Investigating the evolution and application of Optiflow in managing unique patient groups in the perioperative period

PhD Candidate

Rebecca Louise Valentine, BSc
20214038

PhD Supervisors

Prof Jonathan G. Hardman
Dr Marianna Laviola

Anaesthesia and Critical Care, Academic Unit 3 (Injury, Recovery and Inflammation Science),
School of Medicine

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy
July 2023

The work leading to the submission of this thesis was funded by Fisher & Paykel Healthcare

Table of contents

Table of Contents

Abstract

This thesis utilises computational modelling to explore the different applications of High Flow Nasal Oxygenation, specifically, Optiflow (Fisher & Paykel Healthcare, Auckland, New Zealand) device, an oxygen therapy device that delivers high-flow, humidified oxygen via nasal cannula. The thesis explores the strengths and weaknesses of Optiflow being used on a variety of patient groups including: the obese, the pregnant and the older population, and concludes that it is often beneficial and potentially superior to alternative oxygenation techniques such as traditional face mask ventilation.

All of the following studies focus exclusively on supporting subjects during apnoea (i.e. cessation of breathing) in the perioperative period.

All of the research presented in this thesis explore potential improvements that could be made to current pre-oxygenation techniques (i.e. administration of 100% of oxygen before the induction of anaesthesia via a tightly fitting face mask) and concludes that changes to pre-oxygenation times could offer better patient protection against injurious hypoxaemia. There is also discussion of whether Optiflow is the best technique to support patients when compared to tight fitting face masks and low flow nasal oxygenation and it is concluded that it is able to achieve equal to or better safe apnoea times and oxygenation.

All investigations were conducted using the Interdisciplinary Collaboration in System Medicine (ICSM) simulation suite, developed by my supervisors and their collaborators and has already been widely validated to explore apnoea.

As all data are computational in nature and so no true human data were collected, computational patients will be referred to throughout as subjects, so as not to cause ambiguity.

Acknowledgements

I would first like to offer a very warm and deeply deserved thank you to my principal supervisor Dr Marianna Laviola, who has always been so willing to offer me her time and insight. I would also like to give thanks to my co-supervisor Prof. Jonathan Hardman. His confidence and willingness to let me stand on my own has been the backbone of this thesis and taught me that I can indeed fly all by myself. Additionally, my fellow student, Clara Daudre-Vignier, deserves thanks for teaching this old dog new tricks.

Of course, none of this would have been possible without the unwavering belief and support of my soul mate. His tireless patience and graciousness have been fundamental to my work. He remains my North Star, preventing me from ever becoming too lost in the datum. You are truly my better half.

To my brother to whom education is our shared passion, I thank you for your support, your love, your praise, and your sarcasm which has seen me through to the end.

Finally, this would have all stayed a pipe dream if not for the generous sponsorship from Fisher & Paykel Healthcare, for whom I can never thank enough.

These past three years of research have been a blessing to me, and despite being locked in my home office for most of that time, I have repeatedly been shocked by how much I have grown in skill as well as self-confidence. I would not trade this thesis for anything, no matter how many times the creation of it has made me cry.

List of abbreviations

HFNO	High flow nasal oxygen
ICSM	Interdisciplinary Collaboration in Systems Medicine
F_iO_2	Fraction of oxygen in the inspired gas
FO_2	Fraction of oxygen
F_gO_2	Fraction of oxygen at the glottis
$F_{E'}O_2$	End-tidal oxygen fraction
V/Q	Ventilation/Perfusion
FRC	Functional residual capacity
O_2	Oxygen
PEEP	Positive end-expiratory pressure
BMI	Body mass index
CO	Cardiac output
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
in-silico	In-silicon or virtual
kPa	Kilopascal
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
pH	Potential of hydrogen
SaO_2	Arterial oxygen saturation
VO_2	Oxygen consumption
VT	Tidal volume
LFNO	Low Flow Nasal Oxygenation

Chapter 1: Overview

1.1 Thesis Outline

This thesis is organised into 9 chapters. **Chapter 1** explores the aim of the research, and who it may be of benefit to. **Chapter 2** gives a review of the state-of-the-art knowledge attained during the study of this thesis. This knowledge revolves around the pulmonary system as well as high flow nasal oxygenation (HFNO) both of which are the focus of all the subsequent chapters. It will also indicate the gaps in the literature and discuss what is already available. The scholarly articles that were fundamental to this thesis are also highlighted in this chapter. **Chapter 3** describes the computational modelling, i.e. the Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite used for the computational investigations of this thesis and, its strengths and limitations. The main equations of the model are also described focusing on the modelling of the and how the state of apnoea and the virtual subject's configuration. **Chapter 4** is an experiment to understand the capability of the computational model's ability to represent head uptilt, with limited changes to the supine model Using a healthy subject, this study demonstrates that the effects of an upward tilt may be beneficial to a subject being oxygenated as opposed to the supine position. The results obtained are compared with those shown in currently published literature. **Chapter 5** builds upon the previous chapter and investigates the pulmonary changes of an upward tilt on a bank of obese subjects, which is a higher risk demographic. The study demonstrates that the benefits to the functional residual capacity (FRC), by head uptilt, may increase the safety of this patient group. **Chapter 6**

develops upon this exploration of head uptilt. The chapter utilises additional pulmonary changes which further increase the accuracy of the simulation's results bringing them closer to published data. The results further demonstrate that an increase in safe apnoea time for all obese patients might be achieved through head uptilt but considers that the severity of the subject's obesity is relevant to the benefits achieved. **Chapter 7** looks at subjects that were modelled on data from patients over 65, regarding pre-oxygenation and apnoea. Due to the pulmonary and cardiac changes associated with age, the hypothesis of this study was that the increased FRC may mean that patients benefit from a longer pre-oxygenation time, allowing for full denitrogenation to occur. Results show that increasing the pre-oxygenation time did modestly increase apnoea time but that this was not isolated to just older patients. **Chapter 8** considers safe apnoea times in pregnant patients, both those in active labour and those not in labour. It also considers obesity as a factor. The study aimed to compare HFNO *versus* low flow nasal oxygenation (LFNO) and investigated the different levels of achieved $F_{E'}O_2$ and the consequence that has on the safety of the subjects. **Chapter 9** also considers pregnant subjects and explores whether the pulmonary changes brought on by obesity and active labour may result in a longer pre-oxygenation time being required to increase the margin of safe apnoea time during intubation. **Chapter 10** summarises what was achieved from these studies in terms of contribution to the scientific field. It also explores the limitations of this thesis as well as recommendations for future research.

1.2 Aim of the Thesis

The aim of this thesis was to investigate high flow nasal oxygen in both the supine and upright position, across different patients (i.e. obese, pregnant and older patients) using a high-fidelity and highly-integrated computer model of the pulmonary and cardiovascular systems. To focus the scope of this topic, the research specifically investigated the ways in which HFNO can be used in the future to benefit adult patient groups who are at a higher risk of injurious hypoxaemia during the perioperative period. Existing literature in the field suggests that at-risk groups include:

- **Obesity**

  obese patients are likely to suffer quicker desaturation times than healthy subjects and can also present difficulties for airway management[1].

- **Pregnancy:**

  pregnant women also suffer from quicker desaturation times during anaesthesia[2].

- **Older Subjects:**

  this group is prone to issues when using face mask ventilation. Problems include patient participation (as seen in those with dementia) as well as displaying discomfort and poor tolerance to face masks. Compounding these issues is the task of achieving a good seal which is required to effectively use a face mask, but difficult due to the features of older people (missing teeth, loose skin).

I conducted a review of the available published literature for all three of these target groups and found that there were gaps in the knowledge that I believe

could be addressed through experimentation. However, due to ethical limitations, they were well suited for utilising the Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite. I was able to use the pre-existing computational model and contribute to it by writing new protocols to accommodate for my specific experiments as well as adding a new biobank to enable the study of the older subject.

All of this allowed me to observe large cohorts of *in-silico* subjects and produce results with important clinical implications; much faster than would be feasible in a real-world setting.

Chapter 2: Biological Knowledge and Existing Literature review

2.1 Respiratory System

Gas exchange is the process by which oxygen (O_2) is taken from the atmosphere and drawn into the tissues to meet their demands, whilst simultaneously removing the carbon dioxide (CO_2) waste out of the body's tissues.

In complex organisms such as humans, an intricate system is required that allows large amounts of oxygen to reach the target cells. This need is what drove pulmonary and cardiovascular systems to evolve into highly efficient structures. Due to these specialised structures, a single breath can inhale, filter, warm, and humidify around 500 mL of air. This volume is known as the tidal volume (TV) and passes through the nasal cavity, through the pharynx, and into the rigid structure of the larynx and the trachea. The trachea branches to form the bronchi, each leading to a lung. Within the lung the bronchi divide further, getting smaller in diameter, and forming structures called bronchioles. At the end of the bronchioles there are air sacs, which are made up of clusters of alveoli. The cells here are moist when healthy, due to pulmonary surfactant, which is secreted by the type II alveolar cells. This mixture of phospholipids and proteins allows for oxygen to diffuse more effectively and are essential for quality lung function. In the alveoli the O_2 dissolves across four membranes (type I alveolar cells, the specialized extracellular matrices known as the epithelial and endothelial basement membranes, and the endothelial cell) due to pressure gradients. This results in

O_2 reaching the blood within the capillaries which transports it to the target tissues. Pressure gradients also allow carbon dioxide to diffuse from the blood. Without the mechanism of exhalation (as is seen in the perioperative period when a patient stops breathing) the carbon dioxide will eventually balance the gradient meaning that no more oxygen will be drawn down and oxygenation of the tissues can no longer take place. This results in hypocapnia and acidaemia[3].

The lungs themselves are unable to move alone, as they have no contractible muscle tissue, and instead require the use of the diaphragm, which is a thin sheet of skeletal muscle that separates the thorax from the abdomen. Additional force is added by the weight of the ribcage. The amount of pressure applied by this skeletal structure will differ depending on posture. The diaphragm and the ribcage are responsible for the change in pressures that occur within the lungs, which pull air in. This is known as negative pressure breathing. When the diaphragm and the intercostal muscles of the ribcage contract, it causes the space in the chest to expand, causing the pressure inside of the lungs to be lower than the pressure in the atmosphere. Gases travel down the pressure gradient, and so this change draws air in through the conductive zones. The rigid cartilage structure of the trachea and larynx is essential at this stage, as it prevents them from collapsing in on themselves when the negative pressure caused by the contraction of the ribcage and diaphragm occurs.

Unfortunately, this highly evolved system is at risk of failure when patients are put under general anaesthesia, due to the cessation of movement which prevents the mechanism of breathing.

2.2 Breathing and the effect of anaesthesia on the cardiopulmonary system

Breathing is an automated mechanism, controlled largely by the neural circuits in the medulla oblongata. This section of the brain can read the pH of the surrounding tissue fluids (which is largely affected by CO_2 levels) to perceive the demand for oxygen and waste removal. The brain is also able to alter the rate and depth of breathing accordingly and is responsible for preventing physical damage occurring to the lungs by preventing them from overstretching during inhalation. The pons, which is located near the medulla oblongata, is responsible for the regulation of breathing. However, when a patient needs a surgical procedure, it is often necessary to induce unconsciousness via general anaesthesia, as well as paralyzing them with a muscle relaxant, which works by interrupting nerve signals, and causes a cessation of breathing. This is known as being “apnoeic” and the body is no longer able to modulate its oxygen delivery. Anaesthesia also causes the loss of airway patency due to the relaxation of the pharyngeal muscles and a displacement of the tongue. There is also a risk of infection, as the loss of a cough reflex can mean that saliva, mucous and gastric contents can enter the trachea and lungs which can result in an airway obstruction which could then prevent gases from travelling in and out of the lungs. To counteract this, antimuscarinic drugs can be given before the induction to reduce the amount

of saliva in the airway. Additionally, gases can be heated and humidified to help maintain mucous clearance and prevent mucous plugging.

As well as the mechanical issues brought about by anaesthesia, gas exchange can also be hindered. In an awake and healthy patient, the FRC exceeds the closing capacity (the closing capacity is the volume at which small airways collapse, hindering the flow of gas into the alveoli) and prevents collapse during normal expiration. However, in up to 80% of patients (with increased prevalence in the elderly) the effects of anaesthesia can cause the closing capacity to approach the FRC. This causes small airways to collapse during normal expiration and this can result in atelectasis.

In a healthy and awake patient's lung, the distribution of gas in the alveoli (ventilation) is matched by the distribution of blood in the pulmonary capillaries (perfusion). During inspiration, a greater proportion of the inhaled gas volume is circulated to the non-dependent areas at the top of the lung, however the effects of gravity reduce pulmonary blood flow in this region. This means that there is a degree of unevenness between ventilation and perfusion, which is called "ventilation-to-perfusion mismatch (V/Q)". For gas exchange to be successful and efficient, a sufficient supply of oxygen and blood is required (demand and supply). The V/Q ratio is the amount of gas that reaches the alveoli divided by the blood flow to the alveoli. Over the course of 1 minute, 5 litres of air enter the respiratory tract, whilst 5 litres of blood pass through the capillaries, which can be calculated as a V/Q ratio of 1. Any V/Q ratio higher or lower is considered a V/Q mismatch[4]. The more ventilated alveoli are under-perfused, and result in a V/Q > 1. Lack of

ventilation in the alveoli that are perfused with blood result in a V/Q < 1 and this is often the result of alveolar collapse, which prevents ventilation but does not affect perfusion; this is often referred to as a "shunt". Anaesthesia alters the distribution of gas and blood within the lungs which mean that both V/Q mismatch and shunt are increased. This reduces the oxygenation of the blood. The blood from these areas is already almost fully saturated with oxygen, so during anaesthesia, the inspired oxygen concentration is increased to offset the small degree of shunting.

Even during the apnoeic state, it is possible for the body to continue delivering oxygen to its tissues using what is still available within the lungs from the last breath taken. If the patient were breathing room air prior to the cessation of breathing, then tissue demands would mean that they would run out of oxygen in around 2 minutes. By increasing the fraction of oxygen in the inspired gas (FiO_2) mixture, a clinician can extend the amount of time that the patient can stay in this apnoeic state, and this is known as apnoeic oxygenation. The physiology of apnoeic oxygenation includes the supply of oxygen, the clearing of the dead space, and the effect of cardiogenic oscillations.

A patient's oxygen saturation of arterial blood (SaO_2) will steadily decrease until reaching 90-92%, at which point the SaO_2 will reduce at a much sharper rate. This state is known as hypoxaemia and it will lead to brain damage and death, if not addressed[5]. Increasing the risk of hypoxaemia is the event of resorptive atelectasis. This is when the alveoli collapse, limiting the channels

in which oxygen can be passed to the blood and therefore creating a shunt or a V/Q mismatch.

Aggravating factors of atelectasis include sedation[6] and obesity[7,8].

The safety period before the patient's SaO_2 reaches 90–92% is referred to as the safe apnoea time (safe apnoea time)[9]. Through intervention by a clinician, the time until a patient is in a dangerous state of hypoxaemia has been increased on average to 17 minutes, going as far as 65 minutes in some patient groups with certain techniques and equipment[10]. The process cannot continue indefinitely though, even if there were a way to keep the SaO_2 at >92% forever, the removal of carbon dioxide cannot occur, and this will lead to acidosis and death[11]. Levels of arterial carbon dioxide ($PaCO_2$) rise by 0.45 kPa every minute after the cessation of breathing[12]. However, when the airway remains unobstructed, the use of some oxygenation techniques such as HFNO make it possible to achieve a reduction in the rate of carbon dioxide increase to only 0.23 kPa/min[13].

2.3 Pre-oxygenation

Pre-oxygenation is the process of allowing a patient to breath a high FiO_2 gas mixture, thereby artificially increasing their oxygen saturation store, whilst simultaneously removing nitrogen. This takes place over the course of several minutes until the alveoli reach as close to 0% nitrogen as possible[14-16], as opposed to an oxygen saturation level of 100%, as some patients with pre-existing lung disease may never get close to 100% SaO_2. Ultimately, this results in the patient having an oxygen-rich reserve of gas in their lungs from which the blood can draw, whilst the patient is not spontaneously breathing.

This reserve delays the onset of hypoxaemia, which is a lower-than-normal arterial blood oxygen level, measured either as SaO_2 or partial pressure of oxygen (PaO_2). Oxygen will normally be supplied to a patient throughout a surgical procedure through the placement of an artificial airway known as an endotracheal tube and through mechanical ventilation. Whilst the airway is being secured however, oxygen cannot be supplied. Further to this, there can be complications and difficulties whilst placing the tube which can be brought about by a range of factors including: a short and thick neck (circumference > 50 cm), a large thick tongue, impaired mobility of the neck and jaw, an accumulation of fat in the oral cavity and cheeks[17], tooth decay, oropharyngeal tumours[18] and more. Being presented with one or possibly several of the above factors can increase the time needed to place the tube and allow for the re-commencement of oxygenation. Therefore, to prevent severe hypoxaemia and potential death, it is preferable that patients are pre-oxygenated as a failsafe. Although most patients will not present complications, and a skilled anaesthetist may even be able to overcome them if they arise, there exists the ability to extend this safety window, and so there is still merit in doing so for the safety of the patient.

In 2015, Corley and colleagues[19] found that it was possible to increase the safe apnoea time of a healthy weight patient to 14 minutes, using pre-oxygenation. At the time of the publication, the most common technique used to pre-oxygenate a patient was the use of a facemask. This non-invasive technique involves forming a tight fit around a patient's nose and mouth. It remains a common way to pre-oxygenate a patient[20], however, it is not

without its drawbacks. In order to function effectively, the tight seal must be maintained and this can be difficult when a patient has loose skin, facial trauma, spinal injury[20], is claustrophobic or unwilling to cooperate[21]. To combat these drawbacks, a newer technique has surfaced known as the "THRIVE" technique. THRIVE stands for trans-nasal humidified rapid-insufflation ventilatory exchange[10] which involves the use of rapidly insufflated, heated and humidified gases administered at high flow, through a nasal canula, to achieve pre-oxygenation[22]. Due to this method of using a nasal cannula, a tight fit is not required and therefore addresses several of the challenges brought on by the use of face masks.

Which of these two techniques is the most effective, safe, cost effective, and risk limiting is still greatly debated in current literature.

2.4 Nasal High Flow Oxygen Therapy (Optiflow - Fisher & Paykel Healthcare)

Numerous techniques in the administration of apnoeic oxygenation have been described. Optiflow (Fisher & Paykel Healthcare, Auckland, New Zealand) is a recently developed oxygen therapy device that delivers high-flow, humidified oxygen via nasal cannulae. My supervisory team has modelled and validated nasal cannulae delivering high-flow humidified oxygen (HFNO) in a 2019 study[13].

Optiflow is a nasal oxygen delivery device developed by Fisher & Paykel Healthcare, which consists of a double pronged nasal cannula, heated tubing, a humidifier, and an adjustable air and O_2 blender. Whilst it has a range of uses, the device is perfectly suited for pre-oxygenation and the THRIVE

technique. It allows for the fraction of FiO_2 to be adjusted from 21% to 100 % and can be independently titrated based on a patient's flow and FiO_2 requirements[23]. It also has an adjustable flow rate of up to 60 L/min. The inspired gas is heated to 37 ˚C and humidified, a feature that allows for a more comfortable experience for the patient, as well as reducing the risk of lesions and subsequent infections in the airways[24]. The use of warmth and humidity is also what allows this device to have high flow rate without causing damage to the airways. There is evidence to suggest that this high flow rate extends the region of turbulent gas flow in the airway, which results in improved gas exchange, therefore reducing the rate of carbon dioxide accumulation in patients who are anaesthetised and apnoeic[25]. Turbulent gas flow is a chaotic stream of gas that does not travel in flowing parallel layers, which is a crucial mechanism for clearing the dead space within the upper respiratory tract. In 2019, a study was conducted by Hermez and colleagues[25] investigated this mechanism, using a 3D printed trachea. The study was able to identify a supraglottic flow pattern. The turbulence of this flow appeared to cause an enhanced mixing below the glottis and formed the longitudinal mixing of gases in the trachea (this forms part of the "anatomical dead space" in the body). Gas flow from the small fluctuations in pressure and flow produced by the contractions of the heart (known as cardiogenic oscillations) combined with HFNO provide a mechanism for transporting carbon dioxide from the carina to the mouth. The accuracy of the results from this study could be called into question though as the model was not a perfect reproduction of human anatomy. The nose, bronchi, trachea, and pharynx in a true body all

have a degree of elastic compliance not found in the model used in this experiment. In the study, the pharyngeal dilator muscles seemed to play a particularly important role in apnoea[26]. Later in 2019, using the computational model used throughout this thesis, my supervisors (Laviola, Hardman) and colleagues investigated the clearance of carbon dioxide during apnoeic oxygenation[13]. The authors found that micro-ventilations induced by pharyngeal pressure and cardiogenic oscillations, as well as a high degree of mixing of the gases within the anatomical deadspace, appeared to be the key physiological mechanisms that combined to facilitate the clearance of carbon dioxide during the use of HFNO. This partial clearance of carbon dioxide is beneficial; however, it is important to note that it is not 100% clearance. The partial clearance of carbon dioxide using HFNO is still substantially less than the rate of production within the body and so the patient will eventually develop a respiratory acidosis caused by the build-up of carbon dioxide.

The rate of increase in $PaCO_2$ is much less if HFNO is used (i.e. 0.23 kPa/min), in similar agreement with previous clinical studies that found that the clearance of carbon dioxide using HFNO, and specifically Optiflow, is between 0.21 kPa/min[27] and 0.15 kPa/min[10].

Further benefits to the nasal prongs used in Optiflow include the ability to allow for oxygenation to occur without obstruction of the mouth, allowing for a faster airway rescue should intubation fail[28] and avoidance of obstruction during the initial placement of the endotracheal tube, which cannot be said for face mask ventilation.

For over a decade, research has been conducted into the use of Optiflow and

its effectiveness in a variety of scenarios and patient groups including infants[29], nonagenarians,[30] and in obesity [31]. From all of this research it is known that Optiflow can be used to extend the safe apnoea time[32] and is applicable to a multitude of unique patient types.

To fully understand the capability, and to accurately discuss Optiflow as a HFNO device, it is important to understand the process of mechanical ventilation. Therefore, the distinction between strategies, as well as their strengths and weaknesses need to be outlined.

A mechanical ventilator is a machine that performs some, to all, of the work of breathing when a person has difficulty or can no longer spontaneously breathe. The latter is the case when a patient goes under anaesthesia and so cannot breathe by themselves. The role of mechanical ventilation is to control PaO_2, $PaCO_2$ (and therefore the blood's pH) during surgery and to deliver the anaesthetic drugs. Mechanical ventilation can be broken down into "continuous" (does not allow the patient to breath spontaneously, used in anaesthesia) or "intermittent" (does allow for spontaneous breathing and is used when the patient is conscious). Mechanically ventilating a patient allows the physician to have control of:

- Oxygen (thorough the fraction of inspired oxygen (FiO_2)
- Flow rate (volume/time)
- Respiratory/ventilator rate (breaths per minute)
- Pressure
- Tidal volume

Mechanical ventilation is typically controlled by either pressure or volume. In pressure-controlled ventilation the amount of inspiratory pressure that is being generated is the variable. In volume control the constant flow produced in a set time is being controlled. There are many benefits to using mechanical ventilation and one of them is the reduction in the work of breathing, which decreases the amount of CO_2 being produced and the amount of O_2 being used. This is important as the accumulation of CO_2 is one of the dangerous aspects of apnoea.

A form of ventilation known as continuous positive airway pressure (CPAP) is a non-invasive form of ventilation, but it relies on a patient spontaneously breathing through a facemask. CPAP applies a positive pressure continuously to the airway, increasing the pressure inside of the alveoli and keeping them at a positive pressure (e.g. 5–20 cmH_2O). The alveolar pressure will fall and rise, but it will never become negative (or below the pressure set by the CPAP machine); this will prevent the alveoli from collapsing at the end of expiration (i.e., preventing atelectasis). CPAP is an effective method of non-invasive ventilation; however, it does have some drawbacks. Use of CPAP is often poorly tolerated by patients because the tight fitting face mask leads to discomfort[33].

Similar in utilization is positive end expiratory pressure (PEEP), which also prevents the alveoli from collapsing by increasing the intra-alveolar pressure (e.g., 8–10 cmH2O) during the expiratory phase of respiration. This pressure can prevent the alveoli from a cycle of collapsing and opening and therefore prevent lung injury from the ventilator. However it is also associated with

over distending the lung[34] which can result in lung barotrauma, increasing the dead space volume[35].

Optiflow, the technique used in this thesis, can generate low levels of PEEP. In patients with a closed mouth and a flow rate of 60 L/min, PEEP was found to be as high as 7 cmH_2O[36]. In patients whose mouth is closed, every 10 L/min of flow rate increases the mean airway pressure by 0.69 cmH_2O[37], although variations between 0.5[38] and 1 cmH_2O have been reported[36] In those with their mouth open, it increases by only 0.35 cmH_2O increasing the pressure so that at the end of expiration the pressure is still positive preventing the alveoli from collapsing[39]. However, the parameters with which this pressure is generated must be customised to the patient's individual needs. If it is set too low, then the pressure will not be positive, but if the flowrate is set too high then as mentioned previously, the lungs may become over distended, resulting in damage. There are also other drawbacks to the PEEP technique: it lowers the venous return and cardiac output because it creates an intrapleural pressure that is too positive. Some patient groups such as pregnant women have a dramatically increased venous return[40], but it is generally diminished in obese patients[41] who also have increased cardiac output due to an augmented stroke volume and an increase in heart rate[42]. Hypothetically, PEEP in an obese patient could cause poor circulation, resulting in poor oxygenation, which is counterproductive. In a healthy weighted individual, a PEEP of 7 cmH_2O may be enough to prevent atelectasis, however, in an obese patient a PEEP of 10 cmH_2O is most likely required[43,44]. Given the association between obesity and atelectasis[45], the need for a high

level of PEEP may be seen as a weakness in the use of HFNO. Optiflow is capable of between 3.5 cmH_2O to as high as to 7 cmH_2O which theoretically makes it incapable of the reported 10 cmH_2O required in the obese[36]. This is not something that was explored deeply in this thesis but may be worth exploration in future research.

High flow devices have several important features, and are considered a less invasive treatment that is better tolerated by patients[46]. As previously mentioned, HFNO devices such as Optiflow are reported to be capable of washing the expired volume of carbon dioxide from the airway, replacing it with oxygen-enriched gas, therefore decreasing the deadspace and increasing safe apnoea time[47]. With all the capabilities of HFNO, there is of course some detriments. The most prevalent of which is possibly that the use of HFNO requires specialist equipment, which may be unfamiliar which could lead to incorrect usage which would be disastrous to a patient. Additionally, and possibly because of its unfamiliarity, it is time-consuming to set up which is not useful in emergency situations, however a large amount of surgical procedures are scheduled and therefore HFNO may be more suited to these sorts of events.

2.5 Obesity

The definition of obesity is given by the World Health Organization as an "abnormal or excessive fat accumulation that presents risks to a patient's health," and can be more specially defined as a body mass index (BMI) of over 30 $kg.m^{-2}$ with degrees of severity increasing as BMI increases[48].

For all instances within this thesis, weight classification determined by BMI grouping will be categorised in line with the NHS guidelines[49] and can be seen in Table 2.1.

Table 2.1. Description of BMI categories and their associated kg.m^{-2} values using the WHO and NHS guidelines[48,49].

Weight categories	**BMI (**kg.m^{-2}**)**
Underweight	< 18.5
Healthy Weight	18.5-24.9
Overweight	25-29.9
Obese (Class 1)	30-34.9
Severely Obese (Class 2)	35-39.9
Morbidly Obese (Class 3)	40-49.9

Obesity is now considered a worldwide epidemic that does not discriminate between age, ethnicity or gender and its prevalence is increasing[50-53]. While many are aware of the negative side effects that obesity can have on an individual's overall health[54], it is also an important challenge that clinicians need to consider during the perioperative period. A key concern that arises in patients with obesity is a rapidly decreasing safe apnoea time[55,56]. This reduction is brought about by several factors including an obesity-associated reduction in the most important store of oxygen in the body, the functional residual capacity (FRC)[1], which is the amount of gas remaining in the lungs at the end of natural expiration. The FRC is normally around 2.5L for a healthy weighted adult[57,58], but a patient with a BMI of 30 kg.m^{-2} can expect to have an FRC of just 1.87 L[59]. This is caused by the adipose tissue around both the rib cage and in the abdominal cavity, which has the mechanical effect of exerting an undesirable pressure on the lungs, diaphragm, and ribs.

The FRC and how it is affected by obesity is integral to understanding the changes in airway and vascular resistance, increased oxygen consumption and metabolic rate[60], decreased lung and chest wall compliance[61], oxygen reserve, closing capacity, and V/Q mismatch[62]. These have therefore been a key focus in a lot of the experiments in this thesis.

A diminished FRC can be very dangerous to a patient under anaesthesia, and the decrease seen in the obese scales with severity; the more obese the patient, the smaller the FRC. For a healthy weighted patient, FRC is normally reduced by 20% once a patient is under anaesthesia, likely due to the loss of inspiratory muscle tone in the muscles acting on the rib cage which maintains the abdominal contents within the abdomen[63]. A loss of this muscle tone results in a loss of outward elastic recoil of the chest wall[63]. A morbidly obese patient can experience a reduction of around 50% in FRC[64]. Once a patient undergoes general anaesthesia and breathing ceases, the FRC contains the great majority of the oxygen that the body has access to, until ventilation resumes. To complicate matters, it is also understood that obese patients have a higher oxygen consumption rate[65,66], so upon the cessation of breathing, the oxygen that is in the lungs is consumed faster than in a healthy weighted individual, leading to a rapid decrease in oxygen saturation when under anaesthesia.

Obesity must be taken into account in a multitude of ways, specifically, ventilatory strategies[67] and positioning[68] and further complications for the clinician arrive when trying to secure an airway in this difficult patient group[69]. The changes in body composition when a patient has a BMI >30 $kg.m^{-2}$, also

influences the reference range values for arterial blood gas tests. What may be an alarming result for a healthy weighted patient, may be considered normal for an obese patient.

2.7 Pregnancy

Pregnancy may be life-threatening if not managed effectively. Respiratory physiology changes that are seen during the third trimester as well as the consequences of labour, increase the risk of rapid de-oxygenation and therefore reduce the safe apnoea time[70]. Lung volumes undergo considerable alterations with FRC decreasing (by 9.5–25%) and inspiratory capacity increasing to maintain a stable total lung capacity (TLC) [71]. As seen in obese patients, the oxygen consumption of the pregnant patient increases (up to 21%) as does metabolic rate (up to 14%); the smaller oxygen reserve brought by this increase coupled with the decrease in FRC can be disastrous if not managed correctly[72,73]. Making things worse is that reported failed intubation in this demographic is increased, and difficult intubation occurs in 3.3% of cases[70].

Pregnancy can be unpredictable and rarely can it be scheduled conveniently into an operating room. Instead, the use of anaesthesia for pregnancy often happens out-of-hours or in the emergency setting. This presents a potential hurdle in the use of HFNO, as new equipment may be unfamiliar to clinicians, whereas low flow nasal oxygenation (LFNO) is a familiar alternative that is therefore quick to set up in an emergency. However, both technology and technique move on and so at some point staff will need to embrace new technology, and this unfamiliarity should not hinder progress. Whilst there

may be some initial resistance to change, it can offer superior results.

With multiple lives at risk, and the important changes in pulmonary dynamics, the pregnant patient group is a worthwhile demographic that definitely requires further exploration.

2.6 Older Patients

The pulmonary system is considered to have reached maturity by age 20 years[74] and further ageing causes a steady decline in respiratory capability. However, without the intervention of pathology, the lungs will continue to sufficiently perform to fulfil a person's needs for their whole life[75]. The decline in performance is largely associated with the decrease in three variables: the static elastic recoil of the lung, compliance of the chest wall, and the strength of respiratory muscles. However, there is also a decrease in response to hypoxia and hypercapnia[74] which may be related to the increase in FRC and a reduced VO_2 at rest.

An older patient is more accurately described as an individual who is over the age of 65 years. This demographic is certainly worth further consideration and research as we see an increase in our ageing population and life expectancy[76]. Whilst there is a debate to be had on whether medicine should be focusing on longevity or quality, the focus of this thesis is keeping the older patient safe whilst in the perioperative period. When on the operating table, an older patient is much more at risk of complications. This is particularly of note during the placement of an endotracheal tube due to nasal polyps, fragile lips, atrophy of the muscle and connective tissues in the face and mouth, loose, fragile and/or missing teeth, high incidence of throat cancers, increased

likelihood of pharyngeal collapse, rheumatoid arthritis in the cervical vertebrae and more[18]. Many of these obstacles are highlighted when trying to use a tight-fitting face mask to deliver oxygen. This makes them an important patient group to consider when looking at HFNO which does not require a tight-fitting mask to be applied. The dual-pronged nasal design means that it can simply be placed on a patient's face, avoiding most of the previously mentioned difficulties.

Further complications for face mask ventilation and older people lie in the possibility of uncooperative behaviour due to confusion or dementia. In such cases, a large face mask may be difficult to apply and maintaining a good seal could be impossible. It can also be quite frightening and an unpleasant experience for the patient. The discreet design of nasal prongs may be a less intimidating approach, and so may make them better suited to this demographic, if it proves to still be as effective at oxygenation as face-mask alternatives.

Age brings with it many important physiological changes to the pulmonary system, such as a decreased elastic recoil coupled with an increase compliance due to changes in the alveoli. Whilst the total lung capacity does not change[77,78], there is a loss of elasticity and muscle mass, and there is an increase in the work of breathing. It becomes harder to expel air from the lungs and they do not readily return to their usual size after inhalation, causing an increase in FRC. This increase has been shown to result in an FRC of between 2.9 L to 3.14 L in an older person, but otherwise healthy, male[79,80]. As mentioned, despite the change in the FRC, the total lung capacity (the

maximum size of the lungs) does not change with age[77,78]. The increase in FRC and residual volume result in a decrease in the inspiratory capacity and the vital capacity [78], and there is an increase in residual volume. These changes to the pulmonary mechanics may make traditional pre-oxygenation techniques less effective and this is explored in Chapter 7.

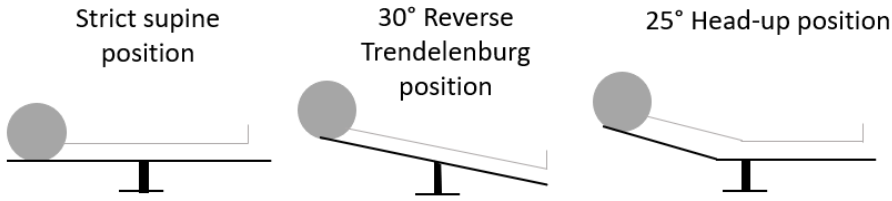
When reviewing the literature for these patients to accurately model them, there became an obvious complication: comorbidity. Older people are so rarely perfectly healthy and so it can be difficult to know what changes are strictly brought on by age and what is a secondary effect of a disease state such as respiratory disease, cancer, cardiovascular problems, arthritis and hypertension[81]. These additional states should be considered more when modelling in the future, but they were not explored in detail in this thesis. My focus was on the changes that were most likely brought on purely by age and to see if those changes could be uniquely catered for by HFNO and what techniques might need to be implemented to further that.

2.8 Posture

Often, a patient is pre-oxygenated and put under general anaesthesia in a supine position[82], and whilst this is effective, it is not necessarily the *most* effective. FRC is greatly affected by changes to the patient's posture[83]. This might be of most relevance in obese patients who already have a diminished FRC that can be exacerbated by the supine position. The induction of general

anaesthesia can also reduce the FRC by 20–50%[63,64] by reducing the muscle tone.

Figure 2.1: Demonstration of different surgical positions



This makes the supine position a less appropriate option for the obese patient. It has been established that a more appropriate posture may be the 30° reverse Trendelenburg position[82]. As shown in **Error! Reference source not found.**.1, this position allows for the head to be higher than the feet, whilst remaining parallel to the bed, as in supine. This change in position can redistribute the additional mass of an obese patient and may allow freedom for the thoracic cage to function with more capability. The 30° reverse Trendelenburg position also does not cause additional weight to "pool" where the waist meets the thighs, as in the 25° head-up position, which relies on a bend of the body which may not be entirely practical depending on their height and weight. In obese patients, this bending may limit the freedom of the thoracic cage in a way that the reverse Trendelenburg position does not. There seems to be little research in the field regarding posture in relation to HFNO; however, there is research on posture in relation to the more traditional face-mask techniques[60,82,84,85], which shows that it is of significance.

Physiological deadspace is the volume of ventilated air that does not participate in gas exchange (found in the nose, trachea, and bronchi), as well

as the volume of air in the alveolar dead space. Physiological deadspace decreases with the supine position and increases during a sitting position[35]. This is due to gravity's greater effect on blood than air, so in the supine position more wasted ventilation occurs and effectively increases the dead space volume[35]. The supine position and the alternatives are an important example of physics and biology working together.

2.9 Gaps in the literature

There is extensive research in the field of pre-oxygenation, however, the overwhelming bulk of that refers to the use of face-mask ventilation. There is considerably less research on HFNO, and there are several areas where more attention is needed, particularly regarding position and the patient groups that this thesis will cover.

Lane's research[85] shows that the uptilt of the back, neck and head of a healthy weighted individual by 20° (25° in the obese[60]) is more effective and efficient compared to the strict supine position. The uptilt of the head, back and neck will be referred to throughout this thesis as the "head-up position" with specification as to the degree of uptilt. Couture's study[84] indicates that the FRC of a patient (when compared to supine or beach chair) can be increased in the reverse Trendelenburg position. This cluster of research is a clear indicator that an elevated position is likely to have the best results for increasing the quality and the duration of the safe apnoea time, in obese and non-obese patients and requires investigation.

Research on the obese focuses heavily on the morbidly obese, whilst ignoring the potential benefits that could be given to those with less severe degrees of

obesity, whose physiology differs. As such, this thesis has looked further into elevated positioning regarding the obese at different BMI classifications. Even with its ability to overcome several of the key problems faced by the older demographic on the operating table, there is not a large amount of research available on the use of HFNO on this patient group. HFNO has many potential benefits for the older patient, and research into pre-oxygenation times to accommodate for the change in physiology must be explored further. Research on the pregnant is vital, as two lives are very often at risk. As such, the conflicting research between LFNO and HFNO should be explored in more detail. Equally important is the pre-oxygenation times, as changes may need to be accommodated for due to the dramatic and temporary change in respiratory physiology.

Chapter 3: Methodology

3.1 Interdisciplinary Collaboration in Systems Medicine

Simulation suite

Computational modelling is an innovative technique that is enabling researchers to conduct work that helps the scientific community gain a better understanding of the human body in a variety of circumstances. The data produced by computational modelling can add weight to arguments, help refine a technique, or aid in deepening the understanding of a bodily interaction that is difficult, time consuming, or unethical to perform on living beings[13,86].

The computational model that was used throughout this thesis (ran on a 64-bit Intel Core i7 3.7 GHz Windows 10 personal computer, running MATLAB version R2018a.v9 (MathWorks Inc, Natick, MA, USA)) is the Interdisciplinary Collaboration in Systems Medicine (ICSM) simulator, a highly integrated suite of high-fidelity computational models of the pulmonary and cardiovascular systems based upon the Nottingham Physiology Simulator[87-89], developed in the last 25 years by my supervisor (Prof Jonathan Hardman) and his team. It was originally created and then improved upon in two stages. The first model was known as the Nottingham Physiology Simulator; it has developed since, with new additions being made such as the model of the cardiovascular system to the pulmonary system and the full integration of the two, until it evolved into its second stage.

This chapter discusses the functionality of the system in detail and how the virtual subjects are configured.

The ICSM simulation suite includes several organ systems i.e. the heart, the blood vessels and blood, as well as the lungs. The ICSM suite is a high-fidelity and highly integrated model of pulmonary and cardiovascular systems in which the result of a calculation in one system feeds back as an input for another.

It is designed as a series deadspace between the airway and 100 alveolar compartments. The series deadspace is programmed as a series of stacked, rigid laminae ($Nlam$=50) of equal volume. The static total volume of the series deadspace can be set by the user and each lamina, known as j, has a known fraction (f ((SD,j))x) of gas x. The gases are comprised of O_2, nitrogen, CO_2, water vapour and another gas that is used to model additives. Gases will shift up or down the stacked laminae, during each iteration, depending on the pressure gradient between the alveoli and the environment.

The individual pressure of each of the alveolar compartments is determined by a cubic function:

$$p_i = S_i\left(\frac{(10\ \cdot v_i - 300)^3}{6600}\right) - P_{ext,i}\ \ v_i > 0\ for\ i = 0, \dots, N_{alv}$$

$$p_i = 0\ otherwise$$

where

$$S_i = \mathrm{k_{stiff}} \cdot \mathrm{N_{alv}^2}/200000$$

[a]

0,…, N_{alv} determines the alveolar pressure p_i (the pressure above atmospheric pressure in cmH_2O) for the i^{th} of N_{alv} alveolar compartments for the given volume of the alveolar compartment, v_i, in millilitres. $P_{ext,}$ (per alveolar unit, in cmH_2O) represents the effective net pressure generated by the effects of factors outside each alveolus. The parameter S_i is a scalar that determines the intra-alveolar pressure for a given volume and is dependent on the parameter K_{stiff} (stiffness co-efficient that represent the stiffness of the alveolar compartments). The units of S_i are cmH_2O.

For an additional breakdown of the equations and physiological principles on which the model is based, further reading can be found[90,91].

3.2 Apnoea model

All the studies in this thesis focus on the perioperative period, during pre-oxygenation and apnoea oxygenation, at which point gas exchange is altered.

To model the physiological mechanisms and the gas exchange during apnoeic oxygenation, four modules have previously been developed, validated[2,92,93], and integrated to the previous version of the model, namely: *i*) cardiogenic oscillations; *ii*) tracheal insufflation; *iii*) anatomical deadspace gas-mixing and *iv*) pharyngeal pressure(when HFNO is used).

Cardiogenic oscillation module

Cardiogenic oscillations are the small 2-3 cmH_2O fluctuations in pressure and flow produced by the contractions of the heart. This results in small volume changes in the alveoli and tracheobronchial airspaces which is likely to be an important physiological mechanism in facilitating gas exchange during

apnoea[13]. In the following equation, $P_{osc,j}$ represents the pressure applied by the heart upon the alveolar compartment *j*. N_{osc} indicates the number of compartments that are being acted upon (usually the number of alveoli for an adult is set to 100).

$$P_{osc,j} = K_{osc} \cdot \varphi \qquad \text{for } i = 0, \dots, N_{osc} \text{ where } N_{osc} \leq N_{alv}$$

[b]

K_{osc}, signifies the strength of the physical compression that occurs on the alveoli by the heartbeat. Lastly, φ denotes the ventricle activation function.

The tracheal insufflation module

Tracheal insufflation is the delivery of gas into the trachea via the nose. This module can be dictated to one of two settings, which alters the insufflation location between the glottis or the carina. The location is determined by the value attributed to l_{insuff} (values 1 to 5). The flow of the gas that is being insufflated is represented by the parameter r_{insuff} and is measured as L/min Insufflation at the lamina is calculated via the equation:

$$f_{SD,i}^{O_2} = \frac{\left(v_i * f_{SD,i}^{O_2}\right) + \left(F_{new} * f_{insuff}\right)}{v_i + F_{new}}$$

$$F_{new} = f_{insuff} * r_{insuff}$$

[c]

In this example, f_{insuff} is the concentration of O_2 in the gas that is being insufflated into lamina *i*. The volume of air in lamina *i* is represented by v_i.

Anatomical deadspace gas-mixing module

Gas mixing in the anatomical deadspace is represented by σ, which allows the user to control what level of gas mixing occurs. The parameter σ can assume

values ranging from 0 to 1, corresponding to no mixing (σ =0) to turbulent mixing (σ =1). Therefore, the fraction of gas in each laminas is calculated as follows:

$$\mathrm{f}_{\mathrm{SD},l}^{x} = \left((1-\sigma) * \mathrm{f}_{\mathrm{SD},l}^{x}\right) + \sigma * \mathrm{f}_{\mathrm{SD},l+1}^{x} \text{ where } l < \mathrm{N}_{\mathrm{lam}}$$

[d]

$\mathrm{f}_{\mathrm{SD},l}^{x}$ is the fraction of gas (shown as *x*) in lamina *l* and $\mathrm{f}_{\mathrm{SD},l+1}^{x}$ is the fraction of that gas in the next lamina in serial.

Pharyngeal pressure module

The delivery of HFNO has been shown to generate positive pressure at the pharyngeal space. The oscillatory pharyngeal pressure ($Pphar$) has been added to the tracheal pressure (equal to the atmospheric pressure):

$$\mathrm{P}_{\mathrm{phar}} = \mathrm{A} \cdot \sin\left(\frac{\pi}{\mathrm{f}}\right)^{2}$$

[e]

A is the amplitude of the pressure in cmH_2O (values 0-2 cm H2O), and f is the frequency in Hz equal to 70 Hz.

In the modelling investigations of this thesis the model parameters on the apnoea modules were set as follows:

- Classical (low flow) apnoeic oxygenation K_{osc} =2; σ = 0.3 and $P_{phar=}$ 0 cmH2O;
- Apnoeic oxygenation with HFNO: K_{osc} =2; r_{insuff}=13 L/min; σ = 1 and $P_{phar=}$ 2 cmH2O.

These values are those found to validate the apnoea modules against literature data during classical apnoeic oxygenation and high flow nasal oxygen (HFNO).[13]

3.3 In-silico (virtual) (in silico) subjects

Throughout this thesis, it was necessary to investigate different populations, both healthy and those who have specific conditions or morbidities.

To conduct the modelling investigations of the different studies presented in the next chapters several biobanks of subjects have been configured. The values chosen are discussed in this paragraph, so as not to repeat them throughout every subsequent chapter in the thesis. Biobank is the term used to describe a large collection of biological data for research purposes. These physiological values can be used to represent different populations of subjects. The biobanks used in this thesis, where possible, are based on published human data. Rather than using a singular value (such as the average reported value across several studies) a range of values are used for each parameter. The computational model randomly selects a value from this range to generate a subject. This means that multiple subjects can be generated, each with different values, meaning that the generated subjects will all be slightly different from each other. This variation is important as it more accurately reflects real world populations. Because the ranges are small, the variation is small enough to still mean that the subject is within a selected demographic (e.g. they may all be subjects with a height above 1.5 metres, but they will all have varying heights between 5-foot 1 inch, and 6-feet.) This

allows studies to be conducted on select demographics and investigation into their individual responses to a stimulus. It also means that we can see the range of effects that the stimuli will have (e.g. what may be true for a child, may not be true for an adult). This is important because it produces more realistic data, multiple subjects in a select demographic are unlikely to be identical and are unlikely to have completely identical responses. It can also show multiple insights into where a limiting factor might be, or where trends might lie.

Whilst averages are useful and pragmatic tools, individual and varied responses offer us a more detailed exploration when studying computational data.

3.3.1 Obesity

As previously mentioned in Chapter 2.5, obesity has been defined here as those individuals with a BMI that falls over 30 $kg.m^{-2}$. However, as obesity increases, further changes occur within the body and so it was necessary to have three different builds that represented three states of obesity. There was also an issue of too much data giving a range that was too wide. This variability clouded accuracy, and so where this was the case, it was necessary to create an interquartile range that gave a better representation of the obesity level, as opposed to the full spectrum.

Subjects were programmed and organised into the following three categories based on 39 different values:

Obesity I:

Subjects were set to randomise between 79–115 kg, whilst the height

randomised to 1.48–1.78 metres which would calculate to a BMI in the category of 30–35 $kg.m^{-2}$.

There was also a change in the respiratory rate, in a healthy subject this is observed as 12–20 breaths per minute (bpm)[94], whereas Obesity I subjects are programmed to 11–15 bpm[95,96]. Their stroke volume (the volume of blood that is pumped out of the left ventricle during each systolic cardiac contraction) and cardiac output (the quantity of blood pumped by the heart) were also affected by the additional weight and were accounted for in the model by reducing the stroke volume[96,97].

A very important change that has a large impact on oxygenation is the rate at which oxygen is consumed by the tissues, in obese subjects this was increased [98,99] and the model reflected this accordingly.

Anatomical shunt, which is in normal lungs because of the bronchial (supplies blood to the conducting airways of the lungs) and thebesian (drains deoxygenated blood into the newly oxygenated blood of the left atrium and ventricle) circulations which accounts for 2–3% of anatomical shunt, was also increased[97].

The external pressure acting upon the lungs was also increased for obese subject which also allowed for the change that is seen in the FRC[95,96,100].

The variables used to configure the subjects and their ranges are shown in Table 3.1

Table 3.1 Physiological data used to represent BMI of 30–35 kg.m^{-2}.

	Range	References
Weight (kg)	79–115	95,98,100,101
Tidal Volume (L)	0.46–0.65	95
Respiration rate (breaths/min)	11.2–15.6	95
FRC (L)	1.1–3.7	95,98,100
VO_2	254–307	99
Heart rate (beats/min)	85–103	97
Stroke volume (mL)	50–93	97
Shunt (%)	4–6	97
Anatomical deadspace (mL)	120–150	100,101

Obesity II

The weight range was again increased to include a range of 116–136 kg. Height was also adjusted and together this gave a BMI range of 35–40 kg.m^{-2}. This group saw a further increase to their stroke volume[97,99]. The physiological deadspace was also increased and scaled with the increase of obesity[100,101], as was the anatomical shunt of these subjects[100]. The FRC[102] and heart rate[99] were also scaled to represent this group. The variables used can be seen in Table 3.2

Table 3.2 Physiological data used to represent BMI of 35–40 kg.m-^{2} .

	Range	References
Weight (kg)	116–136	95,98,100-102
Tidal Volume (L)	0.42–1.05	95,96
Respiration rate (breaths/min)	9.0–22	95,96
FRC (L)	1.0–3.75	95,96,98,100,102
VO_2	309–336	99
Heart rate (beats/min)	72–78	96,97
Stroke volume (mL)	75–104	97,103
Cardiac output (L/min)	6–7	97
Shunt (%)	1.0–12.7	100
Anatomical deadspace (mL)	103–270	100,101

Obesity III:

Subjects were set to randomise between 137–205 kg, whilst the height randomised to 1.7–1.82 metres which would calculate to a BMI in the category of >50 kg.m^{-2}. Again, this group saw a change in their FRC[95,96] due to the additional adipose tissue causing reduced lung expansion, in contrast, VO_2 increased due to the increased body mass[95,98,100]. Heart rate also increased as the increased strain on the heart causes it to beat faster[99]. It is also necessary to increase the stroke volume[96,97] due to an increase in total blood volume. Cardiac output is calculated based on the variables added for heart rate and stroke volume, and the results matched with those seen in the data[97]. The full variables used can be seen in Table 3.3.

Table 3.3 Physiological data used to represent BMI of >50 kg.m^{-2}.

	Range	**References**
Weight (kg)	137–205	95,98,100-102
Tidal Volume (L)	0.44–0.80	95,96
Respiration rate (breaths/min)	15.2–20.6	95,96
FRC (L)	1.3–3.3	95,96,98,100,102
VO_2	339–439	99
Heart rate (beats/min)	66–88	96,97
Stroke volume (mL)	100–119	97
Shunt (%)	3–5	100
Anatomical deadspace (mL)	108–235	100,101

3.3.2 Pregnancy

Pregnancy has a profound effect on the body, and this includes its effect on the respiratory and cardiovascular systems which is discussed in more detail in Chapter 2.7. The virtual subjects describing pregnant women, in and out of labour, were already configured and published in 2021, in work led by my

supervisors[104] and listed here in Table 3.4 and Table 3.5 Where data could not be found, human physiological knowledge was used.

With my team, I have worked in a second research study on pregnancy to compare apnoeic oxygen techniques (LFNO versus HFNO) in term pregnant subjects[105] (in this paper I contributed, as fourth author). All the details are described in Chapter 8.

Table 3.4: Physiological values used to model term pregnant women out of labour. RR, respiratory rate; FRC, functional residual capacity; VO_2, resting energy consumption; Q_S/Q_T, anatomical shunt fraction; CO, cardiac output.

	Pregnant BMI25	Pregnant BMI35	Pregnant BMI40	Pregnant BMI50	References
Weight (kg)	75	94	108	135	
Tidal volume (ml)	630	690	700	730	106-108
RR (breaths/min)	16	16	16	19	106,107,109
FRC (ml)	2800	2289	1808	1697	106,109-112
VO_2 (ml/min)	270	338	388	450	107,113
CO (L/min)	6.9	8	9.2	9.4	106,114
Q_S/Q_T (%)	9	13	15	18	106,113,115

Table 3.5: Physiological values used to model term pregnant subjects during labour. RR, respiratory rate; FRC, functional residual capacity; VO_2, resting energy consumption; Q_S/Q_T, anatomical shunt fraction; CO, cardiac output.

	Labour BMI25	Labour BMI35	Labour BMI40	Labour BMI50	References
Weight (kg)	75	94	108	135	
Tidal volume (ml)	850	900	840	950	106-108
RR (breaths/min)	23	23	23	23	106,107,109
FRC (ml)	2800	2289	1808	1697	106,109-112
VO_2 (ml/min)	322.5	404	464	619	107,113
CO (L/min)	8.3	9.6	10.5	11.3	106,114
Q_S/Q_T (%)	9	13	15	18	106,113,115

3.3.3 Old Patients

To conduct the study in Chapter 7, it was necessary to build a biobank to model older people Literature search on old patients focussed on those

subjects that were not recorded as having been subjected to secondary illnesses that could affect their respiratory system, and who were of a healthy weight. The physiological parameters and their values range describing a population over 65 years old are presented in Table 3.6. Tidal volume does not change significantly with age in the absence of pathology and so remained at around 500 ml or 7ml/kg of body mass. FRC changes are likely because of the effect of age on the elasticity of the lungs, but total lung volumes are not increased. There is an increase in closing capacity, and closing volume, resulting in an intrapulmonary shunt increase.

Table 3.6: Physiological values used to configure subjects over the age of 65 years old.

	Range	**References**
Weight (kg)	65–75	
Tidal Volume (mL)	390–525	77,116,117
Respiration Rate (breaths/min)	12–25	118-120
FRC (L)	2.9–3.14	78-80
VO_2 (ml/min)	149.5–252.5	121,122
Heart rate (beats/min)	63–76	123-125
Stroke volume (mL)	86.5	124,126,127
Cardiac output (L/min)	HR*CO	124,126
Anatomical shunt (%)	15–17	128
Anatomical deadspace (mL)	127–370	77,129,130
Alveolar opening threshold	8–16.8	74,131

3.4 Strengths and limitations of computational modelling

Computational modelling opens a world of possibilities by allowing us to look at demographics and scenarios that would be otherwise unethical, such as recording the data of prolonged durations of apnoea on obese, pregnant, and older patients. It would be inconceivable to allow this to happen to a human being, but through the use of computational modelling, these areas can be explored without lives being on the line.

There are, of course, other ways to explore dangerous scenarios. One tool is animal modelling, which has greatly increased our understanding in areas of disease and genetics. However, animal modelling is considered a poor predictor of human expectations. Even when we look at other primates, the results are often not helpful predictors for human outcomes, as the physiology and biochemistry differ [132]. Computational models use real-life human data wherever possible, and so the results should be specific predictors of what to expect in humans.

Computational modelling lends itself to more progressive research, as it works well within the principles of the 3R's (Replacement, Reduction, Refinement) of animal research, and computational modelling supports the replacement by reducing and replacing the use of research animals, computation modelling is a clean and ethical research tool that will continue to advance and be embraced, particularly with the rise and advancement of artificial intelligence in the last few years.

Another area where computational modelling excels is in timekeeping. Whilst real-world trials and research can take months or years, with the need to screen and schedule human patients, computational modelling can be completed in hours, allowing a researcher to conduct thousands of experiments at a rate that real world experimentation cannot compete with. Another strength is that methods and results are reproducible, and modelling is mechanistic. Living patients run the risk of having undiagnosed medical conditions at the time of the study, causing any number of unknown false positives or unreliable results. Adding to this is the uncertainty that real

patients will turn up on time and can be relied upon for multiple interventions without the passage of time causing unexpected changes to their physiology (for example, taking a new medication, eating a meal before the study, acts outside of their control like broken bones, disease or being distracted by personal issues). Adding to the benefits of timekeeping, is that the recruitment of acceptable and willing patients is instantaneous with computational modelling, with multiple subjects with different and unique characteristics being generated quickly and repeatably.

With all these strengths and more, there can be no doubt that computational modelling is a useful tool in research.

There are, of course, limitations to computational modelling. One area of concern is that modelling often relies upon assumptions- data is not always available and so physiological theory has to be used to create calculations, and these can only be done to the level of current human understanding, as well as the programmers understanding, which can cast doubt upon the results. However, this can be combated through the validation using data from real patients or from literature.

With all the aforementioned strengths, it is easy to assume that computational research is easy to do, and that it is able to be generated easily and without skill, which is untrue. Skill in computing, biology, engineering, and knowing how your particular model works, unfortunately amounts to another weakness. The amount of time it takes to understand how to use the system correctly can hinder progress. Often there is a large learning curve that one must climb to use the system correctly, this is followed by learning how to

interpret the results that are often not displayed through user-friendly interfaces. This can lead to misinterpretations or user-error.

Another area of weakness is the customisability. You could be forgiven for thinking this is purely a strength, however, as previously explained, the user must understand the programming that has gone into the build in order to make meaningful changes that do not break the system. When we wish to change the way a subject ventilates, it is necessary to change multiple functions. The user must know what those functions are, how they affect other calculations that use that integer, what unit it is currently being calculated in, where the variable is found, and what it is termed within the system- this is why a degree of medical theory must be known as well as the computational ability to find and input the desired change. Once customisation of biobanks or updates to algorithmic calculations have been done, it can then be difficult to make these updates universal or "live" and so multiple iterations of the system can exist without unification. This means that a true second version of the software is difficult to create and disseminate, and multiple people working within the same team can find themselves using outdated versions.

For all of its strengths and weaknesses, computational modelling is a useful tool/method, and something that will only become stronger and more robust. As we continue into the digital age, a future where computer literacy, medical understanding and access to education is ever increasing, computational modelling will be wholeheartedly embraced.

Chapter 4: Investigating FRC as the key change during 30° head uptilt in healthy subjects during pre-oxygenation and apnoea and its effect on safe apnoea time.

4.1 Introduction

Positioning can have a considerable effect on multiple variables such as FRC, thoracic cage compliance, distribution of pulmonary blood flow, anatomical dead space, diffusing capacity, and lung compliance[113]. It is known that the supine position decreases FRC [133] and a healthy patient in this position can be expected to have an FRC of 2 litres [134-136]. The reverse Trendelenburg allowed the patient to be tilted whilst they remain flat to the operating bed, and an upward tilt of 30° allows for a 2.5 litres increase in FRC, due to the change in the thoracic volume [113]. Whilst this increase is considerable, it is important to note that simply increasing the FRC does not necessarily increase the safe apnoea time [137].

A study by Lane in 2005 [85] showed that pre-oxygenation with a face mask was more efficient in an elevated head position. This was strengthened by Ramkumar in 2011 [138] who found that a 20° head-up tilt with a tight-fitting face mask, generating 5 cmH_2O PEEP, provided a longer duration of non-hypoxic apnoea than conventional pre-oxygenation. Both of these studies were conducted in healthy weighted adult patients. Additionally, Subedi 2016 [139], also showed a similar pattern by pre-oxygenating patients in a 20° head elevated position for 3 minutes using 5 cmH_2O CPAP, and found that elevated patients were able to extend their safe apnoea time by 67 seconds. Across these papers, on average, elevated patients in the literature were able to

increase their safe apnoea time by 87 seconds.

However, similar results have been found in obese patients when facemasks have been used, as demonstrated by Altermatt in 2005 [1]. They explored obese patients in a sitting position for pre-oxygenation compared to the supine position and found that supine was inferior for extending tolerance to apnoea. This was strengthened by the findings of Dixon [140], also in 2005, who looked at a 20° head uptilt in the obese and found that it increased the safe apnoea time when compared to supine. Together these studies [1,140] show that when the patients back and head are elevated, the FRC is increased by ~25%, the PaO_2 after pre-oxygenation is increased by ~23% and the safe apnoea time increased by ~33%. Positions that have an elevated back and neck appear to have an important impact on pulmonary mechanics regardless of weight, which may predominantly be due to the change in the FRC.

The use of different positions during HFNO pre-oxygenation does not appear to have been investigated in detail. The lack of pre-existing data makes it difficult to explore the topic using computational modelling in a way that can be credible or validated. However, theoretical exploration based on the understanding of human anatomy is still possible.

The aim of this study is to investigate the pre-oxygenation of a healthy weighted virtual subject during apnoea, using HFNO, in a position which tilts the patient's torso such that the chest is higher than the abdomen by 25–30°. Positional change whilst using HFNO may increase the safe apnoea time and the PaO_2 which increases the safety of a surgical procedure. This study considers thoracic cage compliance and diffusion capacity both as single

variables and in combination with the FRC, to determine their importance in the accuracy of the simulation and to see if there is a subsequent tolerance of apnoea in the subject. This will then be used later in this thesis to conduct studies to better simulate the study of position in Chapters 5 and 6.

4.2 Virtual Subjects and protocol

As with all the studies in this thesis, the simulations were conducted in this chapter using the ICSM simulation suite, a comprehensive description of which can be found in Chapter 3. The model has been extensively validated for the investigation of apnoea and hypoxaemia in adults[2,92,93].

This study would have been too dangerous to conduct on a real patient, as allowing the SaO_2 to fall, with no intervention puts a human being at a very real risk of brain damage or even death, and so, computational modelling has been used. A virtual *(in silico)* subject was configured with a weight of 66.5kg and a height of 1.7 metres. The protocol consisted of three interventions:

Intervention 1: Subject is head-up tilted during pre-oxygenation and is also elevated during apnoea.

- **Intervention 2:** Subject is elevated during pre-oxygenation only. Subject is placed in supine for the duration of apnoea.
- **Intervention 3:** Subject is positioned supine during both pre-oxygenation and apnoea.

Only the FRC was adjusted, to represent the change in position. Where the subject is indicated to be in a head-up tilt the FRC was set to 2.5 litres [113]. Where the subject is configured as supine, the FRC of the subject was set to 2.1 litres [134-136].

The three interventions were all run across two ventilation strategies:

(i) patent upper airway with 5 cmH_2O with 60% O_2 for CPAP

(ii) patent upper airway with 70 L/min of humidified 100% O_2 delivered via the nose for HFNO. The modelling of HFNO has been described in Chapter 3.

This is to generate results that can be used to compare to existing literature, as well as theorize the potential of HFNO. A total of six scenarios were simulated.

Pre-oxygenation was simulated at rest, with the subject breathing 100% oxygen for 3 minutes to achieve pulmonary denitrogenation, using HFNO or CPAP. To simulate the induction of anaesthesia, the FRC was decreased by 20% [63]. The pre-oxygenation was followed by apnoea (i.e. cessation of tidal ventilation), with an unobstructed airway, and continued support by CPAP or HFNO respectively. The apnoea simulation ended when the arterial oxygen saturation (SaO_2) reached 40%, though 92% is considered the end of the safe apnoeic time[9].If a subject's SaO_2 did not reach this level then the simulation was ended after 40 minutes. $PaCO_2$ was also recorded, as a build-up of CO_2 in the body is also a safety concern during apnoea, even if SaO_2 continues to be high. A $PaCO_2$ of more than 45 mmHg/6.0kPa is considered hypercapnic.

The time (minutes) was recorded from the start of apnoea (therefore not including the pre-oxygenation time) until 40 minutes had passed and compared across all three interventions. Data were recorded every 5 ms from the start of the pre-oxygenation until the protocol was terminated.

4.4 Results

The results for this investigation are shown in the following tables and figures. Results showed that SaO_2 was an ineffective way of measuring the difference in the interventions, as the changes were less than a single % for both HFNO and CPAP. $PaCO_2$ showed larger changes with Intervention 1 being able to provide the lowest $PaCO_2$ throughout the simulation in both HFNO (4.7/7.5/9.7 kPa) and CPAP ventilation (5.2/8.7/12.0 kPa). HFNO demonstrated the lowest $PaCO_2$ between both ventilation methods.

Table 4.1. Arterial oxygen saturation (SaO_2), arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$) during apnoea, after subjects were pre-oxygenated with CPAP. Min 0 is at the end of 3 minutes of pre-oxygenation, when apnoea began; Min 50 is after 50 minutes of apnoea; Min 100 is after 100 minutes of apnoea.

CPAP			
Time to SaO_2			
		SaO_2= 92%	**SaO_2 = 95%**
Intervention 1 (elevated throughout)		7 min 48 seconds	7 min 6 seconds
Intervention 2 (elevated followed by supine)		7 min 30 seconds	6 min 42 seconds
Intervention 3 (supine throughout)		7 min 27 seconds	6 mins 48 seconds
SaO_2(%)			
	Min 0	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	99.9	99.0	N/A
Intervention 2 (elevated followed by supine)	99.9	98.8	N/A
Intervention 3 (supine throughout)	99.9	9.8	N/A
PaO_2 (kPa)			
	Min 0	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	45.4	21.2	6.3
Intervention 2 (elevated followed by supine)	45.4	19.9	5.6
Intervention 3 (supine throughout)	45.4	20.1	5.7
$PaCO_2$ (kPa)			

	Min 0	Min 5	Min 10
Intervention 1 (elevated throughout)	5.2	8.7	12.0
Intervention 2 (elevated followed by supine)	5.2	8.7	12.1
Intervention 3 (supine throughout)	5.2	8.70	12.1

Table 4.2. Arterial oxygen saturation (SaO_2), arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$) during apnoea, after subjects were pre-oxygenated with HFNO. Min 0 is at the end of 3 minutes of pre-oxygenation when apnoea began; Min 5 is after 5 minutes of apnoea; Min 10 is after 10 minutes of apnoea. Patients SaO_2 did not drop passed 99% as seen in other studies [104]

HFNO			
SaO_2 (%)			
	Min 0	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	99.99	99.98	99.97
Intervention 2 (elevated followed by supine)	99.99	99.98	99.97
Intervention 3 (supine throughout)	99.99	99.98	99.97
PaO_2 (kPa)			
	Min 0	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	82.3	74.1	70.1
Intervention 2 (elevated followed by supine)	82.3	73.4	69.1
Intervention 3 (supine throughout)	82.3	73.6	69.2
$PaCO_2$ (kPa)			
	Min 0	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	4.7	7.5	9.7
Intervention 2 (elevated followed by supine)	4.7	7.6	9.9
Intervention 3 (supine throughout)	4.7	7.6	9.9

4.5 Discussion

The SaO_2 results of this study were ineffective at measuring the interventions as the level of oxygen saturation never fell beneath 99% for the HFNO intervention. However, reflected in the data shown in table 4.1 we can make comparisons to the results obtained by Lane[85]. Lane's elevated patients saw a time of 5 minutes 43 seconds to 7 minutes 9 seconds, for subjects to reach an SaO_2 of 95%. To reach this same level our elevated CPAP subject took 7 minutes and 6 seconds, and so did fit within the expected range. Lane's supine patients took between 4 minutes and 3 seconds to 5 minutes and 22 seconds. The supine subject here took 6 minutes and 48 seconds, which was longer than anticipated, however, both the modelling results and Lane's results show a similar pattern which may suggest some validity to the experiment. There may have also been some variation due to the subjects in question, Lane looked at exclusively female patients who needed a cholecystectomy procedure, whereas the simulated subjects in this investigation did not present any co-morbidities and could be defined healthy patients were healthy.

Future studies should additionally look at what happens when the patient is left apnoeic with no ventilation technique in use. This may give some very useful information.

The results show that using HFNO on a healthy weighted subject with an FRC of 2.5 litres (used to represent a person in a head-up tilted position) for pre-oxygenation and apnoea offers better $PaCO_2$ results, CPAP subjects reached higher levels of $PaCO_2$ faster. The $PaCO_2$ continues to rise, even though in the

case of HFNO, SaO_2 was constant and PaO_2 decreased. Overall, this study adds weight to the argument that up-right tilt offers a more advantageous option for safe apnoea time by delaying hypercapnia, both when using HFNO and when using CPAP.

This work was initially inspired by the findings from Lane [85], a study from 2016 which pre-oxygenated patients with a head uptilt of 25° for 3 minutes, and a control group of supine patients for the same amount of time via standard face mask. Time for the SaO_2 to reach 95% showed elevated patients had 103 seconds longer of safe apnoea time. Additionally, in 1993, Baraka [141] preoxygenated patients at 45° head uptilt via facemask (8 L/min over a period of 3 minutes) and found that the elevated patients took 88 seconds longer to reach 95%.

Unfortunately, none of these studies, looked at HFNO and an upward head tilt and so there is no direct comparison to be made to give weight to the HFNO results. However, HFNO has been modelled in a supine position on a healthy subject and it was also seen in that study that the SaO_2 did not reduce as the time elapsed [104]. In its entirety this study works only as a stepping stone to the next studies explored in Chapter 5 and 6.

In conclusion, whilst the FRC is undeniably an important part of head-up tilt, and CPAP results aligns with published results[85,141], there is a need to improve the accuracy of the results by investigating other factors that change during an upward head tilt (e.g. changes to thoracic cage compliance, distribution of pulmonary blood flow, anatomical dead space, diffusing capacity, and lung compliance [113]) at which point the target demographic (in obesity) can be

investigated in an accurate and meaningful way. Retrospectively, there are also other considerations that could have been included in this study, such as the results of no pre-oxygenation, and no ventilation.

Chapter 5: Investigating the FRC changes brought on by 30° head uptilt during HFNO pre-oxygenation and its effect on safe apnoea time in virtual obese subjects.

5.1 Introduction and Aim

Numerous studies shows that head-up tilt (at various degrees) during pre-oxygenation is more effective than when in supine, in both healthy weighted and obese patients [1,85,113,138,140]. It has been observed by researchers that the positional change may increase FRC which is why the oxygenation is more effective, and a safe level of SaO_2 can be achieved for longer. However, contradicting results from Benedik [142] show that the higher the BMI, the less impact a change in position has on FRC. It also showed that 30° tilt did not improve FRC significantly in either group which contradicts Nunn [113], who observed a marked increase in the FRC of the obese when their position was tilted upright. The aim of this study is to evaluate if an increased FRC (theoretically brought on by a change in position) can offer an extended safe apnoea time and an optimal PaO_2 those with a BMI of >25 kg /m^2.

Obesity is an important challenge that clinicians need to consider during the perioperative period. A key concern is that individuals under this patient group are more likely to have a shorter safe apnoea time, mainly due to an obesity associated reduction in FRC [1]. As discussed in detail in Chapter 2.5, this reduction is due to the additional fatty tissue which mechanically exerts an higher pressure on the lungs, diaphragm, and ribs. The FRC is recorded as 2.5 L for a healthy adult [143], with a BMI of 18.5–24.9 kg.m^{-2}, where as a patient with a BMI of 30 kg.m^{-2} can expect to have an FRC of 1.87 L [59] which is a 25.2%

reduction. During anaesthesia, FRC in a healthy subject falls by 20% [63], compared to a subject with a BMI of >40 $kg.m^{-2}$ who will see a reduction of around 50% [64]. Obese patients have a higher oxygen consumption rate [65,66], so, during apnoea, oxygen is consumed quickly, leading to a rapid decrease in SaO_2.

An additional concern is the increased difficulty a clinician may have in securing the airway in this patient group due to alterations in the upper airway anatomy which reduces glottic visualization, this can cause delay in the placement of the intubation tube. In 2017, a study [144] found that successful first intubation attempts were heavily influenced by the position of the patient, with the success rates being: 65.8% for supine, 77.9% for patients on an incline and 85.6% in upright positions. It is also noted that Khandelwal [145] demonstrated that there was more than a 50% reduction in intubation-related complications in a 30° head and back elevated group when compared to a supine group.

FRC is also sensitive to the surgical positioning of the patient [83,84], in 2018, it was established by Couture et al[84] that position had a 6.4% effect on the FRC of patients with a BMI of 40 $kg.m^{-2}$or above.

Table 5.1 FRC measurements of patients with a BMI of >40 $kg.m^{-2}$ in different positions, from Couture[84]

Position	FRC in Litres (spontaneous breathing)	FRC in Litres (spontaneous breathing + PEEP)
Supine	2.1	2.5
Beach chair 25°	2.2	2.4
Reverse Trendelenburg 25°	2.2	2.6

In 2009, Benedik[142] showed that in patients with a BMI of 30–39 $kg.m^{-2}$, a

change in position could make a 27% difference in FRC, and for those with a BMI of between 25–29 kg.m^{-2} the difference was 31%.

Table 5.2 FRC measurements of patients with a BMI of 25-29 and 30-39 kg.m^{-2} in different positions, from Benedik's study[142]

Position	**FRC (mL) BMI 25-29** kg.m^{-2}	**FRC (mL) BMI 30-39** kg.m^{-2}
Supine	1920	1550
Fowlers at 30°	1980	1570
Sitting at a strict 90°	2520	1980

The results from these studies show that the higher the BMI, the less impact the change in position has. This could be due to the weight of the additional adipose tissue counteracting the benefits of the position. As such, those who are most likely to see the greatest benefit are likely those categorised as "overweight" and "obese", rather than those in the "morbidly obese" category. This should be investigated to see if HFNO at different positions can offer an extended safe apnoea time for those with a BMI of >25 kg.m^{-2}.

5.2 Virtual Subjects and protocol

For this study, 3 groups of 10 *in silico* (virtual) subjects, each group was put through 3 interventions. Subjects were configured with the data shown in Chapter 3.3.1 and the data from Table 5.3:

Table 5.3. Body mass index (BMI) and functional residual value (FRC) values of the 30 virtual subjects used in this study, when the patient is put under anaesthesia.

	BMI (kg.m$^{-2)}$	**FRC decrease after induction (%)**
Obese 1 (30 subjects)	30-24.9	~25
Obese 2 (30 subjects)	35-39.9	~35
Obese 3 (30 subjects)	40-49.9	~50

In line with the previous study in Chapter 4, the subject groups were exposed to three interventions:

Intervention 1: Subjects are tilted upright during pre-oxygenation and are also tilted upright during apnoea.

I**ntervention 2:** Subjects are tilted upright during pre-oxygenation only. They are placed in supine for the duration of apnoea.

Intervention 3: Subjects are placed in supine during both pre-oxygenation and apnoea.

Pre-oxygenation was simulated at rest, with the subject tidal breathing with an FiO_2 of 100% for 3 minutes to achieve pulmonary denitrogenation, via HFNO. To simulate the induction of anaesthesia, FRC was decreased by 25.2% for subjects in Obese 1, by 35% for subjects in Obese 2, and by 50% for those in Obese 3. The FRC change for Obese 2 was estimated between Obese 1 and Obese 3 as there was no available literature for this particular group.

The pre-oxygenation, at 60 L/min, was followed by apnoea, with an unobstructed airway and HFNO was ceased. The simulation was run until SaO_2 reached 92% which is considered the end of the safe apnoeic time [9], or until 60 minutes had elapsed.

5.3 Additional support protocols

To support the findings of the study, additional simulations were run to ensure that results being produced were in line with those found within the existing literature.

Methods used in the study by Ramkumar[138]

Ramkumar's 2011 study[138] used CPAP at 5 cmH_2O for 5 minutes of pre-oxygenation on a healthy, non-obese, patient. Afterwards, apnoea commenced, and the subject was left to desaturate with only room air until an SaO_2 of 93% occurred. A simulation was conducted to mimic this methodology using 5 cmH_2O during 5 minutes of pre-oxygenation on a single non-obese, subject and then allowed to desaturate with fiO_2 21% until SaO_2 reached 93%.

Methods used in the study by Dixon[140]

Dixon's 2005 study[140] observed patients with a BMI> 40 $kg.m^{-2}$, pre-oxygenating them with CPAP at 5 cmH_2O for 5 minutes before allowing them to desaturate with only room air until SaO_2 reached 92%. A study was conducted to allow for comparisons with these results, using a single patient with a BMI of 50 $kg.m^{-2.}$ They were pre-oxygenated for 5 minutes at 5 cmH_2O and then allowed to desaturate with fiO_2 21% until SaO_2 reached 92%.

Data were recorded every 5 ms from the start of the pre-oxygenation until the protocol was terminated.

5.4 Results

Preliminary results of a simulation that modelled the methodology of Ramkumar [138] fell within the range of those shown in the published study, which supports the theory that the changes made to the FRC to replicate a change in position may be accurate.

Table 5.4. Comparison of results between published data[138] and the modelling simulations.

	Time until SaO_2 desaturated to 93%	
	Ramkumar	**Model**
Head up	7 minutes 32 seconds ± 71seconds	6 minutes and 19.2 seconds
Supine	6 minutes 34 seconds ± 83 seconds	5 minutes and 18 seconds

Preliminary results of a simulation that modelled the methodology of Dixon were similar to those reported in the literature, which lends more strength to the validity of the changes that have been made to replicate the change in FRC.

Table 5.5. Comparison of results between published data[140] of subjects with a BMI>40 $kg.m^{-2}$ and the modelling simulations.

	Time until SaO_2 desaturated to 92%	
	Dixons results	**Simulation results**
Supine	2 minutes 35 seconds ± 70 seconds	2 minutes 49.8
Head up	3 minutes 21 seconds± 56 seconds	3 minutes 15.6 seconds

Both studies were able to be similarly replicated through the simulation, which lends credibility to the results that will be produced with HFNO.

The results for this investigation show that HFNO increases the safe apnoea time across all three obese groups. The safe apnoea time decreased as weight increased, but HFNO still provided additional benefit. The data from the investigation are shown by average in tables 5.6, 5.7 and 5.8, and the full range of data for each subject in figures 5.1 to 5.6.

Obese 1:

Table 5.6. Average time take for arterial oxygen saturation (SaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) to reach 92% during apnoea, as well as their average arterial partial pressure of carbon dioxide ($PaCO_2$) after 3, 5 and 10 minutes of apnoea.

Obese 1			
Average time to reach SaO_2 92%			
Intervention 1 (elevated throughout)	8 minutes 51 seconds		
Intervention 2 (elevated followed by supine)	7 minutes 51 seconds		
Intervention 3 (supine throughout)	7 minutes 52 seconds		
Average $PaCO_2$ (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	6.4	7.7	11.2
Intervention 2 (elevated followed by supine)	6.4	7.8	11.3
Intervention 3 (supine throughout)	6.4	7.8	11.3

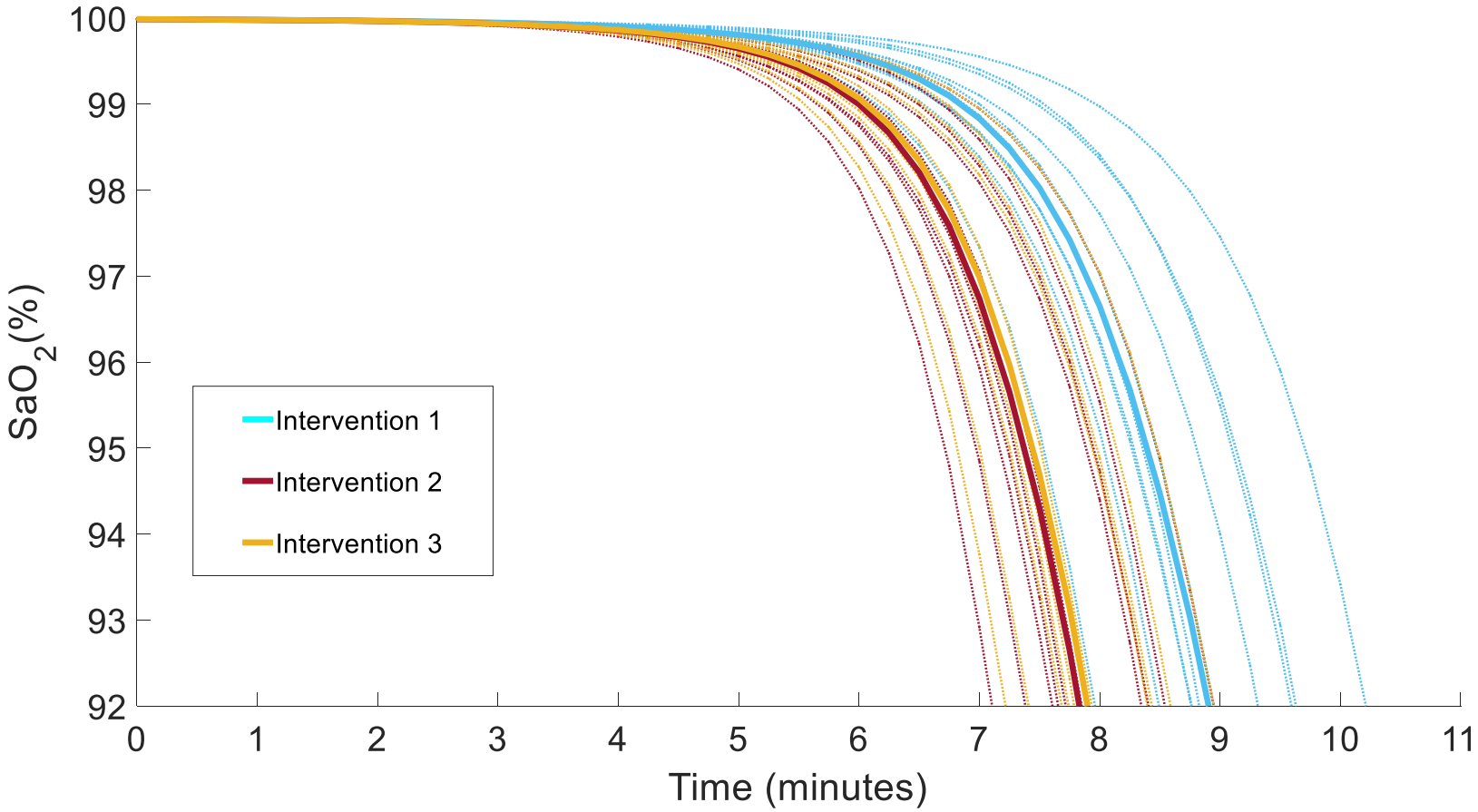


Figure 5.1. Arterial oxygen saturation (SaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines indicate the average.

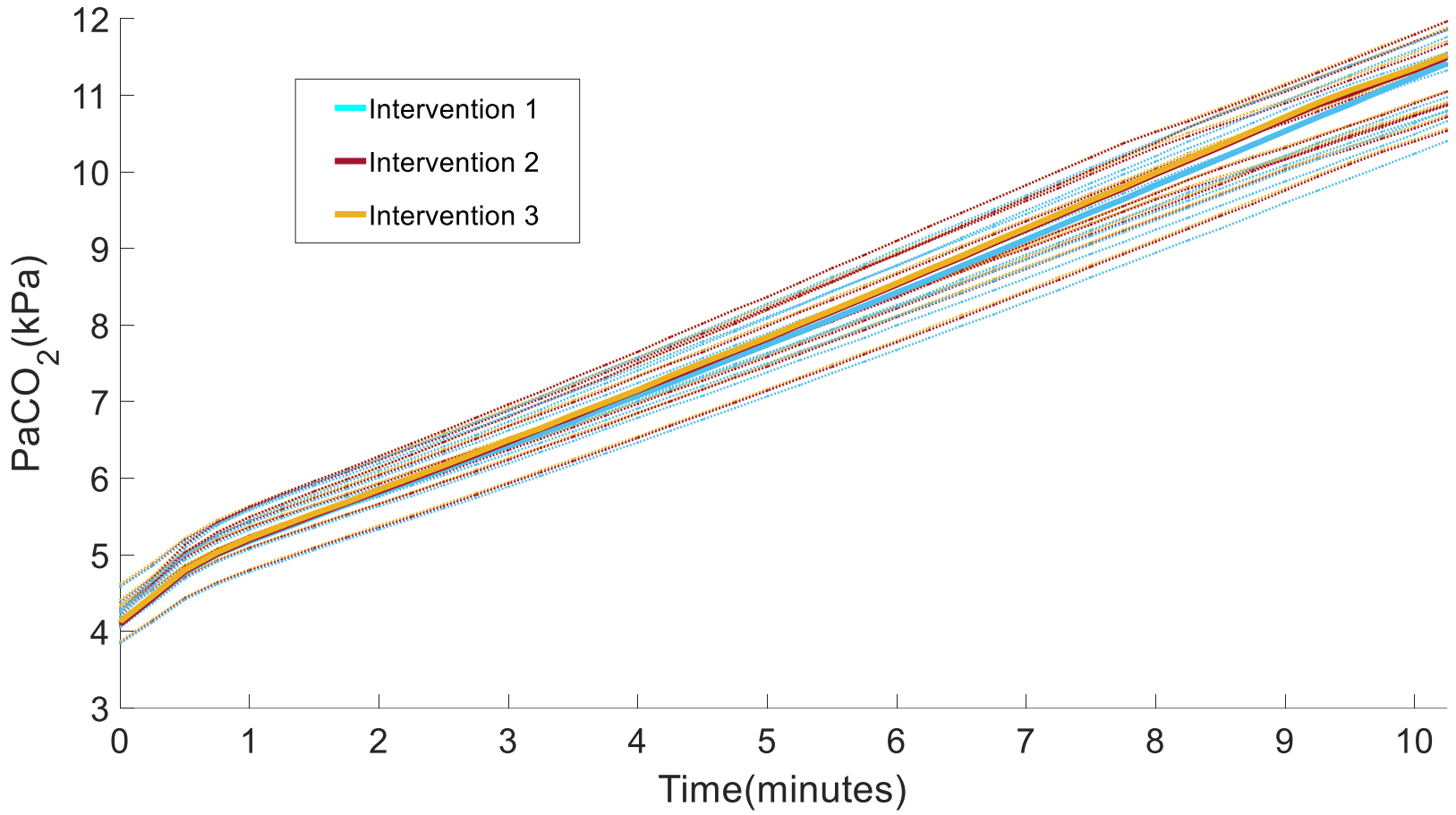


Figure 5.2. Average arterial partial pressure of carbon dioxide ($PaCO_2$) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) during apnoea. Dotted lines represent the individual subjects. Solid lines represent the average.

Obese 2:

Table 5.7. Average time take for arterial oxygen saturation (SaO_2) of Obese 2 (BMI 35-29.9 $kg.m^{-2}$) to reach 92% during apnoea, as well as their average arterial partial pressure of carbon dioxide ($PaCO_2$) after 3, 5 and 10 minutes of apnoea. Where the simulation ended before a value could be taken N/A is used.

Obese 2			
Average time to reach SaO_2 92%			
Intervention 1 (elevated throughout)	7 minutes and 18 seconds		
Intervention 2 (elevated followed by supine)	7 minutes and 1 second		
Intervention 3 (supine throughout)	7 minutes and 1 second		
Average $PaCO_2$ (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated throughout)	6.1	7.3	N/A
Intervention 2 (elevated followed by supine)	6.1	7.3	N/A
Intervention 3 (supine throughout)	6.1	7.3	N/A

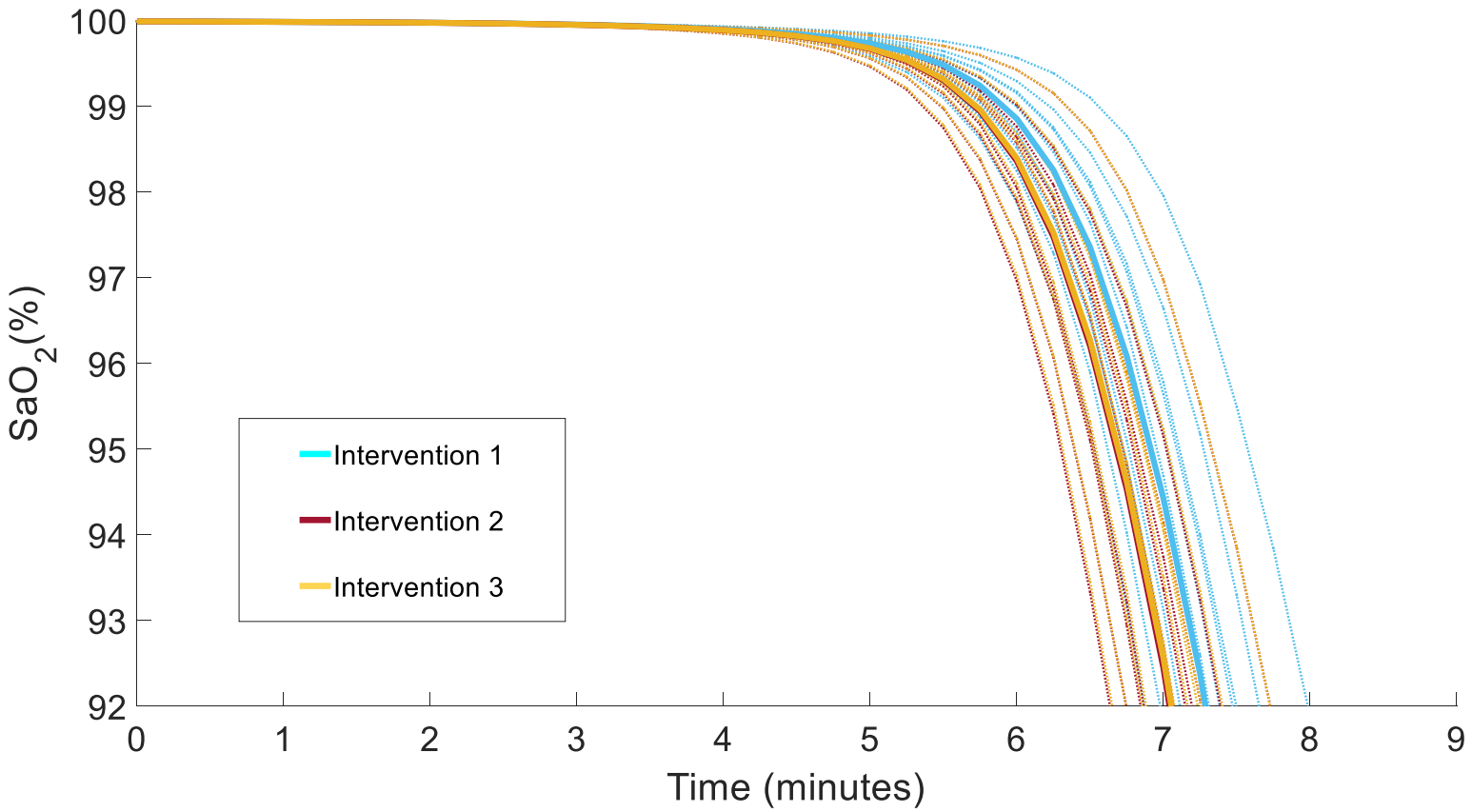


Figure 5.3. Arterial oxygen saturation (SaO_2) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. Intervention 2 is obscured by Intervention 3.

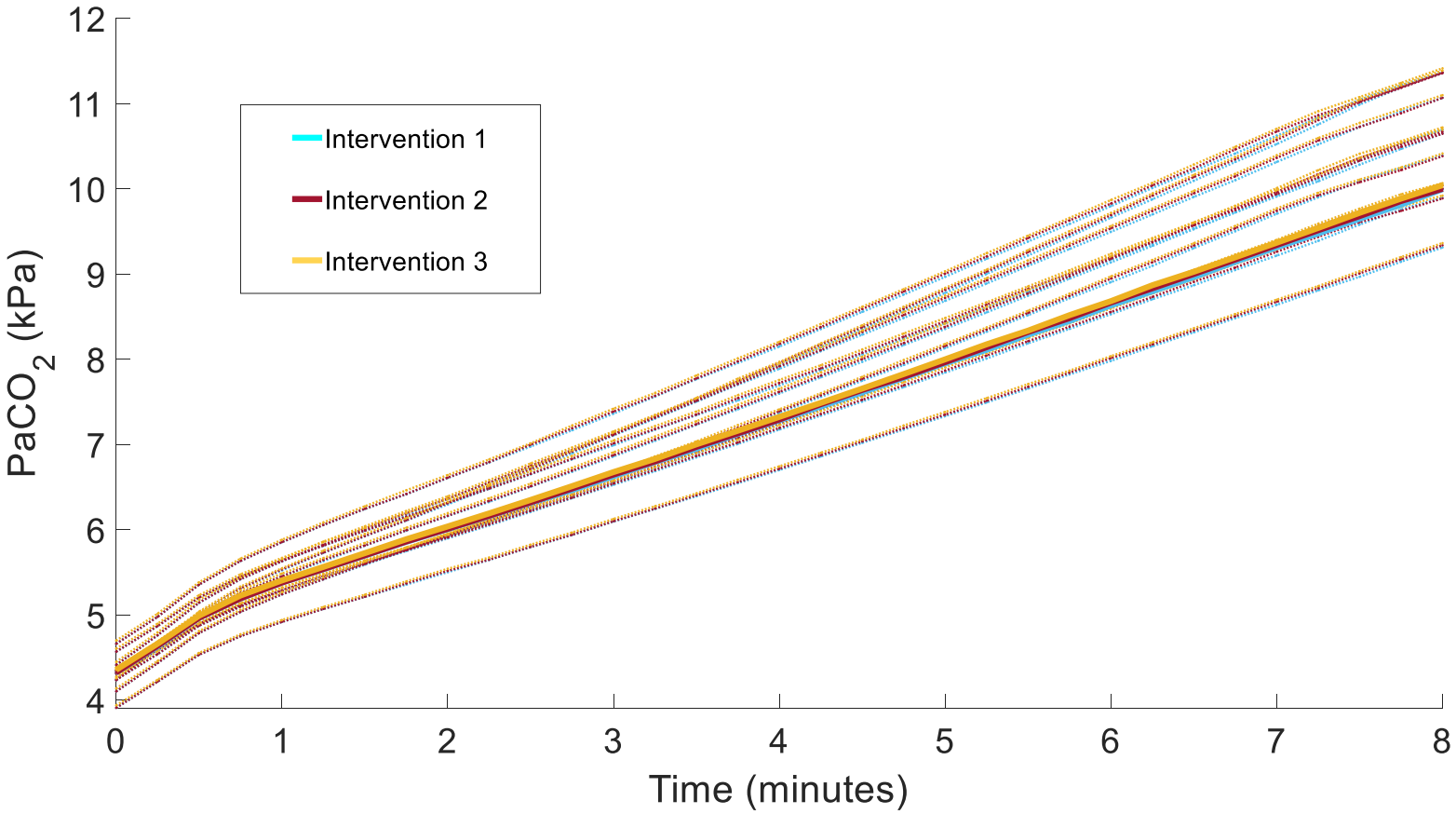


Figure 5.4. Arterial partial pressure of oxygen ($PaCO_2$) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The three averages are overlapping, as well as the three interventions for each of the 10 subjects.

Obese 3:

Table 5.8. Average of the time taken until arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) reached 92% during apnoea, as well as their average arterial partial pressure of carbon dioxide ($PaCO_2$) after 3, 5 and 10 minutes of apnoea. Where the simulation ended due to subject reaching 92% SaO_2 before a value could be taken N/A is used.

Obese 3			
Time to reach SaO_2 92%			
Intervention 1 (elevated throughout)	1 minute 54 seconds		
Intervention 2 (elevated followed by supine)	1 minute 42 seconds		
Intervention 3 (supine throughout)	1 minute 42 seconds		
$PaCO_2$ (kPa)			
	Min 3	Min 5	Min 10
Intervention 1 (elevated throughout)	6.63	8.41	N/A
Intervention 2 (elevated followed by supine)	6.63	8.41	N/A
Intervention 3 (supine throughout)	6.63	8.41	N/A

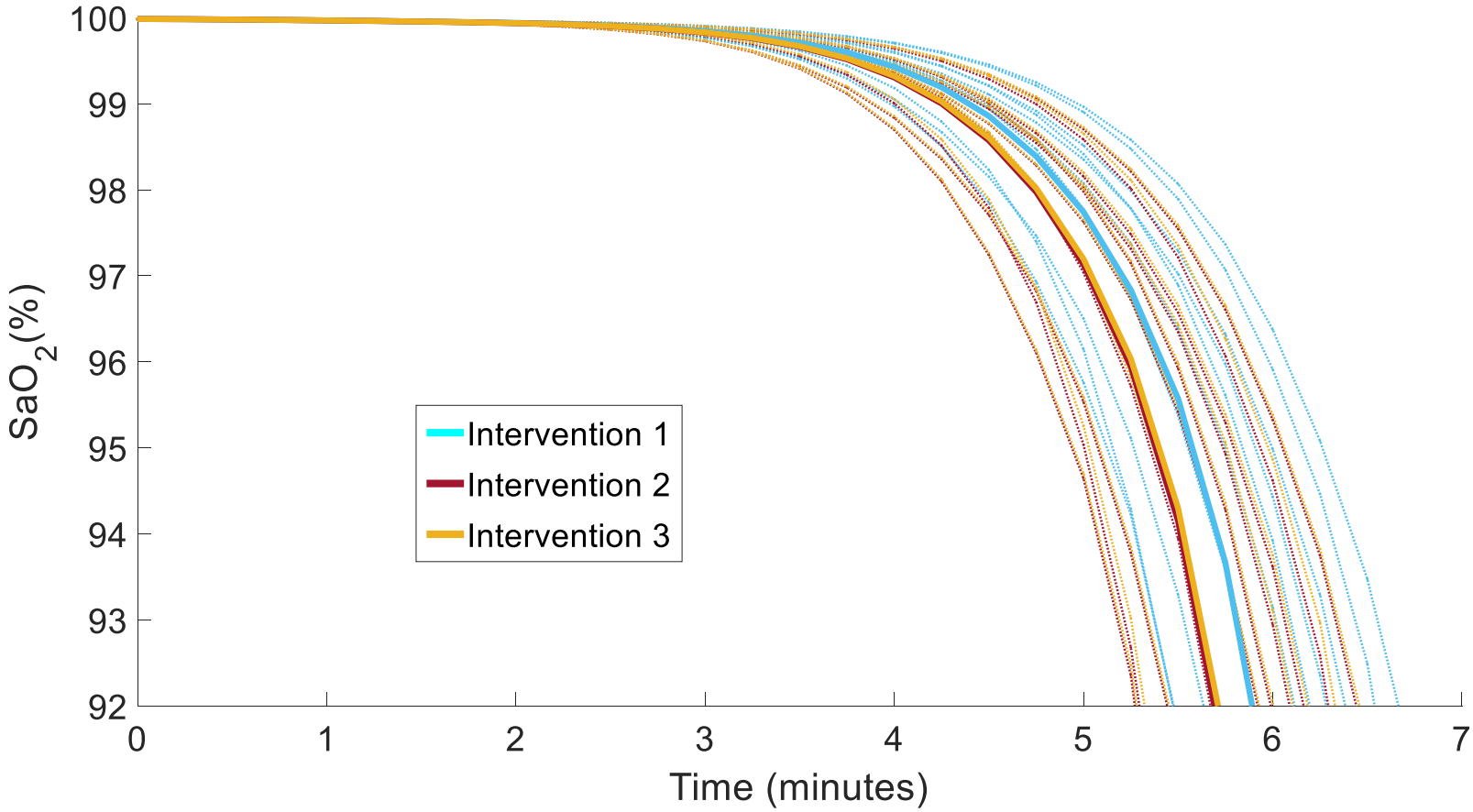


Figure 5.5. Arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average.

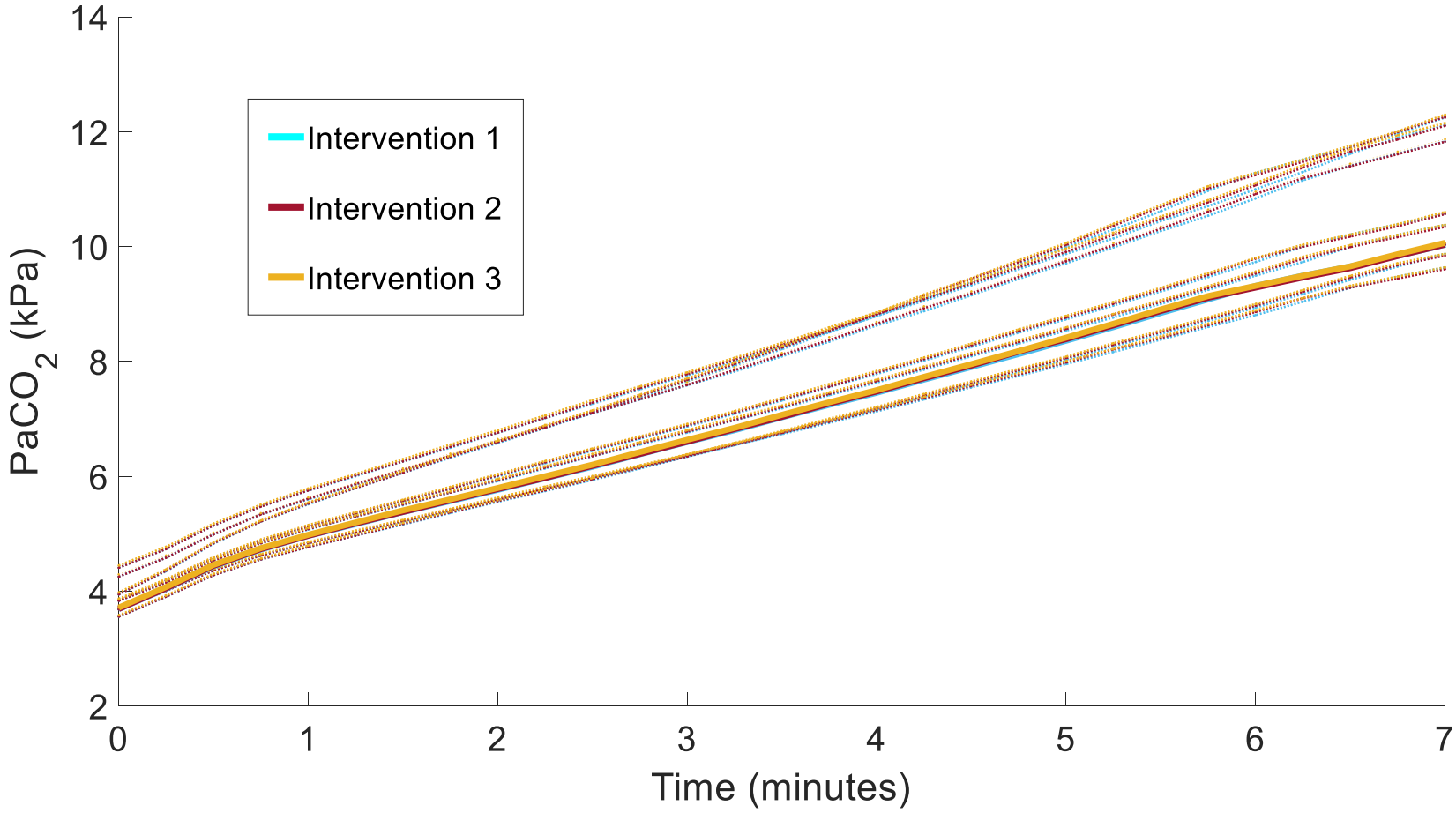


Figure 5.6. Average arterial partial pressure of oxygen ($PaCO_2$) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

5.5 Discussion

It is clear from the results that in all three subject groups, the upright tilt of the patient for both pre-oxygenation and apnoea lead to an increase in the safe apnoea time. The difference between Intervention 1 (entirely elevated) vs Intervention 3 (entirely supine) was on average 59 seconds (Obese 1), 17 seconds (Obese 2), and 12 seconds (Obese 3).

Intervention 2 (upright tilted and then supine) was created to best simulate how a patient may be situated on a surgical table for a procedure as the uptilt of a patient for the placement of an intubation tube seems unfeasible. While the results of intervention 1 seem promising, intervention 2 proved similar to those of intervention 3 which shows that uptilt during pre-oxygenation alone is not enough to increase the safe apnoea time.

It is important to note that as the BMI of the subject increased, the benefit was reduced in seconds, but when looked at as a percentage of the total time, the increase is put into perspective as >12.5%, (59 seconds) 4% (17 seconds), 3.4% (12 seconds), across Obese 1, Obese 2 and Obese 3, respectively. Whilst it may be unclear if an increase of >3.4% to the safe apnoea time for the morbidly obese (Obese 3) is an important amount of time, in a situation such as endotracheal placement, every second counts.

This investigation has shown that uptilt could both provide more time to those who are still obese but in lower BMI such as 35-29.9 $kg.m^{-2}$ (a target group often ignored in the literature), and still be a factor for those who are morbidly obese. Looking at the $PaCO_2$ data, upward tilt does not seem to relieve the burden on the body, but this does add strength to the accuracy of

the data, as the CO_2 build up was not expected to change across interventions. However, it is important to remember that this is still just a change in FRC and that logic dictates that this is not the only variable to change when the body is upward tilted. As such, further studies are needed to better simulate the changes and increase accuracy to real patients. The lack of additional variables such as cardiac output or pharyngeal pressure is a weakness in this study. However, the data obtained from this study agreed with what has been seen in the literature, which adds credibility to the results.

When comparing the results of this study with the preliminary protocol that was run using CPAP (Table 5.5) HFNO offers longer safe apnoea (desaturated to 92%) times, with a supine approach increasing from 195 seconds to 354 seconds, and the uptilt increasing from 169 to 342.This may suggest that HFNO may be the more advantageous and effective option for pre-oxygenation. This study also didn't consider one of the great strengths of HFNO, which is that it does not need to be removed when the endotracheal tube is being placed. This means that it may still be able to supply some oxygenation during placement, though how much oxygen would be successfully delivered whilst the instrumentation is being placed has not been investigated in enough detail for a simulation to be created to investigate this. However, estimations could be made in the future, and this is an important area to because it is one of the major mechanical advantages in the unobstructive nature of HFNO.

Chapter 6: Refined simulation of 30° head uptilt during HFNO pre-oxygenation and its effect on safe apnoea time in obese virtual subjects.

6.1 Notes about this study

Following on from Chapter 5, the aim of this study is to create a more accurate modelling of the 30° head uptilt position, with the intention of being able to better simulate its effects on the obese patient group. It looks at the safe apnoea time that is achieved when HFNO is being used as the oxygenation method. After reviewing basic biological mechanics in more detail, it has been necessary to look at changes in FRC, as before, but with the addition of cardiac output which appears to alter during positional change. It is logical to consider Chapter 4, 5 and 6 as one connected study through multiple chapters. The results could add weight to other research discussed in chapters 4 and 5 that suggests head uptilt is an appropriate position for the obese population in the perioperative period, by measuring the time it takes for the patient's SaO_2 to fall below 92%, compared to the supine position.

6.2 Introduction

A previously discussed, safe apnoea time is the amount of time a patient has from the moment they stop breathing until blood oxygenation decreases to below 92%. Extending this time gives clinicians longer to do life-saving interventions. There is a correlation between a higher BMI and a shorter safe apnoea time window, but these patients are also the more likely to require clinical intervention. Elevating a patient during the pre-oxygenation and apnoea phase could help extend the safe apnoea window. This study explores

this idea by simulating uptilt in virtual (in silico) obese subjects. The first step in modelling this was to try to model uptilt on a healthy model (Chapter 4) and to evaluate what components of a subject's physiology were likely to be changed during this positional change. The accuracy of the results in Chapters 4 and 5 were limited as FRC was the only physiological change that was evaluated. A further literature search has highlighted the need to make additional parameter changes, including hemodynamic changes such as a 33% reduction in venous return[146] which therefore affects cardiac output in healthy weighted patients. There is limited evidence that suggests that uptilt decreases pharyngeal pressure from 2 cmH_2O to 1.8 cmH_20 when a patient is at a 45° angle of uptilt [147] (though the body composition of the patients in this study was not discussed) so this will not be used in the study. As explored previously, FRC is also reduced when a patient goes from an upright, or elevated position, to a supine position [113,133] as well as decreasing the respiratory compliance, resulting in the requirement of higher airway pressures to maintain ventilation. It is logical to assume that with all these positive attributes the intervention of elevating an obese patient would result in an extended safe apnoea time, however, it would expose humans to unacceptable risk to use human patients to explore this topic.

6.3 Virtual subjects and protocols

As with all the studies in this thesis, the research in this chapter was conducted using the ICSM simulation suite, a full description of which can be found in Chapter 3. For this study, the same 3 groups of 10 *in silico* (virtual)

subjects for a total of 30 subjects from Chapter 5 were used.

Cardiac output was adjusted by around 1/3 to the values as shown in Table 6.1:

Table 6.1. The average cardiac output (CO) used across the 30 subjects in both upwards tilt and supine position.

	BMI (kg.m^{-2}**)**	**CO in uptilt (L.min^{-1})**	**CO in supine[97] (L.min^{-1})**
Obese 1	30-24.9	4.7	7.0
Obese 2	35-39.9	4.7	7.0
Obese 3	40-49.9	6.0	9.0

Previous chapters have shown that elevating a patient and then returning them to supine did not meaningfully change the results of safe apnoea time, and so the interventions in this study will be:

Intervention 1: Subject is elevated for the duration of pre-oxygenation and remains elevated for apnoea.

Intervention 2: Subject is in supine position for the duration of pre-oxygenation and remains this way for apnoea.

Pre-oxygenation was simulated at rest, with the subject tidal breathing an inspired FiO_2 of 100% for 3 minutes to achieve pulmonary denitrogenation, via HFNO at 60 L.min^{-1}. To simulate the induction of anaesthesia the FRC was decreased by 25.2% % for subjects in Obese 1, by 35% for subjects in Obese 2, and by 50% for those in group 3. The FRC change for Obese 2 was estimated between Obese 1 and Obese 3 as there was no available literature for this particular group.

The pre-oxygenation was followed by apnoea, with an unobstructed airway and no HFNO support. The simulation was run until 60 minutes had passed or

SaO_2 reached 40%. Data were recorded every 5 ms from the start of the pre-oxygenation until the protocol was terminated.

6.4 Results

Results from this study show that a forward tilt position does influence the safe apnoea time achieved (SaO_2 = 92%). However, the effect varies depending on the level of obesity. Uptilt improved safe apnoea time in Obese 1 but reduced it in Obese 2 and offered no benefit to Obese 3. On average, Obese 1 had an improved safe apnoea by 32 seconds. Obese 2 saw an increase of 12 seconds. Obese 3 saw an increase of 9 seconds. The average data for this investigation are shown in tables 6.2, 6.3 and 6.4 and the full data ranges are shown in figures 6.1 – 6.9.

Obese 1:

Table 6.2. Average of the time (in seconds) taken until arterial oxygen saturation (SaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) reached 92% after 3 minutes of pre-oxygenation with HFNO, as well as the average of the arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$). Min 3 is 3 minutes of apnoea, Min 5 is 5 minutes of apnoea, Min 10 is 10 minutes of apnoea.

Obese 1			
Time to reach SaO_2 92%			
Intervention 1 (elevated followed by supine)	8 minutes		
Intervention 2 (supine throughout)	7 minutes and 28 seconds		
Average PaO_2 (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated followed by supine)	47.2	30.0	5.4
Intervention 2 (supine throughout)	46.4	28.6	4.9
Average $PaCO_2$ (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated followed by supine)	6.3	7.6	11.0
Intervention 2 (supine throughout)	6.3	7.6	11.0

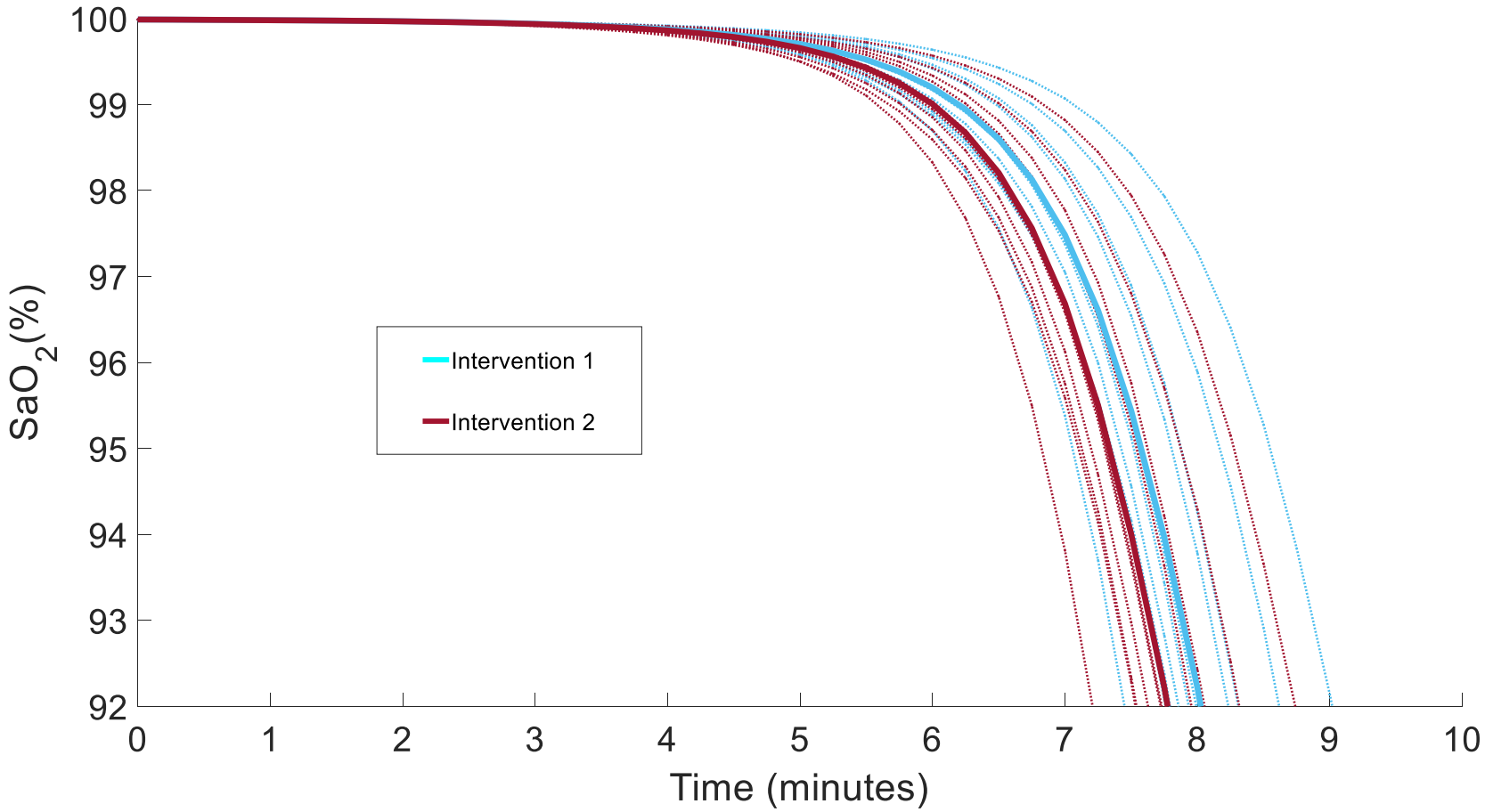


Figure 6.1. Time taken until arterial oxygen saturation (SaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) reached 92% during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

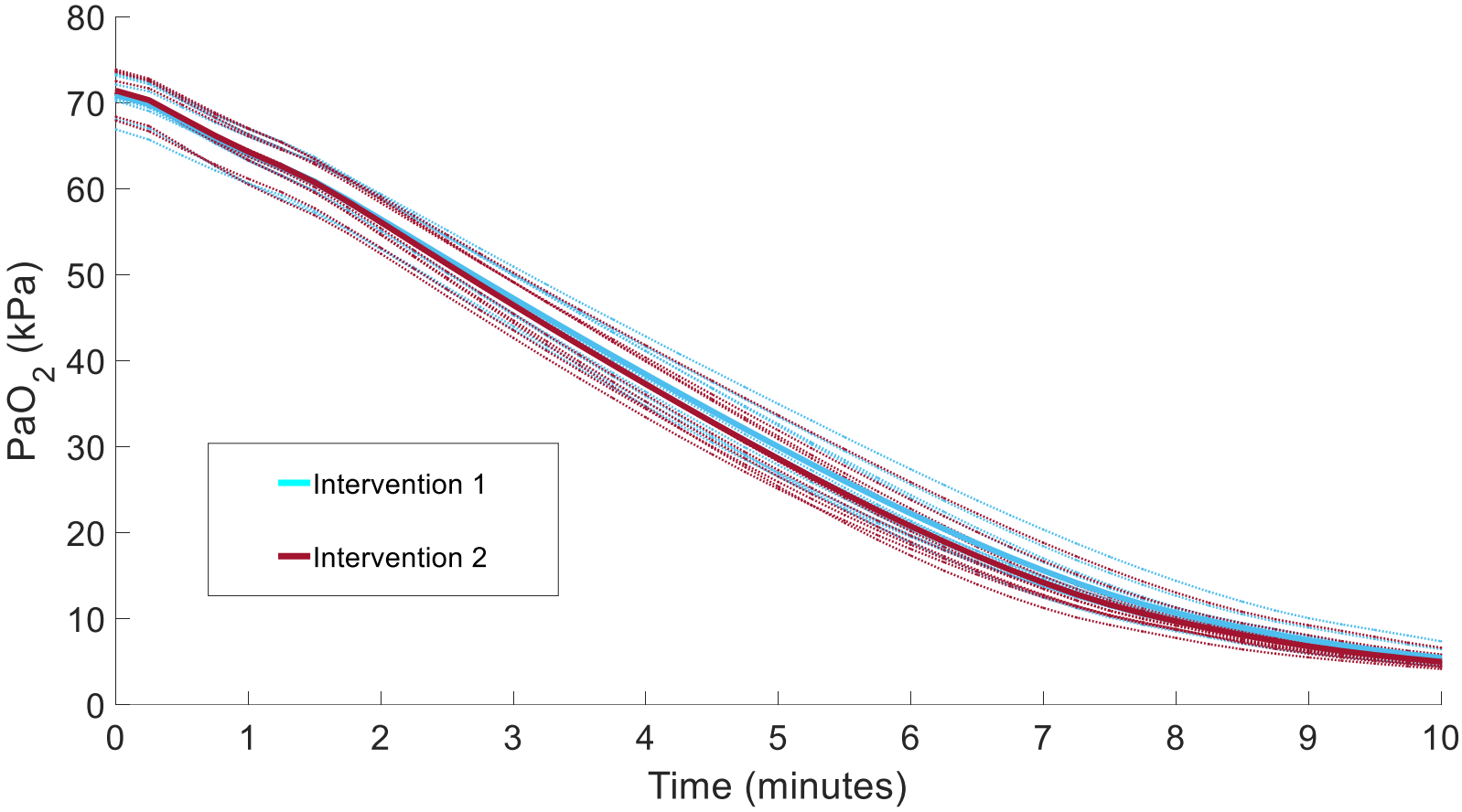


Figure 6.2. Arterial partial pressure of oxygen (PaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap

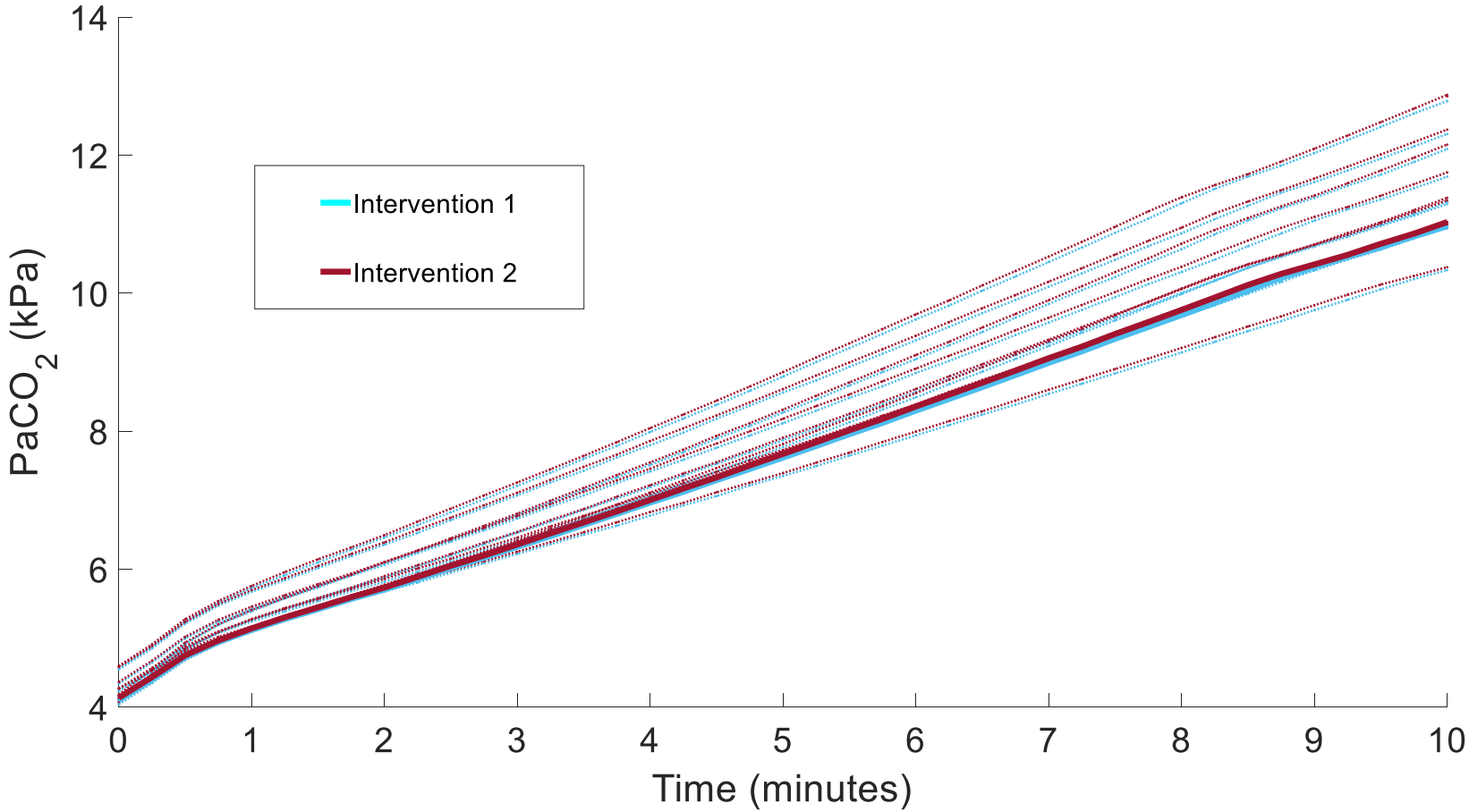


Figure 6.3. Arterial partial pressure of carbon dioxide ($PaCO_2$) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

Obese 2:

Table 6.3. Average of the time taken until arterial oxygen saturation (SaO_2) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) reached 92%, and average of the partial pressure of oxygen (PaO_2) and average of the arterial partial pressure of carbon dioxide ($PaCO_2$) during apnoea. Min 3 is 3 minutes of apnoea, Min 5 is 5 minutes of apnoea, Min 10 is 10 minutes of apnoea. Where the simulation ended before a value could be taken N/A is used.

Obese 2			
Average time (minutes and seconds) to reach SaO_2 92%			
Intervention 1 (elevated followed by supine)	7 minutes and 18 seconds		
Intervention 2 (supine throughout)	7 minutes and 6 seconds		
Average PaO_2 (kPa)			
	Min 3	**Min 5**	**Min10**
Intervention 1 (elevated followed by supine)	52.7	32.4	N/A
Intervention 2 (supine throughout)	51.9	29.5	N/A
Average $PaCO_2$ (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated followed by supine)	6.7	8.1	N/A
Intervention 2 (supine throughout)	6.7	8.2	N/A

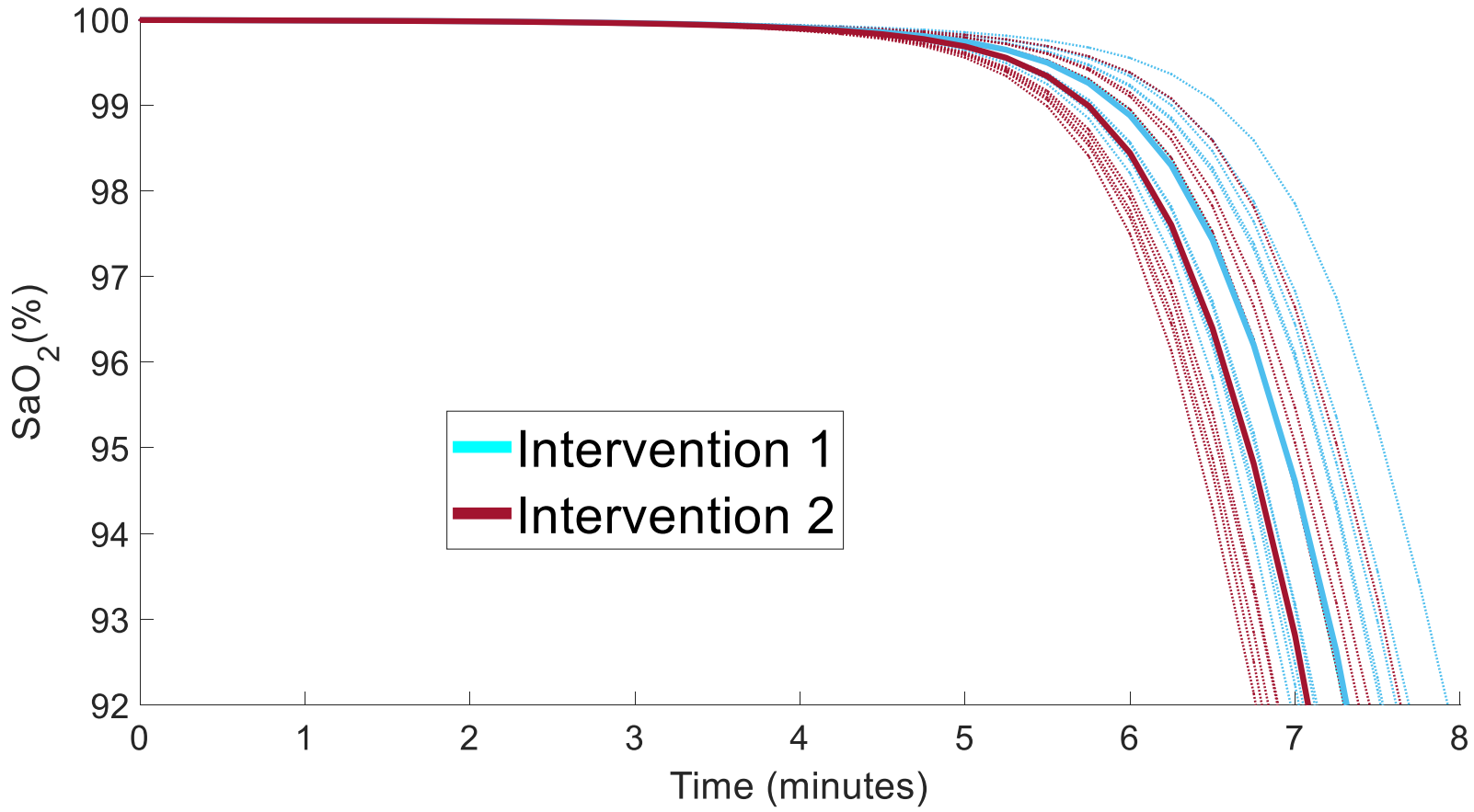


Figure 6.4. Time taken until arterial oxygen saturation (SaO_2) of Obese *2* (BMI 35-39.9 $kg.m^{-2}$) reached 92% during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

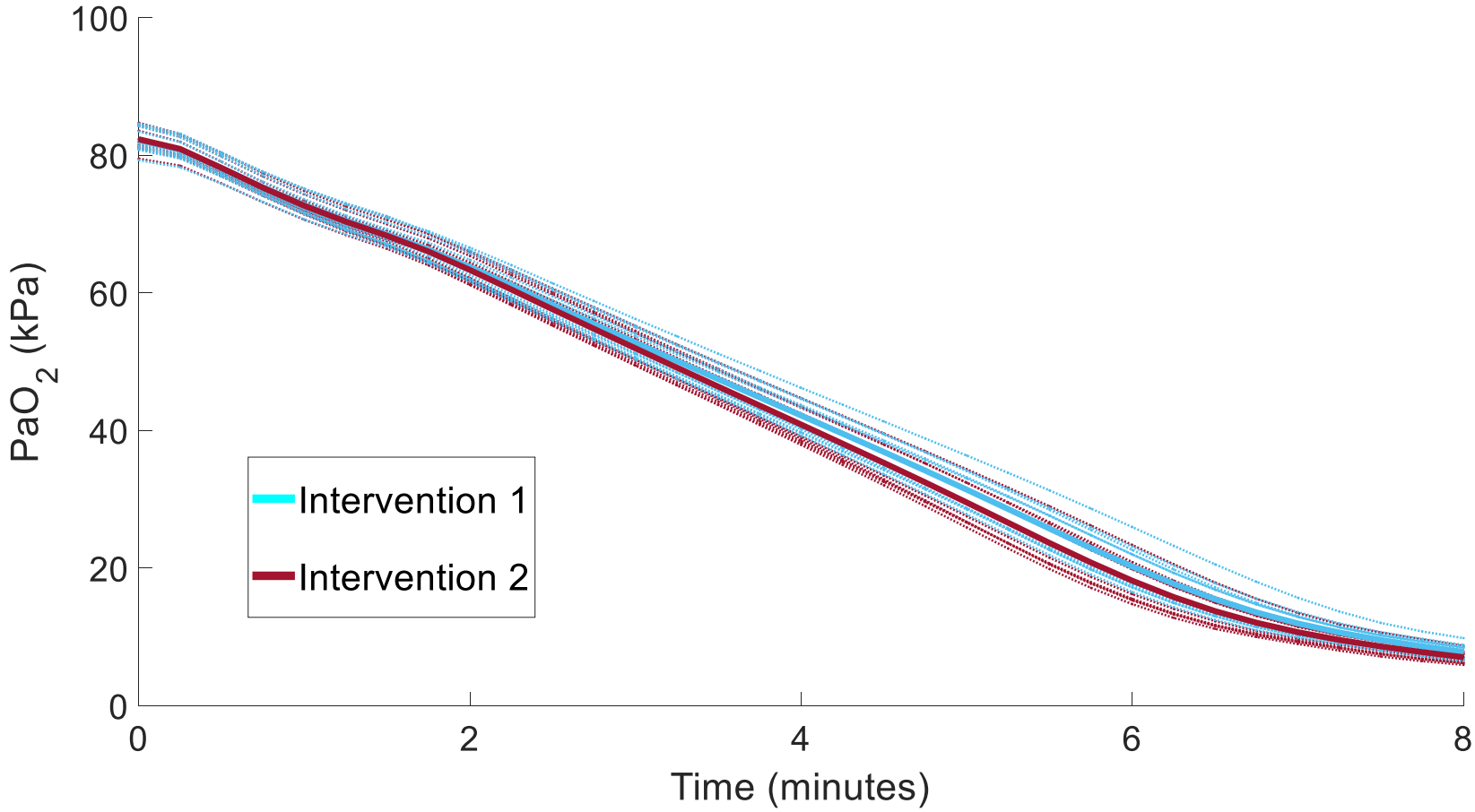


Figure 6.5. The partial pressure of oxygen (PaO_2) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

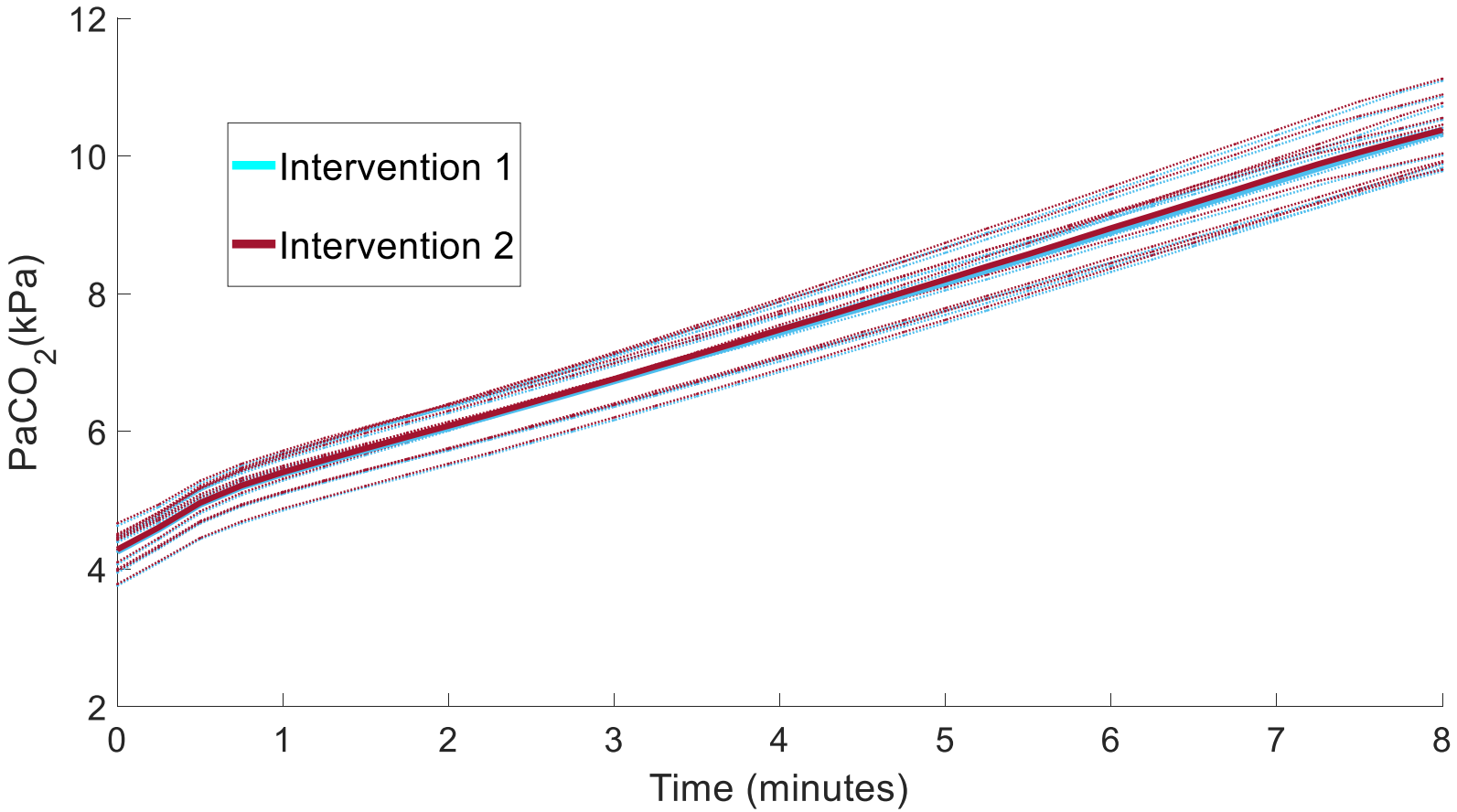


Figure 6.6. The partial pressure of carbon dioxide ($PaCO_2$) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

Obese 3:

Table 6.4. Average time taken until arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) reached 92% during apnoea and the average of the partial pressure of oxygen (PaO_2) during apnoea. Min 3 is 3 minutes of apnoea. Min 5 is 5 minutes of apnoea. Min 10 is 10 minutes of apnoea. Where the simulation ended from reaching SaO_2 92% and so no value could be recorded, N/A is used.

Obese 3			
Time (sec) to reach SaO_2 92%			
Intervention 1 (elevated followed by supine)	5 minutes 21 seconds		
Intervention 2 (supine throughout)	5 minutes 12 seconds		
Average PaO_2 (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated followed by supine)	33.0	14.2	N/A
Intervention 2 (supine throughout)	31.9	13.1	N/A
Average $PaCO_2$ (kPa)			
	Min 3	**Min 5**	**Min 10**
Intervention 1 (elevated followed by supine)	7.5	9.6	N/A
Intervention 2 (supine throughout)	7.5	9.6	N/A

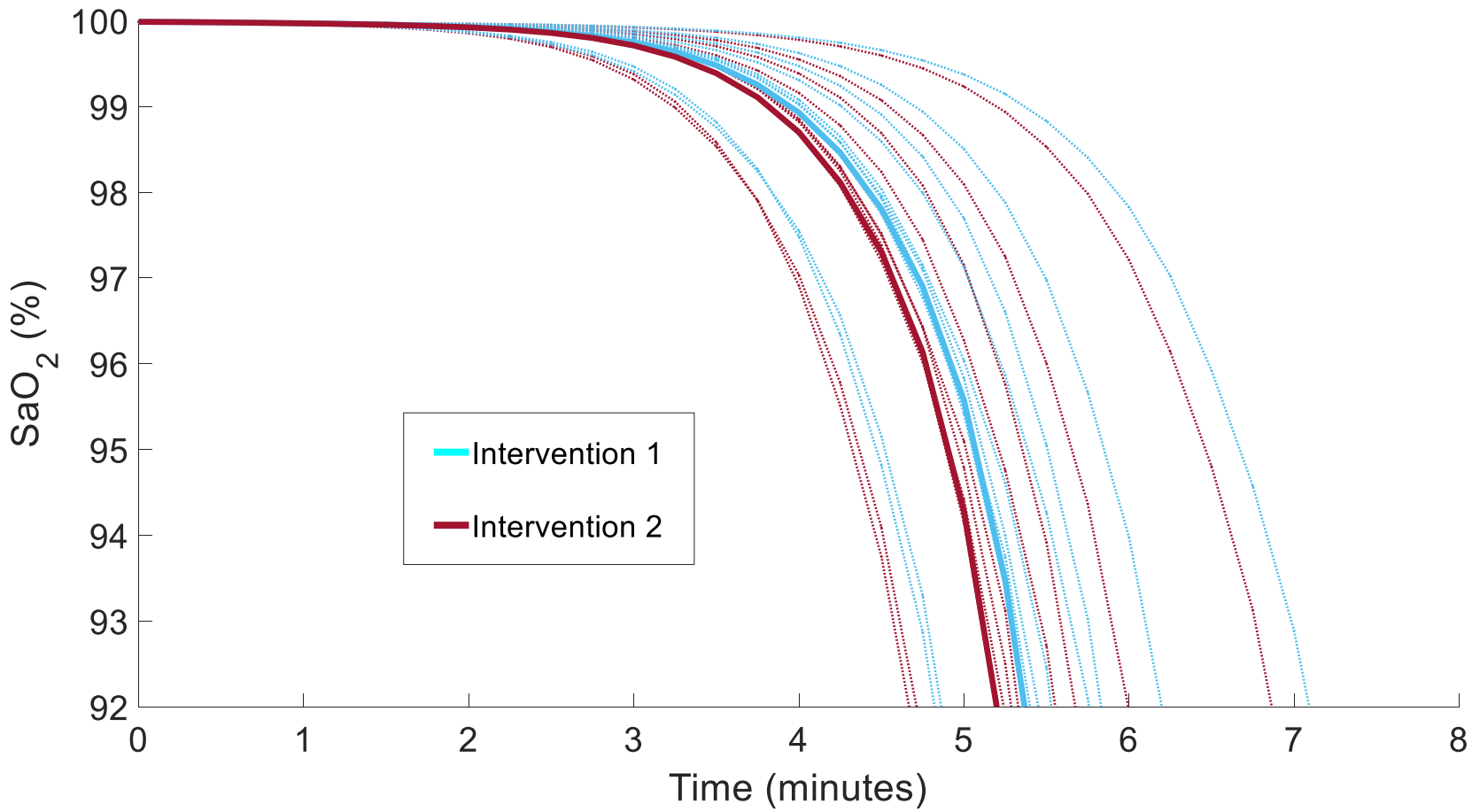


Figure 6.7. Time taken until arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) reached 92% during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

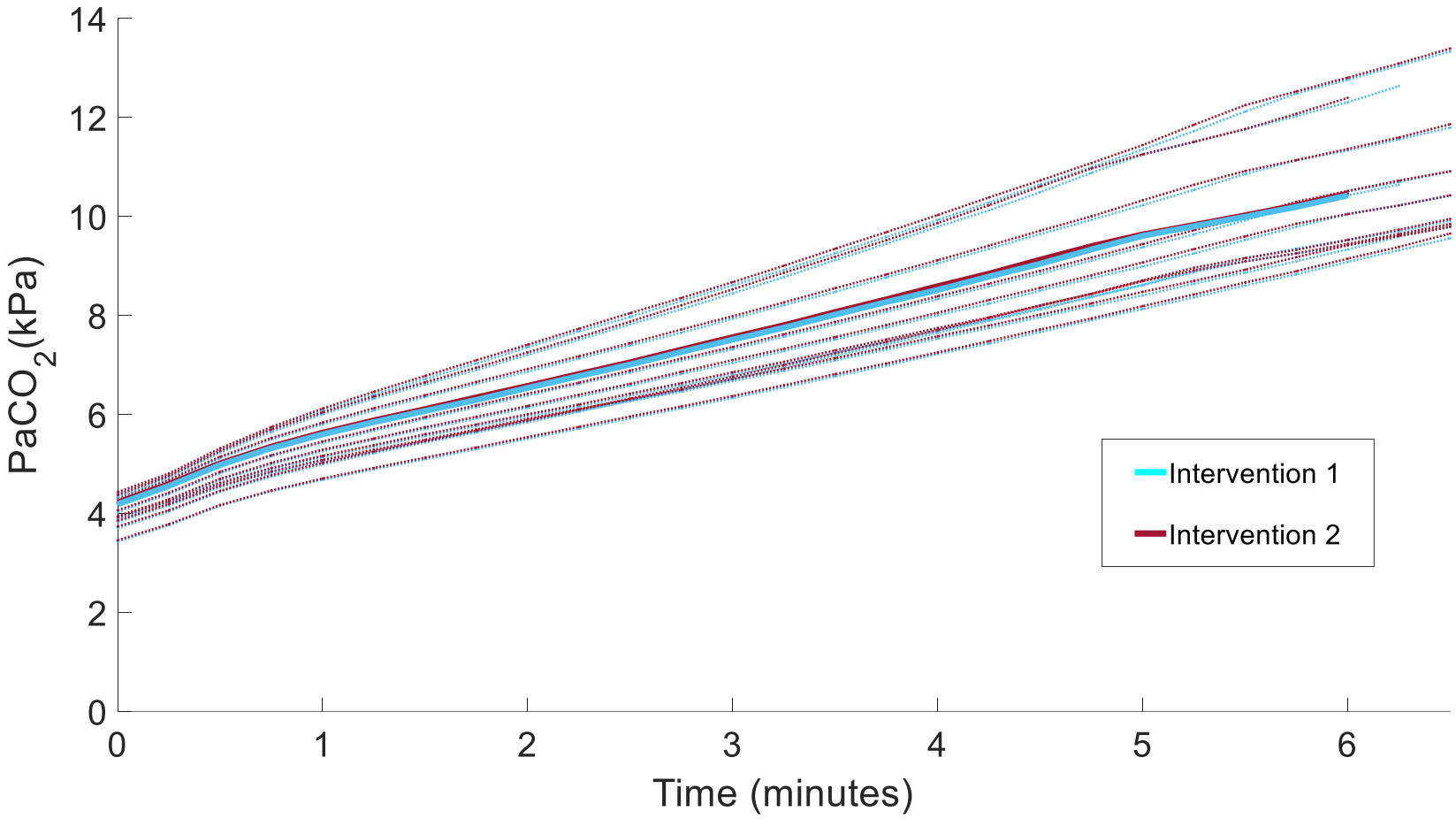


Figure 6.8. The partial pressure of carbon dioxide ($PaCO_2$) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

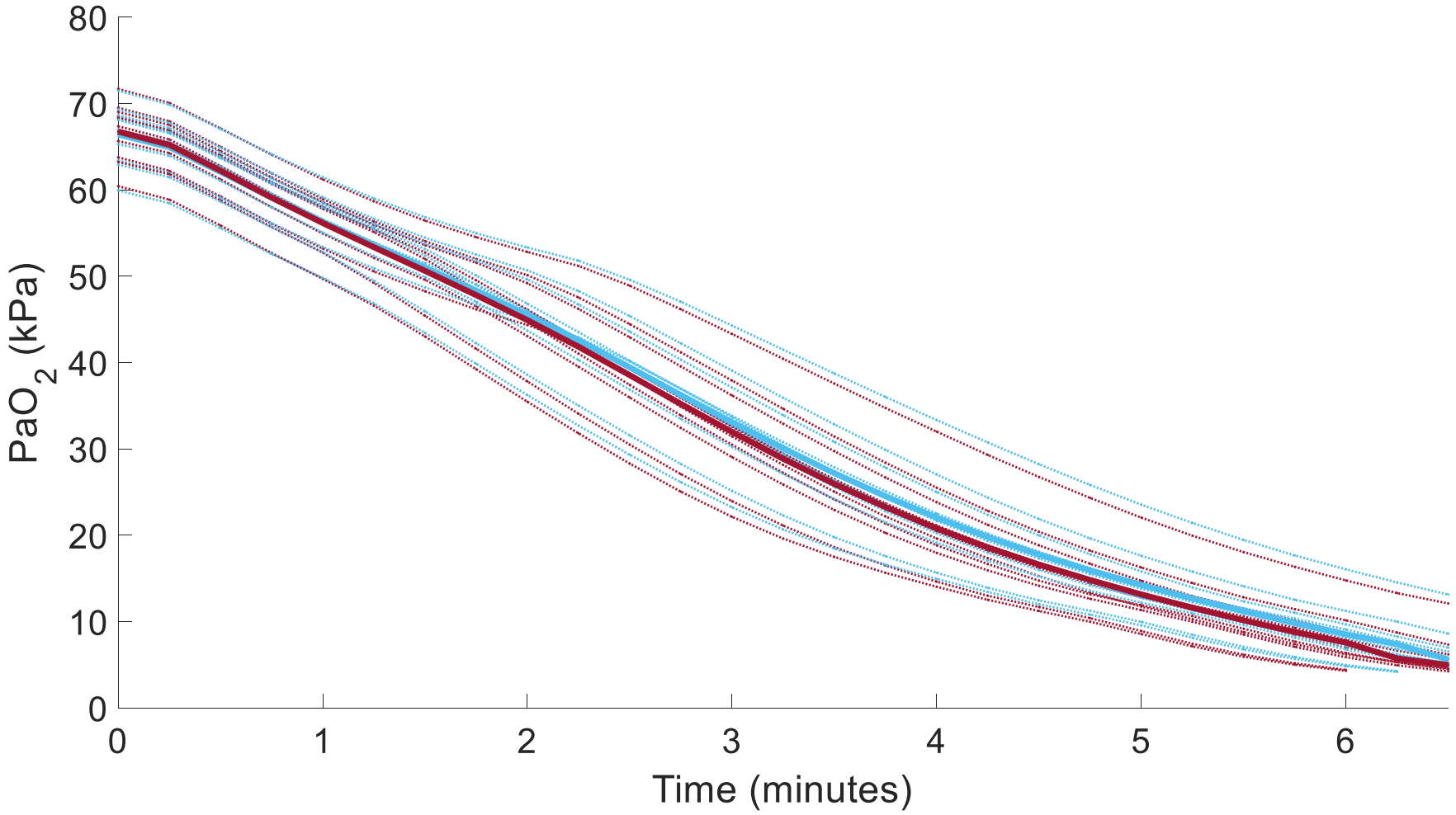


Figure 6.9. The partial pressure of oxygen (PaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

6.5 Discussion

The resulting data suggests that an upright tilt does have an effect on the safe apnoea time, although the benefit is there for all ranges of BMI that were studied, the level of benefit reduced as BMI increased. In Obese 1, which represents patients with the lowest levels of obesity, safe apnoea was improved by 32 seconds. Obese 2 saw an increase of 12 seconds. Obese 3 saw an increase of 9 seconds. The reduced levels of benefit are likely due to the VO_2 increases and the reduced FRC that is present in those with a higher BMI, and so the benefit is minimized. Preliminary protocols run in Chapter 4 show concordance with published data, and the results from Chapter 5 and this study also show a similar trend with those findings. However, this study also shows that HFNO may be able to increase the safe apnoea of patients, and that benefit may be further increased by physically elevating the patient.

There are other known changes in the cardiopulmonary system that occur when the body is elevated, such as thoracic cage compliance, distribution of pulmonary blood flow and lung compliance, all of which were not modelled in this study, however, this is only because the data is currently limited or unavailable. In an ideal scenario, it would have been possible to take a range of measurements from real patients to build an even more robust model. This would strengthen the results even further. Chapter 4, 5, and 6 all showed that an upward tilt of the subject's position results in an increased safe apnoea time, though it indicated weight is a factor to how effective the advantage can be. Additionally, as the results are consistent with similar results found in the literature, there is consistency that suggests there is an element of reliability.

Dixon [140] was able to show that pre-oxygenation in the 25° head-up position achieved an additional 46 seconds of safe apnoea time for those with a BMI>40 Kg m^{-2}, when compared to the supine position. Results in Chapter 4 showed that safe apnoea time in Group 3 (BMI>40 Kg m^{-2}) increased by 26 seconds. In this study elevation increased the safe apnoea time for Group 3 by only 9 seconds, suggesting that the change in CO is either inaccurate or, more likely, requires additional co-changes to also be made to be closure to real world data, which is currently unavailable. Additionally Chapter 4 produced results that also agreed with Subedi [139] who showed that uptilt prolonged the safe apnoea time in non-obese patients. Altogether, this study does adds weight to the importance of a head up tilt, that agreed with previously published data that HFNO may be a beneficial alternative to use for pre-oxygenation. As mentioned before, this study did not look at how long apnoea could continue for if the HFNO was used during apnoea which is one of the strengths of the technique, and this should be studied further when more data becomes available that can result in a stronger more reliable model.

Chapter 7: HFNO and safe apnoea times in old virtual subjects

7.1 Notes on this study

This study has been accepted and presented in a poster presentation at the 33° SMART Conference, Milan, Italy, in May 2022.

7.2 Introduction

As previously discussed in Chapter 2.6, an older patient is more at risk of complications during the placement of an endotracheal tube, due to an array of different medical and mental conditions that have a high comorbidity with old age[18]. Lungs over the age of 20 years (that have no additional pathology) will function well enough to meet the demands of the body[75] but the performance is reduced [74]. This decline in performance is largely associated with the decrease in three variables: the static elastic recoil of the lung, compliance of the chest wall, the strength of respiratory muscles. A result of these changes is an increase in FRC [80] and a reduced metabolic oxygen consumption (VO_2) at rest. However, there is also a decrease in their response to hypoxia and hypercapnia. [74]

This study explores if the changes associated with age could influence the appropriate pre-oxygenation time, based on the understanding that an increased pre-oxygenation time may be required due to a larger FRC. Aged lungs are configured through multiple variables, but the FRC is of particular importance as an increased capacity may require more time to be completely de-nitrogenated. A similar study by Özgültekin has looked at comparing 3

minutes of pre-oxygenation to 4 deep breathes while using a tight fitting face mask [148] as opposed to HFNO, which may be more appropriate given the reported discomfort an older person may have with tight fitting face masks [149], however, these results will be useful for comparison. Older people can be difficult to intubate because of loose skin, but HFNO doesn't require a tight fit to work, and so if it is able to achieve a comparable result to a facemask, then it is arguable that it is the safer and more reliable method for this patient group. Pre-oxygenation normally lasts between 3-5 minutes with HFNO in a healthy younger patient, but there is a question of whether it needs to be 5 minutes or more to compensate for the increased FRC of the older patient group, to allow their lungs to fully de-nitrogenate.

This study explores different, i.e. 3, 5 and 10 minutes, pre-oxygenation times for this older subject group. For comparisons to be made with the literature, simulation with CPAP will also be included.

7.3 Virtual subjects and protocol

As with all the studies in this thesis, the research in this chapter was conducted using the ICSM simulation suite, a full description of which can be found in Chapter 3. For this study, 10 virtual *(in silico)* older subjects were configured as described in Table 3.6. Where values could not be found, or no evidence of change could be found in the literature, the values for a healthy adult patient were used.

The following 4 interventions were run:

Intervention 1: Subjects are pre-oxygenated for 3 minutes, before apnoea, with CPAP at 5cmH_2O, or HFNO.

Intervention 2: Subjects are pre-oxygenated for 5 minutes, before apnoea, with CPAP at 5cmH_2O, or HFNO.

Intervention 3: Intervention 4: Subjects are pre-oxygenated for 10 minutes, before apnoea with CPAP at 5cmH_2O, or HFNO.

As the point of this research is to look at the effects of pre-oxygenation alone, for all 4 interventions, oxygenation is ceased during apnoea.

Pre-oxygenation was simulated at rest, with the subject tidal breathing, a patent upper airway with 5 cmH_2O with 60% O_2 for CPAP or patent upper airway with 3 cmH_2O and 70 L/min of humidified 100% O_2 delivered via the nose for HFNO, for the amount of time indicated by the intervention. To simulate the induction of anaesthesia the FRC was decreased by 20% [63]. This was followed by apnoea, with an unobstructed airway with HFNO determined by the intervention strategy. The simulation ended when the SaO_2 reached 92%, which is considered the end of the safe apnoeic window [9], if the subjects SaO_2 did not reach this level then the simulation was ended after 60 minutes had passed. The results of the SaO_2 were compared across all four interventions.

7.4 Additional protocol comparison:

In the Özgültekin study[148] patients were given 3 minutes of pre-oxygenation with 100% oxygen at 10 L/min and then left to desaturate to 93%. To add

weight to this chapter, Intervention 1 was used which pre-oxygenated subjects for 3 minutes, before apnoea, with CPAP at 5cmH_2O.

Data were recorded every 5 ms from the start of the pre-oxygenation until the protocol was terminated.

7.5 Results

When making a direct comparison between the CPAP technique in the Özgültekin study[148] to the simulation of CPAP we see a similar trend, with a difference of 64 seconds (97%), 55 seconds (95%), and 43 seconds (93%) which can be seen in Table 7.1.

Table 7.1: Average time for arterial oxygen saturation (SaO_2) to reach 97%, 95% and 93% across published literature, simulated CPAP and simulated HFNO for 3 minutes of pre-oxygenation on elderly patients.

	Time taken for SaO_2 to fall after 3 minutes of pre-oxygenating		
SaO_2	**CPAP from literature[148]**	**CPAP simulation**	**HFNO simulation**
97%	5 minutes and 3 seconds	4 minutes	9 minutes 45 seconds
95%	5 minutes and 56 seconds	5 minutes and 1 second	10 minutes and 36 seconds
93%	6 minutes and 19 seconds	5 minutes and 36 seconds	11 minutes and 12 seconds

Table 7.2: Arterial partial pressure oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial oxygen saturation (SaO_2), after pre-oxygenation has completed and apnoea commences, from both literature data and model outputs.

	Average arterial gases and arterial oxygen saturation after pre-oxygenation		
	CPAP from literature	**CPAP simulation**	**HFNO simulation**
PaO_2 (kPa)	34.3	28	53
$PaCO_2$ (kPa)	5.0	5.5	4.6
SaO_2 (%)	99.7	99	99.9

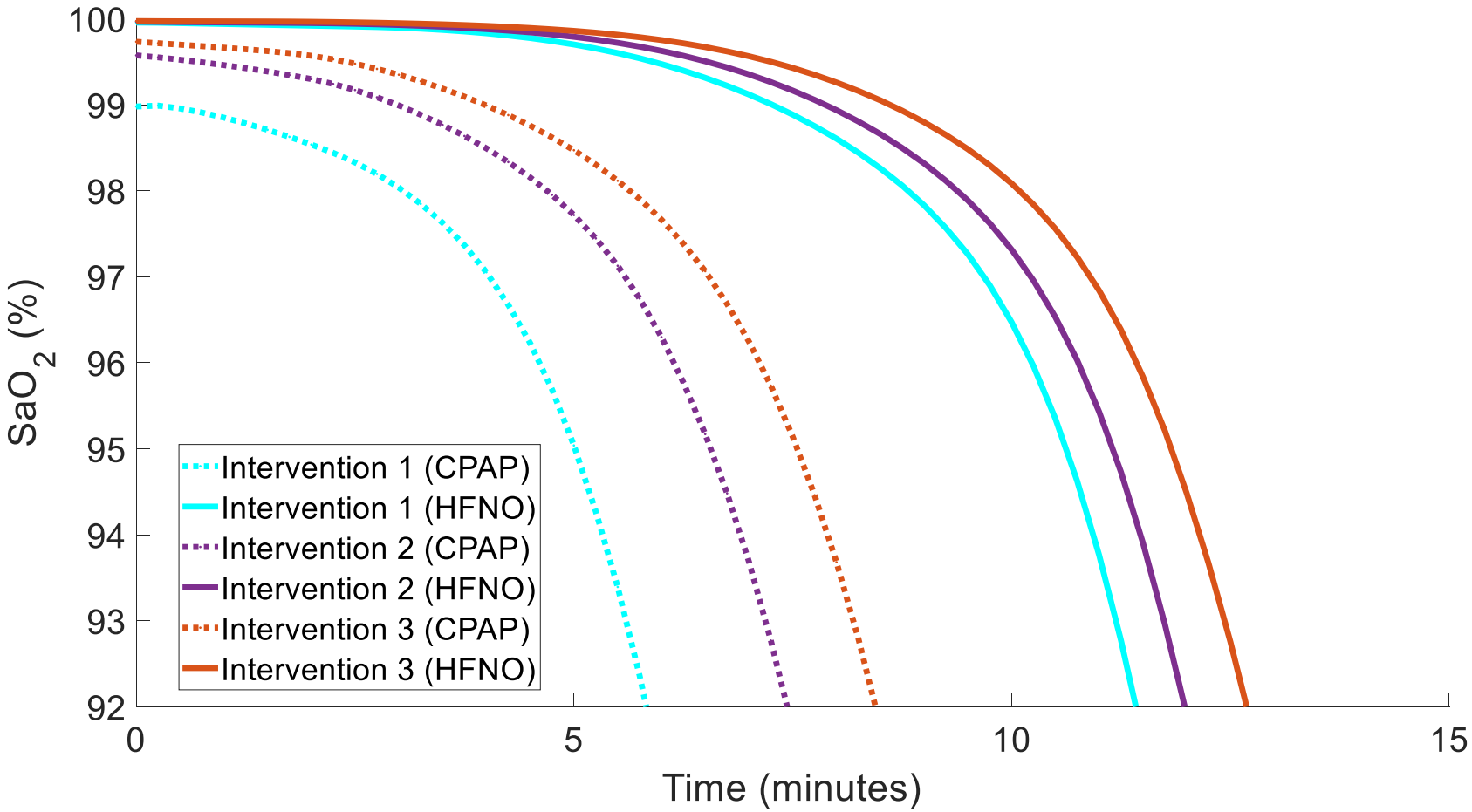


Figure 7.1 Average arterial oxygen saturation (SaO_2) results after pre-oxygenation for 3 minutes for Intervention 1 (average time to 92% was 5 minutes 4 seconds for CPAP and 11 minutes 24 seconds for HFNO), 5 minutes for Intervention 2 (average time to 92% was 7 minutes 27 seconds for CPAP and 11 minutes and 57 seconds for HFNO), and 10 minutes for Intervention 3 (average time to 92% was 8 minutes 27 seconds for CPAP and 12 minutes and 30 seconds for HFNO).

There is an increase in safe apnoea for the older subjects at every stage where the pre-oxygenation time was prolonged.

Table 7.3: Time taken for arterial oxygen saturation (SaO_2) to reach 92% after 3, 5 and 10 minutes of pre-oxygenation with HFNO and CPAP, in minutes(m) and seconds(s).

Time taken for SaO_2 to reach 92% during apnoea						
	CPAP			HFNO		
	Intervention 1	Intervention 2	Intervention 3	Intervention 1	Intervention 2	Intervention 3
Subject 1	4m 3s	5m 28s	6m 21s	10m 26s	10m 56s	11m 3s
Subject 2	5m 11s	7m 6s	7m 54s	10m 35s	11m 8s	11m 34s
Subject 3	5m 46s	7m 25s	8m 15s	10m 38s	11m 12s	11m 38s
Subject 4	6m 0s	7m 42s	8m 29s	10m 47s	11m 25	11m 57s
Subject 5	6m 15s	7m 50s	8m 30s	11m 41s	11m 26s	13m 0s
Subject 6	6m 41s	8m 50s	9m 44s	11m 56s	11m 37s	13m 18s
Subject 7	6m 47s	8m 50s	9m 59s	12m 23s	13m 23s	13m 55s
Subject 8	6m 58s	9m 7s	10m 3s	12m 27s	13m 26s	13m 56s
Subject 9	8m 0s	9m 45s	11m 48s	13m 33s	14m 22s	15m 16s
Subject 10	10m 24s	11m 24s	12m 45s	14m 47s	15m 51s	16m 42s

Three minutes of pre-oxygenation via HFNO gave 684 seconds of safe apnoea time, whereas five minutes was able to achieve 717 seconds (33 seconds more compared to CPAP), and finally ten minutes offered a safe apnoea time of 750 seconds (66 seconds more compared to CPAP) as shown in Figure 7.1.

Increasing pre-oxygenation time from 3 minutes to 5 minutes increased the safe apnoea by 99 seconds, in the CPAP group, but only 33 seconds in the HFNO group. Increasing the pre-oxygenation time from 3 minutes to 10 minutes increased safe apnoea time by 159 seconds in the CPAP group, and by only 66 seconds in the HFNO group.

However, there are diminishing returns: increasing the pre-oxygenation time for HFNO and CPAP by 66% (from 3 to 5 minutes) resulted in an increase of safe apnoea time by 4.8% and 28.4% respectively, when increasing the pre-oxygenation time by a further 100% (from 5 to 10 minutes) the safe apnoea time only increased by 4.6% and 13.4%, respectively. It would appear that CPAP benefits most from increasing the pre-oxygenation time.

Table 7.4: Average arterial partial pressure of oxygen (PaO_2) at 3 minutes, 5 minutes and 10 minutes of apnoea.

	Average PaO_2 (kPa)					
	CPAP			**HFNO**		
	3 min	**5 min**	**10 min**	**3 min**	**5 min**	**10 min**
Intervention 1	23.6	19	10.2	46.8	37.2	19.7
Intervention 2	28.9	22.7	12.7	54.1	44.6	23.4
Intervention 3	34.4	27.1	15.0	58.4	48.9	26.7

Table 7.5: Average arterial partial pressure of carbon dioxide ($PaCO_2$) at 3 minutes (3 min), 5 minutes (5 min) and 10 minutes (10 min).

	Average $PaCO_2$ (kPa)					
	CPAP			**HFNO**		
	3 min	**5 min**	**10 min**	**3 min**	**5 min**	**10 min**
Intervention 1	6.8	7.6	9.6	5.9	6.7	8.7
Intervention 2	6.9	7.6	9.7	5.5	6.3	8.3
Intervention 3	7.0	7.7	9.8	5.0	5.7	7.6

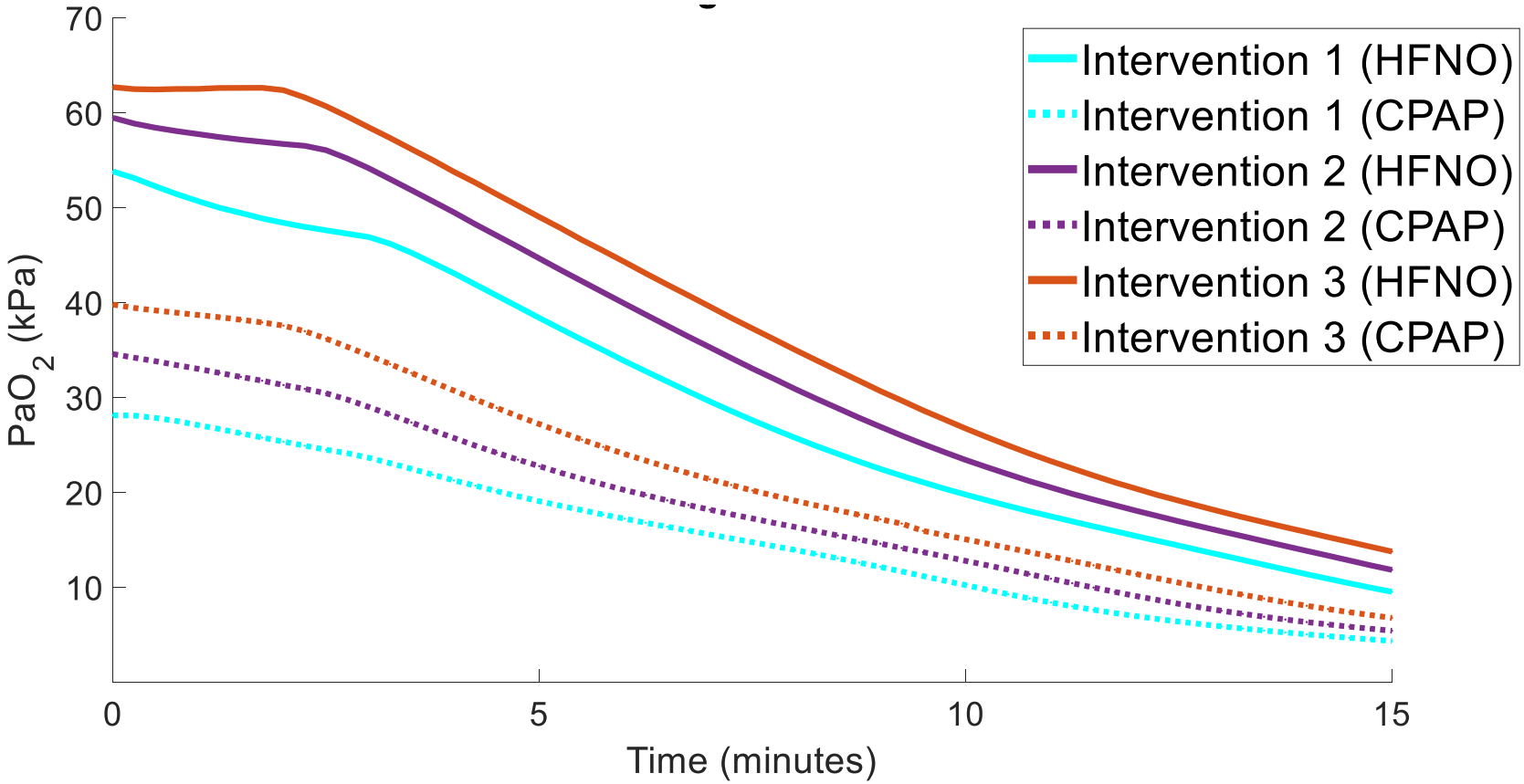


Figure 7.2 Average arterial partial pressure of oxygen (PaO_2) results after 3, 5, or 10 minutes of CPAP or HFNO pre-oxygenation.

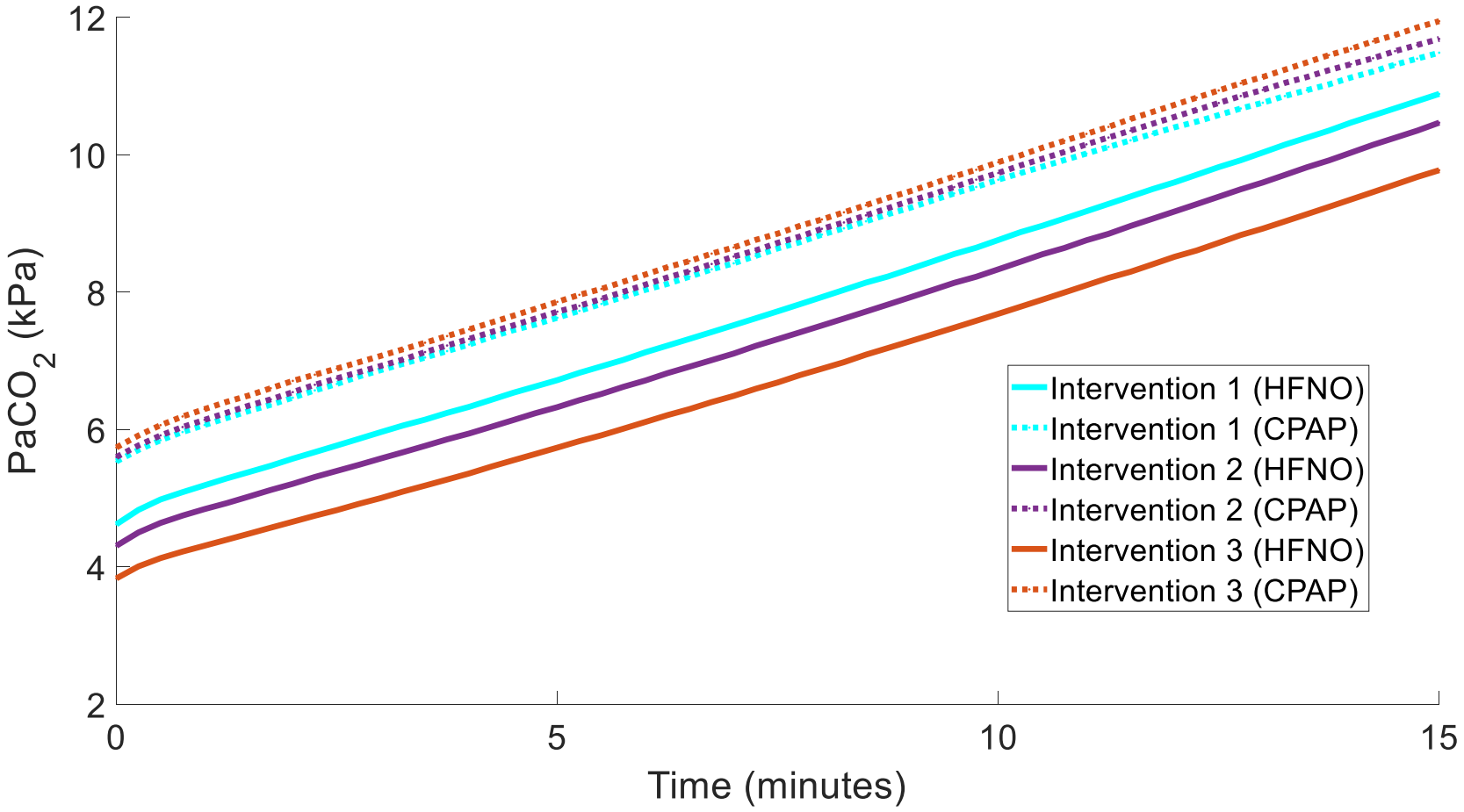


Figure 7.3 Average arterial partial pressure of carbon dioxide ($PaCO_2$) results after 3, 5, or 10 minutes of CPAP or HFNO pre-oxygenation.

Subjects who were pre-oxygenated with CPAP had a higher $PaCO_2$ at the beginning of apnoea compared to those who were preoxygenated with HFNO, across all interventions.

7.5 Discussion

The results of this study suggest that there is merit in increasing the pre-oxygenation times in the older subjects, however, it also highlighted that subjects who are pre-oxygenated using CPAP benefit more from a prolonged pre-oxygenation time, than those who have been pre-oxygenated with HFNO. This may suggest that HFNO is able to achieve a more optimal level of pre-oxygenation sooner than CPAP, perhaps because of its ability to deliver warmed and humidified air at a faster rate than CPAP. It was also noted that subjects who were pre-oxygenated with HFNO started apnoea with a lower level of CO_2, perhaps owing to the carbon dioxide clearance of HFNO.

The dataset for older patients is limited in that it assumes that the older patients are in perfect health. However, older people have very high comorbidities for a range of medical conditions such as asthma, emphysema, chronic bronchitis, bronchiectasis, and chronic obstructive pulmonary disease (COPD)[150]. They are also susceptible to illness of the cardiac system such as coronary heart disease [151]. All these things will affect the efficiency of gas exchange. To increase the accuracy in further research, some of the features of these disease would need to be modelled.

When compared to the work of Özgültekin [148], it would seem that HFNO is more effective for the older person. A direct comparison between the published study, the CPAP modelled in this study *versus* modelled HFNO,

resulted in HFNO producing safer results. Further accuracy and changes could potentially make for more comparative results such as the inclusion of different disease states that are associated with advanced age.

All the data suggests that it could be in the best interest of the older subject to extend their pre-oxygenation times, no matter which technique is being used to pre-oxygenate them, this could increase their safety when on the operating table. As explored in early chapters, there is evidence to show that HFNO is also tolerated better by older patients due to its less intrusive design and because of the physiological changes that are bought about by aging.
It would be wise for future work to be done to validate the model for the older subject and build in additional and optional comorbidities to better represent the demographic such as COPD and heart disease. This would really strengthen the results, but for now it still adds strength to the argument of HFNO being a safer alternative to tight fitting face masks for ventilation in older people and for longer pre-oxygenation times to be utilized.

Chapter 8:
Apnoeic oxygenation using different techniques in pregnancy: a computational modelling study.

8.1 Notes on this study

This study has been published in British Journal of Anaesthesia

Ellis R, Laviola M, Stolady D, Valentine RL, Pillai A, Hardman JG. Comparison of apnoeic oxygen techniques in term pregnant subjects: a computational modelling study. Br J Anaesth. 2022 Oct;129(4):581-587 [105].

It appears here exactly as it did in its final form at publication, including challenges that were posed after publication.

8.2 Introduction

Hypoxaemia during induction of general anaesthesia in the obstetric population has the potential to cause significant Obstetric Anaesthesia maternal and foetal harm. Current recommendations are to use a standard face-mask technique to preoxygenate to an end-tidal oxygen fraction ($F_E'O_2$) of 90%; however, this can be difficult to achieve in clinical practice. [152] Maternal respiratory physiological adaptations seen during the third trimester and the effects of labour increase the risk of rapid deoxygenation and reduce safe apnoea time.[70] Apnoeic oxygenation allows extension of the safe apnoea time. A tight-fitting face mask with continuous oxygen delivery to an open airway can provide apnoeic oxygenation but cannot be utilised during airway instrumentation. Other published apnoeic oxygenation techniques include the use of high-flow humidified nasal oxygen (HFNO) and low-flow nasal oxygen

(LFNO) via standard nasal cannulae. [153] Standard nasal cannulae can also be used in conjunction with face-mask preoxygenation to continue oxygen delivery during tracheal intubation. Studies conducted in healthy pregnant volunteers show that HFNO achieves a lower $F_E'O_2$ after preoxygenation than a face-mask technique. [154-157] After 3 min of tidal breathing, HFNO achieved a mean $F_E'O_2$ of 87% (95% confidence interval: 86-89%), whilst standard face-mask preoxygenation achieved a mean $F_E'O_2$ of 91% (95% confidence interval: 89-93%). [154] Other studies demonstrated that when HFNO is used with up to 20 vital capacity breaths, the median maximum $F_E'O_2$ achieved is 82% with the mouth closed and 73% with the mouth open. [157] Studies have also shown that in healthy pregnant volunteers, even with 8 min of preoxygenation, $F_E'O_2$ 90% is not achieved when using HFNO. [155] However, computational modelling has shown that HFNO extends the safe apnoea time even when an $F_E'O_2$ of only 60% is achieved, when compared with face-mask preoxygenation without apnoeic oxygenation. [158] The use of HFNO presents challenges in the obstetric environment, particularly out of hours or in the emergency setting. Because of the nature of obstetric care, this is often when general anaesthesia is required. Use of HFNO requires specialist equipment, which may be unfamiliar and time-consuming to set up. In contrast, LFNO is cheap, familiar, and quick to set up in an emergency. It allows tight-fitting face-mask preoxygenation, measurement of pre-apnoea $F_E'O_2$, and apnoeic oxygenation even during airway instrumentation. We hypothesised that, in pregnant women, LFNO after face-mask preoxygenation ($F_E'O_2$ 90%) would provide a safe apnoeic

period similar to that provided by HFNO after imperfect preoxygenation ($F_E'O_2$ 60%, 70%, 80%, and 90%).[154,156,157]

8.3 Methodology

We used the Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite, a high-fidelity, highly integrated model of the human respiratory and cardiovascular systems, based on the Nottingham Physiology Simulator, which has been described in detail previously.[159] The ICSM simulation suite has been widely validated and has been used in investigations into preoxygenation and apnoea in adults and pregnancy.[13,92,104,159-161] To model the apnoeic status and the gas exchange accurately during HFNO at a flow rate of 70 L min^{-1} , additional modules have been incorporated, including cardiogenic gaseous oscillations within the tracheobronchial tree and alveoli, complete gas mixing within the respiratory dead space, and pharyngeal pressure oscillations.[13] These have been presented in detail Chapter 3.2. Further details are provided in the supplementary material of our recent paper.[104] Ten virtual subjects were configured to be identical to those used in our previous investigations using established data.[2,159,161-164] Where physiological values could not be obtained for term pregnant subjects, values were extrapolated from a combination of data from non-pregnant subjects and from established physiological theory. Ten subjects were configured in active labour and not in labour, with values of BMI of 24 (BMI 24), 35 (BMI 35), 40 (BMI 40), 45 (BMI 45), and 50 kg m^{-2} (BMI 50). Subjects that were in labour saw an increase in tidal volume, respiration rate, VO_2 and cardiac output. Each subject underwent pulmonary denitrogenation (i.e.

preoxygenation) via tidal breathing with inspired fraction of oxygen (FO_2) 100% to reach $F_E'O_2$ of 60%, 70%, 80%, and 90%. At time zero, apnoea commenced, representing the induction of general anaesthesia. At this time, the functional residual capacity was decreased by 20% in the BMI 24 subject and by 30% in all other subjects, as per published data. [98,162] Also at this time, metabolic oxygen consumption (VO_2) decreased by 65 $mlmin^{-1}$ for all subjects at the onset of apnoea, representing the reduced metabolic oxygen consumption caused by general anaesthesia and muscle paralysis.[165] During apnoea, four interventions were modelled: (i) Complete upper airway obstruction, representing failure of maintenance of a patent airway (ii) No apnoeic oxygenation (i.e. oxygen 21% at the open glottis), representing airway instrumentation without any provision of supplemental oxygen to the airway (iii) Oxygen provision via nasal cannulae (i.e. LFNO), providing periglottic oxygen (FgO_2) 60% or 100% at the open glottis (reflecting perfect insufflation and the effect of dilution with air) (iv) HFNO (i.e. 100% humidified oxygen at 70 $Lmin^{-1}$ HFNO) with an open glottis Apnoea continued until the subject's haemoglobin oxygen saturation (SaO_2) reached 50%. The times taken to reach SaO_2 90% (termed the 'safe apnoea time') and to reach 50% were recorded. Data were recorded every 5 ms from the start of the preoxygenation until the protocol was terminated. The model simulations ran on a 64-bit Intel Core i7 3.7 GHz Windows 10 personal computer, running MATLAB version R2018a.v9 (MathWorks Inc., Natick, MA, USA).

8.4 Results

Times to desaturation (SaO_2 90% and 50%) for the various pre-apnoea $F_E'O_2$ values are shown in **Table 8.1** and **Table 8.2**. Preoxygenation to $F_E'O_2$ 90%, compared with lower values, extended the time taken to reach SaO_2 90% and 50% in all subjects, with exception of those with a BMI of 24 $kg.m^{-2}$ who were not in labour and were receiving HFNO during apnoea (where the safe apnoeic period was very long). In non-labour and in-labour subjects, as BMI increased, there was a reduction in the safe apnoea time. This trend was seen with all apnoeic oxygenation techniques. **Figure 8.1** shows the time course of SaO_2 for two subjects (BMI 24 and BMI 50) in labour. Both HFNO and LFNO apnoeic techniques increased the time to SaO_2 90% and 50% in comparison with absent oxygen supplementation and with upper airway obstruction. This finding was observed in all subjects, in active labour and not in labour. Similar to our previous findings,[104] HFNO alters the speed of haemoglobin desaturation, with slower desaturation with respect to LFNO and all other interventions examined with the same $F_E'O_2$ during the initial fall from SaO_2 100%-90% and the steeper fall from 90% to 50%. Our findings suggest that LFNO offers a slightly smaller but clinically comparable reduction in the speed of desaturation to HFNO. In the subject with BMI 50 kg m^2 who was in labour and preoxygenated to $F_E'O_2$ 90%, LFNO with FgO_2 100% during apnoea had a safe apnoeic period of 9.9 min in comparison with 12 min with HFNO, 7.6 min with LFNO FgO_2 60%, and 3.1 min with no apnoeic oxygenation. For the subjects in labour, LFNO with pre-apnoea $F_E'O_2$ 90% and FgO_2 100% provided a similar or longer apnoeic period to SaO_2 90% and 50% than HFNO with pre-

apnoea $F_E'O_2$ 80%. Moreover, except in BMI 24, LFNO with pre-apnoea $F_E'O_2$ 90% and FgO_2 60% provided a longer safe apnoea time to SaO_2 90% compared with HFNO with $F_E'O_2$ 80% or less **Table 8.2**. A similar trend was seen in the subjects not in labour but only in the subjects with BMI 40 kg m^2 **Table 8.1**.

Figure 8.2 shows the gain in safe apnoea time between HFNO with pre-apnoea $F_E'O_2$ 80% and LFNO (FgO_2 100%) with pre-apnoea $F_E'O_2$ 80% and 90%. With pre-apnoea $F_E'O_2$ 80%, HFNO provided a longer safe apnoea than LFNO in all subjects, although this was less marked with larger BMI. Specifically, with pre-apnoea $F_E'O_2$ 80%, HFNO allows a gain in safe apnoea time ranging from 50.2 to 1.2 min in the subjects not in labour and from 13.5 to 0.7 min in the subjects in labour.

Table 8.1: Time (in minutes) taken to reach arterial oxygen saturation (SaO_2) of 90% and 50% during apnoea for different pre-apnoea end-tidal oxygen fraction ($F_{E'}O_2$) in subjects that were term pregnant but not in labour. FgO_2 (periglottic oxygen); N.A. (not achieved); *t50* represents time from onset of apnoea to SaO_2 50% in minutes; *t90* represents time from onset of apnoea to SaO_2 90% in minutes.

BMI (kg.m^{-2}**)**	**$F_{E'}O_2$ (%)**		**Closed Glottis**		**Glottic FgO_2 21%**		**LFNO, glottic FgO_2 60%**		**LFNO, glottic FgO_2 100%**		**HFNO**	
			t90	***t50***	***t90***	***t50***	***t90***	***t50***	***t90***	***t50***	***t90***	***t50***
24	60		2.1	4.4	2.4	5.0	6.2	14.5	7.0	16.7	66.9	N.A.
	70		3.1	5.4	3.4	6.0	8.5	16.6	9.7	19.4	63.9	N.A.
	80		4.2	6.5	4.5	7.3	11.6	19.8	13.3	22.7	63.8	N.A.
	90		6.5	9.0	7.6	10.6	23.6	31.3	27.7	36.2	65.2	N.A.
35	60		2.0	4.1	2.2	4.5	4.4	11.2	4.9	13.1	19.8	39.6
	70		2.8	4.8	3.0	5.3	5.9	12.9	6.7	15.0	21.4	40.0
	80		3.6	5.7	3.8	6.2	8.1	15.2	9.5	17.6	22.3	41.6
	90		5.3	7.5	6.1	8.8	18.5	25.4	21.9	29.7	34.2	49.0
40	60		1.9	4.2	2.1	4.6	3.8	10.3	4.1	12.5	12.8	28.2
	70		2.6	4.8	2.8	5.2	4.9	11.9	5.5	14.0	13.9	29.1
	80		3.3	5.5	3.4	6.0	6.6	13.6	7.5	15.7	14.9	29.9
	90		4.7	7.1	5.5	8.3	16.8	23.8	20.7	28.8	25.9	37.9
45	60		1.8	3.9	1.9	4.2	3.1	9.2	3.4	10.4	7.9	22.2
	70		2.4	4.4	2.5	4.8	3.9	10.2	4.2	11.7	8.9	23.2
	80		3.0	5.0	2.0	5.4	5.0	11.6	5.7	13.8	9.8	23.5
	90		4.0	6.3	4.4	7.2	12.6	19.5	15.9	24.0	19.5	30.9
50	60		1.6	3.6	1.7	3.9	2.5	7.7	2.6	8.7	3.9	17.7
	70		2.1	4.0	2.2	4.3	3.0	8.5	3.1	9.7	4.3	18.3
	80		2.6	4.5	2.6	4.8	3.6	9.7	3.8	11.4	4.9	19.3
	90		3.3	5.5	3.5	6.07	8.1	16.0	10.2	19.6	12.1	24.8

Table 8.2: Time (in minutes) taken to reach arterial oxygen saturation (SaO_2) of 90% and 50% during apnoea for different pre-apnoea end-tidal oxygen fraction ($F_{E'}O_2$) in subjects that were term pregnant and in active labour. FgO_2 (periglottic oxygen); N.A. (not achieved); *t50* represents time from onset of apnoea to SaO_2 50% in minutes; *t90* represents time from onset of apnoea to SaO_2 90% in minutes.

BMI (kg.m-2)	**$F_{E'}O_2$ (%)**		**Closed Glottis**		**Glottic FgO_2 21%**		**LFNO, glottic FgO_2 60%**		**LFNO, glottic FgO_2 100%**		**HFNO**	
			t90	***t50***	***t90***	***t50***	***t90***	***t50***	***t90***	***t50***	***t90***	***t50***
24	60		2.2	4.4	2.5	4.9	5.6	12.5	6.5	14.8	22.7	39.8
	70		3.1	5.3	3.3	5.8	7.7	14.7	8.9	17.1	23.7	40.5
	80		3.9	6.1	4.1	6.8	10.2	17.1	11.9	19.9	25.4	41.6
	90		5.7	8.1	6.8	9.6	21.1	17.7	25.4	32.7	33.9	47.4
35	60		2.4	4.1	2.6	4.4	5.2	10.2	5.9	12.0	11.4	20.5
	70		2.8	4.5	3.0	4.9	6.3	11.2	7.3	13.2	12.6	21.7
	80		3.1	4.7	3.2	5.2	7.0	11.9	8.1	14.1	14.3	22.9
	90		4.4	6.2	5.2	7.4	15.6	20.7	19.3	24.9	23.6	31.6
40	60		2.2	3.7	2.3	4.0	3.94	8.56	4.3	9.9	8.6	17.5
	70		2.5	4.1	2.6	4.4	4.6	9.5	5.3	11.0	9.4	17.9
	80		2.8	4.3	2.8	4.6	5.1	10.1	6.0	11.7	9.9	18.2
	90		3.8	5.5	4.4	6.4	12.5	17.5	15.6	21.4	18.7	25.7
45	60		2.1	3.6	2.1	3.9	3.0	7.7	3.2	8.9	4.9	15.7
	70		2.4	3.9	2.4	4.2	3.4	8.4	3.7	9.9	5.5	16.2
	80		2.6	4.1	2.6	4.4	3.7	8.9	4.0	10.5	6.3	17.0
	90		3.3	5.1	3.6	5.7	9.3	15.3	11.7	19.0	13.4	22.9
50	60		1.5	3.5	1.6	3.7	2.4	6.8	2.5	7.8	3.7	14.1
	70		2.0	3.8	2.1	4.1	2.8	7.6	3.0	8.9	4.0	14.3
	80		2.4	4.2	2.4	4.5	3.3	8.6	3.5	10.1	4.3	14.7
	90		2.9	4.9	3.1	5.5	7.6	14.3	9.9	17.9	12.0	21.8

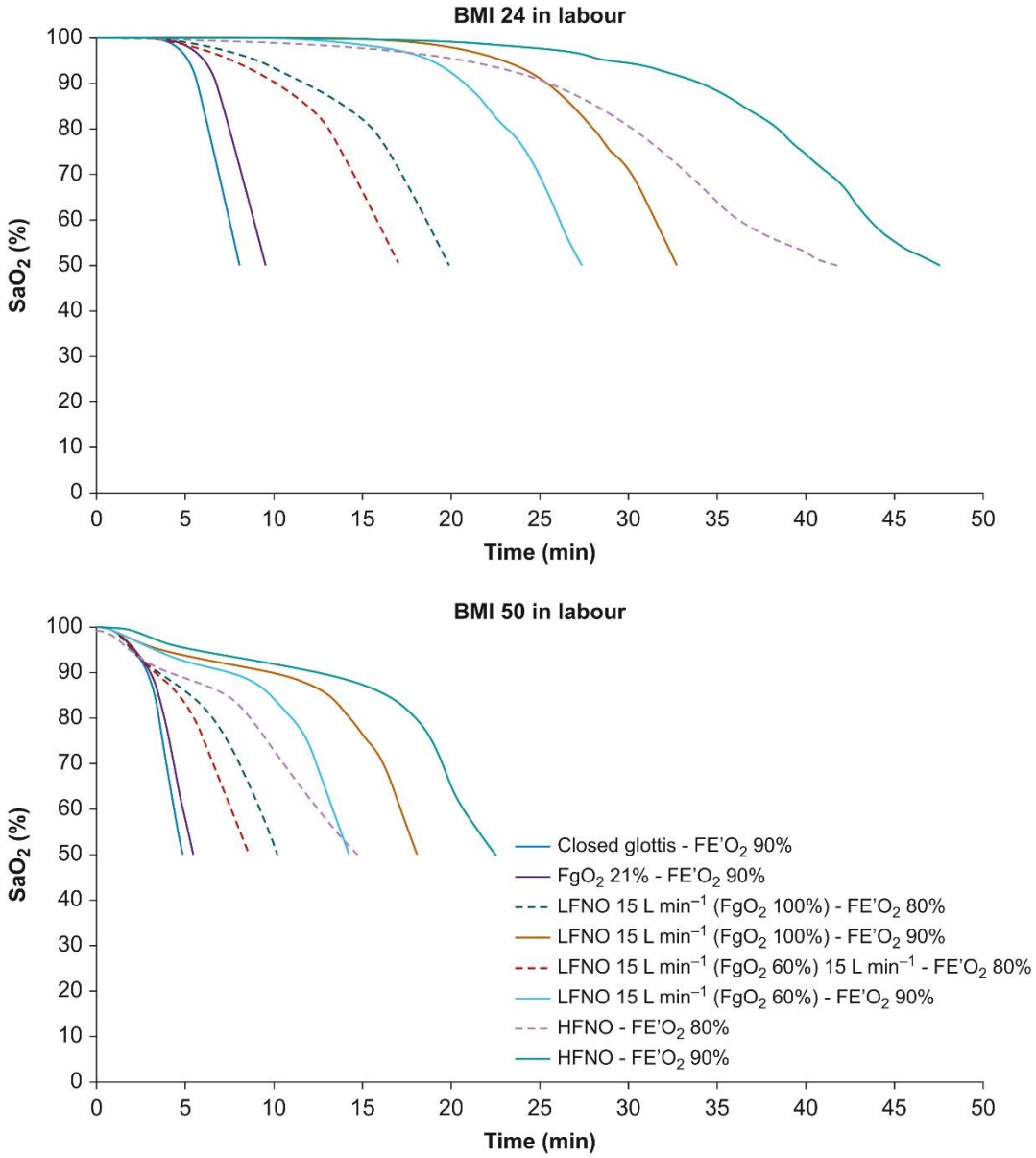


Figure 8.1: Arterial oxygen saturation (SaO_2) during apnoea in the virtual subjects with BMI of 24 and BMI of 50 $kg.m^{-2}$ in labour, with a closed glottis, open airway with fraction of oxygen (FO_2) 21%, LFNO, and HFNO with an end-tidal oxygen fraction ($F_{E'}O_2$) of 80% and 90%. The closed glottis simulates a failure of LFNO and HFNO, whereas FO_2 21% $F_{E'}O_2$ of 90% simulates the face-mask technique during airway instrumentation with no oxygenation supplementation.

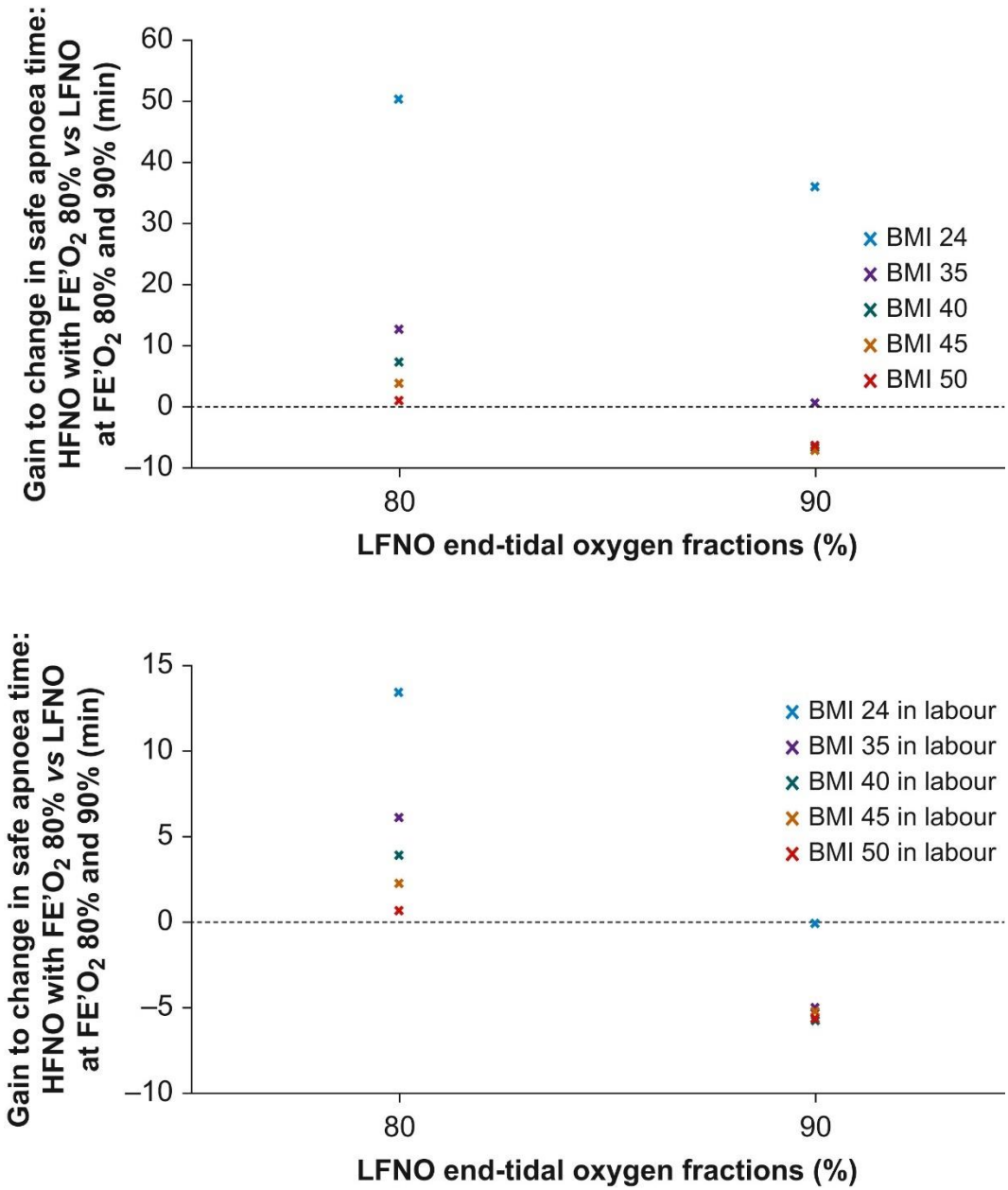


Figure 8.2: Gain in safe apnoea time, calculated as the difference in minutes to reach arterial oxygen saturation (SaO_2) 90% between HFNO with an end-tidal oxygen fraction ($F_{E'}O_2$) 80% and LFNO at $F_{E'}O_2$ 80% and 90% with FiO_2 100% at the open glottis in the subjects not in labour (upper panel) and in labour (lower panel).

8.5 Discussion

The results of this computational modelling investigation demonstrate that, with good preoxygenation ($F_{E'}O_2$ 90%), HFNO provides the most effective apnoeic oxygenation, delivering the longest safe apnoea time in all subjects. These findings concur with other studies [104,160] [10,27,92]. In 2015, Patel and

Nouraei [10] found apnoea times of up to 65 min and no desaturation below 90% using nasal oxygenation at a rate of 70 L/min in adult patients with difficult airways who were undergoing general anaesthesia for hypopharyngeal or laryngotracheal surgery. In 2017, Gustafsson and colleagues,[27] oxygenating adult patients undergoing shorter laryngeal surgery under general anaesthesia with 100% of oxygen 40-70 L/min , found a mean apnoea time of 22.5 (4.5) min. The extension of the safe apnoeic period is reduced when a patient is in labour.[104] However, studies of preoxygenation with HFNO have shown an $F_{E'}O_2$ of 90% is unlikely to be achieved.[154] There are also barriers to the routine use of HFNO. The equipment is time-consuming to set up, requires training, and is likely to impede face-mask ventilation. In contrast, standard nasal cannulae can deliver LFNO, and the equipment required is cheap, accessible, familiar, easy to set up, and does not impede face-mask ventilation. LFNO also can be provided during face-mask preoxygenation, facilitating measurement of $F_{E'}O_2$. We found that LFNO after preoxygenation to $F_{E'}O_2$ 90% produced equivalent or better safe apnoeic times compared with HFNO with preoxygenation to $F_{E'}O_2$ of 80% in all subjects. Because of the challenges of achieving $F_{E'}O_2$ 90% with HFNO, LFNO may provide a suitable alternative for apnoeic oxygenation, with lower cost and ease of use. Use of LFNO to achieve comparable apnoeic oxygenation is dependent on achieving a preoxygenation $F_{E'}O_2$ of 90% with a face-mask technique. Under clinical study conditions, only 70% of term pregnant women were able to achieve $F_{E'}O_2$ 90% with a face-mask technique and up to 20 vital capacity breaths, and an average of 3.6 min of tidal breathing was needed to

achieve $F_{E'}O_2$ 90% in 90% of term parturients. [154-157] Therefore, in real-world clinical situations, $F_{E'}O_2$ 90% may be difficult to achieve, particularly in emergency scenarios, where the parturient is in pain or distress and maintaining a tight face-mask seal becomes difficult. A more clinically relevant comparison of apnoeic oxygenation between LFNO and HFNO may be from a baseline of $F_{E'}O_2$ 80% for both techniques, instead of 90% **Figure 8.2.** In this situation, our data suggest that the extension in safe apnoea time seen with LFNO will be less than HFNO. At a smaller BMI, HFNO may provide twice the time to SaO_2 90% compared with LFNO at the same starting $F_{E'}O_2$. There are, however, diminishing gains in safe apnoeic time using HFNO as BMI increases. The increase in metabolic oxygen consumption that occurs with increasing BMI and active labour may explain this reduction in safe apnoea time. In the subject with the largest BMI (50 kg m^2), both HFNO and LFNO provided a comparatively small increase in safe apnoea time, as seen in **Figure 8.1**, even with preoxygenation to $F_{E'}O_2$ 80%. This group is also at risk of failure of apnoeic oxygenation because of the increased risk of airway obstruction and increased shunt fraction caused by alveolar collapse. This scenario was modelled within the study (as airway obstruction), and when this occurs, a very short safe apnoeic period follows. There is also an increased risk of failed intubation and difficult face-mask ventilation in this group, amplifying the risks. The modest increase in safe apnoea time gained with HFNO or LFNO, whilst buying critical thinking time, may not prevent the need for attempted rescue ventilation if intubation requires multiple attempts or fails in this group. LFNO provides easier access to bag-and-mask rescue ventilation, and

unlike HFNO, which needs to be removed to allow safe bag-mask ventilation, LFNO can be left in place to restart apnoeic oxygenation during further attempts at intubation. As such, despite the modest increase in safe apnoeic times, LFNO may be a better strategy for providing apnoeic oxygenation in subjects with large BMI. Consequently, we recommend that HFNO should be used with caution in those who have high BMI; there may be more benefit in LFNO techniques that allow the measurement of $F_{E'}O_2$ during preoxygenation and the use of rescue bag mask ventilation. One assumption within this simulation model is that oxygen 100% may be provided at the glottis when LFNO at 15 L/min is administered. To the authors' knowledge, there are no data to refute or confirm this. Previous studies in non-pregnant patient groups have shown that oxygen 15 L/min via standard nasal cannulae achieves FgO_2 60% at the glottis during 'quiet breathing', as inspired oxygen is diluted by inspiration of surrounding air.[166] We accounted for the effect of this dilution in LFNO by creating an alternate model with FgO_2 60% at the glottis during apnoea. With pre-apnoea $F_{E'}O_2$ 90%, there is still benefit in using 'imperfect' LFNO (i.e. FgO_2 60%), with only small reductions in the safe apnoeic period compared with 'perfect' LFNO (i.e. FgO_2 100%). The extension in safe apnoea remains greater than that seen with HFNO with pre-apnoea $F_{E'}O_2$ <90%. During apnoea, air is unlikely to be entrained to dilute inspired oxygen, so we would expect the glottic FgO_2 to be higher than 60%. Further work is required to establish the FgO_2 achieved at the glottis during apnoea when using LFNO.

This study utilised computational modelling to investigate an issue that is clinically difficult to address. The assumptions built into this model are a

potential weakness of this approach; however, the simulation suite has been validated within obstetric and non-obstetric populations.[13,92,159-161] Studying intentionally inadequate preoxygenation and the limits of apnoeic hypoxaemia in the obstetric population would be ethically unacceptable; this modelling technique provides a safe and reproducible approach to this challenging issue.

In summary, our modelling investigation shows that whilst high-flow nasal oxygenation with good preoxygenation ($F_{E'}O_2$ 90%) provides the most effective extension in safe apnoea time, using low-flow nasal oxygenation after good preoxygenation ($F_{E'}O_2$ 90%) provides a comparable benefit to that provided by high-flow nasal oxygenation with preoxygenation to $F_{E'}O_2$ less than 90% (the expected result in clinical situations). The ease of performing face-mask ventilation during low-flow nasal oxygenation apnoeic oxygenation and the ability to monitor $F_{E'}O_2$ during preoxygenation are likely to provide clinically significant benefits, especially in subjects with BMI40 kg m^2.

8.6 Commentary on the Publication

The following is a printed commentary made by Lyons C:

Ellis and colleagues published a computer modelling exercise in this journal on apnoeic oxygenation at induction of anaesthesia for parturients. They concluded that there is likely to be clinical benefit to using low-flow nasal oxygen (LFNO) over high-flow nasal oxygen (HFNO) in this population. I have a number of concerns regarding the methodology used, and I disagree with the conclusion reached.

The authors stated that 'with good preoxygenation ($F_{E'}O_2$ 90%), HFNO provides the most effective apnoeic oxygenation, delivering the longest safe apnoea time in all subjects'. However, the authors deemed that 'an $F_{E'}O_2$ of 90% is unlikely to be achieved' with HFNO. As a result, from the multiple comparisons made, a favoured comparison that utilised an $F_{E'}O_2$ of 80% for HFNO and FE'O2 90% for LFNO was selected. As $F_{E'}O_2$ was the data input used to reflect pre-oxygenation efficacy in this study, the oxygenation of the HFNO group was modelled as inferior to the LFNO group at the onset of apnoea. This resulted in a shorter time to desaturation in the HFNO group despite apnoeic oxygenation. A key question is therefore, 'Was it appropriate to designate HFNO as an inferior pre-oxygenation device by assigning a lower $F_{E'}O_2$ value?'

The authors reference four studies to support the judgement that an $F_{E'}O_2$ of 80% rather than 90% is the best reflection of pre-oxygenation efficacy with HFNO.[154-157] However, $F_{E'}O_2$ measurement in these studies did not take place in a manner consistent with the clinical use of HFNO. In all cases, HFNO delivery was interrupted; a period of breath-holding was requested; followed by the application of a nose clip in two studies [154,155]; and finally, exhalation into an alternative device (face mask or mouthpiece). None of the studies used the LFNO plus face mask combination, the method advocated by the modelling, and one study did not have a face mask comparator in any form.[156] One study allowed as few as five vital capacity breaths for pre-oxygenation 'because three to five breaths is often employed by clinicians prior to emergency induction of anaesthesia'[157], also contrasting with the tidal respiration used in this modelling. Additionally, none of the studies correlated

$F_{E'}O_2$ measurement with PaO_2 attained, safe apnoea time, or incidence and severity of hypoxaemia. None of the assessments took place at induction of anaesthesia. Only one study had randomised methods, [154] and not-withstanding the limitations mentioned previously, reported mean $F_{E'}O_2$ values of 87.4% and 91% for HFNO and face-mask pre-oxygenation, respectively, differing from the 80% and 90% inputs used to form the headline comparison in this modelling study.

A recent RCT showed that pre-oxygenation with HFNO was equivalent to that with a face mask when time to desaturation was used as the endpoint in healthy patients attending for elective surgery.[167] All oxygenation devices were removed at the onset of apnoea such that the outcome could be attributed to the pre-oxygenation period alone. A third group showed enhanced pre-oxygenation through the use of an HFNO plus mouthpiece combination, which may be of added benefit to obstetric patients who often become familiar with a mouthpiece during labour and who could pre-oxygenate autonomously by this method, allowing the anaesthetist to undertake another task, such as preparation of medicines or performance of neuraxial block.

The authors of this modelling study state that HFNO use is limited by specialist equipment, which may be unfamiliar and time-consuming to prepare. The device is easy to assemble, and this can be done in advance rather than at the time of need. The use of a face mask for pre-oxygenation or bag-mask ventilation does not preclude the use of HFNO during apnoea. This can be achieved by resting the cannulae on the forehead when mask use is desired

and lowering them on the nares before airway instrumentation. A novel nasal oxygen delivery system, Optiflow™ Switch (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) enables concomitant face mask and HFNO use. When a face mask is applied, the nasal tubing flattens to improve the seal, and the device temporarily diverts oxygen away from the nasal cannulae to avoid barotrauma, and automatically restores nasal oxygen delivery upon removal of the face mask.

The authors state that 'studying intentionally inadequate preoxygenation and the limits of apnoeic hypoxaemia in the obstetric population would be ethically unacceptable' and that their modelling 'provides a safe and reproducible approach to this challenging issue'. However, comparing the efficacy of optimised face mask and HFNO pre-oxygenation in the obstetric environment, both commonly undertaken techniques, is ethical and a more appropriate arena for determining their relative risks and benefits. In my view, apnoeic oxygenation with standard nasal oxygen should not be judged as superior (or equivalent) to apnoeic oxygenation with HFNO on the basis of this study.

8.7 Response to the commentary

The following was the printed response to this commentary:

We thank Lyons for his recent comments on our work. First, we should state that our research group has no bias against high-flow nasal oxygen (HFNO); indeed, our group has previously published research highlighting its potential benefits.[104,168]

The key concern raised by Lyons is the use of pre-oxygenation endpoints that differ between HFNO and tidal pre-oxygenation ($F_{E'}O_2$ 80% vs 90%, respectively). Lyons suggests that our findings might be substantially affected by that decision and suggests that the assumption of a lower alveolar oxygen content after HFNO pre-oxygenation is not reasonable.

As we described, a range of pre-oxygenation endpoint $F_{E'}O_2$ values were used, based carefully on the evidence available in pregnant subjects.[154-157] These studies demonstrated lower $F_{E'}O_2$ after HFNO pre-oxygenation in comparison with tidal pre-oxygenation. Whilst we appreciate that measurement of $F_{E'}O_2$ requires interruption of HFNO, we considered that this would not substantially affect alveolar oxygen content; we do acknowledge that this assumption should be tested with further research.

The cited evidence indicates the possibility that clinicians may, unknowingly, be providing inadequate pre-oxygenation with HFNO before induction of anaesthesia, due at least in part to the inability to measure the completeness of alveolar denitrogenation. Whilst $F_{E'}O_2$ cannot be considered a perfect representation of the completeness of alveolar denitrogenation, it remains the most useful (and most accurate) method in clinical practice.

We stand by our decision to use $F_{E'}O_2$ 80% as the pre-oxygenation endpoint during HFNO, and we trust that this response allays concerns regarding the use of that value in our modelling investigation. However, we do acknowledge that further work is needed to establish the profile of alveolar denitrogenation during various methods of pre-oxygenation, including HFNO.

8.8 Editorial accompaniment

The publication was also printed with the following editorial companion [169]:

Pregnant women are at high risk of developing hypoxaemia during rapid-sequence induction of anaesthesia, with haemoglobin oxygen saturation decreasing to <90% in up to 17% of women.[170,171] Failed or difficult tracheal intubation, high BMI, pre-eclampsia, and labour are recognised risk factors for hypoxaemia. Preoxygenation or peri-intubation oxygenation techniques such as oxygen administration using a face mask, high- or low-flow nasal cannula, and gentle mask ventilation (as opposed to apnoeic oxygenation) have recently been recommended to reduce the risk of hypoxaemia during induction of general anaesthesia, especially in the setting of emergency Caesarean delivery.[172,173]

Clinical studies comparing methods for peri-induction oxygen administration in pregnant women are challenging to perform because of ethical concerns. It is difficult to obtain informed consent for study participation in the setting of emergency Caesarean delivery. Indeed, these studies are also difficult to perform in the non-pregnant population. To address this challenge, an investigator group has used a high-fidelity model of the human respiratory and cardiovascular system based on the Nottingham Physiology Simulator to study apnoeic oxygenation in non-pregnant and pregnant patients.[159] In the current issue of the British Journal of Anaesthesia, this group has published a welcome addition to their previous studies, specifically modelling and comparing the apnoeic administration of low-flow (LFNO) and high-flow nasal oxygen (HFNO) in simulated pregnant patients.[105]

Preoxygenation with a tight-fitting mask using oxygen flows of 10–15 L/min, optimally to achieve an end-tidal oxygen concentration (ETO_2) of 90% before intravenous induction of anaesthesia, is arguably the gold standard preoxygenation technique during rapid-sequence induction of anaesthesia. However, evidence suggests that an ETO_2 of 90% is frequently not achieved.[174] Poor preoxygenation technique (poor mask seal, inadequate time) can contribute to the high incidence of hypoxaemia during rapid-sequence induction of anaesthesia. Additional factors might include poor oxygen delivery during the initial period of apnoea (apnoeic oxygenation) and no oxygen delivery after muscle relaxation is achieved and the face mask is removed to facilitate laryngoscopy. The resultant hypoxaemia can adversely affect both the mother and (already compromised) fetus. Thus, investigators have searched for other techniques to mitigate oxygen desaturation and improve safety for the mother and fetus.

Historically, mask ventilation during rapid-sequence induction has been discouraged because of the fear of causing gastric insufflation and subsequent increased risk of pulmonary aspiration. However, studies have shown that if the peak inspiratory pressure during mask ventilation is limited to <20 cm H_2O, with or without correctly applied cricoid pressure, gastric insufflation does not occur.[175,176] Therefore, gentle mask ventilation was recommended in the 2015 Obstetric Difficult Airway Guidelines published by the Obstetric Anaesthetists' Association (OAA)/Difficult Airway Society (DAS) as part of the master algorithm for safe obstetric general anaesthesia.[152]

In the non-obstetric population, evidence suggests that the use of LFNO can have beneficial effects in prolonging the safe apnoea period.[153] Computational modelling studies using simulated pregnant women also support this strategy.[168] The 2015 OAA/DAS Obstetric Difficult Airway Guidelines recommended the use of LFNO at 5 L/min.[152] Use of LFNO with oxygen flows of 10–15 L/min could be more effective than 5 L/min,[168] but, unfortunately, non-humidified oxygen flows of 10–15 L/min can cause discomfort and is poorly tolerated in awake patients.[177] Currently no clinical studies in pregnant women have compared LFNO at 5, 10, or 15 L/min.

In non-obstetric settings, evidence is growing to support the use of HFNO during induction of anaesthesia.[167,178-180] However, the results of clinical trials in pregnant women have been less consistent in showing benefit. Four trials comparing preoxygenation with face mask to HFNO failed to show superiority of HFNO, and a high proportion of patients failed to attain ETO_2 >90%. [154-157] A possible explanation is the higher oxygen consumption in pregnancy and the entrainment of room air, resulting in lower ETO_2 compared with face mask preoxygenation. However, a limitation of these studies is the technical difficulty of measuring ETO_2 during the use of HFNO.

In contrast, studies that have measured arterial blood gases in pregnant and non-pregnant patients have demonstrated higher oxygen partial pressures after 3 min of preoxygenation with HFNO compared with face mask preoxygenation.[167,181,182] Currently, only one small study (n=34) assessed this outcome in pregnant women; the investigators concluded that

preoxygenation with HFNO provided superior oxygenation during rapid-sequence induction compared with face mask preoxygenation.[181] A limitation of the study was the lack of inclusion of women with morbid or supermorbid obesity. Thus, the computer modelling study by Stolady and colleagues[104] published last year in the British Journal of Anaesthesia, and the current study by Ellis and colleagues,[105] are welcome additions to the literature. Modelling in the first study showed that HFNO was superior to face mask preoxgenation with ETO_2 values ranging from 60% to 90% with the mouth both open and closed, although the improvement in safe apnoea time (time for saturation to reach 90%) was significantly less in women with high BMI.[104] The new study assumed preoxygenation to reach ETO_2 ranging from 60% to 90%, and then compared LFNO and HFNO commencing at the onset of apnoea.[105]6 Although safe apnoea time was generally longer in the HFNO compared with the LFNO model, this depended on the starting ETO_2, BMI, and whether or not the simulated patient was labouring. Overall, the investigators concluded that LFNO prolongs the period of safe apnoea to a similar degree to HFNO and might be a preferred alternative because of ease of use and ability to combine face mask preoxygenation with LFNO.

Both of these model studies are cautious about the use of HFNO in pregnant women with BMI >50 kg m^2.[104,105] It is unclear why HFNO appears less effective, or not effective, in this group. Findings in the non-pregnant population are also not consistent. Schutzer-Weissmann and colleagues[183] explored use of HFNO in non-pregnant patients with morbid obesity (BMI >45 kg m^2). They showed that in experienced hands, with a head-up position of

45°, careful patient selection (ability to mask ventilate), meticulous maintenance of a patent airway, and ensuring a closed mouth, 88% of patients were able to maintain oxygen saturation >92% at 18 min in the HFNO group compared with 62% in the face mask group. These are encouraging data, but the results should be interpreted with caution. In addition to controlled experimental conditions, the authors noted that some patients desaturated rapidly despite optimal preoxygenation and adequate oxygen delivery, and it might be difficult to identify these patients in advance. In contrast to the findings of Schutzer-Weissmann and colleagues,[183] Hamp and colleagues[184] found no differences in the time for oxygen saturation to decrease to ≤95% or in arterial blood gas parameters when LFNO (10 L/min) was compared with HFNO (120 L/min) in patients scheduled for elective bariatric surgery (BMI >40 kg m^2).[184]

The efficiency of preoxygenation with HFNO may depend on whether the patient maintains an open or closed mouth.[157,185] Breathing with the mouth closed can result in higher pharyngeal pressures, leading to better oxygenation. However, flow rates influence patient tolerance to using HFNO with the mouth closed,[155] with 38% of women able to tolerate breathing HFNO with their mouths closed with flows of 50 L/min compared with 24% at 70 L/min. In two studies that showed a benefit of HFNO compared with other methods of preoxygenation, patients were instructed to breathe with their mouth closed.[181,183] Thus, inconsistent results among studies of the benefits of HFNO might be explained by whether patients breathe with their mouth open or closed.

HFNO generates continuous positive pressure that increases proportionally with flow rate. Concerns have been raised that the positive airway pressure generated by HFNO causes gastric insufflation, with resultant increased risk of regurgitation and pulmonary aspiration. HFNO administered to healthy volunteers at 50 or 70 L/min with their mouth closed resulted in nasopharyngeal pressures of up to 6.8 and 10.1 cm H_2O, respectively.[186] Gastric ultrasound studies in spontaneously breathing non-pregnant volunteers and CT imaging in non-pregnant patients undergoing general anaesthesia showed that use of HFNO in these settings did not increase gastric distension or gastric volume.[187,188] Whether HFNO results in gastric distension and increased risk for aspiration in pregnant women has not been studied, but given the physiological changes of pregnancy, including the angle and position of the stomach, and anatomic and hormonally induced decreases in lower oesophageal sphincter pressure, this question is critical.

Ultimately, our goal is to identify a peri-intubation oxygenation technique that prolongs the safe apnoea period without increasing the risk for pulmonary aspiration. The optimal peri-induction oxygen administration technique may differ among patients with different body habitus, and with and without labour. Although the use of HFNO may be appealing, it requires extra equipment that might not be readily available for emergency induction of general anaesthesia for Caesarean delivery. Thus, the findings of Ellis and colleagues[105] that LFNO compares favourably to HFNO supports a modified multimodal technique for peri-intubation oxygen administration. The ability to

perform face mask preoxygenation and gentle face mask ventilation after onset of apnoea, while simultaneously administering LFNO and then continuing administration of LFNO during laryngoscopy, makes this technique adaptable to all operating room theatres. Combined use of face mask preoxygenation and LFNO at 5 L/min with an increase in flow rate to 15 L/min after the patient is unconscious overcomes the limitation of patient discomfort associated with administration of LFNO 15 L/min in awake patients. The future may bring modified HFNO delivery systems that make switching from face mask ventilation to HFNO easier.

Future clinical studies in pregnant women comparing HFNO and LFNO in both obese and non-obese patients are needed. In the meantime, with the knowledge currently available, we know that both LFNO and HFNO prolong safe apnoea time and one or the other should be exploited to reduce the incidence of peri-intubation hypoxaemia. The current modelling study by Ellis and colleagues[105] has shed more light on the use of apnoeic oxygenation techniques in the pregnant population, including women with obesity. Attention to details such as airway patency, mouth closure, patient selection (ease of mask ventilation), and head-up positioning influence the effectiveness of our peri-intubation oxygen administration techniques. Finally, studies of oxygenation techniques during tracheal extubation are lacking.

Chapter 9: Investigation into the appropriate pre-oxygenation times in pregnant patients using HFNO

9.1 Introduction

Throughout this thesis, safe apnoea time as the time until SaO_2 reaches 92% has been discussed. However, after many years of studying and further consideration it as at this point that it must now be considered how safety can be defined. Whilst SaO_2 is a good indication of how much oxygen is in the patient blood, there are also other factors that can cause danger, such as acidosis. A dangerous pH in the blood is defined as <7.35.

As explored in Chapter 8, the goal of extending the safe apnoea time is to give clinicians additional time to secure the airway, reducing airway management complications such as hypoxaemia which poses considerable risk of harm to both the mother and the foetus. Unfortunately, the risk of hypoxaemia in this demographic is increased due to the physiological changes that occur during pregnancy; the effects of active labour on the body's oxygen supply; and the increased risk of failed intubation[70,189,190]. In some demographics, such as morbidly obese patients in labour, it is likely that there will only be time for one intubation attempt before oxygen desaturation begins[191].

Pre-oxygenation with HFNO has been compared to face mask ventilation before and has been shown to have comparable efficacy[185]. The performance of HFNO when compared to LFNO was compared in Chapter 8, showing that when both devices achieve the same $F_{E'}O_2$, HFNO can provide the superior

safe apnoea time across different BMIs, as well as in active and non-active labour [105]

In the obstetric population, 3 minutes of face mask ventilation has been shown to achieve 2 minutes 53 seconds ± 4.8 seconds of safe apnoea time before SaO_2 reaches 95% [141]. In labour, when a patient is experiencing pain and stress, HFNO may be a more comfortable technique for pre-oxygenation, and therefore, more reliable than a traditional face mask ventilation technique, which requires a tight seal for success and is poorly tolerated by patients due to reported discomfort [33]. However, to be considered a true competitor HFNO will need to be able to provide similar or superior safe apnoea time results. This may be achieved by increasing the pre-oxygenation time. An increase in the pre-oxygenation time has been shown to increase the safe apnoea time achieved in other demographics, such as the older subjects in Chapter 7, but the physiological variations that occur during pregnancy are novel and so the results from one demographic may not translate.

This study looks at the pregnant subjects and investigates whether an increase in pre-oxygenation time is of benefit. It will look at a range of different weight classes and qualify the safe apnoea time by ensuring that the blood of the subject is still within a healthy pH range.

9.2 Methodology

The subjects modelled in this study used the same data as shown in Chapter 8.3.

The modelling suite was used to simulate and compare the effect of HFNO pre-oxygenation, at different durations, on the safe apnoea time of 10 virtual

subjects.

Eight subjects were configured with a BMI of 24kg m^{-2} (BMI24), 30 kg m^{-2} (BMI35), 40 kg m^{-2} (BMI40), 50 kg m^{-2} (BMI50), in active labour and not in labour. Subjects that were in labour were modelled with an increased tidal volume, respiration rate, metabolic oxygen consumption VO_2 and cardiac output. Subjects starting pH level, before preoxygenation was 7.41 both in labour and out of labour.

Each subject underwent pulmonary denitrogenation (i.e., pre-oxygenation) via tidal breathing with a FiO_2 of 100% at 70 $Lmin^{-1}$. The interventions were:

Intervention 1: 1 minute of pre-oxygenation prior to apnoea;

Intervention 2: 2 minutes of pre-oxygenation prior to apnoea;

Intervention 3: 3 minutes of pre-oxygenation prior to apnoea;

Intervention 4: 5 minutes of pre-oxygenation prior to apnoea;

Intervention 5: 10 minutes of pre-oxygenation prior to apnoea.

At time zero, apnoea commenced, representing the induction of general anaesthesia. At this time, the FRC was decreased by 20% in the BMI24 subject and by 30% in all other subjects, as per published data [13,14]. Also at this time, VO_2 decreased by 65 ml min^{-1} for all subjects at the onset of apnoea, representing the reduced metabolic oxygen consumption caused by general anaesthesia and muscle paralysis [15].During apnoea subjects will be modelled with (FiO_2 100%) and without (FiO_2 21%) apnoeic oxygenation, modelling airway instrumentation with and without any provision of supplemental oxygen to the airway. Additionally, complete upper airway obstruction will also be modelled which will represent the failure to maintain a patent airway.

Apnoea continued for 40 minutes. Data were recorded every 5 ms from the start of the pre-oxygenation until the protocol was terminated.

9.3 Additional protocol for comparison

Baraka's study[141] looked at non obese pregnant patients and preoxygenated them for 3 minutes using CPAP and then left to deoxygenate until SaO_2 95% occurred. In order to replicate this to make comparisons and increase the validity of the results, a subject was pre-oxygenated for 3 minutes simulating CPAP at 5 cmH_2O with 100% O_2, and then left to deoxygenate during apnoea.

9.4 Results

Comparison data

In the literature [141] patients took 2 minutes and 57 seconds to drop to SaO_2 95%. Simulation of a subject in similar conditions resulted in 3 minutes and 42 seconds until 95%. This means that time until 95% SaO_2 (with acceptable blood pH) after 3 minutes of pre-oxygenation increased with HFNO when compared to face mask techniques[141].

Computational data

Subjects both in labour and out labour who had a BMI of 35 $kg.m^{-2}$ and under showed improvement when pre-oxygenation times were extended, but the increase was always less than a minute. Patients with a BMI of over 40 $kg.m^{-2}$ did not see an improvement.

Table 9.1. Time (in minutes and seconds) that oxygen demand was met without blood pH falling below 7.35 in subjects with a BMI of 35/40/50 $kg.m^{-2}$ out of labour (pregnant) and in active labour (labour).

Minutes of pre-oxygenation	**Time until SaO_2 reached 92% and blood pH above 7.35**	
	Pregnant BMI of 24 $kg.m^{-2}$	**Labour BMI of 24 $kg.m^{-2}$**
1 minute	3 min 55 sec	3min 35 sec
2 minutes	4 min 5 sec	3 min 55 sec
3 minutes	4 min 12 sec	4 min 5 sec
5 minutes	4 min 27 sec	4 min 25 sec
10 minutes	4 min 45 sec	4 min 38 sec
	Pregnant BMI of 35 $kg.m^{-2}$	**Labour BMI of 35 $kg.m^{-2}$**
1 minute	3 min 15 sec	3 min 0 sec
2 minutes	3 min 18 sec	3 min 6 sec
3 minutes	3 min 19 sec	3 min 14 sec
5 minutes	3 min 19 sec	3 min 20 sec
10 minutes	3 min 26 sec	3 min 24 sec
	Pregnant BMI of 40 $kg.m^{-2}$	**Labour BMI of 40 $kg.m^{-2}$**
1 minute	3 minutes 10 seconds	2 minutes 48 seconds
2 minutes	3 minutes 5 seconds	2 minutes 45 seconds
3 minutes	3 minutes	2 minutes 42 seconds
5 minutes	2 minutes 57 seconds	2 minutes 34 seconds
10 minutes	2 minutes 37 seconds	2 minutes 24 seconds
	Pregnant BMI of 50 $kg.m^{-2}$	**Labour BMI of 50 $kg.m^{-2}$**
1 minute	3 min 6 sec	2 min 27 sec
2 minutes	2 min 55 sec	2 min 13 sec
3 minutes	2 min 45 sec	2 min 1 sec
5 minutes	2 min 30 sec	1 min 45 sec
10 minutes	2 min 16 sec	1 min 23 sec

Subject BMI 24

In subjects with a BMI of 24 kg m^{-2}, SaO_2 remained above 99% for the full 40-minute duration of simulated apnoea, as shown in figure 9.1, and in previous studies [104]. This meant that any improvement brought on by the additional pre-oxygenation time, when just looking at SaO_2 alone, was undetectable.

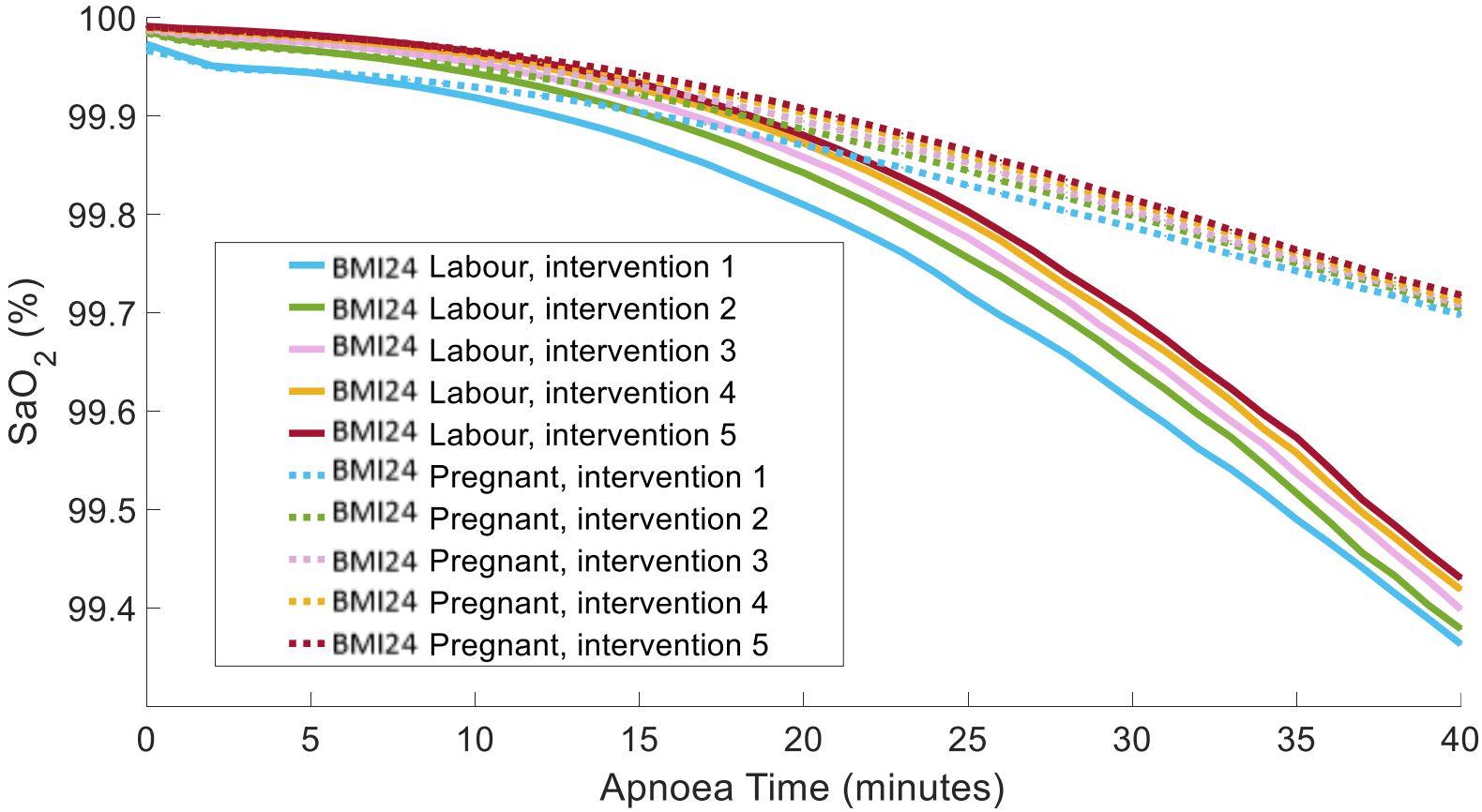


Figure 9.1. Time-course of arterial oxygen saturation (SaO_2) during apnoea in pregnant and active labour subjects with a BMI of 24 $kg.m^{-2}$.

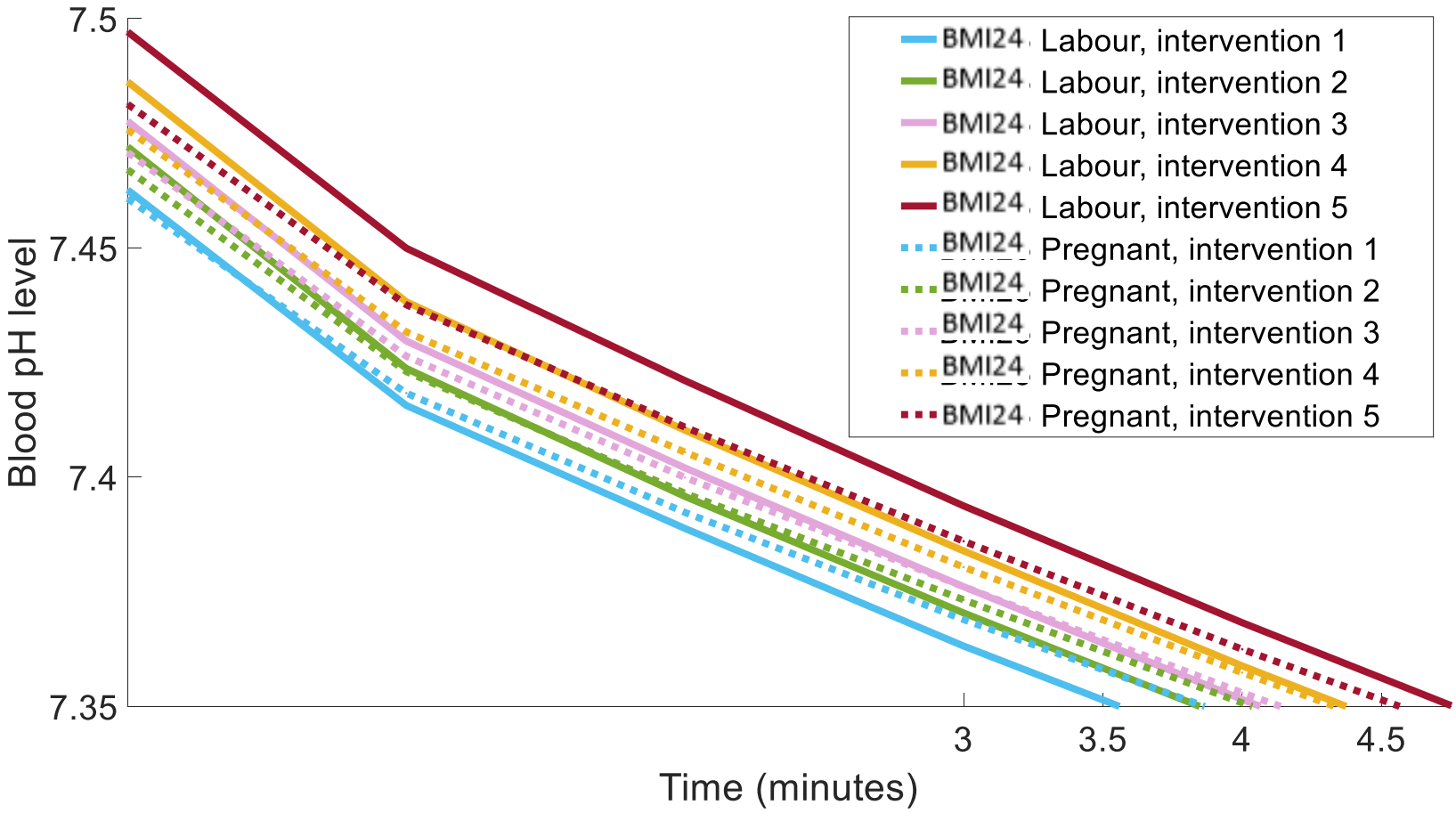


Figure 9.2. Time-course of the blood pH during apnoea subjects with a BMI of 24 kg m^{-2} out of labour (pregnant) and in active labour (labour).

Subject BMI35

In both labouring and non-labouring states, the subject showed improvement by extending the pre-oxygenation time, though the improvements were only a maximum of 11 seconds (non-labouring) and 24 seconds (labouring).

Subject BMI40

In subjects with a BMI of 40 $kg.m^{-2}$ increasing the pre-oxygenation time did not prove to be beneficial across labouring or non-labouring, when considering both SaO_2 and pH. When comparing the standard 3-minute technique with 10 minutes, the additional 7 minutes of pre-oxygenation added 2 minutes of safe apnoea time to subjects when looking at SaO_2 alone. However, when the subject's blood pH was considered, there was no improvement, and the longer the pre-oxygenation the more detrimental it became.

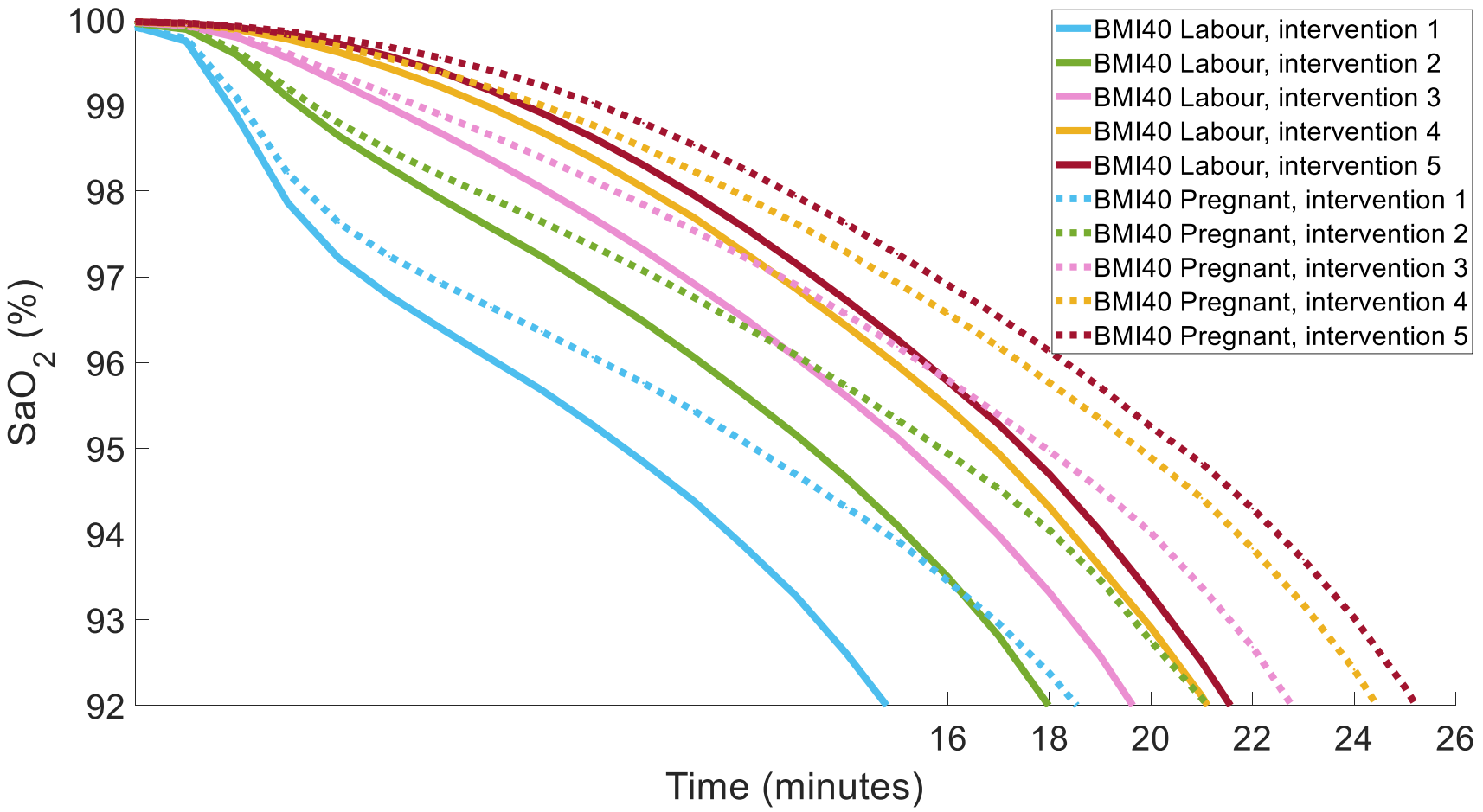


Figure 9.3 Time-course of arterial oxygen saturation (SaO_2) during apnoea in subjects with a BMI of 40 $kg.m^{-2}$ out of labour (pregnant) and in active labour (labour).

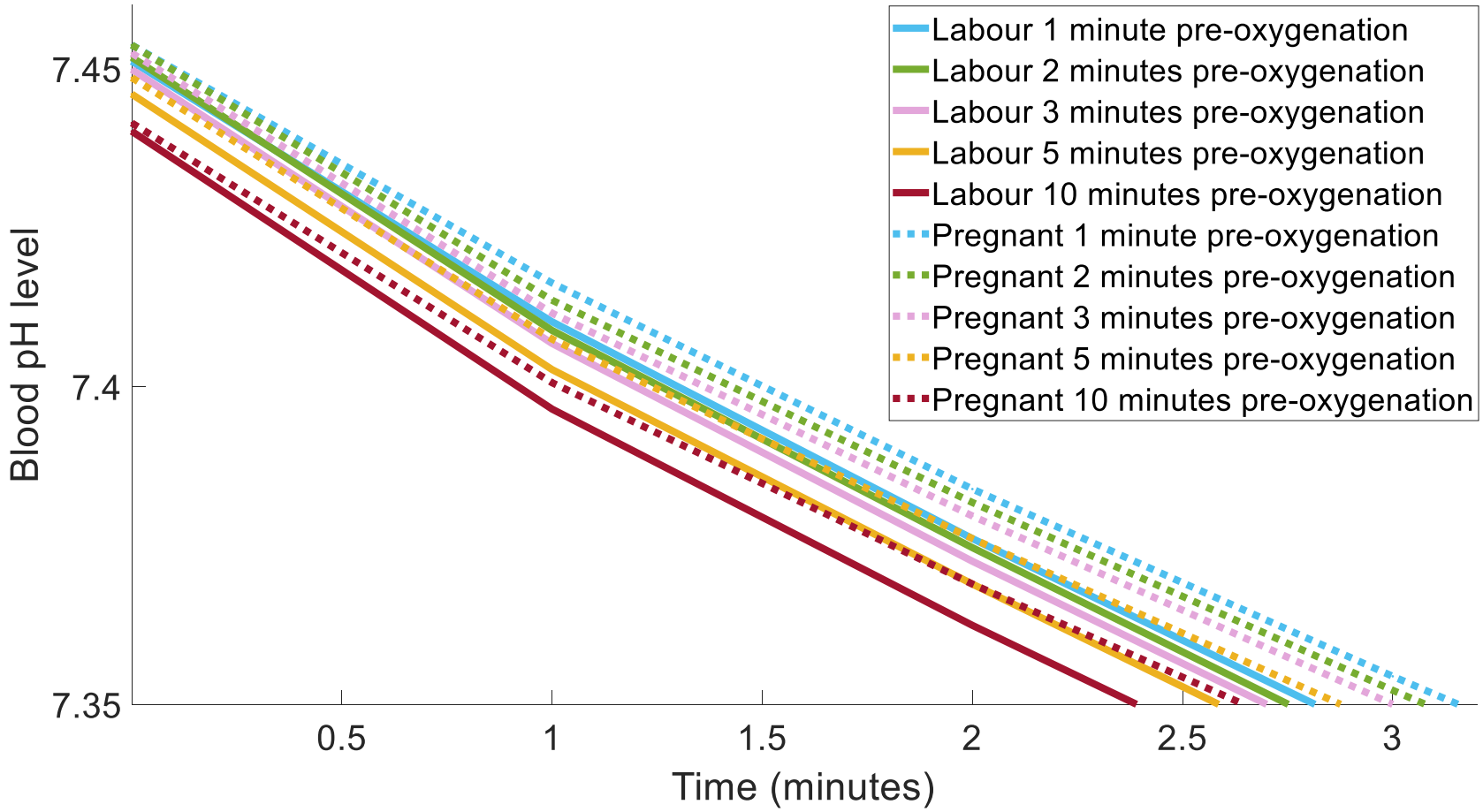


Figure 9.4 Time-course of Blood pH during apnoea in subjects with a BMI of 40 kg.m^{-2} out of labour (pregnant) and in active labour (labour).

Subjects BMI50

In the subject with a BMI of 50 $kg.m^{-2}$, 10 minutes of pre-oxygenation time was only able to sustain 83 seconds of true safe apnoea, whereas 3 minutes was able to achieve 121 seconds. Following a similar pattern to that of BMI 40 $kg.m^{-2.}$

Observation

After reviewing the pH level starting points, it was notable that in BMI24, the starting pH for intervention 5 (a pre-oxygenation time of 10 minutes) had a very high starting pH at the beginning of apnoea. A theory for why it has become so high, is due to respiratory alkalosis, a condition that occurs when a subject's blood does not have enough carbon dioxide (hypocapnia). This may have been brought about through the pre-oxygenation going on for an extended time. The starting pH showed that all BMI24 subjects began pre-oxygenation with the same pH of 7.41, but as pre-oxygenation times increased, so did the pH by the time apnoea had started. This was mirrored in both active labour subjects and non-active labour subjects, with the issue exaggerated in those in active labour. One explanation for why we don't see this as obesity increases is due to the changes in the cardiopulmonary system brought about by obesity, which increases CO_2 production.

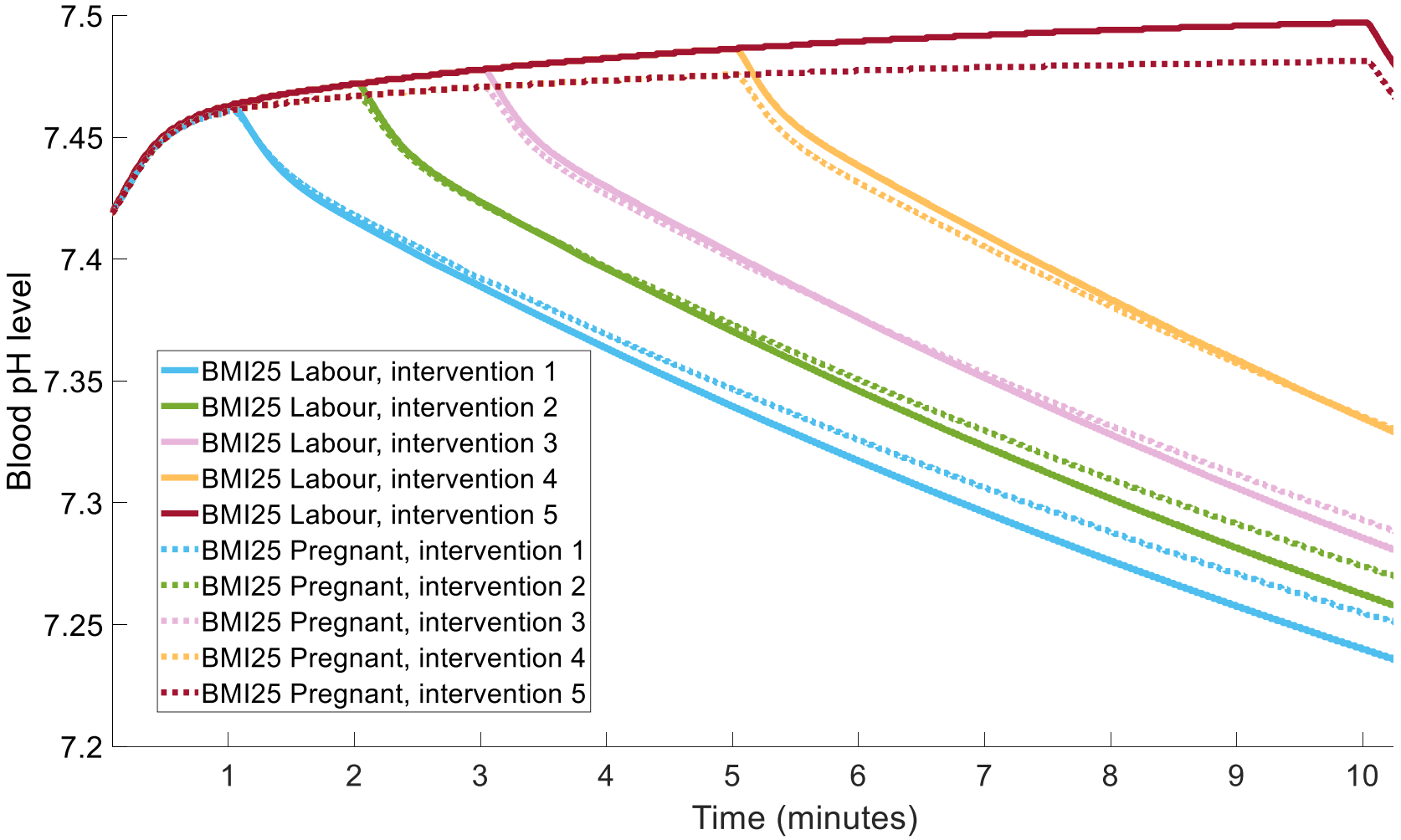


Figure 9.5 Time-course of blood pH during pre-oxygenation in pregnant and active labour subjects with a BMI of 25 kg.m^{-2}.

9.4 Discussion

A healthy blood pH is 7.35 – 7.45, with even mild excursion outside of this range having deleterious effects with fatality often occurring at >7 [192]. Pregnant patients often experience mild respiratory alkalosis due to the stimulation of the respiratory centre by progesterone; as a result, the pH remains slightly high (7.40 – 7.45)[193].

An increase in the acidity of the blood can be caused by an increase in carbon dioxide levels, which is seen in apnoea.

Whilst HFNO can meet the oxygen demands of a healthy patient that is in apnoea [10], and there may be some wash out of the carbon dioxide that builds within in the system during apnoea via cariogenic oscillations [13], apnoea will ultimately cause a build-up that will be fatal. This is all to say that pH is an important factor to consider when looking at safe apnoea time, and research should consider it in conjunction with SaO_2 before making conclusions on whether new techniques that are being modelled are truly increasing the *safe* apnoea time.

The results of this study showed that in healthy weighted pregnant subjects, extending pre-oxygenation times to 5 and 10 minutes provided an extended safe apnoea time in pregnant subjects (26 seconds) and those in labour (40 seconds), when compared to the standard 3 minutes of pre-oxygenation. When the BMI of the subject increased, the benefit was minimized or even reversed. The most obese subject (BMI50) showed a better safe apnoea time at 1 minute of pre-oxygenation than at 3 or 10, as the acid levels in the blood

appear to increase very quickly. This is likely because of a combination of a reduced FRC minimizing the reserve of oxygen available and an increase in VO_2, generating a quicker build-up of CO_2. A smaller FRC means that de-nitrogenation of the lungs is achieved faster and so waste begins to build quickly.

In all instances, when looking at just SaO_2 in isolation, it appears that the increased pre-oxygenation times are giving a longer safe apnoea time. This shows the importance of looking at multiple system responses when modelling and is one of the strengths of a mechanistic model such as the ICSM simulation suite.

This study suggests that extending the pre-oxygenation times for healthy weighted pregnant subjects may be worth clinical consideration, though it is unclear if there is 10 minutes of time available to pre-oxygenate a patient when they are in the emergency situation of requiring surgery during labour. In this instance, it may serve to know what safe apnoea time is available at the lower pre-oxygenation times of 1 and 2 minutes. Reducing the pre-oxygenation time to 1 minute in an emergency situation with a healthy weighted patient, may only lose 17 seconds (pregnant) and 20 seconds (labour) of safe apnoea time in that subject and that HFNO appears to a safer alternative to face masks in this demographic, as it extended the time to SaO_2 95% that was presented in the literature[141].

It may also be important to consider that obese patients appeared to benefit from a lower pre-oxygenation time, and this may be important to consider in an emergency situation, as on the operating table, these patients often

present with other conditions such as maternal diabetes, high blood pressure, big babies and increased risk of caesarean section due to complications during labour and delivery [194]. With this in mind, obesity during pregnancy may require further study to consider the best pre-oxygenation techniques.

Chapter 10: Summary of the results and discussion of the contribution of this thesis

In summary, this thesis has shown that HFNO may have a more important role in the future of pre-oxygenation than a CPAP counterpart. This study has shown evidence through simulations, that suggests that in most scenarios, HFNO is able to provide longer safe apnoea times than when compared to simulated CPAP. This appeared to be true in a range of patient groups including obese, older subjects, and pregnant women. However, in Chapter 7 there was particularly strong evidence for the use of HFNO over CPAP in both 3 minutes of pre-oxygenation as well as when extended the time (10 minutes). CPAP would appear to require an increased time to be more effective in the older population.

These positive implications should be considered further when looking at the device's weaknesses such as the requirement for additional training within a hospital setting. Technology is also improving and a future design that allows for the use of face mask rescue techniques to be used without removing the nasal cannulae (as is seen in LFNO) is an improvement that will likely be made soon, only strengthening its position as an important part of the preoxygenation process. The benefits demonstrated cannot be ignored, and the chapters in this thesis could be considered a trial run that needs to now be explored in flesh and blood patients.

Chapter 4 considered the use of HFNO in an elevated position and showed that it improved safe apnoea time, with Chapter 5 expanding this into the obese subjects and showing a similar trend. Chapter 6 agreed with these results further, though any further progress on modelling changes in positioning is hindered until more patient data is available, which will allow for more detailed simulations of the different positions of a patient.

This thesis also looked at the importance of pre-oxygenation as its own topic. Chapter 7 showed that the most appropriate pre-oxygenation time was heavily dependent on the demographic being investigated, by showing that older patients may benefit from an increased pre-oxygenation time to accommodate for the changes in their lungs. This further opens additional questions about what is the "ideal" preoxygenation technique and if it should be catered depending on the patient on the table. In emergency situations, time is of the essence, and whilst Chapter 7 started an exploration into the diminishing returns on "time gained" *versus* "time invested" in pre-oxygenating a patient, the risk/reward ratio may be different in other demographics, and this could be explored further with more computational modelling. Extension of the pre-oxygenation time is particularly important to older subjects, and Chapter 9 showed that in the pregnant obese it was detrimental. Chapter 8 considered the benefits of HFNO in comparison to LFNO and found that it was able to easily compete when it came to results, but that its weakness of design and familiarity still hold it back.

This thesis adds weight to the argument that HFNO has a significant application within the perioperative setting and highlights as well as

underlining the importance of the pre-oxygenation process. Additionally, though, the thesis shows the power and strength of computational modelling and how it can be used effectively to investigate areas that are otherwise too dangerous to approach. That is not to say that there are no limitations. Computational modelling as a tool is only effective when the person who wields it has a great deal of understanding of both computational modelling, coding, and biology which is a trifecta of skills in short supply. There is an argument that educational providers could help the future of biology by incorporating these skills into traditional courses. However, a more user-friendly interface would make this tool more accessible, and would no doubt drastically increase the amount of research being conducted with it and open up the tool to brilliant minds with ideas that may currently be intimidated by the prospect of having to learn a complicated and difficult new system. Regardless, this tool is incredibly powerful and is being improved making an high-fidelity model of pulmonary and cardiovascular systems. Whilst it is not a perfect replacement for living patients, it can add weight to arguments and save time and money at the planning stages of a large human study.

There is also an ethical argument to be made for the use of computational modelling, many animals are sacrificed for scientific endeavours when their application to humans is debateable. When compared to using animal modelling, there is also the factor of cost. Computational modelling does not require feeding, housing, or maintenance. It is instead built from real human data, which makes the results more applicable for their intended use.

This thesis and its contained study also add to the field of computational modelling by starting the build for a model of older subjects which can be further expanded upon as more data becomes available.

Computational modelling should be embraced, critiqued, and improved upon more abundantly in the future as it has a great deal to add to the overall scientific field. We are standing at the beginning of its use, and it is only going to get better, stronger, and more refined.

Chapter 11: Conclusions, reflections, and suggestions for further work.

The conclusion of this work is that HFNO is an important ventilation strategy with huge amounts of potential, future research into its design and engineering improvements will no doubt make it an even more powerful tool going forward. Its use within the perioperative period cannot be ignored and its suitability to the older patient is of particular note. As technology moves on, it would not be outside the realm of possibility to see it become the preferred and more common form of ventilation used for pre-oxygenation. Whilst cost, familiarity with the technology, and some current functionality flaws hold it back at this present time, they will no doubt be overcome.

In regard to future research, finding a way to facilitate interactions between new organ systems paired with improvements to the user interface could really give the ICSM a much-deserved boost, opening up the possibility for much more research. However, even in its current state it is very powerful, as a research tool.

It would be beneficial to see the ICSM used in the future to investigate topics such as the obese pregnant demographic, which is already (without the intervention of anaesthetic and surgery) a delicate and precarious situation to manage as the birth approaches. This thesis has analysed the SaO_2 in conjunction with blood pH, PaO_2 and $PaCO_2$, but only starts asking the question of what other parameters need to be reviewed in order to call something a “safe” amount of time for apnoeic oxygenation. Future studies should always consider the carbon dioxide levels of the subject, rather than

just the SaO_2 as this can paint a limited picture. In a real life setting the SaO_2 is never monitored in isolation, but it can be difficult for someone without clinical experience to be aware of all the variables that need to be considered when considering if a technique is truly effective or beneficial, when being researched with a computational model.

Additionally, more data needs to be obtained for the older subject biobank that was built for this study, and for it to be validated further. During its construction it was noted that this demographic does not receive as much attention as it perhaps should. The biological changes brought on by aging are an important topic, and this demographic appears to make up a large portion of surgical procedures. It may be that this demographic does not feel as important or as immediately rewarding as the work done to save the lives of newborns, pregnant patients, and others, however older patients deserve both our respect and our consideration when it comes to research. If we are lucky, we will all fall into this demographic at some point, and only too late may we truly understand its significance.

In addition to the more age ranges, additional states of disease need to be built within the modelling system to truly have accurate results. As the chapters revolving around the older subject and the morbidly obese pregnant have alluded, there is rarely a "healthy" subject in these demographics, and so for the results to be of use, a way to build in additional, validated, states of disease would be very useful and would open new avenues of research. Some research into this already exists for ARDS [195] and Chronic obstructive

pulmonary disease [196], but even these would need to be customised to the different age ranges, to make a more accurate model.

Looking back at the work I have done in this thesis, I can say that I have enjoyed my work immensely, and only wish I had more time to work on and improve my understanding of the computational model and the research that I have done here. It is strange that after 3 years of active research it feels like only the beginning of a story. I have learnt so much about what it means to be a researcher and to add to the body of knowledge of science. If I had the time again, I would have done things differently, as modelling position with only a small amount of data was very time consuming and challenging. However, as I have written my chapters, I am reminded of all the different topics and additional variables that I wish I had investigated at the time, but I hope upcoming researchers, and my team at Nottingham University, will delve into these topics in the future.

References

1. Altermatt, F.R., Muñoz, H.R., Delfino, A.E. & Cortínez, L.I. Pre-oxygenation in the obese patient: effects of position on tolerance to apnoea. *BJA: British Journal of Anaesthesia* **95**, 706-709 (2005).
2. McClelland, S.H., Bogod, D.G. & Hardman, J.G. Apnoea in pregnancy: an investigation using physiological modelling. *Anaesthesia* **63**, 264-269 (2008).
3. Lyons, C. & Callaghan, M. Uses and mechanisms of apnoeic oxygenation: a narrative review. *Anaesthesia* **74**, 497-507 (2019).
4. Rivas, E.*, et al.* Ventilation/Perfusion distribution abnormalities in morbidly obese subjects before and after bariatric surgery. *Chest* **147**, 1127-1134 (2015).
5. Olayan, L., Alatassi, A., Patel, J. & Milton, S. Apnoeic oxygenation by nasal cannula during airway management in children undergoing general anaesthesia: a pilot randomised controlled trial. *Perioper Med (Lond)* **7**, 3-3 (2018).
6. Saraswat, V. Effects of anaesthesia techniques and drugs on pulmonary function. *Indian J Anaesth* **59**, 557-564 (2015).
7. Hedenstierna, G. & Rothen, H.U. Atelectasis Formation During Anesthesia: Causes and Measures to Prevent It. *Journal of Clinical Monitoring and Computing* **16**, 329-335 (2000).
8. Ray, K., Bodenham, A. & Paramasivam, E. Pulmonary atelectasis in anaesthesia and critical care. *Continuing Education in Anaesthesia Critical Care & Pain* **14**, 236-245 (2013).
9. Sahay, N.*, et al.* Effect of nasal oxygen supplementation during apnoea of intubation on arterial oxygen levels: A prospective randomised controlled trial. *Indian J Anaesth* **61**, 897-902 (2017).
10. Patel, A. & Nouraei, S.A.R. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* **70**, 323-329 (2015).
11. Riva, T.*, et al.* Carbon Dioxide Changes during High-flow Nasal Oxygenation in Apneic Patients: A Single-center Randomized Controlled Noninferiority Trial. *Anesthesiology* **136**, 82-92 (2022).
12. Stock, M.C., Schisler, J.Q. & McSweeney, T.D. The PaCO2 rate of rise in anesthetized patients with airway obstruction. *J Clin Anesth* **1**, 328-332 (1989).
13. Laviola, M., Das, A., Chikhani, M., Bates, D.G. & Hardman, J.G. Computer simulation clarifies mechanisms of carbon dioxide clearance during apnoea. *British Journal of Anaesthesia* **122**, 395-401 (2019).
14. Kesavan, R.*, et al.* Efficiency and Efficacy of Two Techniques of Preoxygenation during Modified Rapid Sequence Intubation. *Anesth Essays Res* **12**, 754-757 (2018).
15. Bouroche, G. & Bourgain, J.L. Preoxygenation and general anesthesia: a review.
16. Tanoubi, I., Drolet, P. & Donati, F. Optimizing preoxygenation in adults. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie* **56**, 449-466 (2009).

17. Cierniak, M.*, et al.* The degree of intubation difficulties and the frequency of complications in obese patients at the Hospital Emergency Department and the Intensive Care Unit: Case-control study. *Medicine (Baltimore)* **95**, e5777-e5777 (2016).
18. Johnson, K.N., Botros, D.B., Groban, L. & Bryan, Y.F. Anatomic and physiopathologic changes affecting the airway of the elderly patient: implications for geriatric-focused airway management. *Clin Interv Aging* **10**, 1925-1934 (2015).
19. Corley, A., Bull, T., Spooner, A.J., Barnett, A.G. & Fraser, J.F. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥30: a randomised controlled trial. *Intensive Care Medicine* **41**, 887-894 (2015).
20. Thiele, E.L. & Nemergut, E.C. Miller's Anesthesia, 9th ed. *Anesthesia & Analgesia* **130**, e175-e176 (2020).
21. Azam Danish, M. Preoxygenation and Anesthesia: A Detailed Review. *Cureus* **13**, e13240 (2021).
22. Jagannathan, N. & Burjek, N. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a step forward in apnoeic oxygenation, paradigm-shift in ventilation, or both? *Br J Anaesth* **118**, 150-152 (2017).
23. Lodeserto, F.J., Lettich, T.M. & Rezaie, S.R. High-flow Nasal Cannula: Mechanisms of Action and Adult and Pediatric Indications. *Cureus* **10**, e3639-e3639 (2018).
24. La Fauci, V.*, et al.* Humidifiers for oxygen therapy: what risk for reusable and disposable devices? *J Prev Med Hyg* **58**, E161-e165 (2017).
25. Hermez, L.A.*, et al.* A physiological study to determine the mechanism of carbon dioxide clearance during apnoea when using transnasal humidified rapid insufflation ventilatory exchange (THRIVE). *Anaesthesia* **74**, 441-449 (2019).
26. Du, X., Yang, C., Pan, P. & Yu, X. Effect of high-flow nasal cannula oxygen therapy on improving the atelectasis in adults after cardiac surgeries: a Meta-analysis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* **30**, 748-753 (2018).
27. Gustafsson, I.M., Lodenius, Å., Tunelli, J., Ullman, J. & Jonsson Fagerlund, M. Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) - a physiological study.
28. Frerk, C.*, et al.* Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *British journal of anaesthesia* **115**, 827-848 (2015).
29. Humphreys, S., Rosen, D., Housden, T., Taylor, J. & Schibler, A. Nasal high-flow oxygen delivery in children with abnormal airways. *Pediatric Anesthesia* **27**, 616-620 (2017).
30. Muldoon, S., Onwochei, D., Bille, A. & Ahmad, I. Successful use of transnasal humidified rapid-insufflation ventilatory exchange during rigid bronchoscopy in a nonagenarian. *Anaesthesia Cases* **6**, 20-24 (2018).

31. Guy, L*., et al.* The effect of transnasal humidified rapid-insufflation ventilator exchange (THRIVE) versus nasal prongs on safe apnoea time in paralysed obese patients: a randomised controlled trial. *Br J Anaesth* **128**, 375-381 (2022).
32. Weingart, S.D. & Levitan, R.M. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med* **59**, 165-175.e161 (2012).
33. Spoletini, G. & Hill, N.S. High-flow nasal oxygen versus noninvasive ventilation for hypoxemic respiratory failure: Do we know enough? *Ann Thorac Med* **11**, 163-166 (2016).
34. Miller, R.R., 3rd*, et al.* Point: should positive end-expiratory pressure in patients with ARDS be set on oxygenation? Yes. *Chest* **141**, 1379-1382 (2012).
35. Quinn, M., St Lucia, K. & Rizzo, A. Anatomy, Anatomic Dead Space. BTI - StatPearls.
36. Groves, N. & Tobin, A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Australian Critical Care* **20**, 126-131 (2007).
37. Ritchie, J.E., Williams Ab Fau - Gerard, C., Gerard C Fau - Hockey, H. & Hockey, H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures.
38. Parke, R., McGuinness, S. & Eccleston, M. Nasal high-flow therapy delivers low level positive airway pressure. *British Journal of Anaesthesia* (2009).
39. Dres, M. & Demoule, A. What every intensivist should know about using high-flow nasal oxygen for critically ill patients. *Rev Bras Ter Intensiva* **29**, 399-403 (2017).
40. Hall, M.E., George, E.M. & Granger, J.P. [The heart during pregnancy]. *Rev Esp Cardiol* **64**, 1045-1050 (2011).
41. van Rij, A.M*., et al.* Obesity and impaired venous function. *Eur J Vasc Endovasc Surg* **35**, 739-744 (2008).
42. Vasan, R.S. Cardiac function and obesity. *Heart* **89**, 1127-1129 (2003).
43. Hedenstierna, G. & Edmark, L. Protective Ventilation during Anesthesia: Is It Meaningful? *Anesthesiology: The Journal of the American Society of Anesthesiologists* **125**, 1079-1082 (2016).
44. Reinius, H.M.D*., et al.* Prevention of Atelectasis in Morbidly Obese Patients during General Anesthesia and Paralysis: A Computerized Tomography Study. *Anesthesiology: The Journal of the American Society of Anesthesiologists* **111**, 979-987 (2009).
45. Pelosi, P., Croci, M., Ravagnan, I., Vicardi, P. & Gattinoni, L. Total Respiratory System, Lung, and Chest Wall Mechanics in Sedated-Paralyzed Postoperative Morbidly Obese Patients. *Chest* **109**, 144-151 (1996).
46. Pedersen, M.B. & Vahlkvist, S. Comparison of CPAP and HFNC in Management of Bronchiolitis in Infants and Young Children. *Children (Basel)* **4**, 28 (2017).

47. Helviz, Y. & Einav, S. A Systematic Review of the High-flow Nasal Cannula for Adult Patients. *Critical Care* **22**, 71 (2018).
48. WHO, W.H.O. Obesity. Overview (2022).
49. (NHS), N.H.S.U. Obesity Overview. (2022).
50. Moreno, J.P., Crowley, S.J., Alfano, C.A. & Thompson, D. Physiological mechanisms underlying children's circannual growth patterns and their contributions to the obesity epidemic in elementary school age children. *Obesity reviews : an official journal of the International Association for the Study of Obesity* (2019).
51. Curry, G.D. The Impact of Educational Attainment on Black Women's Obesity Rate in the United States. *Journal of racial and ethnic health disparities* (2019).
52. Watson, M.C. & Lloyd, J. Obesity epidemic: bold and decisive action needed. *BMJ (Clinical research ed.)* **367**, l6396 (2019).
53. Lin, L.Y.*, et al.* Gender difference in the association of dietary patterns and metabolic parameters with obesity in young and middle-aged adults with dyslipidemia and abnormal fasting plasma glucose in Taiwan. *Nutrition journal* **18**, 75 (2019).
54. Carbone, S., Lavie, C.J., Elagizi, A., Arena, R. & Ventura, H.O. The Impact of Obesity in Heart Failure. *Heart failure clinics* **16**, 71-80 (2020).
55. Cavallone, L.F. & Vannucci, A. Review article: Extubation of the difficult airway and extubation failure. *Anesthesia and analgesia* **116**, 368-383 (2013).
56. Langeron, O., Birenbaum, A., Le Saché, F. & Raux, M. Airway management in obese patient. *Minerva Anestesiol* **80**, 382-392 (2014).
57. Benumof, Jonathan L., M.D. Preoxygenation : Best Method for Both Efficacy and Efficiency? *Anesthesiology: The Journal of the American Society of Anesthesiologists* **91**, 603-603 (1999).
58. Siriwardena, M. & Fan, E. Chapter 1 - Descent into heart and lung failure. in *Mechanical Circulatory and Respiratory Support* (eds. Gregory, S.D., Stevens, M.C. & Fraser, J.F.) 3-36 (Academic Press, 2018).
59. Jones, R.L. & Nzekwu, M.M. The effects of body mass index on lung volumes.
60. Dixon, Benjamin J., M.B.B.S.*, et al.* Preoxygenation Is More Effective in the 25° Head-up Position Than in the Supine Position in Severely Obese Patients: A Randomized Controlled Study. *Anesthesiology: The Journal of the American Society of Anesthesiologists* **102**, 1110-1115 (2005).
61. Rochester, D.F. & Enson, Y. Current concepts in the pathogenesis of the obesity-hypoventilation syndrome: Mechanical and circulatory factors. *The American Journal of Medicine* **57**, 402-420 (1974).
62. Hopkins, E.S., Sandeep. Physiology, Functional Residual Capacity. Vol. 2023 (ed. StatPearls) (National Library of Medicine, https://www.ncbi.nlm.nih.gov/books/NBK500007, 2022).
63. Wahba, R.W.M. Perioperative functional residual capacity. *Canadian Journal of Anaesthesia* **38**, 384-400 (1991).

64. Hodgson, L.E., Murphy, P.B. & Hart, N. Respiratory management of the obese patient undergoing surgery. *J Thorac Dis* **7**, 943-952 (2015).
65. Bray, G., Schwartz, M., Rozin, R. & Lister, J. Relationships between oxygen consumption and body composition of obese patients. *Metabolism* **19**, 418-429 (1970).
66. Rajalakshmi, R., Vageesh Vy Fau - Nataraj, S.M. & Nataraj, S.M. Myocardial oxygen consumption at rest and during submaximal exercise: effects of increased adiposity.
67. Kim, K.M.*, et al.* Effects of ventilatory strategy on arterial oxygenation and respiratory mechanics in overweight and obese patients undergoing posterior spine surgery. *Scientific reports* **9**, 16638 (2019).
68. Nakhwa, C. & Verma, S. Positioning of a morbidly obese patient during retinal surgery. *Indian journal of ophthalmology* **67**, 1153-1154 (2019).
69. Thota, B., Jan, K.M., Oh, M.W. & Moon, T.S. Airway management in patients with obesity. *Saudi J Anaesth* **16**, 76-81 (2022).
70. Douglas, M.J. & Preston, R.L. The obstetric airway: things are seldom as they seem. *Can J Anaesth* **58**, 494-498 (2011).
71. LoMauro, A. & Aliverti, A. Respiratory physiology of pregnancy: Physiology masterclass. *Breathe (Sheff)* **11**, 297-301 (2015).
72. Weinberger, S.E., Weiss, S.T., Cohen, W.R., Weiss, J.W. & Johnson, T.S. Pregnancy and the lung. *Am Rev Respir Dis* **121**, 559-581 (1980).
73. Jensen, D.*, et al.* Physiological mechanisms of hyperventilation during human pregnancy. *Respiratory physiology & neurobiology* **161**, 76-86 (2008).
74. Janssens, J.P., Pache, J.C. & Nicod, L.P. Physiological changes in respiratory function associated with ageing. *European Respiratory Journal* **13**, 197 (1999).
75. Krumpe, P.E., Knudson, R.J., Parsons, G. & Reiser, K. The aging respiratory system. *Clin Geriatr Med* **1**, 143-175 (1985).
76. Brown, G.C. Living too long: the current focus of medical research on increasing the quantity, rather than the quality, of life is damaging our health and harming the economy. *EMBO Rep* **16**, 137-141 (2015).
77. Sharma, G. & Goodwin, J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging* **1**, 253-260 (2006).
78. Pride, N.B. Ageing and changes in lung mechanics. *European Respiratory Journal* **26**, 563 (2005).
79. Garcia-Rio, F.*, et al.* Lung Volume Reference Values for Women and Men 65 to 85 Years of Age. *American journal of respiratory and critical care medicine* **180**, 1083-1091 (2009).
80. Sprung, J., Gajic, O. & Warner, D. Review article: Age related alterations in respiratory function - Anesthetic considerations. *Canadian journal of anaesthesia = Journal canadien d'anesthésie* **53**, 1244-1257 (2007).
81. Yancik, R.*, et al.* Report of the national institute on aging task force on comorbidity. *J Gerontol A Biol Sci Med Sci* **62**, 275-280 (2007).
82. Falempin, A.-S., Pereira, B., Binakdane, F., Bazin, J.-E. & Smirdec, M. Investigator-initiated, multicentre, open-label, two-arm, randomised controlled trial comparing intubating conditions in 25° head-up

position and supine: the InSize25 study protocol. *BMJ Open* **9**, e029761 (2019).
83. Coleman, M.D. CHAPTER 2 - Respiratory and Pulmonary Physiology. in *Anesthesia Secrets (Fourth Edition)* (ed. Duke, J.) 17-23 (Mosby, Philadelphia, 2011).
84. Couture, E.J.*, et al.* Effect of position and positive pressure ventilation on functional residual capacity in morbidly obese patients: a randomized trial. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie* **65**, 522-528 (2018).
85. Lane, S.*, et al.* A prospective, randomised controlled trial comparing the efficacy of pre-oxygenation in the 20° head-up vs supine position*. *Anaesthesia* **60**, 1064-1067 (2005).
86. Das, A.*, et al.* In Silico Modeling of Coronavirus Disease 2019 Acute Respiratory Distress Syndrome: Pathophysiologic Insights and Potential Management Implications. *Critical care explorations* **2**, e0202 (2020).
87. Hardman, J., Bedforth, N., Ahmed, A., Mahajan, P. & Aitkenhead, A.R. A physiology simulator: Validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation. *British journal of anaesthesia* **81**, 327-332 (1998).
88. Bedforth, N.M. & Hardman, J.G. Predicting patients' responses to changes in mechanical ventilation: a comparison between physicians and a physiological simulator. *Intensive Care Med* **25**, 839-842 (1999).
89. Das, A., Gao, Z., Menon, P.P., Hardman, J.G. & Bates, D.G. A systems engineering approach to validation of a pulmonary physiology simulator for clinical applications. *J R Soc Interface* **8**, 44-55 (2011).
90. Das, A.*, et al.* Hemodynamic effects of lung recruitment maneuvers in acute respiratory distress syndrome. *BMC Pulm Med* **17**, 34-34 (2017).
91. Chikhani, M.*, et al.* High PEEP in acute respiratory distress syndrome: quantitative evaluation between improved arterial oxygenation and decreased oxygen delivery. *British journal of anaesthesia* **117**, 650-658 (2016).
92. McNamara, M.J. & Hardman, J.G. Hypoxaemia during open-airway apnoea: a computational modelling analysis. *Anaesthesia* **60**, 741-746 (2005).
93. Pillai, A., Chikhani, M. & Hardman, J.G. Apnoeic oxygenation in pregnancy: a modelling investigation. *Anaesthesia* **71**, 1077-1080 (2016).
94. Bhardwaj, C.C.A. Physiology, Respiratory Rate. Vol. 2023 (StatPearls[Internet], Natonal Library of Medicine, 2022).
95. Sampson, M.G. & Grassino, A.E. Load compensation in obese patients during quiet tidal breathing. *Journal of Applied Physiology* **55**, 1269-1276 (1983).
96. Pankow, W.*, et al.* Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. *J Appl Physiol (1985)* **85**, 1236-1243 (1998).
97. de Divitiis, O.*, et al.* Obesity and cardiac function. *Circulation* **64**, 477-482 (1981).

98. Damia, G., Mascheroni D Fau - Croci, M., Croci M Fau - Tarenzi, L. & Tarenzi, L. Perioperative changes in functional residual capacity in morbidly obese patients.
99. Robert I. White, J. & Alexander, J.K. Body oxygen consumption and pulmonary ventilation in obese subjects. *Journal of Applied Physiology* **20**, 197-201 (1965).
100. Barrera, F.M.D.R., Marcus M. M.D.Winters, William L. M.D. PULMONARY FUNCTION IN THE OBESE PATIENT. *American Journal of the Medical Sciences* **254**, 785–796 (1967).
101. Bedell, G.N., Wilson, W.R. & Seebohm, P.M. Pulmonary function in obese persons. *J Clin Invest* **37**, 1049-1060 (1958).
102. Sharp, J.T., Henry, J.P., Sweany, S.K., Meadows, W.R. & Pietras, R.J. THE TOTAL WORK OF BREATHING IN NORMAL AND OBESE MEN. *J Clin Invest* **43**, 728-739 (1964).
103. Alexander, J.K.*, et al.* Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. *Cardiovasc Res Cent Bull* **1**, 39-44 (1962).
104. Stolady, D., Laviola, M., Pillai, A. & Hardman, J.G. Effect of variable pre-oxygenation endpoints on safe apnoea time using high flow nasal oxygen for women in labour: a modelling investigation. *British Journal of Anaesthesia* **126**, 889-895 (2021).
105. Ellis, R.*, et al.* Comparison of apnoeic oxygen techniques in term pregnant subjects: a computational modelling study. *Br J Anaesth* **129**, 581-587 (2022).
106. Saravanakumar, K., Rao, S.G. & Cooper, G.M. Obesity and obstetric anaesthesia. *Anaesthesia* **61**, 36-48 (2006).
107. Dempsey, J.A., Reddan, W., Balke, B. & Rankin, J. Work capacity determinants and physiologic cost of weight-supported work in obesity. *J Appl Physiol* **21**, 1815-1820 (1966).
108. Villar, J., Kacmarek, R.M. & Hedenstierna, G. From ventilator-induced lung injury to physician-induced lung injury: why the reluctance to use small tidal volumes? *Acta Anaesthesiol Scand* **48**, 267-271 (2004).
109. Cheun, J.K. & Choi, K.T. Arterial oxygen desaturation rate following obstructive apnea in parturients. *J Korean Med Sci* **7**, 6-10 (1992).
110. Eng, M., Butler, J. & Bonica, J.J. Respiratory function in pregnant obese women. *Am J Obstet Gynecol* **123**, 241-245 (1975).
111. Ibañez, J. & Raurich, J.M. Normal values of functional residual capacity in the sitting and supine positions. *Intensive Care Med* **8**, 173-177 (1982).
112. Mills, G. Respiratory physiology and anaesthesia. *Continuing Education in Anaesthesia, Critical Care & Pain* **1**, 35-39 (2001).
113. Lumb, A.B. *Nunn's applied respiratory physiology*, (2017).
114. Veille, J.C. & Hanson, R. Obesity, pregnancy, and left ventricular functioning during the third trimester. *Am J Obstet Gynecol* **171**, 980-983 (1994).
115. Söderberg, M., Thomson, D. & White, T. Respiration, circulation and anaesthetic management in obesity. Investigation before and after jejunoileal bypass. *Acta Anaesthesiol Scand* **21**, 55-61 (1977).

116. John Knight, Y.N. Anatomy and physiology of ageing 2: the respiratory system. *Nursing Time* **113**, 53-55 (2017).
117. Zimmerman, B.P.F.J.J. Pediatric Critical Care (Third Edition). in *Pediatric Critical Care (Third Edition)* (eds. Fuhrman, B.P. & Zimmerman, J.J.) v (Mosby, Philadelphia, 2006).
118. Mark E. Williams, M. The Basic Geriatric Respiratory Examination. Vol. 2023 (Medscape Anesthesiology, Medscape Anesthesiology, 2009).
119. McFadden, J.P., Price, R.C., Eastwood, H.D. & Briggs, R.S. Raised respiratory rate in elderly patients: a valuable physical sign. *Br Med J (Clin Res Ed)* **284**, 626-627 (1982).
120. Rodríguez-Molinero, A., Narvaiza, L., Ruiz, J. & Gálvez-Barrón, C. Normal Respiratory Rate and Peripheral Blood Oxygen Saturation in the Elderly Population. *Journal of the American Geriatrics Society* **61**, 2238-2240 (2013).
121. Sergi, G.*, et al.* Resting VO2, maximal VO2 and metabolic equivalents in free-living healthy elderly women. *Clin Nutr* **29**, 84-88 (2010).
122. Kwan, M., Woo, J. & Kwok, T. The standard oxygen consumption value equivalent to one metabolic equivalent (3.5 ml/min/kg) is not appropriate for elderly people. *International Journal of Food Sciences and Nutrition* **55**, 179-182 (2004).
123. Marks, R.G., Hale, W.E., Moore, M.T., May, F.E. & Stewart, R.B. Resting heart rates in an ambulatory elderly population: an evaluation of age, sex, symptoms, and medication. *Gerontology* **35**, 210-217 (1989).
124. Houghton, D.*, et al.* The effect of age on the relationship between cardiac and vascular function. *Mech Ageing Dev* **153**, 1-6 (2016).
125. Li, K., Yao, C., Yang, X. & Dong, L. Effect of Resting Heart Rate on All-Cause Mortality and Cardiovascular Events According to Age. *Journal of the American Geriatrics Society* **65**, 989-994 (2017).
126. Weisfeldt, M. Aging, changes in the cardiovascular system, and responses to stress. *Am J Hypertens* **11**, 41s-45s (1998).
127. Wasserman, K. Preoperative Evaluation of Cardiovascular Reserve in the Elderly. *Chest* **104**, 663-664 (1993).
128. Stone, J.G., Khambatta, H.J., Donham, R.T. & Sullivan, S.F. Pulmonary shunting during anaesthesia in man. *Can Anaesth Soc J* **22**, 647-652 (1975).
129. Jared Cadogan, D.J.M., MD, . Pulmonary Changes with Aging. Vol. 2023 (Open Anesthesia, Open Anesthesia, 2023).
130. Tenney, S.M. & Miller, R.M. Dead Space Ventilation in Old Age. *Journal of Applied Physiology* **9**, 321-327 (1956).
131. Niewoehner, D.E., Kleinerman, J. & Liotta, L. Elastic behavior of postmortem human lungs: effects of aging and mild emphysema. *Journal of Applied Physiology* **39**, 943-949 (1975).
132. Suntharalingam, G.*, et al.* Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412.
133. Mezidi, M. & Guérin, C. Effects of patient positioning on respiratory mechanics in mechanically ventilated ICU patients. *Ann Transl Med* **6**, 384-384 (2018).

134. Modak, R.K. *Anesthesiology Keywords Review*, (Wolters Kluwer Health, 2013).
135. Karlet, M. *Nurse Anesthesia Secrets*, (Elsevier Mosby, 2005).
136. Stannard, D. Nurse Anesthesia Pocket Guide. *AORN Journal* **94**, 211-211 (2011).
137. Hardman, J.G., Wills, J.S. & Aitkenhead, A.R. Factors determining the onset and course of hypoxemia during apnea: an investigation using physiological modelling. *Anesthesia and analgesia* **90**, 619-624 (2000).
138. Ramkumar, V., Umesh, G. & Philip, F.A. Preoxygenation with 20º head-up tilt provides longer duration of non-hypoxic apnea than conventional preoxygenation in non-obese healthy adults. *Journal of Anesthesia* **25**, 189-194 (2011).
139. Subedi, A., Dhakal, Y., Bhattarai, B. & Khatiwada, S. Abstract PR576: Effectiveness of Preoxygenation with Positive Airway Pressure in Non-Obese Healthy Patients: A Comparison of the Supine And 25 Degree Head Up Position. *Anesthesia & Analgesia* **123**, 734 (2016).
140. Dixon, Benjamin J.M.B.B.S*., et al.* Preoxygenation Is More Effective in the 25° Head-up Position Than in the Supine Position in Severely Obese Patients: A Randomized Controlled Study. *Anesthesiology: The Journal of the American Society of Anesthesiologists* **102**, 1110-1115 (2005).
141. Baraka, A.S*., et al.* Preoxygenation of pregnant and nonpregnant women in the head-up versus supine position.
142. Benedik, P.S*., et al.* Effects of body position on resting lung volume in overweight and mildly to moderately obese subjects.
143. Siriwardena, M. & Fan, E.
144. Turner, J.S*., et al.* Feasibility of upright patient positioning and intubation success rates At two academic EDs. *Am J Emerg Med* **35**, 986-992 (2017).
145. Khandelwal, N., Khorsand, S., Mitchell, S.H. & Joffe, A.M. Head-Elevated Patient Positioning Decreases Complications of Emergent Tracheal Intubation in the Ward and Intensive Care Unit. *Anesthesia and analgesia* **122**, 1101-1107 (2016).
146. Min, J.H*., et al.* The correlation between the Trendelenburg position and the stroke volume variation. *Korean J Anesthesiol* **67**, 378-383 (2014).
147. Rosen, S.P., Abdelhalim, S.M., Jones, C.A. & McCulloch, T.M. Effect of Body Position on Pharyngeal Swallowing Pressures Using High-Resolution Manometry. *Dysphagia* **33**, 389-398 (2018).
148. Özgültekin, A. Preoxygenation in the elderly: Comparison of three minutes and four deep breath tecniques. *Haydarpasa Numune Training and Research Hospital Medical Journal* (2018).
149. Bansal, R., Kaloria, N., Bhatia, P. & Sharma, A. Modified E-C technique for edentulous geriatric patients. *Saudi J Anaesth* **13**, 257-258 (2019).
150. Lowery, E.M., Brubaker, A.L., Kuhlmann, E. & Kovacs, E.J. The aging lung. *Clin Interv Aging* **8**, 1489-1496 (2013).
151. Rodgers, J.L*., et al.* Cardiovascular Risks Associated with Gender and Aging. *J Cardiovasc Dev Dis* **6**, 19 (2019).

152. Mushambi, M.C*., et al.* Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. *Anaesthesia* **70**, 1286-1306 (2015).
153. Ramachandran, S.K., Cosnowski, A., Shanks, A. & Turner, C.R. Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of nasal oxygen administration. *J Clin Anesth* **22**, 164-168 (2010).
154. Shippam, W*., et al.* High-flow nasal oxygen vs. standard flow-rate facemask pre-oxygenation in pregnant patients: a randomised physiological study. *Anaesthesia* **74**, 450-456 (2019).
155. Au, K., Shippam, W., Taylor, J., Albert, A. & Chau, A. Determining the effective pre-oxygenation interval in obstetric patients using high-flow nasal oxygen and standard flow rate facemask: a biased-coin up-down sequential allocation trial. *Anaesthesia* **75**, 609-616 (2020).
156. Tan, P.C.F., Millay, O.J., Leeton, L. & Dennis, A.T. High-flow humidified nasal preoxygenation in pregnant women: a prospective observational study. *Br J Anaesth* **122**, 86-91 (2019).
157. Al-Sulttan, S*., et al.* A prospective, up-down sequential allocation study investigating the effectiveness of vital capacity breaths using high-flow nasal oxygenation versus a tight-fitting face mask to pre-oxygenate term pregnant women. *Int J Obstet Anesth* **45**, 28-33 (2021).
158. Stolady, D., Laviola, M., Pillai, A. & Hardman, J.G. Effect of variable pre-oxygenation endpoints on safe apnoea time using high flow nasal oxygen for women in labour: a modelling investigation. *Br J Anaesth* **126**, 889-895 (2021).
159. McClelland, S., Bogod, D. & Hardman, J. Pre-oxygenation in pregnancy: an investigation using physiological modelling. *Anaesthesia* **63**, 259-263 (2008).
160. Hardman, J.G., Wills, J.S. & Aitkenhead, A.R. Investigating hypoxemia during apnea: validation of a set of physiological models. *Anesthesia and analgesia* **90**, 614-618 (2000).
161. McClelland, S., Bogod, D. & Hardman, J. Pre-oxygenation and apnoea in pregnancy: changes during labour and with obstetric morbidity in a computational simulation. *Anaesthesia* **64**, 371-377 (2009).
162. Wahba, R. Perioperative functional residual capacity. *Canadian Journal of Anaesthesia* **38**, 384-400 (1991).
163. Knuttgen, H.G. & Emerson Jr, K. Physiological response to pregnancy at rest and during exercise. *Journal of Applied Physiology* **36**, 549-553 (1974).
164. Eliasson, L.A.H., Phillips, L.Y.Y., Stajduhar, M.K.C., Carome, M.M.A. & Cowsar Jr, L.J.D. Oxygen consumption and ventilation during normal labor. *Chest* **102**, 467-471 (1992).
165. Jakobsson, J., Vadman, S., Hagel, E., Kalman, S. & Bartha, E. The effects of general anaesthesia on oxygen consumption: A meta-analysis guiding future studies on perioperative oxygen transport. *Acta Anaesthesiologica Scandinavica* **63**, 144-153 (2019).

166. Gibson, Robert L., Comer, Paul B., Beckham, Richard W. & McGraw, C.P. Actual Tracheal Oxygen Concentrations with Commonly Used Oxygen Equipment. *Anesthesiology* **44**, 71-73 (1976).
167. Lyons, C*., et al.* Pre-oxygenation with facemask oxygen vs high-flow nasal oxygen vs high-flow nasal oxygen plus mouthpiece: a randomised controlled trial.
168. Pillai, A., Chikhani, M. & Hardman, J. Apnoeic oxygenation in pregnancy: a modelling investigation. *Anaesthesia* **71**, 1077-1080 (2016).
169. Wong, C.A. & Mushambi, M. Peri-intubation oxygenation for Caesarean delivery: is there an optimal technique? *British Journal of Anaesthesia* **129**, 468-471 (2022).
170. Bonnet, M.-P*., et al.* Incidence and risk factors for maternal hypoxaemia during induction of general anaesthesia for non-elective Caesarean section: a prospective multicentre study. *British Journal of Anaesthesia* **125**, e81-e87 (2020).
171. Tomlinson, J., Bishop, D., Hofmeyr, R., Cronje, L. & Rodseth, R. The incidence and predictors of hypoxaemia during induction of general anaesthesia for caesarean delivery in two South African hospitals: a prospective, observational, dual-centre study. *Southern African Journal of Anaesthesia and Analgesia* **26**, 183-187 (2020).
172. Patel, A. & El-Boghdadly, K. Facemask or high-flow nasal oxygenation: time to switch? *Anaesthesia* **77**(2022).
173. Mushambi, M. Facemask or high-flow nasal oxygenation: time to switch? *Anaesthesia* **77**, 716-717 (2022).
174. Porter, R., Wrench, I. & Freeman, R. Preoxygenation for general anaesthesia in pregnancy: is it adequate? *International Journal of Obstetric Anesthesia* **20**, 363-365 (2011).
175. Cajander, P., Edmark, L., Ahlstrand, R., Magnuson, A. & de Leon, A. Effect of positive end-expiratory pressure on gastric insufflation during induction of anaesthesia when using pressure-controlled ventilation via a face mask: a randomised controlled trial. *European Journal of Anaesthesiology| EJA* **36**, 625-632 (2019).
176. Lawes, E., Campbell, I. & Mercer, D. Inflation pressure, gastric insufflation and rapid sequence induction. *British journal of anaesthesia* **59**, 315-318 (1987).
177. Brainard, A., Chuang, D., Zeng, I. & Larkin, G.L. A randomized trial on subject tolerance and the adverse effects associated with higher- versus lower-flow oxygen through a standard nasal cannula. *Annals of Emergency Medicine* **65**, 356-361 (2015).
178. Mir, F., Patel, A., Iqbal, R., Cecconi, M. & Nouraei, S. A randomised controlled trial comparing transnasal humidified rapid insufflation ventilatory exchange (THRIVE) pre-oxygenation with facemask pre-oxygenation in patients undergoing rapid sequence induction of anaesthesia. *Anaesthesia* **72**, 439-443 (2017).
179. Lodenius, Å., Piehl, J., Östlund, A., Ullman, J. & Jonsson Fagerlund, M. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) vs. facemask breathing pre-oxygenation for rapid sequence induction

in adults: a prospective randomised non-blinded clinical trial. *Anaesthesia* **73**, 564-571 (2018).
180. Wong, D.T.*, et al.* High-flow nasal oxygen improves safe apnea time in morbidly obese patients undergoing general anesthesia: a randomized controlled trial. *Anesthesia & Analgesia* **129**, 1130-1136 (2019).
181. Zhou, S.*, et al.* The efficacy of high flow nasal oxygenation for maintaining maternal oxygenation during rapid sequence induction in pregnancy: a prospective randomised clinical trial. *European Journal of Anaesthesiology| EJA* **38**, 1052-1058 (2021).
182. Heinrich, S.*, et al.* Benefits of Heated and Humidified High Flow Nasal Oxygen for Preoxygenation in Morbidly Obese Patients Undergoing Bariatric Surgery: A Randomized Controlled Study. *Journal of Obesity and Bariatrics* **1**, 7 (2014).
183. Schutzer-Weissmann, J.*, et al.* Apnoeic oxygenation in morbid obesity: a randomised controlled trial comparing facemask and high-flow nasal oxygen delivery. *British Journal of Anaesthesia* **130**, 103-110 (2023).
184. Hamp, T.*, et al.* Duration of safe apnea in patients with morbid obesity during passive oxygenation using high-flow nasal insufflation versus regular flow nasal insufflation, a randomized trial. *Surgery for Obesity and Related Diseases* **17**, 347-355 (2021).
185. Pillai, A.*, et al.* High-flow humidified nasal oxygenation vs. standard face mask oxygenation. *Anaesthesia* **71**, 1280-1283 (2016).
186. Parke, R.L., Bloch, A. & McGuinness, S.P. Effect of very-high-flow nasal therapy on airway pressure and end-expiratory lung impedance in healthy volunteers. *Respiratory care* **60**, 1397-1403 (2015).
187. McLellan, E.*, et al.* High-flow nasal oxygen does not increase the volume of gastric secretions during spontaneous ventilation. *British Journal of Anaesthesia* **125**, e75-e80 (2020).
188. Sud, A., Athanassoglou, V., Anderson, E. & Scott, S. A comparison of gastric gas volumes measured by computed tomography after high-flow nasal oxygen therapy or conventional facemask ventilation. *Anaesthesia* **76**, 1184-1189 (2021).
189. Hägerdal M Fau - Morgan, C.W., Morgan Cw Fau - Sumner, A.E., Sumner Ae Fau - Gutsche, B.B. & Gutsche, B.B. Minute ventilation and oxygen consumption during labor with epidural analgesia.
190. McDonnell, N.J., Paech Mj Fau - Clavisi, O.M., Clavisi Om Fau - Scott, K.L. & Scott, K.L. Difficult and failed intubation in obstetric anaesthesia: an observational study of airway management and complications associated with general anaesthesia for caesarean section.
191. McClelland, S.H., Bogod, D.G. & Hardman, J.G. Preoxygenation and Apnea in Pregnancy: Changes During Labor and With Obstetric Morbidity in a Computational Simulation. *Obstetric Anesthesia Digest* **30**, 48 (2010).
192. Allyn, J.*, et al.* Prognosis of patients presenting extreme acidosis (pH <7) on admission to intensive care unit. *Journal of Critical Care* **31**, 243-248 (2016).
193. Ahmed, A. Fetomaternal Acid-Base Balance and Electrolytes during Pregnancy. *Indian J Crit Care Med* **25**, S193-s199 (2021).

194. Ayabe., J.K.A. Obesity In Pregnancy. Vol. 2023 (ed. StatPearls) (StatPearls, National Library of Medicine, 2022).
195. McCahon, R., Columb, M., Mahajan, P. & Hardman, J. Validation and application of a high-fidelity, computational model of acute respiratory distress syndrome to the examination of the indices of oxygenation at constant lung-state. *British journal of anaesthesia* **101**, 358-365 (2008).
196. Wang, W*., et al.* Can computer simulators accurately represent the pathophysiology of individual COPD patients? *Intensive Care Med Exp* **2**, 23 (2014).

List of Tables

Table 5.5. Comparison of results between published data[140] of subjects with a BMI>40 $kg.m^{-2}$ and the modelling simulations.

Table 5.6. Average time take for arterial oxygen saturation (SaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) to reach 92% during apnoea, as well as their average arterial partial pressure of carbon dioxide ($PaCO_2$) after 3, 5 and 10 minutes of apnoea.

Table 5.7. Average time take for arterial oxygen saturation (SaO_2) of Obese 2 (BMI 35-29.9 $kg.m^{-2}$) to reach 92% during apnoea, as well as their average arterial partial pressure of carbon dioxide ($PaCO_2$) after 3, 5 and 10 minutes of apnoea. Where the simulation ended before a value could be taken N/A is used.

Table 5.8. Average of the time taken until arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) reached 92% during apnoea, as well as their average arterial partial pressure of carbon dioxide ($PaCO_2$) after 3, 5 and 10 minutes of apnoea. Where the simulation ended due to subject reaching 92% SaO_2 before a value could be taken N/A is used.

Table 6.1. The average cardiac output (CO) used across the 30 subjects in both upwards tilt and supine position.

Table 6.2. Average of the time (in seconds) taken until arterial oxygen saturation (SaO_2) of Obese 1 (BMI 30-34.9 $kg.m^{-2}$) reached 92% after 3 minutes of pre-oxygenation with HFNO, as well as the average of the arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$). Min 3 is 3 minutes of apnoea, Min 5 is 5 minutes of apnoea, Min 10 is 10 minutes of apnoea.

Table 6.3. Average of the time taken until arterial oxygen saturation (SaO_2) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) reached 92%, and average of the partial pressure of oxygen (PaO_2) and average of the arterial partial pressure of carbon dioxide ($PaCO_2$) during apnoea. Min 3 is 3 minutes of apnoea, Min 5 is 5 minutes of apnoea, Min 10 is 10 minutes of apnoea. Where the simulation ended before a value could be taken N/A is used.

Table 6.4. Average time taken until arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) reached 92% during apnoea and the average of the partial pressure of oxygen (PaO_2) during apnoea. Min 3 is 3 minutes of apnoea. Min 5 is 5 minutes of apnoea. Min 10 is 10 minutes of apnoea. Where the simulation ended from reaching SaO_2 92% and so no value could be recorded, N/A is used.

Table 7.1: Average time for arterial oxygen saturation (SaO_2) to reach 97%, 95% and 93% across published literature, simulated CPAP and simulated HFNO for 3 minutes of pre-oxygenation on elderly patients.

Table 7.2: Arterial partial pressure oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial oxygen saturation (SaO_2), after pre-oxygenation has completed and apnoea commences, from both literature data and model outputs.

Table 7.3: Time taken for arterial oxygen saturation (SaO_2) to reach 92% after 3, 5 and 10 minutes of pre-oxygenation with HFNO and CPAP, in minutes(m) and seconds(s).

Table 7.4: Average arterial partial pressure of oxygen (PaO_2) at 3 minutes, 5 minutes and 10 minutes of apnoea.

Table 7.5: Average arterial partial pressure of carbon dioxide ($PaCO_2$) at 3 minutes (3 min), 5 minutes (5 min) and 10 minutes (10 min).

Table 8.1: Time (in minutes) taken to reach arterial oxygen saturation (SaO_2) of 90% and 50% during apnoea for different pre-apnoea end-tidal oxygen fraction ($F_{E'}O_2$) in subjects that were term pregnant but not in labour. FgO_2 (periglottic oxygen); N.A. (not achieved); *t50* represents time from onset of apnoea to SaO_2 50% in minutes; *t90* represents time from onset of apnoea to SaO_2 90% in minutes.

Table 8.2: Time (in minutes) taken to reach arterial oxygen saturation (SaO_2) of 90% and 50% during apnoea for different pre-apnoea end-tidal oxygen fraction ($F_{E'}O_2$) in subjects that were term pregnant and in active labour. FgO_2 (periglottic oxygen); N.A. (not achieved); *t50* represents time from onset of apnoea to SaO_2 50% in minutes; *t90* represents time from onset of apnoea to SaO_2 90% in minutes.

Table 9.1. Time (in minutes and seconds) that oxygen demand was met without blood pH falling below 7.35 in subjects with a BMI of 35/40/50 $kg.m^{-2}$ out of labour (pregnant) and in active labour (labour).

List of Figures

Figure 6.6. The partial pressure of carbon dioxide ($PaCO_2$) of Obese 2 (BMI 35-39.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

Figure 6.7. Time taken until arterial oxygen saturation (SaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) reached 92% during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

Figure 6.8. The partial pressure of carbon dioxide ($PaCO_2$) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

Figure 6.9. The partial pressure of oxygen (PaO_2) of Obese 3 (BMI 40-49.9 $kg.m^{-2}$) during apnoea. Dotted lines show individual subjects. Solid lines represent the average. The averages overlap.

Figure 7.1 Arterial oxygen saturation (SaO_2) results comparing the simulated older subject and the healthy younger subjects, after 3, 5 and 10 minutes of pre-oxygenation with continuous HFNO.

Figure 8.1: Arterial oxygen saturation (SaO_2) during apnoea in the virtual subjects with BMI of 24 and BMI of 50 $kg.m^{-2}$ in labour, with a closed glottis, open airway with fraction of oxygen (FO_2) 21%, LFNO, and HFNO with an end-tidal oxygen fraction ($F_{E'}O_2$) of 80% and 90%. The closed glottis simulates a failure of LFNO and HFNO, whereas FO_2 21% $F_{E'}O_2$ of 90% simulates the face-mask technique during airway instrumentation with no oxygenation supplementation.

Figure 8.2: Gain in safe apnoea time, calculated as the difference in minutes to reach arterial oxygen saturation (SaO_2) 90% between HFNO with an end-tidal oxygen fraction ($F_{E'}O_2$) 80% and LFNO at $F_{E'}O_2$ 80% and 90% with FiO_2 100% at the open glottis in the subjects not in labour (upper panel) and in labour (lower panel).

Figure 9.1. Time-course of arterial oxygen saturation (SaO_2) during apnoea in pregnant and active labour subjects with a BMI of 24 kg.m-^{2}.

Figure 9.2. Time-course of the blood pH during apnoea subjects with a BMI of 24 kg m^{-2} out of labour (pregnant) and in active labour (labour).

Figure 9.3 Time-course of arterial oxygen saturation (SaO_2) during apnoea in subjects with a BMI of 40 $kg.m^{-2}$ out of labour (pregnant) and in active labour (labour).

Figure 9.4 Time-course of Blood pH during apnoea in subjects with a BMI of 40 $kg.m^{-2}$ out of labour (pregnant) and in active labour (labour).

Figure 9.5 Time-course of blood pH during pre-oxygenation in pregnant and active labour subjects with a BMI of 25 $kg.m^{-2}$.

List of publications and presentations

List of publications:

1. Ellis R, Laviola M, Stolady D, **Valentine RL**, Pillai A, Hardman JG. Comparison of apnoeic oxygen techniques in term pregnant subjects: a computational modelling study. Br J Anaesth. 2022 Oct;129(4):581-587.
2. Ellis R, Laviola M, Stolady D, **Valentine RL**, Pillai A, Hardman JG. Comparison of apnoeic oxygen techniques in term pregnant subjects: a computational modelling study. Response to Br J Anaesth 2022; 129: 581-7. Br J Anaesth. 2023 Apr;130(4)

Research presentations:

1. Poster presentation: 'HFNO pre-oxygenation times in the older subject: a computational modelling study' at the 33° SMART Conference, MiCo Milano, May 2022

2. Oral presentation: 'Investigating the evolution and application of Optiflow in managing unique patient groups in the perioperative period' at the Sue Watson Event, School of Medicine, University of Nottingham, March 2022

3. Oral presentation: 'Investigating the evolution and application of Optiflow in managing unique patient groups in the perioperative period' Fisher and Paykel annual meeting review, New Zealand, March 2022

4. Poster presentation: "Investigating the evolution and application of Optiflow in managing unique patient groups in the perioperative period" at the Research Impact Forum, School of Medicine, University of Nottingham, September 2021

5. Oral presentation: "Investigating the FRC changes brought on by 30° head elevation during HFNO pre-oxygenation and its effect on safe apnoea time for an Obese subject." at the N-trans Training Programme Sandpit series, University of Nottingham 2021

6. Oral presentation to the Anaesthesia & Critical Care group at the ICSM Digest 3rd session, University of Nottingham December 2020