean of 91 ± 2% (this was lower than the SpO_2 usual LTOT and the conserver system, which is not surprising given its design and SpO_2 target), had a lower variation in SpO_2 over the time period tested than the other two systems and non-significantly reduced intermittent hypoxia (percentage of time spent with SpO_2 <88%). In addition to maintaining SpO_2 at a clinical acceptable level, the $AccuO_2$ system delivered significantly less oxygen than the other two delivery system and over a longer period of time this could reduce cost associated with oxygen use. These results of were published in 2011 with the study having been performed between 1999 and 2000. There has have been no further publications of this oxygen delivery system and as far as I am aware this system is not being commercially developed.

The O_2 flow regulator, developed in Italy, was tested in COPD patients on LTOT during cycle exercise tests (Cirio and Nava, 2011). In a cross-over study, patients were asked to complete two exercise tests, one in which a respiratory therapist titrated oxygen flow rates to maintain a constant SpO_2 and the second in which oxygen flow rates were adjusted by the O_2 flow regulator. The outcomes studied were the percentage of time spent with SpO_2 <90% and the number of interventions needed by the respiratory therapist. The O_2 flow regulator significantly reduced the percentage of time spent with SpO_2 <90% during the exercise tests and required less input from a respiratory physiotherapist compared to fixed flow oxygen. The O_2 flow regulator is available to purchase in Italy and has two models which can supply up to 10 litres/minute or 20 litres/minute of oxygen. The system has a physical connection from the O_2 regulator to the patient and the regulator can be strapped to a patients' arm much like a iPod is strapped to the arm whilst running (https://www.dimaitalia.com/en/o2-flow-regulator/).

The $FreeO_2$ system has been the most extensively published auto-titrating oxygen system with studies in healthy adults during induced hypoxia, during field exercise tests in patient with COPD, in patients with acute respiratory failure in the emergency department and on general medical wards in patients with acute exacerbation of COPD (Lellouche and L'Her, 2012b, Lellouche et al., 2016a, Lellouche et al., 2016b, L'Her et al., 2017). The system has been shown to significantly reduce intermittent hypoxia compared to fixed-flow oxygen during field walking tests but without any increases in walking distance. The system also increased the percentage of time spent within a pre-specified SpO_2 range compared to fixed-flow oxygen in patients admitted with respiratory failure and in patients recovering from exacerbations of COPD. The system has recently gained CE marking in Europe. It is approximately the size of a

computer screen, is intended for hospital use and can supply oxygen flow rates of up to 20 litres/minute.

Consistent with the clinical studies involving the three other systems, the primary outcomes with the iO_2Ts described in this thesis have the percentage of time spent with SpO_2<90% or SpO_2 levels within a predefined SpO_2 range. As with the two commercially available system described, this thesis has shown that the iO_2Ts significantly reduced intermittent hypoxia in patients on oxygen therapy during a 6MWT in patients with COPD and during activities of daily living. However, the magnitude of reduction with the iO_2Ts, especially during exercise, is not as significant as that shown by the O_2 flow regulator or the FreeO_2 systems. Consistent with studies involving the Free O_2 system, the optimisation of oxygen delivery during exercise did not increase walking distance with the iO_2Ts. The biggest difference between the iO_2Ts and the other two systems is that the two other systems can deliver oxygen flow rates of up to 20 litres/minute whereas the iO_2Ts is flow limited at just 5 litres/minute. The other two systems have an advantage as they already have a CE marking and are commercially available. The challenge for the iO_2Ts, as with any other commercial product introduced into the market where there are existing competitors, is to have unique selling point/s. I think that for iO_2Ts the unique selling points would be the combinations of its' size and weight, its wireless connectivity, its portability, the fact it can records SpO_2 and flow rates and has the potential for telemonitoring, all of which would be ideally suited for the delivery of domiciliary and ambulatory LTOT. However, significant developments are required in order to produce a commercially available product and significant limitations which need to be overcome.

8.4 Limitations of the device

The biggest limitations of the iO_2Ts are the flow limitation of 5 litres/minute, the rate of change of flow rates in response to changes in oxygen desaturations and the external watchdog timer and bypass flow valve.

The flow limitation, as previously discussed, was introduced for two main reasons: firstly, because most patients on domiciliary oxygen do not require flow rates of greater than 5 litres/minute and secondly, to minimise the size of iO_2Ts by having a small flow meter so that the system can a viable option of ambulatory oxygen. What I have discovered through my studies is that many patients require ambulatory oxygen flow rates of greater than 5 litres/minute with the consequence that this flow limitations needs to be removed for the system to be a viable system for ambulatory oxygen. This is a relatively simple problem to solve as the new generation of commercially available flow meters can now deliver oxygen flow rates of 20

litres/minute and are the same weight and size as ones which had previously delivered 5 litres/minute.

The second limitation of the iO_2Ts is that the rate of increase of oxygen flow in response to desaturations is slower than expected and the change in oxygen flow rate at times does not seem proportional to the degree of desaturation. It takes 34 seconds for the iO_2Ts to increase its oxygen flow rate from 0 to 3.0 litres/minute for a 10% difference in the actual SpO_2 and the set-point SpO_2. However, the increase in oxygen flow rate slows down markedly as the flow rate reaches the maximum output of the system, with the consequence that it takes 35 seconds to go from 3 to 4 litres/minute and 128 seconds to go from 4 to 5 litres/minute. The slow change in oxygen flow rates as the oxygen flow rate requirement increases, is in all likelihood, a significant cause as to why patients with ILD did not experience a reduction in intermittent hypoxia and why patients with COPD still experienced a significant degree of hypoxia despite being on the iO_2Ts during the 6MWTs. This is in part as a result of the original algorithm being damped to avoid very large fluctuations in oxygen flow rates to small changes in SpO_2 which were initially observed. However, the system is now over-damped and need adjustment.

The third limitation of the device is the watch dog timer and bypass flow valve. The external watch-dog timer and flow valve were built into the system as safety features to ensure oxygen delivery to the patient in event of complete battery or system failure. However, the watch dog timer was very difficult to engage when used in chapter 6 and often required multiple attempts before it could be activated appropriately. This issue adversely affects the reliability of the system and one's confidence that it is safe to use in a domiciliary setting without any medical personnel being present. In addition, the bypass flow valve is currently a manual device which needs to be adjusted by hand to the desired flow rate for each patient before any application. Going forward, the issues with the watchdog timer and bypass flow valve need to be addressed before any more clinical studies are conducted.

8.5 Auto-titrating oxygen systems in the context of other developments in oxygen delivery

The mainstays of oxygen delivery for self-ventilating patients have been nasal prongs, oxygen masks (Hudson or non-rebreathe) and the venturi system with very few new developments in the past 50 years. However, parallel to the development of auto-titrating oxygen systems has been the development of high flow oxygen therapy through nasal cannulae (HFNC). HFNC oxygen therapy is the delivery a warmed and humidified oxygen/air mixture at high flows rates (up to 60 litres/minute) with variable fraction of inspired oxygen (FiO_2) (between 0.21 – 1.0). The delivery is via large bilateral nasal prongs through a humidified single limb circuit. HFNC

has been utilised extensively in children with hypoxaemic respiratory failure as an alternative to continuous positive airway pressure (CPAP) but is now fast gaining in popularity in critically ill adult patients (Hutchings et al., 2015).

In the most significant clinical trial date, the FLORALI trial, HFNC was compared to non-invasive ventilation (NIV) and standard mask oxygen therapy in patients with type 1 respiratory failure (Frat et al., 2015). The results showed no difference in the primary end-point of intubation rates between the three interventions, but did demonstrate a reduction in 30-day mortality in favour of HFNC compared to the other two groups.

In a recently completed multicentre, randomised cross-over study from Japan, patient with COPD on LTOT, were randomised to either nocturnal HFNC with daytime usual LTOT or usual LTOT during the day and night over a period of 6 weeks (Nagata et al., 2017). The study showed that the addition of nocturnal HFNC reduced daytime hypercapnia and improved health related quality of life.

In a randomised cross-over study, Fraser *et al*., studied a number of physiological parameters in patients with COPD on LTOT whilst the patients were on their usual LTOT or HFNC for 20 minutes each. They demonstrated that even with a short time of 20 minutes, HFNC reduced transcutaneous carbon dioxide and respiratory rate compared to usual LTOT low flow rate oxygen (Fraser et al., 2016). Hasani *et al*., demonstrated that domiciliary HFNC could be utilised for a short time period (3 hours per day for 3 hours per day for 7 days) to enhance mucociliary clearance in patients with bronchiectasis (Hasani et al., 2008).

There is very limited data on the use of HFNC for patients with acute hypercapnic respiratory failure. In one case report from the UK, Millar *et al*., utilised HFNC in a patient with an acute exacerbation of COPD associated with hypercapnia and respiratory acidosis for which the patients declined NIV (Millar et al., 2014). The patient tolerated HFNC very well and after 6 hours there was a significant reduction in her carbon dioxide and the pH normalised. Braunlich *et al*., assessed the impact of HFNC on ventilatory parameter changes in patients with stable hypercapnic COPD whilst at rest. They showed that HFNC resulted in increases in tidal volume, reduction in respiratory rate and a reduction in carbon dioxide with greater reductions seen with higher flow rates (Braunlich et al., 2016). Therefore, there may be a rationale for utilising HFNC is patients with hypercapnic respiratory failure as an alternative to NIV for acute exacerbation of COPD and a number of current studies are exploring this rationale (NCT02371564, NCT02439333).

From the above described studied, it can be appreciated that high flow oxygen therapy is being trialled in the acute setting in patient with hypoxaemic respiratory failure and in patients with hypercapnic respiratory failure. Furthermore, it is also being trialled as an alternative to usual fixed-flow domiciliary LTOT. These are all the indications for which auto-titrating oxygen systems are also being developed. It is therefore foreseeable, not too long in the future, that for all the above indications there maybe three alternatives forms of oxygen therapy: usual fixed-flow oxygen, auto-titrating oxygen system and high flow nasal cannuale.

8.6 The process of ethical and NHS approval and impact on studies

The biggest disappointment from my perspective was the failure to recruit sufficient patients to complete the sleep studies described in chapter 6. As described before, this was due to a combination of having a strict inclusion criterion initially, working in a hospital with a large number of patients who are on NIV and LTOT and patients declining to having two domiciliary sleep studies. In addition to this, there was also an impact from the process of setting up the clinical studies and the time taken in gaining local NHS approval. Between 2013 and 2016 when the clinical studies were initiated, to begin a clinical study, one needed ethical approval and subsequently separate NHS approval from the trust/trusts where the research would be conducted. Gaining ethical approval for the studies in chapter 4, 5 and 7 was relatively straight forward. However, gaining NHS permission to undertake research at the Royal Brompton NHS Foundation Trust added between 3 to 6 months at a time to each of the projects. The cause of this delay was due to several factors the important of which was the drawing up of appropriate contracts between the sponsor of the study (Imperial College London) and the NHS host as this was a non-CE marked device. These added delays at various stages in the thesis contributed to a lack of time towards the end of my research.

8.7 The unmet expectations of the redesigned and upgraded iO_2Ts

There were two main expectations which could not be delivered for the redesigned iO_2Ts. First, we had initially planned to utilise a bespoke Arduino as the control centre for the iO_2Ts. However, this proved very technologically challenging and due to time constraints, the decision was taken to utilise a more readily available smartphone system. I think that in the longer term we will need to go back to utilising a bespoke system rather than smartphones due to expense, space (smaller microcontrollers) and ease of programming.

Secondly, we had envisaged an iO_2Ts which had the capability of tele-monitoring. We utilised Bluetooth technology to link/pair the pulse oximeter to the smartphone. However, we could not simultaneously pair another device (laptop) to show the real-time data. Therefore, we have not

been able to incorporate a tele-monitoring capability into our current system. This particular capability would be very useful within a hospital setting to allow remote constant monitoring of patients from a nursing station.

8.8 Conclusions

Oxygen is a lifesaving drug delivered every day in clinical practice. This thesis has reviewed the evidence of its use in patient with chronic respiratory failure and the evidence for LTOT reducing mortality in these patients and investigated the current shortfalls in its delivery. To optimise the delivery of oxygen therapy, a novel portable iO_2Ts was developed and tested in patient with chronic respiratory failure. The iO_2Ts reduced intermittent hypoxia and improved oxygenation compared to usual fixed-flow oxygen therapy in patients with COPD on LTOT during a 6MWT and during ADL in patients on LTOT. However, several other outcomes such as breathlessness and fatigue were unchanged by the delivery of optimal oxygen therapy. In a pilot study, the iO_2Ts did not change overnight transcutaneous carbon dioxide compared to usual LTOT. Further developments of the iO_2Ts are necessary to make the system into a commercially viable product, and further clinical research is necessary to demonstrate that clinical outcomes such changes in pulmonary artery pressure and in the longer-term, mortality, are improved with optimised oxygen therapy.

9 Chapter 9 – Future directions

There are three major areas for future development of the iO_2Ts: 1) further technological developments, 2) subsequent clinical studies and 3) involvement of patients to assess how best to further develop the iO_2Ts.

9.1 Further technological developments of the iO_2Ts

There are two main aspects of the iO_2Ts which need further technical development: the algorithm and software which controls the system and the integration of the different components into a single device.

9.1.1 Algorithm development

When the current algorithm for the iO_2Ts was devised, it incorporated into its design is a flow limitation of 5 litres/minute. During my research, I have seen that many patients require oxygen flow rates of >5 litres/minute for ambulatory oxygen and therefore if the iO_2Ts is to be used widely for both LTOT and particularly ambulatory oxygen, then the flow limitation must be removed. This can be achieved in two ways. Firstly, technology has now moved on a pace and the mass flow controllers which could previously only deliver 5 litres/minute can now deliver up 20 litres/minute. In effect, much higher flow rates can now be delivered without any additional increase in size or weight of the mass flow controller. The second solution is to incorporate a bespoke flow meter into the iO_2Ts which has higher flow rates than the existing mass flow controller and could potentially be much smaller. This is obviously a much larger undertaking but may be more fruitful in the longer term in designing a bespoke system which is smaller in size and lighter in weight.

As previously discussed, the change in oxygen flow rate with oxygen desaturation is much slower than expected especially at higher oxygen flow rates. This needs to be amended to ensure that the change in oxygen flow rate with oxygen desaturation is truly proportional to the desaturation and that the change in oxygen flow rate is fast enough to keep up with the desaturation episodes.

As noted in the domiciliary sleep study (chapter 6), the iO_2Ts needs improved software to allow continuous recording of data rather than the current system of recording data (this only happens when the app is closed). The software also needs to be modified so that the system continues to function even in the events of prolonged periods of time without any input from a pulse oximter.

9.1.2 Integration of components

The iO_2Ts consists of different commercially available components connected to make a unique product. It is acceptable in its current format as a research tool. However, this is not a commercial product which could be delivered to patients on oxygen therapy. The most important next step is to integrate the flow meter, the smartphone and battery into a single device. Ideally, this should be no large than an iPad and should have a touch screen menu to allow the system to be user friendly (as many patients with chronic respiratory failure have some degree of cognitive impairment). There should be an input for the oxygen supply and an output to the patient which are clearly marked. The battery of the system must be able to provide power for at least 12 hours.

9.2 Clinical studies

It is imperative that we continue with further clinical studies of the iO_2Ts. Once the device is integrated into one unit and the above stated challenges overcome, the system would be a in position to be put forward for CE marking (as mentioned in the external review). This is because the current regulations for device development require that the device acts as intended, that there is some evidence from pre-clinical studies and some clinical research and evidence that the device is safe (Frigerio, 2016). The iO_2Ts is going a long way to fulfilling these criteria. This is in complete contrast to how drugs are developed and licenced as they require not only safety data, but in addition, clinical trials which show superiority or equivalence against current standards of care. However, the current method of evaluating devices are changing and therefore we must be mindful that in the future a greater burden of proof may be necessary before CE marking is allowed so we should continue with further clinical studies to meet any future standards (Tarricone et al., 2016). In addition, it must also be remembered that just because devices act as they are intended, they can still cause harm as has recently been highlighted from the large multicentre SERVE-HF study (Cowie et al., 2015).

Further clinical studies of the iO_2Ts can be divided into those in which the system is tested in the short term, the medium term or in long-term studies.

9.2.1 Short term studies

iO_2Ts during sleep In the short term, the priority would be to finish the project investigating the effects of the iO_2Ts on intermittent hypoxia during sleep. The current data I have are only a case series and therefore finishing this project and collecting further data should be a priority.

iO_2Ts during pulmonary rehabilitation Oxygen therapy is currently used in pulmonary rehabilitation programmes for patients who demonstrate exercise induced oxygen desaturation. A study could be conducted to investigate whether optimised oxygen delivery to maintain a pre-set SpO_2 target (iO_2Ts) could improves outcomes during pulmonary rehabilitation when compared to fixed-flow oxygen therapy.

iO_2Ts for patients with ILD Once the iO_2Ts has its algorithm upgraded, the study on the effects of auto-titrating oxygen therapy in patients with IPF could be repeated. This is important as there is little evidence for the use of ambulatory oxygen in patients with IPF. Most of the published studies have had one crucial issue: that the delivery of oxygen was not adequate to completely eliminate oxygen desaturation. If the iO_2Ts could be optimised, it may be able to overcome this shortfall and become potentially useful in patients with ILD.

iO_2Ts as an oxygen assessment tool During the two studies in which patients completed 6MWTs, the iO_2Ts could not be used as an oxygen assessment tool as many patients required oxygen flow rates greater than that which could be delivered. If the system is redesigned with an updated algorithm and without any flow limitation, another study investigating its use an oxygen assessment tool for ambulatory oxygen could be conducted. The study would in two parts: the first part would have an exploratory study and the second part a validation study. Patients who had oxygen desaturation during the 6MWT and fulfilled the criteria for ambulatory oxygen would be recruited and asked to complete 2 further 6MWTs. In the first 6MWT, the oxygen flow rate would be titrated manually to maintain $SpO_2 \geq 90\%$. The second 6MWT would be done with the iO_2Ts. Flow-time data would be analysed using Bland and Altman analysis to investigate which percentiles of time agree best with the manual 6MWT oxygen flow data. These results could then be taken forward and tested in a validation cohort of patients

9.2.2 Medium term studies

iO_2Ts for exacerbations of COPD Once the iO_2Ts is in an integrated format, the system could be used to investigate whether automated control of oxygen delivery to meet a specified SpO_2 target leads to better outcomes than manual titration of oxygen in patients with acute exacerbations of COPD. This study would recruit patients with exacerbations of COPD who require oxygen therapy and randomise the patients to either manual titration of oxygen therapy or the iO_2Ts from when they are first given oxygen therapy (most likely by an ambulance crew). Oxygen therapy would then be continued in the accident and emergency department and medical wards as necessary. There are many outcomes which could be measured in this study with the most important being overall mortality and the need for NIV.

iO_2Ts for pulmonary hypertension In one early study, it was demonstrated that LTOT could reduce pulmonary hypertension in patients with chronic hypoxaemia (Stark et al., 1972). This reduction in pulmonary hypertension was replicated to only a small degree in the NOTT and very little change was demonstrated in the MRC study (NOTT, 1980, MRC, 1981). The changes in pulmonary hypertension were measured by right heart cathetrisations at specified time intervals. We now have the technology to implant a haemodynamic pressure monitor in the pulmonary artery and measure pulmonary pressures continuously over a period of up to 12 weeks (Kjellstrom et al., 2014). Therefore, we could investigate if the optimal delivery of oxygen with the iO_2Ts in patients eligible for LTOT with co-existing pulmonary hypertension, could result in reductions in pulmonary artery pressure over a period of week to months compared to fixed-flow LTOT.

9.2.3 Long-term studies

The iO_2Ts was originally designed to optimise the delivery of domiciliary LTOT. Therefore, a study investigating the effect of optimisation of LTOT with the iO_2Ts assessed against usual LTOT in patients with COPD with chronic hypoxamic respiratory failure would be interesting. The study would be over a much longer period, ideally between 1-4 years and have a primary outcome of overall mortality. Other outcomes from this study would include cardiovascular events, volume of oxygen delivered and effects on quality of life. The data collected during this study would include heart rate and SpO_2 data and these could also be analysed to investigate whether such data can be used to predict COPD exacerbations.

9.3 Patient involvement in further development

In respect of the research presented in this thesis, patients were involved in the design phase of the clinical studies. Expert patients were asked to review the proposed projects and asked to comment of various aspects including reviewing the lay summary and assessing the burden placed on the participants in the study.

The aim of the iO_2Ts is to optimise the delivery of domiciliary and long-term and ambulatory oxygen. Once the final product is made, it will be used by patients in their homes and will involve the patient wearing a pulse oximeter at all times to gain the maximum benefit. Therefore, it is essential that we involve patients in the further development of the device at this stage to understand patient expectations and needs in order to design a product which not only delivers optimised oxygen therapy but is acceptable to patients. The theme of patient empowerment in the design process of medical devices is one which has been highlighted in a

publication from the European Commission and recently by the MHRA (MHRA, 2017, Commision, 2010).

The best method to explore patients' opinions would be through a qualitative approach. This could take the form of focus groups (made up of patients on oxygen) and individual patient interviews. There are several themes which need to be explored and these include:

- What size and weight should the device by for the patients to be happy and use this when they are walking? Would they prefer a device which can be strapped to the arm whilst walking?
- How the patients feel about wearing a pulse oximeter 24 hours a day?
- How likely patients are wear the pulse oximeter 24 hours a day?
- Are there particular times during the day that patients would be more likely to wear the pulse oximeter than others?
- Would patients prefer to wear an oximeter on the ear or the finger?
- How patients feel about not being able to adjust their oxygen flow rates and a machine adjusting it for them?
- Would patients wish to have information such as oxygen saturations and oxygen flow rates displayed and how that feel about this?
- Would patients be happy to have their data on oxygen saturation and heart rate sent to their doctor?
- What safety features would patients like to see in the device?

Within the focus groups and individual interviews, there may be other ideas, concerns which develop and this is all part of the process of product development.

10 References

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11 Appendices

11.1 Appendix 1 – Functional specification for the iO_2Ts

Imperial College London	iO_2T system	Doc No.	iO2-SPC-001
	Design Document	Revision	1
	Functional Specification	Page 1	OF 4

AMENDMENT RECORD

DATE	REVISION	CHANGES
	A	First Draft
	1	Issued – Included nocturnal use

Prepared By : M.Moghal	
Approved By : R Dickinson	DATE OF ISSUE: 21/7/2015

QUALITY STATEMENT

This document is a mandatory requirement and forms part of the quality system. Amendments are not permitted without the prior authorisation of the Clinical Investigator.

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1.1 Scope

This Functional Specification gives details of the design and function of the intelligent Oxygen Therapy System (iO_2T). The software for the iO_2T system is currently based in a laptop computer and cannot be utilised effectively for ambulatory or home care use. This functional specification describes the process of making the system mobile (which can be utilised in an ambulatory and home setting) by transferring the system onto a mobile phone.

1.2 Background and Overview

The iO_2T system is designed to titrate oxygen flow rates to meet a specific oxygen saturation (SpO_2) target. It is based on a closed-loop design and the controller is based on a proportional-integral-derivative controller. The system measures a patients' SpO_2 using a pulse oximeter. This information is transmitted via Bluetooth to a control unit based inside a smartphone. The output from the smartphone produces changes in a flow control hence changing the oxygen flow rate. The system should also be able to supply fixed-flow oxygen therapy as one would deliver from an oxygen cylinder so that the system can be used in clinical trials.

2.1 Intended Use

The iO_2T system is intended for use in clinical trial in patients with chronic respiratory failure requiring oxygen therapy. It can be utilised in an ambulatory setting, for nocturnal oxygen delivery and during activities of daily living.

2.2 Classification

The device is classified according the Medical Devices Directive as Class IIb . Rule 11 applies.

2.3 User Profile

The device will be set up by the clinician.

2.4 Use Environment

The device will be used in a hospital setting (ward or outpatient clinic) or in the patient's home.

3. System Overview and Architecture

The system consists of an electrically operated gas flow valve connected between a portable oxygen cylinder and the nasal delivery tube. The valve is connected to an Android phone which acts as the controller. An earlobe mounted pulse oximeter sensor detects a patients' SpO_2 which is then feeds data via a Bluetooth to the Android controller. The devices are battery operated with a rechargeable battery, in addition to the phone battery.

4. Functional requirements

1. The system must be based on a mobile phone preferably Android as currently this is the most common mobile phone platform.
2. The phone must be pin protected.
3. The phone should a stand-alone phone.
4. The system must be in the form of an Application (app).
5. The app must be placed on the home screen on the mobile phone.
6. The application should have two methods of activation: 1) by touching the app and 2) by connecting a micro USB cable (which in turn connects to the flow controller).
7. The system must be able to deliver both fixed-flow oxygen
8. The system must be able to deliver variable flow oxygen according the SpO_2 set-point.
9. The choice of which type of oxygen to deliver (fixed-flow or variable flow) must be clear at the start of the app.
10. Each experiment conducted must have a unique ID.
11. The experiments must be ID protected to stop unwanted interference.
12. For fixed-flow oxygen: the use must be able to select an oxygen flow rate between 0 and 5 litres per minute
13. For fixed-flow oxygen: if there is loss of Bluetooth signal, after 20 seconds, the system must continue to supply fixed-flow oxygen at the pre-set level.
14. For variable flow oxygen: the user must be able to select the target SpO_2 for any given experiment in the range 0 to 100%.
15. For variable flow oxygen: the user must be able to define a back-up flow rate at 0 to 5 litres per minute. The system must revert to this flow rate 20 seconds after loss of Bluetooth signal i.e. it must supply fixed flow oxygen. The system must then be able to revert back to variable flow oxygen when Bluetooth connection is re-established.
16. If communication between the flow controller is lost, or the power fails, or the Android software hangs up (crashes) the system should revert to a pre-set flow of between 1 and 5 litre per minute.
17. The system must be able to synchronise with a Nonin Bluetooth pulse oximeter.
18. The Alicat flow meter must be able to function from a portable battery source.
19. All data from each experiment must be recorded.
20. Data collection for variable flow: The experimental settings must be recorded. The date and time of the experiment must be recorded. The SpO2 and heart rate must be recorded every second.
21. Data collection for variable flow: the experimental settings must be recorded. The data and time of the experiment must be recorded. The SpO2 and heart rate must be recorded every second. The calculated error from the set-point must be recorded. The oxygen flow rate every second must be recorded.
22. The app on the mobile phone should be able to synchronise with a laptop computer in order that other users may observe an experiment.
23. If the Bluetooth is disconnected the data output should read an easily recognisable error code.
24. Weight: as light as possible but no more than 5.0 kilograms

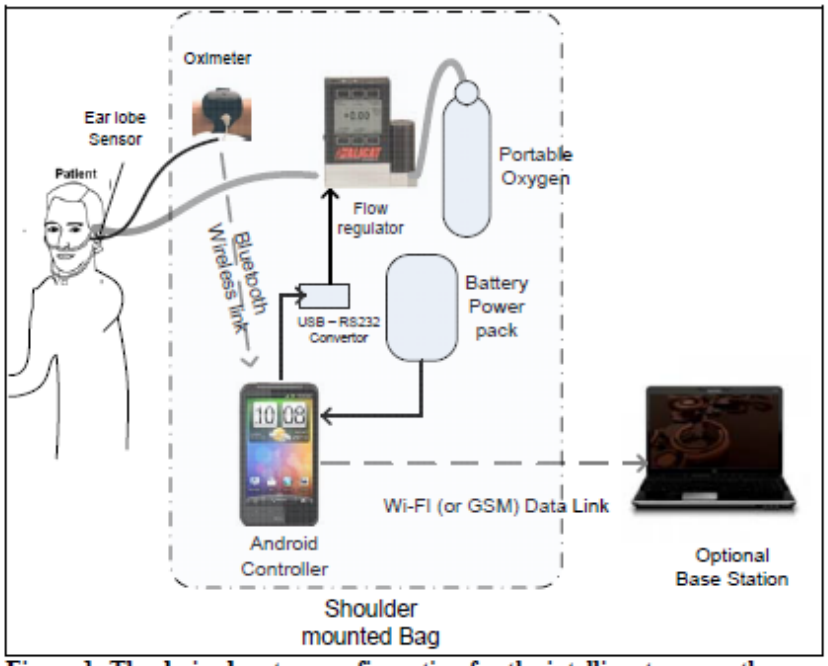

Figure 1: The desired system configuration for the intelligent oxygen therapy system

References

1. Hardinge M, Annandale J, Bourne S, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax 2015;70 Suppl 1:i1-i43.
2. Iobbi G. SATURATION DRIVEN FLOW CONTROLLER FOR OXYGEN THERAPY. London: Imperial College London; 2007.

11.2 Appendix 2 – Letter for external assessment of the iO_2Ts

Royal Brompton & Harefield NHS
NHS Foundation Trust

Royal Brompton Hospital
Sydney Street
London
SW3 6NP

Tel: 020 7352 8121
Fax: 020 7351 8473

Professor Anita Simonds
National Heart and Lung Institute
Royal Brompton Hospital
Fulham Road
London

CLINICAL ENGINEERING DEPARTMENT
Tel.: 020 7351 8662
Fax.: 020 7351 8663

16th October 2015

Dear Professor Simonds,

The design process and testing of the Auto-Titrating (Intelligent) Oxygen Therapy (iO_2T) system has been independently reviewed by Clinical Engineering at the Royal Brompton through the inspection of the design and test documentation and is considered safe to use by participants when used according to the supplied instructions for use.

The risk assessments have been carried out in a manner consistent with *EN ISO 14971:2012, Medical devices — Application of risk management to medical devices*, which is the applicable standard for the safe development of medical equipment. Risks have been appropriately identified, evaluated and, where required, reduced by design or operational mitigations. The residual risks are considered low and are outweighed by the benefits.

The design and development of the iO_2T system has been carried out at a standard considered sufficient for submission to a CE mark testing house, as is appropriate for all medical devices intended to be used on patients.

Stephen Squire
Clinical Engineering Services Manager
Royal Brompton and Harefield NHS Foundation Trust

11.3 Appendix 3 – REC confirmation of study approval - 14/WM/0130

NHS
Health Research Authority

National Research Ethics Service

NRES Committee West Midlands - South Birmingham
HRA NRES Centre Manchester
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7819

29 April 2014

Dr Mohammad Moghal
Clinical Research Fellow
Royal Brompton and Harefield NHS Trust
Department of Sleep and Ventilation
2nd Floor, Fulham Wing
Royal Brompton Hospital
SW3 6HP

Dear Dr Moghal,

Study title:	**The assessment of intelligent oxygen therapy (iO2t) in patients with chronic obstructive pulmonary disease on long term oxygen therapy**
REC reference:	**14/WM/0130**
Protocol number:	**V1**
IRAS project ID:	**141974**

Thank you for your e-mail of 29th April 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 28 April 2014.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant Information Sheet	2	28 April 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering Letter		31 March 2014
GP/Consultant Information Sheets	1.0	10 January 2014
Investigator CV	Anita Simonds	
Investigator CV	Mary Morrell	
Investigator CV	Moghal Mohammad	
Letter from Sponsor	Imperial College London	27 March 2014

11.4 Appendix 4 – REC approval for study amendment to include patients with IPF

NHS
Health Research Authority
National Research Ethics Service

NRES Committee West Midlands - South Birmingham
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7827
Fax: 0161 625 7299

04 November 2014

Dr Mohammad Moghal
Clinical Research Fellow
Royal Brompton and Harefield NHS Trust
Department of Sleep and Ventilation
2nd Floor, Fulham Wing
Royal Brompton Hospital
SW3 6HP

Dear Dr Moghal

Study title:	**The assessment of intelligent oxygen therapy (iO2t) in patients with chronic obstructive pulmonary disease on long term oxygen therapy**
REC reference:	**14/WM/0130**
Protocol number:	**V1**
Amendment number:	**2**
Amendment date:	**16 September 2014**
IRAS project ID:	**141974**

The above amendment was reviewed by the Sub-Committee in correspondence.

Favourable opinion

Approval was sought for a change to the inclusion criteria to include patients with IPF and for the new documents for patients with IPF and their GPs.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [IPF]	2.0	18 September 2014
Notice of Substantial Amendment (non-CTIMP)	2	16 September 2014
Participant consent form [IPF]	2.0	18 September 2014
Participant information sheet (PIS) [IPF]	3.0	18 September 2014

11.5 Appendix 5 - REC confirmation of study approval – 15/WM/0137

NHS
Health Research Authority
West Midlands - South Birmingham Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 883 9428

26 October 2015

Professor Anita Simonds
Department of Sleep and Ventilation
2nd Floor, Fulham Wing
Royal Brompton Hospital
London
SW3 6HP

Dear Professor Simonds

Study title:	**The assessment of an auto-titrating oxygen system (intelligent oxygen therapy [iO2T]) in patients with hypercapnic respiratory failure on long-term oxygen therapy during sleep**
REC reference:	**15/WM/0137**
IRAS project ID:	**177788**

Thank you for your letter of 23 October 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 23 October 2015

Documents received

The documents received were as follows:

Document	*Version*	*Date*
IRAS Checklist XML [Checklist_23102015]		23 October 2015
Other [Patient information sheet]	3.0	23 October 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Signed cover letter]		25 March 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor Insurance]		21 July 2014
GP/consultant information sheets or letters [GP letter_io2t sleep]	1.0	02 February 2015

11.6 Appendix 6 – REC confirmation for study approval 15/LO/1435

NHS
Health Research Authority

London - Stanmore Research Ethics Committee
Ground Floor
NRES/HRA
80 London Road
London
SE1 6LH

Telephone: 020 7972 2554

21 September 2015

Dr Moghal
Imperial College London
Department of Sleep and Ventilation
2nd Floor, Fulham Wing
Royal Brompton Hospital
SW3 6HP

Dear Dr Moghal

Study title:	**The assessment of intelligent oxygen therapy (iO2T) in patients on long-term oxygen therapy during activities of daily living**
REC reference:	**15/LO/1435**
IRAS project ID:	**184986**

Thank you for your letter of 21st September 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 18 September 2015

Documents received
The documents received were as follows:

Document	*Version*	*Date*
Participant information sheet (PIS) [Participant information sheet_activities of daily living_Imperial_Post REC review]	1.1	21 September 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Signed letter for activities of daily living]		24 July 2015

11.7 Appendix 7 – Email from MHRA

From: Higgins, Rob
To: Simonds Anita
Sent: Tue Jan 21 15:50:23 2014
Subject: Evaluation of intelligent oxygen therapy

Dear Professor Simonds,

Further to your enquiry I can confirm that there is no need to notify MHRA of this project as the study is being solely performed within your own trust and there is no commercial intention.

Kind regards.

Rob Higgins

From: Simonds Anita [mailto:A.Simonds@rbht.nhs.uk]
Sent: 19 December 2013 15:40
To: MB-MDA-ERA@mhra.gsi.gov.uk
Subject: Evaluation of intelligent oxygen therapy
FAO Dhruti Patel, MHRA

Dear Dhruti
RE: The evaluation of intelligent oxygen therapy (iO2T) in patients with chronic obstructive pulmonary disease
Many thanks for the helpful discussion today about this project which is funded by an Imperial College 'Confidence in Concept' grant. The research compares standard oxygen therapy with a new concept of oxygen therapy delivered according to the patient's own oxygen level. We will test the systems during a standard exercise test.

I confirm that this is an educational study, performed on patients in my own healthcare establishment, Royal Brompton & Harefield NHS Foundation Trust. There is no commercial intention and we do not intend to apply for a CE mark.
As discussed this is in accordance with the item below on the MHRA website:
2. A healthcare establishment manufactures a medical device solely for use on its own patients and does not see the possibility of placing that device on the market.
Because the device is being used in-house and will not be commercialised, a notification to the MHRA will not be required.
I would be grateful if you could confirm this is the case and we **do not** have to notify MHRA formally. That will enable us to procede with our IRAS application secure in that knowledge and be able to convey this information to the Ethics Committee.
Many thanks for your help.
Kind regards
Anita Simonds
Prof A K Simonds PI
Consultant in Respiratory & Sleep Medicine
Royal Brompton & Harefield NHS Foundation Trust

11.8 Appendix 8 – Permission to republish all the third party copyrighted works

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