Strategies mitigating hypoxaemia in high-risk populations during anaesthesia and respiratory critical care: computational modelling studies

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Abstract

Assessing interventions applied during clinically-encounterable extreme scenarios is vital to enhance the quality of care. However, the studies that examine these situations are rare, ethically and clinically challenging. Computational modelling offers a reliable, efficient and almost ethical-free approach to investigate high-risk scenarios. This thesis evaluated interventions applied during *(i)* prolonged apnoea in obesity, *(ii)* airway obstruction in emergency crises, and *(iii)* hyperbaric oxygen therapy in severe hypoxaemic respiratory failure patients through a series of high-fidelity computational modelling studies.

Worldwide, there are more than 650 million obese individuals and anticipated to increase. In the context of anaesthesia and critical care, obese subjects are at increased risks during general anaesthesia, such as airway difficulties and apnoea intolerance (rapid occurrence of hypoxaemia). Developing and quantifying methods to extend the safe (non-hypoxaemic) apnoea time would increase their safety remarkably during this procedure. The thesis showed that the use of high-flow nasal oxygen significantly delayed the safe apnoea time in a bank of obese virtual subjects.

Persistent airway obstruction is not common in anaesthesia practice, but it could lead to catastrophic outcomes. Complete blockage of the upper airway was simulated until life-threatening hypoxaemia occurred, followed by relieving the obstruction and delivery of multiple patterns of tidal ventilation. Larger tidal volume did not achieve faster re-oxygenation compared to lower tidal volume.

Globally, up to 20 million acute respiratory failure patients receive mechanical ventilation annually. The mortality of acute respiratory distress syndrome (ARDS) remains considerably high

despite the implementation of the lung-protective ventilation strategy. A bank of severe ARDS virtual patients was configured and underwent maximum lung-protective ventilation strategy at atmospheric pressure (with high positive end-expiratory pressure [PEEP]) and hyperbaric pressure (with low PEEP). The hyperbaric oxygen significantly increased the oxygen delivery to tissues even with a low fraction of inspired oxygen.

The thesis's original contributions to knowledge are: first, it quantified the impact of airway obstruction and patency, high oxygen concentration and high-flow nasal oxygen, applied during apnoea, on the safe apnoea time in obesity. Second, it demonstrated that larger tidal ventilation during airway rescue is not necessary. Finally, it highlighted that hyperbaric oxygen therapy could provide adequate tissue oxygen delivery and may be considered as a rescue option for severe ARDS patients who remain hypoxaemic despite maximum lung-protective ventilation strategy.

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List of publications and scientific presentations

List of publications:

Conference Proceedings

1. **Alahmadi, H**., Laviola, M., Bates D.G and Hardman, J.G, *The effects of high-flow nasal oxygen during apnoea in obesity: a computational modelling investigation.* Trends in Anaesthesia and Critical Care, 2020. **30**: p. e26.
2. Laviola, M., Niklas, C., **Alahmadi, H**., Das, A., Bates D.G and Hardman, J.G, *High oxygen fraction during airway opening is key to effective airway rescue in obese subjects*. In 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2019. IEEE.

Research Articles

I am currently working towards publishing the work described in Chapter 8 (the role of hyperbaric oxygen in rescuing severe ARDS with refractory hypoxaemia: a computational modelling investigation) in a peer-reviewed journal.

Research presentations:

1. Abstract first author: "High-flow nasal oxygen delays hypoxaemia during apnoea in virtual obese subjects" oral presentation delivered by my co-supervisor, i.e. co-author at the 42nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, held virtually, July 2020.
2. Oral presentation: "High-flow nasal oxygen delays hypoxaemia during apnoea in obesity: A computational modelling study" at the Sue Watson Postgraduate Presentation Event, School of Medicine, University of Nottingham, July 2020.
3. Poster presentation: "The effects of high-flow nasal oxygen during apnoea in obesity: a computational modelling investigation" at the 2nd World Airway Management Meeting in Amsterdam, Netherland, November 2019. (*Awarded a prestigious prize bestowed by the International Airway Management Society*)
4. Poster presentation: "The effects of high-flow nasal oxygen during apnoea in obesity: a computational modelling investigation" Division of Clinical Neuroscience (DCN) Research & Social Event, University of Nottingham, September 2019.
5. Oral presentation to the Anaesthesia & Critical Care group at the academic lunchtime meeting, University of Nottingham, May 2019.

List of abbreviations

ARDS	acute respiratory distress syndrome
ATA	atmosphere absolute
BPAP	bilevel positive airway pressure
BMI	body mass index
BVM	bag valve mask
CO	cardiac output
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DAS	difficult airway society
DO_2	oxygen delivery
ECMO	extracorporeal membrane oxygenation
$FetO_2$	end-tidal fractional oxygen concentration
FiO_2	fraction of oxygen in the inspired gas
FRC	functional residual capacity
HBOT	hyperbaric oxygen therapy
HFNO	high-flow nasal oxygen
ICU	intensive care unit
in-silico	*in-silico*n or virtual
kPa	kilopascal
NC	nasal cannulae
NIV	non-invasive ventilation
NRM	non-rebreather mask
O_2	oxygen
OHA	obesity-hypoventilation syndrome
OSA	obstructive sleep apnoea
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PAO_2	partial pressure of oxygen in the alveoli
PAP	positive airway pressure
PEEP	positive end-expiratory pressure
$PetCO_2$	partial pressure of end-tidal carbon dioxide
pH	potential of hydrogen

PIP	peak inspiratory pressure
P_{platu}	end-inspiratory plateau pressure
PS	pressure support
Q_S/Q_T	shunt fraction
RR	respiratory rate
SaO_2	oxygen saturation in haemoglobin
SpO_2	pulse oximetry
THRIVE	transnasal humidified rapid-insufflation ventilatory exchange
VD_{phys}	physiological deadspace
VO_2	oxygen consumption
V_T	tidal volume

Chapter 1: Overview

1.1 Thesis outline

Chapter 1 encompasses the thesis potential beneficiaries and stakeholders, the importance of the investigated research area, and the original contributions to knowledge. Additionally, it states the overall aims of the thesis. **Chapter 2** provides an introduction to the respiratory gas exchange, respiratory failure, pre-oxygenation, and apnoeic oxygenation. Moreover, this chapter briefly covers the ARDS, hyperbaric oxygen therapy (HBOT) and extracorporeal membrane oxygenation (ECMO).

Chapter 3 offers a comprehensive literature review of the scholarly articles that investigated the pulmonary pathophysiology of obesity and ARDS and state of the art underpinning apnoeic oxygenation. Further, the chapter highlights gaps in the literature as well as limitations to implement apnoeic oxygenation and HBOT in clinical practice. **Chapter 4** presents the methodology used, i.e. computational modelling. It covers its background, common terminologies, strengths, and limitations. Additionally, the Interdisciplinary Collaboration in Systems Medicine (ICSM) model is described, which is used to conduct a series of computational modelling studies reported in the thesis.

Chapter 5 examines gas exchange during apnoea while undergoing several scenarios pertaining to the patency of the upper airway and various apnoeic oxygenation strategies. **Chapter 6** compares gas exchange during three interventions *(i)* high-flow nasal oxygen (HFNO), *(ii)* classical (low-flow non-heated) apnoeic oxygenation, and *(iii)* no provision of oxygen during patent-airway apnoea. This study was conducted on a bank (n=90) of virtual subjects with multiple obesity severity levels.

Chapter 7 investigates various patterns of tidal ventilation, following the opening of an obstructed airway, on the re-oxygenation period to a safe level in obese virtual subjects. **Chapter 8** evaluates the use of HBOT in virtual patients suffering from severe ARDS who remain hypoxaemic despite maximum lung-protective ventilation strategy. **Chapter 9** summarises *(i)* the main findings obtained from the thesis studies, *(ii)* the thesis original contributions to the scientific and clinical fields, and *(iii)* the limitations, recommendations and the proposed future research.

1.2 Who might benefit from the thesis?

Professionals that might be interested in the thesis are researchers, healthcare practitioners and medical equipment manufacturers who are involved in airway management and ARDS treatment. These include anaesthetists, intensivists, respiratory therapists, ED physicians, and critical care nurses. Additional beneficiaries include hospital quality and safety officers, upper management and policymaker personnel.

1.3 Why is this area of research important?

It may be helpful to offer a perspective of the scale and the sensitivity of the issues involved. First, obesity is common, harmful and costly. Universally, according to the world health organization (WHO) [1], there are approximately two billions overweight adults and more than half a billion obese individuals. Moreover, the prevalence of obesity has almost tripled since 1975 [1]. In the UK, about a third of the adult population is obese [2] and, by 2030, an additional 11 million subjects are projected to become obese, which is estimated to add £1.9-2 billion a year as a consequence of obesity-related health costs [3].

Therefore, obesity is expected to be managed more frequently in settings where anaesthesia is administered. In 2011, it was estimated that approximately three million patients undergo general anaesthesia annually in the UK [4], and hypoxia has been identified as the mechanism responsible for the leading cause of anaesthesia-related mortality [4].

Secondly, obesity increases two serious risks during anaesthesia. Firstly, anaesthetised obese subjects are at an increased risk for rapid oxygen desaturation. Secondly, obesity is associated with increased complexity in airway management that may require a longer time to secure an airway. Therefore, developing methods to extend the non-hypoxaemic apnoea time in obese patients would be very useful to increase their safety. This would positively impact a large portion of the community as well as save an excessive amount of financial capital.

Worldwide, it has been estimated that up to 20 million acute respiratory failure patients receive mechanical ventilation per year [5]. The mortality of ARDS remains considerably high despite the implementation of the lung-protective ventilation strategy [6]. It is urgently imperative to research how can we improve the survival and the quality-of-life of ARDS patients.

1.4 How does the thesis contribute to the relevant field?

The first two modelling investigations (Chapter 5 and 6) provided quantitative insights into the gas exchange during apnoea. Diverse scenarios (e.g. airway obstruction) and treatments (e.g. HFNO) in a spectrum of obesity severity levels were simulated. The findings revealed informative data such as the safe apnoea time and the hypoxaemia progression rate until life-threatening degrees in a bank of obese virtual subjects. The implication of the knowledge generated

by these studies underlines the efficacity of multiple apnoeic oxygenation strategies and recommend HFNO to airway managers, as it showed to provide longer safe apnoea time in obesity, respect to classical apnoeic oxygenation.

The third investigation (Chapter 7) provided evidence that during the rescue of airway obstruction, the delivery of larger tidal volume does not lead to a faster re-oxygenation rate compared to smaller tidal volume. The implication of this finding could inform clinicians that massive tidal ventilation in this scenario is not necessary and might risk patients for undesirable complications; instead, the emphasis on delivering a high concentration of oxygen is much more crucial.

The last study (Chapter 8) answered a question that was previously unknown that pertains to the capability of the hyperbaric oxygen therapy to rescue severely hypoxaemic respiratory failure patients who failed maximum lung-protective mechanical ventilation. The implication of this finding may encourage researchers to consider HBOT in ARDS future trials.

1.5 Aims of the thesis

The overall aims of the thesis are to develop new rescue strategies in order to evaluate and quantify oxygenation and ventilation in banks of *in-silico* (virtual) patients suffering from obesity and critical respiratory illness.

Chapter 2: Introduction

2.1 Gas exchange

The primary function of the respiratory system is gas exchange, i.e. oxygen (O_2) and carbon dioxide (CO_2). Alveoli are the terminal functional units that are responsible for this process. They unload oxygen to the pulmonary capillaries as well as load CO_2 from the pulmonary capillaries by diffusion. Then, oxygen-rich blood is eventually circulated to the tissues and CO_2, on the other hand, is expelled outside the body [7].

2.1.1 Oxygenation

Oxygen is a vital requirement for the 37.2 trillion cells in a human body [8]. The precise structure of the pulmonary system was designed to not only fulfil but exceed the oxygen demand of these many cells. There are about 500 million alveoli surrounded by 620 miles length of pulmonary capillaries resulting in a large surface area available for gas exchange of about 75 m^2 [9]. The lungs supply one litre of oxygen every minute while the total O_2 demand is only a quarter of it (i.e. 0.25 $L \cdot min^{-1}$) in healthy adults during rest.

Tissue oxygen delivery (DO_2) is the cardiac output (CO) multiplied by the arterial oxygen content (CaO_2). The three most influential factors that affect tissue oxygenation at atmospheric pressure are cardiac output, haemoglobin concentration, and oxygen saturation in arterial haemoglobin.

2.1.2 Respiratory failure

Respiratory failure refers to the inability to maintain either adequate tissue oxygenation (hypoxaemic respiratory failure) or carbon dioxide elimination (hypercapnic respiratory failure) [10]. It is diagnosed via the arterial blood gas (i.e. PaO_2 and $PaCO_2$). Campbell

[11] has established the values associated with each failure type. Respiratory failure could present as acutely or chronically.

2.1.2.1 Hypoxaemic respiratory failure

Hypoxaemia refers to the low oxygen content in the arterial blood below normal values. Hypoxaemic failure is defined as PaO_2 of less than 8 kPa while breathing room air at atmospheric pressure. Hypoxaemia is the most commonly encountered complication during endotracheal intubation [12-15]. It is considered the highest risk factor for cardiac arrest and death during emergency intubation [16]. Scenarios that can cause hypoxaemia are *(i)* upper airway obstruction leading to delayed/failed intubation, *(ii)* oesophageal intubation, and *(iii)* aspiration.

During anaesthesia and apnoea (cessation of breathing), maintaining an adequate level of oxygen is crucial and is, unarguably, among the top priorities (if not the top priority) of the airway manager. Emergency airway management that takes place outside the operating theatre has been identified to be associated with a higher rate of airway complications, including hypoxia, failed intubation, oesophageal intubation and cricothyroidotomy, than elective intubation [4]. Moreover, it was reported that hypoxia was not only common, but it also led to significant untoward outcomes, i.e. brain damage and death (61% in ICU and 33% in emergency departments) [4]. This may be due to the deranged physiology of this population as well as the unavailability of trained staff and appropriate equipment.

More than 50% of claims in anaesthesia-related deaths were found to be related to hypoxia [17]. There are four physiological derangements that can cause hypoxaemia: *(i)* ventilation/perfusion mismatch, *(ii)* shunt, *(iii)* diffusion limitation, and *(vi)* alveolar hypoventilation [18].

Ventilation to perfusion mismatch

The normal ventilation to perfusion (V/Q) ratio is 0.8, which is the alveolar minute ventilation of 4 $L \cdot min^{-1}$, divided by the cardiac output of 5 $L \cdot min^{-1}$ [7]. V/Q inequality has been identified as the most common cause of hypoxaemia [19]. The V/Q mismatch lays between two extreme physiological abnormalities, dead space (ventilation with no perfusion) and shunt (perfusion with no ventilation), as depicted in Figure 2.1.

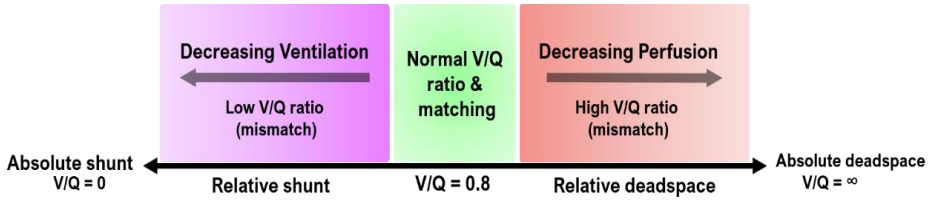

Figure 2.1. Illustration of the shunt-dead space continuum. Redrawn from [7].

Shunt

The shunt of the blood can be classified as anatomical shunt and pathophysiological shunt. Anatomical shunted blood accounts for about 2-3% of the cardiac output and is resulted from the shunted blood through the bronchial and thebesian veins that supply the lungs and heart [20]. Pathophysiological shunt presents either as an intra-cardiac or intra-pulmonary shunt that could be caused by pulmonary oedema, atelectasis and alveolar consolidation [18]. An absolute intra-pulmonary shunt is called an alveolar shunt. The merge of anatomical and alveolar shunted blood, with the oxygenated blood, on the left side of the heart is called venous admixture [20]. The total amount of intra-pulmonary shunted blood is called physiological shunt [20]. The anatomical shunt is responsible for the three-fourths of the difference between alveolar oxygen pressure and arterial oxygen pressure, that

is present in healthy young subjects, while the remaining difference is due to normal V/Q inequality [20].

2.1.2.2 Hypercapnic respiratory failure

Hypercapnic failure is defined as a $PaCO_2$ of more than 6.6 kPa [20]. Some conditions that could cause this failure include inadequate ventilation manifested by abnormal neural drive or muscular strength and abnormal pulmonary or thoracic mechanics [11].

2.2 Pre-oxygenation

2.2.1 Definition & purpose

Pre-oxygenation refers to the brief administration of a high concentration of oxygen before anaesthesia induction. The purpose of pre-oxygenation is to maximise the time of non-hypoxaemic apnoea to enable successful placement of invasive artificial airway. Difficult Airway Society has recommended pre-oxygenation not only before the induction of anaesthesia but also before endotracheal extubation [21, 22].

2.2.2 Physiological background

Oxygen can be stored in several places in the human body, such as blood, tissues, and lungs. Nitrogen occupies about 79% of the lungs' volume. Table 2.1 demonstrates the powerful impact of pre-oxygenation with 100% oxygen. The oxygen depletion time would be increased significantly, from 1.3 to 9.0 min, when 100% O_2 is breathed compared to room air.

A healthy subject breathing 100% O_2 would have a non-hypoxaemic apnoea time (i.e. SpO_2 = 90%) of about 6.9 min as compared with 5.1 min when breathing 80% O_2, 3.6 min when breathing 60% O_2 and less than 1 min when breathing room air [23].

Morbidly obese patients were found to have a non-hypoxaemic apnoea time of only 2.7 minutes despite receiving appropriate pre-oxygenation [24, 25]. The absence of pre-oxygenation is the main predictor of intubation-related cardiac arrest [26].

Table 2.1. A comparison of oxygen content in FRC in a healthy adult male, when breathing room air (21%) and 100% oxygen, using the alveolar gas equation.

$$\mathrm{PAO_2} = \mathrm{FiO_2}(\mathrm{P_{ATM}} - PH2O) - \frac{PaCO_2}{\mathrm{RER}}$$

	breathing 21 % O_2	**breathing 100 % O_2**
	$\mathrm{PAO_2} = .21(101.3 - 6.2) - \frac{5.3}{.8}$ $\mathrm{PAO_2} = 13.3\ \mathrm{kPa}$	$\mathrm{PAO_2} = 1.0(101.3 - 6.2) - \frac{5.3}{.8}$ $\mathrm{PAO_2} = 88.5\ \mathrm{kPa}$
O_2 in FRC (%)	13.3 / 101.3 0.13	88.5 / 101.3 0.87
O_2 in FRC (ml)	0.13 * 2,400 312	0.87 * 2,400 2,088
O_2 depletion time (min)	312 / 230 1.3	2,088 / 230 9.0

PAO_2: the alveolar partial pressure of oxygen, FiO_2: the fraction of inspired oxygen, P_{ATM}: the atmospheric pressure at the sea level, PH_2O: the water vapour pressure when relative humidity is 100% at normal body temperature, $PaCO_2$: the arterial partial pressure of carbon dioxide, RER: the respiratory exchange ratio, 230 ml oxygen consumption [27]; 2,400 ml FRC[28].

2.2.3 Pre-oxygenation optimisation

The efficacy of the pre-oxygenation (i.e. denitrogenation) is assessed by the concentration of the expired O_2 ($F_{ET}O_2$ > 90%), nitrogen ($F_{ET}N_2$ < 5%) [25], where SaO_2 during apnoea reflect the pre-oxygenation efficiency [27]. The SpO_2 is not an appropriate measure to evaluate the pre-oxygenation efficacy. For instance, Rudlof and Hohenhorst [29] reported a COPD case with diffusion limitation. Although the patient had a SpO_2 of only 94% after proper denitrogenation, but tolerated 45 minutes of non-hypoxaemic apnoea (with 0.5 $L{\cdot}min^{-1}$ of O_2 insufflation at the carina), indicating an effective pre-oxygenation despite the initial low SpO_2. Increasing the FRC and

filling it with high O_2 concentration via a leak-free interface are essential factors for optimal pre-oxygenation [30].

2.2.3.1 The role of body position in pre-oxygenation

When lying flat, FRC is decreased by 20-25% (about 0.8 L) [31]. The highest and lowest FRC values were observed during sitting and supine position, respectively [32]. Moreover, Lane and co-workers [33] found a safe apnoea time of about 100 seconds longer in the head-up elevation than the supine position. Two other studies [34, 35] were in agreement with this finding.

Despite proper positioning and O_2 supplementation, some critically ill patients may remain hypoxaemic during the pre-oxygenation phase. This may be due to the pulmonary shunt physiology, which could be improved by augmenting the mean airway pressure [36].

2.2.3.2 The role of positive airway pressure in pre-oxygenation

Positive airway pressure (PAP), e.g. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), and positive end-expiratory pressure (PEEP), have been shown to improve the efficacy of pre-oxygenation. BPAP demonstrated to increase FRC in morbid obesity [37]. BPAP was associated with higher SpO_2 and a lower incidence of critical hypoxaemia than bag valve mask (BVM) in hypoxaemic respiratory failure patients [38]. CPAP of 7.5 cm H_2O was linked with a longer safe apnoea time by approximately 35 seconds in 20 morbidly obese women [39]. A substantially (3.7 minutes) longer safe apnoea time was observed in non-obesity while receiving CPAP of 5 cm H_2O [40].

Appropriate pre-oxygenation has been described as the main method to extend the safe apnoea time [27]. However, another

technique could significantly prolong the safe apnoea time, which is called apnoeic oxygenation.

2.3 Apnoeic oxygenation

2.3.1 History and definition

Apnoeic oxygenation is an interesting phenomenon that was first observed by Hook in 1666 [41] when he blew air into an apnoeic dog's airway. The dog remained alive for over an hour, and as soon as the air ceases, the dog fell in convulsive fits. Two and a half centuries later, Volhard [42] provided a mechanistic explanation of apnoeic oxygenation. In curarized dogs and rabbits with patent airway, he noticed a significate sub-atmospheric intrapulmonary pressure (-20 cm H_2O) [43]. The early experiments of apnoeic oxygenation were conducted by Hirsch in 1905 [44] and by Volhard in 1908 [42]. On rabbits, the authors observed a continued O_2 saturation during 1 to 2 hours of apnoea. The rabbits received atmospheric 100% O_2 via a tracheal catheter, and when the supplemental O_2 was replaced by air, rabbits died rapidly within a few minutes.

Many other researchers, since the early 20th century, have investigated this occurrence [45, 46]. It was termed differently over time, "diffusion respiration" [47], "apnoeic diffusion oxygenation" [48], "aventilatory mass flow" [43] and finally "apnoeic oxygenation" [46].

Apnoeic oxygenation is the mass inflow of O_2 that occurs during apnoea if there are an open airway and a continuous O_2 supply [49]. Apnoeic oxygenation is performed after the induction of anaesthetic and paralytic agents that cause hypoventilation and/or apnoea in patients undergoing invasive interventions such as endotracheal intubation, endoscopy, or laryngeal surgeries [29, 50, 51].

2.3.2 Physiological mechanism and application

Oxygen moves from alveoli to blood capillaries by passive diffusion, which is driven by the pressure gradient of the O_2 available between the alveoli and the pulmonary capillaries. In order to achieve and maintain apnoeic oxygenation, three conditions are required: *(i)* airway patency, *(ii)* alveolar PO_2 that is higher than pulmonary capillaries PO_2, which can be achieved by the continuous provision of oxygen-rich gas, and *(iii)* the presence of the negative alveolar pressure that drives the airflow '*en masse'* from the upper airway to the alveoli [48].

The transairway pressure (P_{TA}) is the pressure gradient between the airway opening and the alveoli that drives the air in and out of the respiratory system. P_{TA} determines the direction and intensity of the gas flow. If P_{TA} is positive, the gas will flow from the upper to the lower airways and vice versa. The higher the P_{TA} value, the higher the flow rate enter or exit the respiratory system [20].

Figure 2.2 illustrates some of the differences in pulmonary mechanics and gas exchange during spontaneous breathing and apnoea. The pressure at the airway opening (e.g. mouth) is relatively constant at atmospheric pressure, while the alveolar pressure value varies during inspiration and expiration. In a healthy individual, the active contraction of the diaphragm during inspiration generates an alveolar pressure of about 1 cm H_2O below the atmospheric pressure [52]. However, during apnoea, the loss of the pressure gradient between alveolar and pulmonary capillary PCO_2 causes an extreme limitation for CO_2 to diffuse to the alveoli. The amount of CO_2 diffused to the alveoli become only 4% or 8 $ml \cdot min^{-1}$ of its normal amount of 200 $ml \cdot min^{-1}$, while the majority of the produced CO_2 (i.e. 96%) dissolves in tissue water that can contain 20 times more CO_2 as the

FRC can hold [53]. As a result of this dramatic gaseous net imbalance, alveolar pressure may reach up to 20 cm H_2O below the atmospheric pressure (i.e. 20 times more negative than normal inspiration), which plays the paramount role in establishing the underlining force that drives the gas (e.g. O_2) inflow downwards that maintains oxygenation during apnoea [42].

During apnoea, O_2 uptake continues to diffuse approximately at a rate of 228 ml·min^{-1} [53], which is derived as the following *(i)* the gas inflow equals the O_2 uptake minus the CO_2 excretion, so if O_2 uptake is assumed to be 250 ml·min^{-1} and CO_2 excretion 8 ml·min^{-1}, then the net difference is 242 ml·min^{-1}. Then if 100% O_2 is delivered and water vapour is considered, O_2 uptake equals gas inflow minus water vapour (approximately 6% of the inhaled gas pressure, 14 ml). So, 242 ml·min^{-1} minus 14 ml gives an O_2 uptake of 228 ml·min^{-1}.

If we assume that an individual consumes a total of 250 ml·min^{-1} of O_2, then the amount of the O_2 uptake during apnoea would fulfil about 91% of the total O_2 demand, which will delay hypoxaemia, especially if the subject has been appropriately pre-oxygenated.

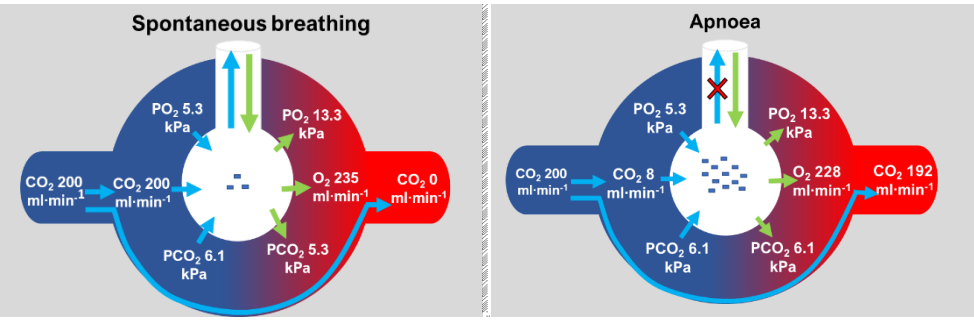

Figure 2.2. Schematic illustration of the gas exchange during spontaneous breathing and apnoea.

Accumulation of gases other than O_2 (e.g. CO_2 or N_2) in the alveoli decreases the space for O_2 to occupy, hence limit the continuous O_2 uptake, which eventually diminishes the negative alveolar pressure that drives the apnoeic oxygenation inflow [54].

Ultimately CO_2 will build up in the alveoli, which will cause the PAO_2 to be less than the O_2 tension in the pulmonary capillaries, which will prevent O_2 diffusion to the blood, resulting in hypoxaemia.

2.4 Acute Respiratory Distress Syndrome

2.4.1 Definition, history, and epidemiology

According to the Berlin definition [55], Acute Respiratory Distress Syndrome (ARDS) is defined as *(i)* an acute insult, *(ii)* bilateral pulmonary opacities that are caused by neither cardiac failure nor fluid overload, and *(iii)* significant arterial hypoxaemia. The ARDS severity has been classified as mild, moderate and severe, based on the magnitude of hypoxaemia in relation to the O_2 requirement, which is objectively represented as the ratio of the partial pressure of O_2 in arterial blood to the fraction of inspired O_2 (PaO_2/FiO_2, or PF ratio) measured while a minimum of 5 cm H_2O of positive airway pressure is being applied. The PF ratios for mild, moderate and severe ARDS are listed in Table 2.2. The ARDS was first described by Ashbaugh and colleagues in 1967 [56].

Table 2.2. The classification of the Acute Respiratory Distress Syndrome severity according to the Berlin definition [55].

Mild	**26.6 kPa <** PaO_2/FiO_2 **≤ 39.9 kPa**
Moderate	**13.3 kPa <** PaO_2/FiO_2 **≤ 26.6 kPa**
Severe	**13.3 kPa ≥** PaO_2/FiO_2

PaO_2, the partial pressure of oxygen in arterial blood; FiO_2, the fraction of inspired oxygen
Note: all PF values must be obtained while receiving a minimum of 5 cm H_2O of positive airway pressure.

A large observational study that collected data from 50 countries has shown that the prevalence of ARDS accounts for 10% of all ICU admission and 23% of those receiving mechanical ventilation. Hospital mortalities were 35%, 40% and 46%, in mild, moderate and severe

ARDS patients, respectively [57]. Factors that are likely to affect survival from ARDS include age, the severity of lung injury, intensity of inflammatory response, degree of vital organs' dysfunction, comorbidity, and the quality of supportive care [58-60].

2.4.2 Aetiology and pathophysiology

ARDS is a syndrome rather than a disease entity. It can originate from either a pulmonary or non-pulmonary insult. Pulmonary insults include pneumonia, aspiration of gastric content, pulmonary contusion, toxic and smoke inhalation, and near-drowning. Non-pulmonary insults include sepsis, major trauma, massive blood transfusion, and acute pancreatitis [7].

The current understanding suggests that the main pathophysiological manifestation in ARDS is the increased permeability of the pulmonary capillaries. A subsequent leakage of protein-rich fluid (e.g. oedema) enters the pulmonary interstitium then the alveoli. This often initiates a release of inflammatory mediators' cascade (e.g. prostaglandins, endotoxins, and cytokines) that activate neutrophils and attract them in. Neutrophils release toxic substances that further increase the permeability of the capillaries as well as destroy tissues [7]. The flooding in the airspaces results in *(i)* deactivation of the surfactant (that plays a crucial role in preventing lung collapse during expiration), *(ii)* disruption of the ventilation to perfusion matching (low V/Q ratio), causing a shunt-like effect in lung areas that are under-aerated, but not collapsed, *(iii)* hyperinflation of the healthy regions of the lung leading to excessive ventilation relative to perfusion (high V/Q ratio), causing an increase in alveolar deadspace.

The intrapulmonary shunt is the result of the alveolar filling and the considerable atelectasis that causes a reduction in the lung

compliance (thus require higher work of breathing), refractory hypoxaemia, while the increased alveolar deadspace may induce hypercapnia if alveolar minute ventilation is not increased for compensation [61]. The magnitude of pulmonary shunting (i.e. hypoxaemia) is further worsened by the diminished hypoxic pulmonary vasoconstriction (HPV) that is likely present in ARDS [62]. HPV is an astonishing physiological mechanism of the pulmonary capillaries that decreases the blood flow to the poorly aerated regions of the lungs. HPV is activated when the alveolar PO_2 is less than 9.3 kPa [7]. Moreover, acidemia is an independent factor to increase pulmonary vascular resistance (even at normal PAO_2) irrespective of PAO_2 value [63]. A shunt fraction of more than 30% is considered life-threatening and require immediate mechanical ventilatory support [7].

2.5 Hyperbaric oxygen therapy

2.5.1 Definition and history

The Undersea and Hyperbaric Medical Society (UHMS) defines hyperbaric oxygen as "an intervention in which an individual breathes near 100% O_2 intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute, or ATA)". According to the UHMS, the therapeutic pressure level must be at least 1.4 ATA while breathing near 100% O_2. The British Hyperbaric Association categories hyperbaric chambers into four classes. Class I is defined as a hyperbaric facility capable of supporting ICU patients and offers Advanced Life Support in or out of the chamber (if needed).

Paul Bert thoroughly described the physiological changes caused by the elevation and reduction of ambient pressure [64]. The cardiac surgeon Boerema and co-workers [65] demonstrated that dogs tolerated longer durations of cardiac arrest when they were

cooled and exposed to 3 ATA O_2. In 1959, Boerema and co-workers [66] performed cardiac surgeries using a hyperbaric operating theatre with an ischemic clamp time of 14 minutes was successfully achieved on humans. Many similar operating chambers were soon built across the world. Gradually, these hyperbaric operating theatres became obsolete due to the development of extracorporeal cardiovascular circulation machines.

2.5.2 Mechanism and relevant physical laws

There are several consequences of increasing the ambient pressure governed by physical laws. For instance, Boyle's law describes that, at a constant temperature, the volume is inversely related to pressure. Increasing ambient pressure reduces the cavities that are filled with air like the lungs, middle ear, and sinuses. Additionally, hyperbaric pressure compresses the particles, thus decreasing their diameters, which is the reason HBOT is recommended in treating conditions like decompression sickness and gas embolism. Henry's law explains that the amount of dissolved gas in a defined volume is proportional to the gas partial pressure. As ambient pressure increases, the partial pressure of the inhaled gases (e.g. O_2) increase as well, which increases the pressure gradient across the alveolar-capillary membrane, thus enables higher diffusion rates.

Normally, the overwhelming majority of O_2 is transported via bonding to haemoglobin, and a negligible amount of O_2 is transported by dissolving in plasma. Once haemoglobin is fully saturated with O_2, it cannot carry any further O_2 molecules despite increasing PO_2 in alveoli. Nevertheless, PO_2 will continue to diffuse into the plasma as long as the PO_2 gradient between alveoli and plasma is positive.

Table 2.3 illustrates the influence of increased barometric pressure and FiO_2 on the amount of O_2 dissolved in the plasma in a healthy subject and a subject with diseased lungs. If we assume that a healthy subject is exposed to a 3 ATA of hyperbaric O_2 and has a cardiac output of 5 $L \cdot min^{-1}$, then the amount of the O_2 dissolved in the plasma (excluding those bond with haemoglobin) would fulfil and exceed the average resting O_2 demand. This has been confirmed by animal model experiments [67].

Table 2.3. The estimated impact of the ambient pressure and inspired oxygen concentration on the amount of dissolved oxygen in plasma in a healthy subject and a subject with diseased lungs.

	PB (ATA)	**FiO_2**	**PAO_2** (kPa)	**PaO_2** (kPa)	**O_2 in plasma*** ($mL \cdot L^{-1}$)
Healthy	1	0.21	14	12	2.8
	1	1.0	90	82	18.9
	2	1.0	185	177	40.8
	3	1.0	280	272	62.7
ARDS with Q_S/Q_T of 50%	1	1.0	90	45	10.1
	2	1.0	185	92	21.2
	3	1.0	280	140	32.2

PB, barometric pressure; FiO_2, the fraction of inspired oxygen; PAO_2, the alveolar partial pressure of oxygen; PaO_2, the arterial partial pressure of oxygen; Q_S/Q_T, shunt fraction.
* The solubility coefficient used to determine the amount of oxygen in plasma is 0.023 ($mL \cdot dL^{-1} \cdot kPa^{-1}$) [68].

2.5.3 Potential benefits and risks of HBOT

When hyperbaric oxygen therapy is conducted correctly, the severe untoward effects are rare [69], and if they occur, they are almost always reversible [70]. There is no doubt that HBOT could cause hyperoxia, and hyperoxia is thought to cause benefits and carry

some risks. Some advantages of hyperoxia include *(i)* enhanced wound healing induced by the high amount of O_2 at the tissue level as well as angiogenesis (i.e. forming new blood vessels), *(ii)* reduces tissue inflammation [71], and *(iii)* kills and/or inhibits the growth of some anaerobic bacteria [72] and suppresses the release of their toxins [73].

On the other hand, risks of hyperoxia include *(i)* O_2 toxicity affecting several organ systems like the central nervous and the pulmonary systems, *(ii)* barotrauma of the middle ear, sinus, teeth, or lungs, and *(iii)* myopia (i.e. short-sightedness). An additional extremely important hazard of HBOT is the high potential of fire, which many individuals have sadly lost their lives in terrifying catastrophic incidences around the world [74]. Moreover, in the event of an emergency, it is likely that rapid decompression will be needed, risking decompression sickness, which would be extremely risky in critically ill, severely hypoxaemic patients considering their poor oxygenation reservoir. However, the use of mechanical ventilation per se has been deemed safe in hyperbaric chambers [75].

2.5.3.1 Oxygen toxicity

Two factors determine the likelihood of developing O_2 toxicity, *(i)* the partial pressure of O_2 in the inhaled gas, which is determined by (and proportional to), the ambient pressure as well as the FiO_2, and *(ii)* the duration of exposure. The higher the values of these two factors, the more likely O_2 toxicity will occur. However, the exact upper threshold could not be precisely defined due to the high degree of variability of O_2 tolerance not only among different subjects but also within the same subject at different times [76]. Nonetheless, in order for CNS O_2 toxicity to develop, it requires higher PO_2 than pulmonary O_2 toxicity.

The most common manifestation of CNS O_2 toxicity (i.e. the Bert effect) is nausea followed by seizures [77]. Sometimes, seizures that occur during an HBOT session are caused by HBOT-induced hypoglycaemia rather than O_2 toxicity. Therefore, to minimise CNS O_2 toxicity, one should consider thorough patient assessment pre and post-treatment, close monitoring during treatment, vitamin E, air breaks, and appropriate selection of PO_2 and exposure time.

Hypercapnia has been reported to accelerate the occurrence of CNS O_2 toxicity [78]. A proposed mechanism responsible was the hypercapnia-induced cerebral vasodilation which enabled higher O_2 tension delivery to the brain [79]. Additional factors that foster O_2 toxicity include premature birth, viral pneumonia, humidity, fever, and vitamin E deficiency. On the other hand, some factors that protect against O_2 toxicity include lower FiO_2 or intermittent 100% O_2, chronic hypoxia, young age, surfactant and nitric oxide [64].

Pulmonary O_2 toxicity has been first described by James Lorrain Smith in 1899 when he exposed mice to FiO_2 of 0.4 at an ambient pressure of 4.5 atmospheres. He notices lung inflammation and massive lung congestion at the postmortem examination [80]. Subsequently, other studies on humans revealed that prolonged exposure to O_2 caused tracheobronchitis, nausea, and alteration in pulmonary parameters such as a reduction in vital capacity and in the diffusing capacity of the lungs for carbon monoxide (DI_{CO}) [80].

Oxygen is quite reactive, and it is most stable when it is bond with hydrogen to produce water. In this cellular respiration chemical process, reactive (or sometimes referred to as radical) oxygen species (ROS), i.e. superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-), are produced. During normoxia, the cells are capable of neutralizing ROS, while in hyperoxic states, ROS

overwhelm the antioxidant defence. ROS targets and damage various biological sites such as cell membranes, proteins, nucleic acid, and enzymes [81]. A natural protective mechanism is that the lungs are equipped with an increased concentration of antioxidants to endure a higher concentration of O_2 [82].

Lambertsen and colleagues [83] developed a means to quantify the O_2 toxicity, which is called the Unit Pulmonary Toxic Dose (UPTD). Basically, one UPTD is equal to breathing 100% O_2 at 1 ATA for 1 minute. An upper cut-off of the UPTD has been determined based on the reversible 10% reduction of vital capacity that occurs when receiving 1440 UPTD, which equals breathing pure O_2 for 24 hours at sea level. To minimise the occurrence of the CNS O_2 toxicity, international organisations recommend that the PO_2 level does not exceed 2.8 bar absolute.

2.6 Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) became available in 1972 to support patients suffering from severe acute hypoxemic respiratory failure. ECMO can be set up to support either haemodynamic and gas exchange (veno-arterial abbreviated as VA ECMO) or only gas exchange (veno-venous abbreviated as VV ECMO) [20]. ECMO requires invasive vascular cannulation as well as administration of systematic anticoagulation, and bleeding is considered the predominant complication of ECMO with an incidence rate of 4-8%, 13%, and 17%, intracranial haemorrhage, surgical site bleeding, and cannulation site bleeding, respectively [84]. Other complications include clotting disorders like platelet dysfunction [85] and others.

On the other hand, some features of ECMO are being portable, no risk or discomfort for staff, and predisposes lower risk for O_2

toxicity as well as lung injury as the intensity of the ventilator support will be decreased, allowing the lungs to rest.

Chapter 3: Literature review

3.1 Aims of the literature review

The literature review chapter is intended to enhance my understanding of the physiological processes underpinning apnoeic oxygenation, pulmonary alterations in obesity, and the use of HBOT in ARDS. Additionally, identify what is not yet known and recognise what is urgent to be investigated.

3.2 Literature search technique

I conducted a thorough, non-systematic, electronic review of scholarly journal articles on search databases including, but not limited to, EMBASE, MEDLINE, Web of Science and Ovid Journals. Examples of search keywords were apnoeic oxygenation, pre-oxygenation, obesity, ARDS, airway management, intubation, safe apnoea time, HFNO, THRIVE, and HBOT. The search was limited to neither a particular time nor a language. The literature review aimed to cover the very first experiments in humans and animals up to the era of modern and sophisticated methods of apnoeic oxygenation.

3.3 Respiratory alterations in obesity

Obesity is a condition characterised by an excessive amount of total body fat [86]. Obesity severity is commonly classified via the Body Mass Index (BMI). A BMI is calculated as the weight in kg divided by the height in meter^2. A BMI of ≥ 30, ≥ 35, and ≥ 40 kg·m^{-2} are classified as obese class I, class II, and class III, respectively [87].

The effects of obesity on the respiratory functions seem to be heterogeneous and incompletely explained, but the most consistent alterations appear to be a reduction in the total respiratory system compliance [18, 88-90] and the functional residual capacity (FRC), which is prominently due to a decrease in the expiratory reserve

volume (ERV) [90-93]. The severity of the respiratory abnormalities caused by obesity tend to be associated with the excessiveness of tissue adiposity, its distribution in the body and obesity-hypoventilation syndrome (OHS) [18, 94].

3.3.1 Lung volumes

The lungs consist of several volumes and capacities. Capacity is defined as a sum of two lung volumes or more. A schematic illustration of the lung volumes and capacities for a normal subject is presented in Figure 3.1.

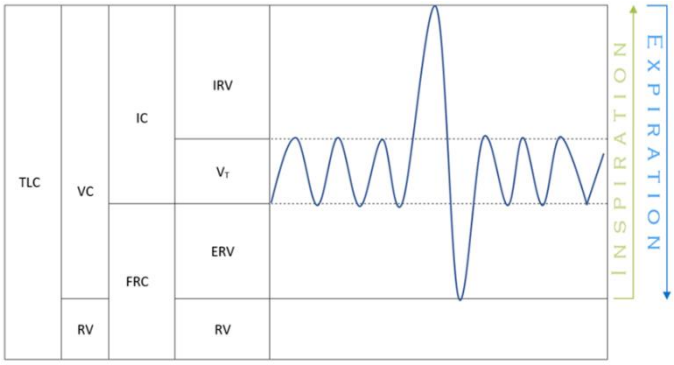

Figure 3.1. Lung volumes and capacities: TLC, total lung capacity; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; V_T tidal volume; IRV, inspiratory reserve volume; ERV, expiratory reserve volume.

There is sufficient evidence indicating that as obesity increases, expiratory reserve volume (ERV) and functional residual capacity (FRC) continue to decrease [90-93]. Jones and Nzekwu [91] evaluated pulmonary function tests (PFT) of various awake obese subjects using BMI. They found a negative exponential relationship between BMI and FRC and ERV. The ERV values (% of predicted) for BMI 20-25, 25-30, 30-35, 35-40 and >40 $kg \cdot m^{-2}$ were 95.6%, 72.3%, 42.4%, 29.3% and 24.6%, respectively. Furthermore, another study by Biring and co-workers [92] supported the previous study's finding by showing that patients with BMI ≥ 62 $kg \cdot m^{-2}$ had an ERV of only 17.8 - 22 % of

predicted. Three factors independently contribute to the reduction of FRC, obesity, general anaesthesia, and supine position.

3.3.2 Closing capacity

Figure 3.2 illustrates the closing capacity (CC) with the FRC in non-obese, obese subjects and during anaesthesia. The CC is the sum of closing volume (CV) and RV, where CV is the amount of vital capacity (VC) that can be exhaled after airway closure begins.

When FRC drops below the CC, patients may develop distal absorption atelectasis, thus resulting in ventilation-perfusion mismatch and pulmonary shunt, leading to hypoxaemia. In such conditions, patients may require PAP to increase the FRC above the CC. Factors that increase CV and CC are advanced age, smoking, congestive heart failure and obesity [95]. In contrast, factors that decrease FRC include anaesthesia, supine position and any restrictive pulmonary disease, e.g. obesity, [28, 32, 96].

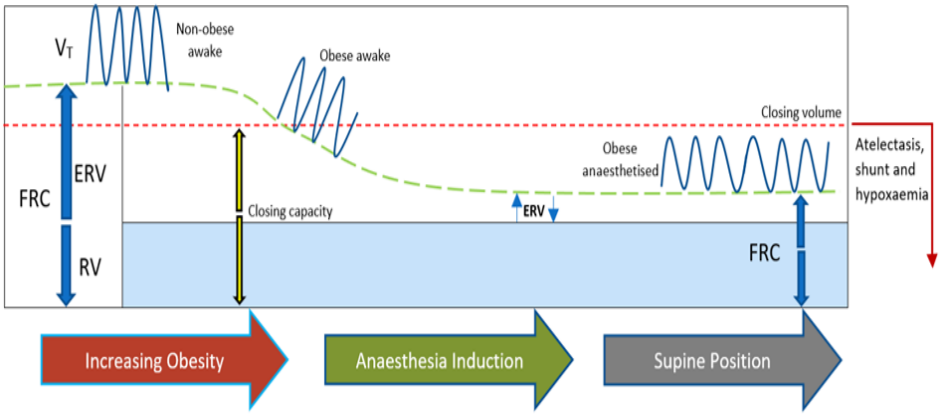

Figure 3.2. Illustration of functional residual capacity (FRC) and closing capacity (CC). Increasing obesity, supine position and anaesthesia induction are independent factors that decrease the FRC.

3.3.3 Fat distribution

Central obesity, where fat is stored mainly in the abdominal and chest walls, is believed to impact the respiratory mechanics more than

peripheral obesity. The excessive adipose tissue stored in the abdomen and chest decreases the respiratory compliance and increase the intra-abdominal pressure [97]. Canoy and co-workers [98] evaluated PFTs of a large UK cohort of more than 21,000 subjects. They found that abdominal obesity had an inverse relation with forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) across the entire cohort. Similarly, Chen and co-workers [99] found that waist circumference had a consistent negative correlation with FEV_1 and FVC.

3.3.4 Obesity-Hypoventilation Syndrome

Obesity-hypoventilation syndrome (OHS) is characterised by morbid obesity (BMI >40 $kg \cdot m^{-2}$) and chronic hypercapnia ($PaCO_2$ > 6 kPa) during wakefulness. The overall effects of obesity on respiratory mechanics appear to be worse in OHS than in those with similar obesity but without chronic CO_2 retention, as reported in Table 3.1.

Table 3.1. Respiratory Mechanics in Simple Obesity (SO) and Obesity Hypoventilation Syndrome (OHS) [18]

	Non-obese	SO	OHS
BMI ($kg \cdot m^{-2}$)	24	45	46
TLC (% predicted)	100	95	83
CRS ($L \cdot cm\ H_2O^{-1}$)	0.11	0.05	0.06
RRS ($cm\ H_2O \cdot L^{-1} \cdot sec^{-1}$)	1.2	4.0	7.8
Work ($J \cdot L^{-1}$)	0.43	0.74	1.64
MVV ($L \cdot min^{-1}$)	159	129	89
PI_{max} ($cm\ H_2O$)	100	95	60

CRS = compliance of the respiratory system; RRS = respiratory system resistance; PImax = maximal inspiratory pressure; MVV = maximum voluntary ventilation.

3.3.5 Respiratory mechanics

It is well known that obesity decreases total respiratory system compliance (CRS) [18, 88-90]. Naimark and Cherniack [100] found

that the CRS of obese subjects was almost entirely due to a reduction in chest wall compliance and was further decreased in the supine position. On the other hand, Sharp and co-workers [89] found, in SO subjects, that lung compliance (0.16 L·cm H_2O^{-1}) is more pronouncedly reduced as compared to thoracic compliance (0.20 L·cm H_2O^{-1}), wheres in OHS patients, thoracic compliance (0.08 L·cm H_2O^{-1}) was more declined than lung compliance (0.12 L·cm H_2O^{-1}).

3.3.6 Control of breathing

In eucapnic morbidly obese patients, Burki and Baker [90] found a significant increase in minute ventilation at rest due to increased inspiratory neuromuscular drive and high respiratory rate without a large difference in tidal volume. Also, another study [101] found a strong positive relationship between obesity and neuromuscular respiratory drive. The hypercapnic ventilatory response was reported to be reduced by 40% in SO and by 65% in OHS, while SO could have a normal or higher ventilatory response to hypoxaemia than non-obese subjects [102].

3.3.7 Oxygen consumption

Obese subjects consume approximately 25% higher O_2 content at rest than non-obese individuals [94]. Compared to non-obese subjects, the O_2 demand required for the increased work of breathing is about 60% higher in SO subjects and up to 250% higher in OHS patients. Additionally, the O_2 cost of breathing at rest increases to approximately five folds in SO and close to 10 folds in OHS [18]. Hypoxaemia is a manifestation of OHS patients but is not present in SO subjects except in severe SO or during supine position [18].

3.3.8 Anaesthesia effects on respiratory function

The induction of anaesthesia was observed to reduce the FRC by approximately 20% in non-obese subjects [103] and 50% in obese patients with BMI > 40 $kg \cdot m^{-1}$ [96]. A possible explanation for the anaesthesia-induced FRC reduction is the loss of the tonic activity present in the inspiratory muscles, allowing the diaphragm cephalad displacement into the thoracic cavity and further restricting the lung volume, as illustrated in Figure 3.3. Ketamine was documented to be the only anaesthetic that does not affect the muscular tone, thus preserve FRC and prevent subsequent atelectasis [103].

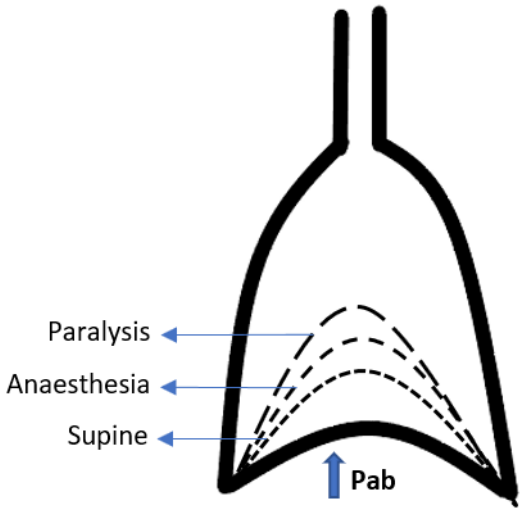

Figure 3.3. Progressive cephalad displacement of the diaphragm; Pab abdominal pressure, FRC functional residual capacity. Redrawn from Hagberg and Benumof's airway management, Chapter 5, Page 138

In anaesthetised obese patients, the intra-pulmonary shunt found to be 10% - 25%, as compared to 2% - 5% in lean subjects [104], which explain why obese patients are at high risk for rapid hypoxaemia shortly after the administration of general anaesthesia [105].

3.3.9 Body position

Dixon and co-workers [106] found, in severely obese patients, that the inclined position had about 50 seconds longer safe apnoea time and 11 kPa higher PaO_2 than the supine position group.

Additionally, ramped position significantly improved the laryngeal view in morbidly obese patients as compared to the sniffing position [107]. Another study [108] showed a more than 50% reduction of intubation-related complications in the 30° back-up head-elevated (BUHE) group than the supine group. Furthermore, Turner and co-workers [109] found a 65.8%, 77.9% and 85.6% first intubation attempt success in the supine, inclined and upright positions, respectively.

3.3.10 Airway difficulty in obesity

Face mask and laryngeal mask ventilation, tracheal intubation and emergency surgical airway have been identified to be more difficult when obesity is accompanied by obstructive sleep apnoea (OSA) [4, 110]. Obesity, particularly around the neck, is a significant risk factor for OSA and strongly correlates with increasing BMI [111, 112]. A 10% increase in body weight risks for devolving moderate to severe OSA by six-fold [113]. A study found that the prevalence of OSA in obese subjects undergoing bariatric surgery is between 73% to 83 % [114].

Obesity has been identified as an independent risk factor for airway complications. The 4th National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society (NAP4) have found that approximately 50% of the severe airway complications occurred to obese patients [115].

Table 3.2. Summary of the anatomical, cardiopulmonary and metabolic alterations imposed by obesity

Parameter	Effect	Ref
CRS	decreased	[89]
RS	increased	[89]
WOB	increased	[89]
$P_{0.1}$	increased	[116]
P_{IMAX}	decreased	[116]
V_T	decreased	[116]
RR	increased	[116]
V_E	increased	[117]
FRC	decreases as BMI increases	[91]
FVC	decreases as BMI increases	[98]
FEV_1	decreases as BMI increases	[98]
CC	increased	[95]
Q_S/Q_T	increased	[104]
PaO_2	decreases as BMI increases	[93]
VO_2	increases as BMI increases	[118]
CO	increased	[119]
SV	increased	[119]
HR	normal	[119]
Airway	- Difficult FMV and ESA - SGA failure	[120]

CRS, respiratory system compliance; RS, respiratory resistance; WOB, work of breathing; $P_{0.1}$ occlusion pressure (represent respiratory drive); P_{IMAX}, maximal inspiratory pressure; V_T tidal volume; RR, respiratory rate; V_E, minute ventilation; FRC, functional residual capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; CC, closing capacity; Q_S/Q_T, shunt fraction; PaO_2, partial pressure of oxygen in arterial blood; VO_2, oxygen consumption; CO, cardiac output; SV, stroke volume; HR, heart rate; FMV, face mask ventilation; LMA, laryngeal mask airway; ESA, emergency surgical airway. Ref, reference.

3.4 Apnoeic oxygenation

3.4.1 Safe apnoea time

Safe apnoea time refers to the time between the onset of apnoea and up until a certain O_2 desaturation level is reached, e.g. SpO_2 = 90-92%.

3.4.1.1 Apnoeic oxygenation during elective procedures

The first apnoeic oxygenation experiment that was conducted on humans was performed by Enghoff and co-workers [121] in 1951. The subjects were sedated and paralysed, then a cuffed endotracheal tube (ETT) was inserted in the trachea followed by a 10 min of 100% O_2 inhalation (i.e. denitrogenation) via the anaesthetic machine. Next, the ETT was disconnected from the anaesthetic machine and connected to a spirometry expiratory hose that provided 100% O_2 with no artificial respirations nor positive pressure. The subjects tolerated a period of 5 to 7 minutes of apnoea with no hypoxaemia.

Similarly, Frumin and co-workers [46] have investigated apnoeic oxygenation, but for extended periods of apnoea, with a mean apnoea time of 40 min and a range of 18 to 55 min. First, the eight healthy patients received a 100% O_2 via facemask for 5 minutes. Next, they were sedated and paralysed, and then ETT was inserted. Then, manual breathing started, which consisted of airflow ≥ 8 $L{\cdot}min^{-1}$ of 100% O_2 for a period of ≥ 30 min. After that, manual compression stopped, and apnoea was allowed to persist while the ETT is connected to the circular anaesthesia apparatus. The reservoir bag was filled with approximately 2-3 litres of O_2 every 15 minutes (i.e. 133-200 $ml{\cdot}min^{-1}$). All participants had a non-hypoxaemic apnoea time ≥ 30 min except for one subject. All subjects had a $SaO_2 \geq 98\%$ throughout the study. No cardiac arrhythmia was observed except in two subjects that had ventricular extrasystole. Moderate to severe

hypertension occurred during apnoea and followed by mild hypotension after the commencement of artificial respiration.

Rudlof and Hohenhorst [29] observed a SpO_2 of ≥ 98% for up to 45 minutes of apnoea in 47 subjects who received 0.5 $L \cdot min^{-1}$ of O_2 via an intra-tracheal catheter. Three subjects had O_2 desaturation, which was due to obesity, inadequate pre-oxygenation and spontaneous breathing. In 12 healthy individuals, Teller and co-workers [122] examined less invasively apnoeic oxygenation delivered via pharyngeal insufflation. They found that all the subjects that received 3 $L \cdot min^{-1}$ of O_2 during apnoea had completed the full allocated apnoea duration (10 min) with $SpO_2 \geq 97\%$, as compared to a mean safe apnoea time of 6.8 min in the control group. Lee [123] investigated non-invasive apnoeic oxygenation via nasal prongs. He reported that the PaO_2 had dropped less sharply in the patients that received 5 $L \cdot min^{-1}$ O_2 (from 65±6 kPa at baseline to 46±10 kPa at 3^{ed} minute of apnoea) than the control group (from 64±8 kPa at baseline to 35±11 kPa at 3rd minute of apnoea).

Finally, Rajan and co-workers [124] studied the effects of CPAP applied during the pre-oxygenation phase and apnoea. The CPAP group received 20 cm H_2O with O_2 supplement during the pre-oxygenation and the apnoeic periods, while the control group received only 6 $L \cdot min^{-1}$ of 100% O_2 during the pre-oxygenation and the apnoeic periods. The CPAP group had a significantly longer safe apnoea time (SpO_2 = 90%) of 816±30 sec as compared to 348±122 sec in the control group. A summary of the studies that investigated apnoeic oxygenation during elective procedures is presented in Table 0.1 in the appendix.

THRIVE during elective procedures

THRIVE is an acronym for "Transnasal Humidified Rapid-Insufflation Ventilatory Exchange", which refers to the use of HFNO during apnoea. Gustafsson and co-workers [51] conducted a physiological case series of 30 subjects planned for minor surgeries. The majority of the subjects were non-obese (i.e. BMI < 25 $kg \cdot m^{-2}$), while several were overweight, and a few were mildly obese. The subjects were pre-oxygenated using HFNO 40 $L \cdot min^{-1}$ of 100% O_2 for at least 3 minutes. Next, the subjects were sedated and paralysed, and the HFNO flow was increased to 70 $L \cdot min^{-1}$ of 100% O_2. The apnoea duration ranged from 11 to 33 min, with a mean of 22.5 min. All the subjects completed their procedures while maintaining adequate oxygenation throughout the apnoeic period except in one subject, which was due to hypercapnia.

Similarly, Lyons and Callaghan [125] performed a case series of 28 patients undergoing elective laryngeal or tracheal surgeries. All the subjects were pre-oxygenated for 3 minutes using 80 $L \cdot min^{-1}$ via HFNO. During apnoea, the same set up remained unchanged. The median apnoea time was 19 min, with a range of 9-37 min. All patients had a SpO_2 of ≥ 92% except for four patients that had mild hypoxaemia with the lowest SpO_2 of 85%. The subject that had the longest apnoea duration (i.e. 37 min) was an overweight subject and had a SpO_2 of 87%.

Joseph and co-workers [126] compared the efficiency of CPAP and HFNO, delivered during apnoea, in 20 non-obese patients undergoing general anaesthesia. The subjects in the CPAP group received a CPAP of 15 cm H_2O with O_2 supplementation, while the subjects in the HFNO group received 30 $L \cdot min^{-1}$ of 100% O_2 for 3 min. After induction and neuromuscular blockade, the O_2 flow rate was

increased to 10 L·min^{-1} with the same CPAP level in the CPAP group, while the O_2 flow was increased to 60 L·min^{-1} in the HFNO group. Both groups have completed the full allocated apnoea time of 12 min without hypoxaemia. However, the CPAP group had a significantly higher PaO_2 at the end of apnoea, 54 kPa, as compared to 28 kPa in the HFNO group. However, it is questionable how these two studies [124, 126] found the same PaO_2 rate of decrease (i.e. 1.0 kPa·min^{-1}) in the CPAP group despite using two different levels of CPAP (i.e. 15 and 20 cmH_2O). A summary of the studies that investigated THRIVE during elective procedures is presented in Table 0.2 in the appendix.

3.4.1.2 Apnoeic oxygenation during emergency intubation

Dyett and co-workers [15] conducted a prospective observational study to evaluate apnoeic oxygenation in 129 critically ill patients. Respiratory failure was the most common indication for intubation. Strategies of pre-oxygenation and apnoeic oxygenation were quite varied. Their findings showed that the hypoxaemia incidence in the non-respiratory failure patients who received apnoeic oxygenation via NC 15 L·min^{-1} was 0.0% as compared to 16.7% in those who did not receive it. Apnoeic oxygenation did not prevent hypoxaemia in respiratory failure patients. There was indeed considerable variability in the strategies used in both phases (i.e. pre-oxygenation and apnoeic oxygenation), so it is difficult to conclude as to which device offers a higher efficacy during each phase. However, the overall effect of apnoeic oxygenation in the non-respiratory failure patients was significantly positive.

The effectiveness of apnoeic oxygenation is supported by Wimalasena and co-workers [127], who evaluated 728 patients in the pre-hospital setting, mainly due to trauma. The cohort that received apnoeic oxygenation via NC 15 L·min^{-1} of O_2 had a hypoxaemia

incidence of 16.5%, while it was 22.6% in the cohort that did not receive apnoeic oxygenation.

Moreover, Sakles and co-workers [128] found that 82.1% of the patients that received apnoeic oxygenation had a first-attempt intubation success without hypoxaemia, as compared to 69.0% in the cohort that did not receive apnoeic oxygenation. In this study, the observed benefit is evident even though the patients in the apnoeic oxygenation group had more risk factors for hypoxaemia, such as respiratory failure (17% vs 12%) and obesity (57% vs 49%).

Further, Sakles and co-workers [129] showed that the incidence of mild (SpO_2 < 90%), moderate (SpO_2 < 80%) and severe (SpO_2 < 70%) hypoxaemia was remarkably lower in the patients that received apnoeic oxygenation, 7% vs 29% in mild, 4% vs 18% in moderate and 3% vs 9% in the severe hypoxaemia. An essential limitation of this study is that the study data were entered by the clinicians and were not extracted directly from the monitors, which may have caused inaccurate data reporting or recall bias. A summary of the studies that investigated apnoeic oxygenation during emergency intubation is presented in Table 0.3 in the appendix.

THRIVE during emergency procedures

Miguel-Montanes and co-workers [130] examined two methods of apnoeic oxygenation, 60 $L \cdot min^{-1}$ O_2 via HFNO and 6 $L \cdot min^{-1}$ via a nasopharyngeal catheter. The investigators found a median SpO_2 of 100%, while it was 94% in the HFNO and the other group, respectively. The incidence of critical hypoxaemia (SpO_2 < 80%) was 2% in the HFNO group and 14% in the other group. The study failed to properly examine the efficacy of the two devices used for pre-oxygenation, as end-tidal O_2 concentration was not used. It is worth noting that these results may have been affected by the uneven

distribution of the patient population, in particular, respiratory failure. It is unknown whether the increased SpO_2 was related to the pre-oxygenation or the apnoeic oxygenation techniques since the investigators implemented two different pre-oxygenation and apnoeic oxygenation strategies.

Furthermore, Semler and co-workers [131] randomised 150 ICU patients, mainly due to respiratory failure, to either receive 15 $L \cdot min^{-1}$ of 100% O_2 via HFNO or receives nothing during laryngoscopy. They found no difference in the median lowest SpO_2 between the two groups. However, there are a few concerns regarding the study's methods. First, the researchers did not prohibit manual ventilation after the onset of apnoea in all patients, which can affect the primary outcome (lowest SpO_2). Secondly, the prescribed flow rate was not high enough. It is well known that many of the physiological benefits of using HFNO are originated from its ability to deliver high flow (e.g. 70 $L \cdot min^{-1}$). Some benefits are flow-dependent, like the dead space flushing and the positive airway pressure, which is proportionally correlated with flow rate, reaching up to 16 cm H_2O with 100 $L \cdot min^{-1}$ [132]. I postulate that the increased positive airway pressure may have positively affected this patient population (i.e. respiratory failure) by increasing the FRC and improving the V/Q matching hence delay the hypoxaemia onset.

Finally, Jaber and co-workers [133] conducted an interesting proof-of-concept RCT in severely hypoxaemic respiratory failure patients. The researchers randomised patients to receive either 60 $L \cdot min^{-1}$ of 100% O_2 via HFNO, combined with PS of 10 cm H_2O and PEEP of 5 cm H_2O and FiO_2 1.0 for 4 min, or receive the same NIV settings but without HFNO. During apnoea, the NIV mask was removed, and HFNO kept in place in the interventional arm, where the reference group received no O_2 during apnoea. Although the median

apnoea time in the interventional group was double as compared with the reference group, the interventional group had a significantly higher lowest SpO_2 of 100% vs 96% in the reference group.

To sum up, both techniques of apnoeic oxygenation, i.e. classical and HFNO, appear to be effective in improving the oxygenation during the laryngoscopy period. However, both techniques seem not to be effective in respiratory failure patients. However, I would argue that HFNO may still offer clinical benefits, even in this population, but with the addition of PAP as demonstrated by Jaber and co-workers [133]. The benefit may be attributed to the partial restoration of the FRC that may have been profoundly reduced due to the intrapulmonary shunt induced by the disease process and by the induction of general anaesthesia.

The superior efficiency of HFNO over classical apnoeic oxygenation appears more clearly in the anaesthesia literature than in the ICU and ED literature. This inconsistency may be due to *(i)* the deranged physiology, *(ii)* sub-optimal pre-oxygenation, and *(iii)* the relatively short apnoea duration that may conceal the benefits of apnoeic oxygenation. A summary of the studies that investigated THRIVE during emergency procedures is presented in Table 0.4 in the appendix.

3.4.1.3 Apnoeic oxygenation in obese patients

The effect of obesity on safe apnoea time has been well demonstrated by Jense and co-workers [24]. The researchers examined normal-weight, obese, and morbidly obese. All the patients were properly pre-oxygenated. After induction of anaesthesia and paralytic agent administration, the patients left apnoeic to room air. The safe apnoea time (i.e. SpO_2 of 90%) were 6.0, 4.1 and 2.7 min in the normal, obese and morbidly obese groups, respectively. This

finding reveals a significant inverse relationship between the severity of obesity and the safe apnoea time.

Numerous apnoeic oxygenation methods have been evaluated in various obesity severities. For instance, Ramachandran and co-workers [134] conducted an RCT in mild obesity (i.e. 30 $kg \cdot m^{-2}$ < BMI < 35 $kg \cdot m^{-2}$). The authors assigned the patients to receive either 5 $L \cdot min^{-1}$ O_2 via nasal prongs or not receive O_2. They found that apnoeic oxygenation significantly increased the time to reach SpO_2 of 95%, 5.29 min in the interventional arm, where it was 3.49 min in the control group.

Heard and co-workers [135] performed an RCT of 40 mildly to moderately obese individuals. The patients received either 10 $L \cdot min^{-1}$ O_2 via a modified 3.5 ETT placed in the buccal area or received no O_2. The researchers found a clinically important and statistically significant increase in the safe apnoea time in the group that received apnoeic oxygenation. The median apnoea time with $SpO_2 \geq 95\%$ was 12.5 min in the interventional arm, while it was 4.9 min in the control group. To date, this finding is considered the longest safe apnoea time for both groups, interventional and control, reported in a randomised control trial in the obese population.

I believe this method of apnoeic oxygenation is novel and overcomes a number of challenges faced during apnoeic oxygenation. First, nasopharyngeal insufflation may provide O_2-rich gas in the supra-laryngeal region, but it may not allow an adequate route for exhalation, which could cause barotrauma even at a low flow rate (e.g. 4 $L \cdot min^{-1}$) [136]. Nasal cannulae may not be effective in obese patients who may develop retropalatal obstruction after anaesthesia induction. However, as the HFNO generates positive pressure, it may be reasonable to anticipate partial or complete relief

of the airway obstruction that occurs in the retropalatal area. The buccal apnoeic oxygenation method also allows the insertion of various airways such as Guedel, nasopharyngeal, and laryngeal mask airways without affecting the O_2 delivery.

In morbidly obese apnoeic patients, Baraka and co-workers [137] assigned patients to receive either 5 $L \cdot min^{-1}$ O_2 via a nasopharyngeal catheter or no O_2. The subjects in the apnoeic oxygenation group completed the entire allocated apnoea time (i.e. 4 min) with SpO_2 of 100%, while the control group had a mean safe apnoea time of 2.4 min.

Moon and co-workers [138] randomised 135 obese patients to receive either, *(i)* control group (not receive any intervention), *(ii)* received 15 $L \cdot min^{-1}$ O_2 during apnoea, and *(iii)* received 15 $L \cdot min^{-1}$ of air during apnoea using a nasal cannulae via a nasopharyngeal airway. The authors found a median safe apnoea time (SpO_2 95%) of 4.4, 2.5, and 2.7 min in the subjects that received O_2, air, and the control group, respectively. It is worth noting that ten subjects in the O_2 group have completed the entire allocated apnoea time (8 minutes) with SpO_2 values higher than 95 %. The finding of this study confirms the paramount importance of the provision of a high concentration of O_2 as well as the patency of airway to successfully extend the safe apnoea time in obesity. A Summary of apnoeic oxygenation studies during elective procedures on obese patients is presented in Table 0.5 in the appendix.

THRIVE in obesity

There are currently a few clinical studies that evaluated the use of HFNO during apnoea in obesity. For instance, Patel and Nouraei [50] conducted a landmark observational study, which revealed that the use of HFNO prevented the hypoxaemia onset up to 65 min of

apnoea without signs of CO_2 toxicity. The researchers observed 25 patients with a median BMI of 30 $kg.m^{-2}$ who were deemed difficult airway. The patients were scheduled for hypopharyngeal or laryngotracheal surgeries. They received 70 $L \cdot min^{-1}$ with FiO_2 1.0 via HFNO for 10 minutes during the pre-oxygenation phase and remained unchanged during apnoea. The authors termed this technique Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE). After anaesthesia induction and neuromuscular blockade, jaw thrust was maintained throughout the procedure to ensure airway patency. All the patients had a safe apnoea time (i.e. $SpO_2 \geq 90\%$) between 5 to 35 min, except one patient who had a 65 min of apnoea with an O_2 saturation of 95%. O_2 desaturation, but not hypoxaemia, was encountered in two cases who suffered from severe obesity and severe tracheobronchomalacia and obesity.

Further, Gustafsson and co-workers [51] case series included four subjects with mild obesity. Table 3.3 highlights the SpO_2 at the end of apnoea of the four obese patients reported by Gustafsson and co-workers [51] and Lyons and Callaghan [125]. These data provide evidence that the use of HFNO during apnoea in mild obesity does delay the onset of hypoxaemia for ≥19 minutes. Regarding the occurrence of hypoxaemia that occurred to subject # 3, the authors mentioned that the desaturation was reversed by opening the airway and increasing the flow rate from 80 to 120 $L \cdot min^{-1}$. This desaturation could be caused by some degree of airway obstruction rather than the inefficiency of the HFNO. These data are in agreement and support the claim that HFNO can provide long non-hypoxaemic apnoea time, up to 30 minutes in mild obesity.

Table 3.3. SpO_2 at the end of apnoea of the obese patients reported by Gustafsson et al. and Lyons and Callaghan during apnoeic HFNO.

Author	Subject	BMI ($kg \cdot m^{-2}$)	Apnoea duration (min)	Lowest SpO_2 (%)
Gustafsson et al. [51]	1	30.5	25	99
	2	32.2	21	91
	3	30.3	23	98
	4	32.2	29	100
Lyons and Callaghan [125]	1	31.1	24	99
	2	30.2	19	92
	3	32.8	13	87
	4	32.7	30	93

BMI, body mass index; SpO_2, pulse oximetry

Finally, Lee and Quek [139] reported a morbidly obese case that successfully maintained the SpO_2 above 98% during the entire procedure, which lasted 14 min of apnoea. They implemented HFNO of 60 $L \cdot min^{-1}$ and FiO_2 of 1.0. Although this is only a case report, it adds to the available evidence that HFNO does extend the time of non-hypoxaemic apnoea, even in severe obesity.

3.4.1.4 Apnoeic oxygenation in computational modelling

In 1996, Farmery and Roe [140] constructed a computational model that consisted of three compartments that represented deadspace, shunt and ideal alveoli. They examined the rate of O_2 desaturation during apnoea. The authors simulated multiple values of pre-oxygenation, FRC, O_2 consumption, shunt fraction, cardiac output, and haemoglobin concentration. The importance of FRC and pre-oxygenation in delaying hypoxaemia was highlighted. The researchers quantified that pre-oxygenation increased the time to

reach SaO_2 85% from 1.4 to 8.4 minutes in the non-obese subject and from 0.8 to 2.9 minutes in the obese (i.e. low FRC) subject.

Benumof and co-workers [141] have criticised the difficult airway algorithm issued by the American Society of Anesthetists, which recommend "consider the advisability of awakening the patient" if the initial intubation attempt is unsuccessful. In this article, the authors demonstrated, using the data from Farmery and Roe [140], that critical hypoxaemia will occur before patients return to the unparalysed state. The author concluded that applying the awakening element is not a safe option. Nevertheless, apnoeic oxygenation has not been evaluated nor considered in these studies.

In 2000, Hardman and co-workers [142] examined apnoeic oxygenation and several physiological factors that influence the hypoxaemia occurrence during apnoea, using high-fidelity multi-compartmental computational modelling. The authors found that when apnoeic oxygenation was not applied (i.e. FiO_2 0.21), the time taken to reach SaO_2 50% was 11 min 37 sec in the patent-airway virtual subject, while it was 8 min 13 sec when the airway was obstructed. Patent-airway apnoeic oxygenation with 100% O_2 resulted in a significant increase (66 min 20 sec) in the time taken to reach SaO_2 50%. Apnoeic oxygenation, FRC, O_2 consumption and airway patency were identified as the most potent factors in determining hypoxaemia onset during apnoea.

Moreover, McNamara and Hardman [143] revealed an interesting finding of the pivotal role of high FiO_2 during apnoea. They found that increasing the FiO_2 from 0.9 to 1.0 causes a remarkable delay in hypoxaemia occurrence (more than double) as compared to the FiO_2 increase from 0.21 to 0.9. They numerically explained why and how this benefit is established. An additional finding was, as the

FiO_2 increases, the hypoxaemia is delayed, regardless of the shunt fraction.

Pillai and co-workers [49] modelled different virtual clinical scenarios for *in-silico* patients. They found that the conditions that had the longest time to 90% desaturation were average parturient, anaemia, twin pregnancy, obesity, sepsis, morbid obesity and average parturient in labour, respectively. Increasing FiO_2 from 0.8 to 1.0 significantly prolonged the time to 40% O_2 desaturation (from ~23 min to ~75 min) during apnoea with an open airway. Even though much research has underpinned the benefits of apnoeic oxygenation, but there is still a significant element that hinders its use for an extended period of time, hypercapnia.

3.5 Apnoeic ventilation

Apnoea-induced hypercapnia and its clinical consequences (e.g. respiratory acidemia) play a significant role in limiting the wide use of apnoeic oxygenation in clinical practice, especially for a long duration of apnoea. Apnoeic ventilation refers to the increased clearance of CO_2 during the apnoeic period with no artificial ventilation. The efficiency of apnoeic ventilation could be affected by anatomical (airway patency), physiological (cardiogenic oscillations), and interventional factors (method of apnoeic oxygenation).

3.5.1 Physiological background

Gas diffusion is inversely proportional to its molecular weight, and directly proportional to its solubility, and to the pressure gradient available across the diffusion area. Even though oxygen's molecular weight (32 $g \cdot mol^{-1}$) is lighter than CO_2 (44 $g \cdot mol^{-1}$) [144], making O_2 1.17 times faster to diffuse but, on the other hand, CO_2 is about 24 times more soluble than O_2. By considering the combined properties,

weight and solubility, the overall rate of CO_2 diffusion is about 20 times faster than O_2 [7], making it a much easier gas to diffuse than O_2. However, the diffusion pressure gradient for O_2 (8 kPa) is substantially (10 times) higher than CO_2 (0.8 kPa) [7].

During apnoea, few mechanisms are thought to prevent CO_2 elimination, thus cause hypercapnia. Shortly after the onset of apnoea, the CO_2 pressure gradient that drives CO_2 from pulmonary capillaries to alveoli is lost. Therefore, a small amount of CO_2 is diffused to the lungs (8-20 ml out of 200 ml·min^{-1}) [145]. The second mechanism was described by Holmdahl [48], which claims that the alveolar sub-atmospheric pressure that occurs during apnoea create a unidirectional (from upper airway towards alveoli) convective gas stream that is strong enough to not allow the CO_2 to move against.

3.5.2 The CO_2 rate of increase

There are several factors that may affect the CO_2 rate of increase and its clearance during apnoea, such as airway patency, pre-apnoea hyperventilation, metabolic statues (e.g. hypothermia, pregnancy), and apnoeic oxygenation delivery method [45, 47, 145-147]. The CO_2 values are also affected by the measurement method of CO_2 obtained via arterial or venous blood gas, capnography and transcutaneous CO_2 [51].

3.5.2.1 The CO_2 rate of increase during apnoeic oxygenation

Holmdahl and co-workers [48] studied apnoeic oxygenation in ten dogs and found an almost linear increase at an approximate rate of 0.9 kPa·min^{-1} during the first 40 min of apnoea. Afterwards, during the next 20 minutes, the rate of rise has decreased. The same research group [48] investigated the $PaCO_2$ rate of rise in humans and found a rate of 0.68 kPa·min^{-1} during 6 min of apnoea. Frumin and co-workers [46] conducted one of the most extended apnoeic

oxygenation studies on human up to 55 minutes of apnoea. They delivered, via an ETT, approximately 133-200 ml·min^{-1} of O_2 on eight subjects. The authors found an average CO_2 rate of rise of 0.45 kPa·min^{-1}, with a range of 0.35 to 0.65 kPa·min^{-1}, and the highest recorded value of CO_2 was 33.3 kPa corresponding with an arterial pH of 6.72. Lee [123] has examined the effect of low-flow apnoeic oxygenation using 5 L·min^{-1} via nasal prongs. He found a significant reduction in the mean $PaCO_2$ rate of rise in the apnoeic oxygenation group, 0.5 as compared to 0.8 kPa·min^{-1}. The duration of apnoea lasted between 3-4 min.

3.5.2.2 The CO_2 rate of increase during HFNO

Patel and Nouraei [50] found even a lower end-tidal CO_2 rate of rise of 0.15 kPa·min^{-1}, but with an O_2 flow rate of 70 L·min^{-1} delivered nasally. Gustafsson and co-workers [51] found a similar rate of rise of end-tidal CO_2 of 0.12 kPa·min^{-1}, while the arterial CO_2 rate of rise was 0.24 kPa·min^{-1}. However, capnography was identified, by the authors, to underestimate the actual value of CO_2 during apnoeic oxygenation, unlike transcutaneous CO_2, as it showed a good correlation to arterial CO_2.

3.5.2.3 The CO_2 rate of increase during CPAP

Joseph and co-workers [126] found the arterial CO_2 rate of rise in lean subjects was lower when using a CPAP of 15 cm H_2O, as compared with HFNC of 60 L·min^{-1}, during the 12 min of apnoea. The CPAP group had a mean $PaCO_2$ rate of 0.3 kPa·min^{-1}, while it was 0.5 kPa·min^{-1} in the HFNC group. Nevertheless, their finding is not in agreement with the previous study [51].

3.5.2.4 The CO_2 rate of increase during intra-tracheal insufflation

Rudlof and Hohenhorst [29] found a median end-tidal CO_2 rate of rise of 0.24 kPa·min^{-1} while delivering 0.5 L·min^{-1} O_2 at the carina. The non-invasive HFNO produced higher CO_2 clearance than this strategy.

3.5.2.5 The CO_2 rate of increase during endo-bronchial insufflation

The lowest levels of CO_2 rate of increase, during apnoea, have been achieved via endobronchial insufflation. Babinski and co-workers [148] investigated five non-obese women. Two catheters were placed 2 cm below the carina, one catheter in each main bronchus. Heated and humidified O_2 was delivered at a flow rate of 24-28 L·min^{-1}. The $PaCO_2$ rate of rise was 0.08 kPa·min^{-1}. Interestingly, one patient's $PaCO_2$ remained within the normal range after 30 min of apnoea.

Watson and co-workers [146] have used the same technique but with a higher O_2 flow rate (i.e. 45 L·min^{-1}). They revealed that the $PaCO_2$ had increased significantly during the first 5 min of endobronchial insufflation, from 4.2 to 5.8 kPa, and then remained relatively unchanged. The arterial pH was 7.3±0.02, and $PvCO_2$ was 6.8±0.4 kPa, after 20 min of apnoea. Moreover, three patients had a $PaCO_2$ of less than 5.0 kPa, throughout the entire 25 min of apnoea. Mackenzie and co-workers [149] studied the required flow rate of room air (not O_2) to achieve near acceptable gas exchange on six dogs. They found the average flow rate required maintaining a PaO_2 above 6 kPa and a $PaCO_2$ below 8.6 kPa was 2.5 L·min^{-1} (0.25 L·kg^{-1}·min^{-1}). All dogs survived, with no neurologic dysfunction, for the two hours of apnoea, using these flow rates of room air.

3.5.2.6 The CO_2 rate of increase during airway obstruction

Stock and co-workers [150] analysed the CO_2 rate of rise, during apnoea, in 14 patients while their airway was completely obstructed. They found that the $PaCO_2$ rate of rise during the first minute of apnoea was 1.6 $kPa \cdot min^{-1}$ and 0.45 $kPa \cdot min^{-1}$ thereafter. They concluded that the $PaCO_2$ raises in a logarithmic manner. Similarly, Cheun and Choi [147] examined the $PaCO_2$ rate of rise during apnoea and total airway blockage and found a mean rate of 0.37 $kPa \cdot min^{-1}$ in the non-pregnant group and 0.90 $kPa \cdot min^{-1}$ in the parturient group. They concluded that this finding is due to the increased O_2 consumption induced by pregnancy, thus increasing the production of CO_2.

3.5.2.7 The role of hyperventilation and hypothermia on the CO_2 rate of increase

Eger and Severinghaus [145] investigated pre-apnoeic hyperventilation (average initial end-tidal CO_2 1.8 kPa) and hypothermia (31.7°C) on the CO_2 rate of rise during apnoea on five healthy subjects. They found that the CO_2 rate of rise during the first minute of apnoea is significantly higher (more than triple) than the subsequent apnoea duration. Hyperventilation did reduce the CO_2 rate of rise during the initial and the subsequent apnoea duration. Its overall rate was 0.40 $kPa \cdot min^{-1}$ as compared to 0.55 $kPa \cdot min^{-1}$ in the normal ventilation. Hypothermia has further decreased the rate of rise, from 2.3 $kPa \cdot min^{-1}$ at a core body temperature of 35.5° C to 0.8 $kPa \cdot min^{-1}$ at 31.7° C. After the first minute of apnoea, at normal temperature, the rate of rise was 0.6 $kPa \cdot min^{-1}$ compared to 0.3 $kPa \cdot min^{-1}$ when hypothermia was applied. A summary of the studies that investigated the CO_2 rate of increase during apnoea is presented in Table 0.6 in the appendix.

3.6 Acute Respiratory Distress Syndrome

3.6.1 Management and evidence-based practice

Since the hypoxaemia in ARDS responds poorly to conventional O_2 therapy, the obvious next level of respiratory support is mechanical ventilation. Compared to negative pressure ventilation, positive pressure mechanical ventilation has shown to decrease mortality from 87% to 40% in non-ARDS patients with respiratory insufficiency during the Copenhagen poliomyelitis epidemic [151]. Nevertheless, positive pressure ventilation can induce serious lung injury that increases mortality if the ventilator parameters' settings (e.g. tidal volume, plateau and driving pressure) are not set in accordance with the lung-protective ventilation strategy.

3.6.1.1 Lung injuries

Ventilator-induced lung injury (VILI), as the name implies, is an insult caused by the forces applied by the mechanical ventilator to the lungs, which can be as harmful as the syndrome itself. Abundant literature underpins the basis of VILI [152]. Generally, the current understanding suggests that VILI is categorised into three main mechanisms *(i)* alveolar stretch beyond its anatomical capability (i.e. overdistension), which can be caused by either excessive lung volume or excessive pressure (volutrauma/barotrauma) respectively, *(ii)* repetitive cyclic inflation (during inspiration) and collapsing (during expiration) of the diseased alveolar units (atelectrauma), which could be caused by a positive airway pressure level that is not high enough to prevent lung collapse during expiration, and not low enough to prevent inflation of the affected lung regions during inspiration, and *(iii)* toxic substances released by the inflammatory mediators (biotrauma), that might be aggravated by the alveolar overdistention, which will cause a vicious cycle.

Increased airway pressure in itself may not cause lung injury (trumpet players can normally endure an expiratory airway pressure of 150 cm H_2O [153]), but rather the increased alveolar transpulmonary (distending) pressure.

3.6.1.2 Lung-protective ventilation strategy

ARDS is a complex syndrome and is challenging to manage due to its heterogeneity [154]. Even though through basic, animal and clinical research, scientists now know few interventions that increase survival, such as using lower tidal volume [155], lower plateau pressure [155], lower driving pressure [156], and prone positioning [157]. However, the optimal safe thresholds for these interventions are to be determined.

The ARMA trial [155] compared the effects of ventilating ARDS patients using a tidal volume of 6 $ml \cdot kg^{-1}$ of predicted body weight (PBW) limited to a plateau pressure of 30 cm H_2O *versus* 12 $ml \cdot kg^{-1}$ of PBW limited to a plateau pressure of 50 cm H_2O. The mortality rate in the group that received lower tidal volume was 31% as compared with 40% in the group that received higher tidal volume.

It is commonly referred to the delivery of a tidal volume of 6 $ml \cdot kg^{-1}$ of PBW as a "low" tidal volume strategy, while in fact, the normal tidal volume in mammals (including in healthy human) is 6.3 $ml \cdot kg^{-1}$ [158]. However, in ARDS, a significant portion of the lung units are not available to accept volume (termed as *baby lung*) due to either alveolar collapsed or filled with fluids. Therefore, I would argue that even 6 $ml \cdot kg^{-1}$ of PBW may still be injurious in some ARDS patients in which the received tidal volume exceeds its maximal stretch capability since the vast majority of the delivered tidal volume will be received by the remaining "functional" lung units [159].

Consequently, Amato and co-workers [156] retrospectively analysed data of 3,562 patients extracted from 9 major ARDS clinical trials. They concluded that the driving pressure (i.e. plateau pressure – total PEEP) is a better predictor of mortality (and maybe a better indicator of lung protection) than tidal volume and respiratory compliance. The driving pressure positively correlated with mortality rate irrespective of plateau pressure levels. An exponential increase in mortality was depicted at driving pressure higher than 15 cm H_2O. The driving pressure is the ratio of tidal volume to the static respiratory system compliance (which roughly represent the amount of "functional" lung unites) rather than predicted body weight.

3.6.1.3 What is the evidence of the ECMO outcomes in severe ARDS?

In the past four decades, only four randomised trials [160-163] have been conducted to assess the efficacy of ECMO in severe ARDS patients. The first two trials were performed before the publication of the ARMA trial in 2000 that demonstrated a survival benefit in the lower V_T and P_{plat} group. The CESAR trial [162] concluded that the mortality and severe disability at six months were significantly lower in the patients transferred to an ECMO centre than those who were not transferred to an ECMO centre. However, it is not clear if the patients in the control group received a lung-protective ventilation strategy and not all the patients assigned to the ECMO group received ECMO. In the EOLIA trial [163], the 60-day mortality was lower in the ECMO group. However, it was not statistically significant (p=0.09). Nevertheless, the trial was underpowered due to futility after the enrolment of 249 patients, as supposed to the planned 331 patients.

A more recent systematic review and meta-analysis [164] assessed the outcomes of severe ARDS patients undergoing ECMO. The authors synthesised the results obtained from the CESAR and

EOLIA trials as well as three observational studies, and they have demonstrated that ECMO was linked with a decreased risk of 30-day mortality (RR 0·69 [95% CI 0·50–0·95), and moderate risk of substantial bleeding. However, this systematic review is limited by the inclusion of only two randomised trials as well as the potential bias that may have originated from the lack of patients' randomisation for ECMO in the observational studies.

3.6.1.4 What is the optimal target for oxygen in ARDS?

Hypoxia and hyperoxia are harmful. The optimal target for O_2 level in ARDS remains unknown. However, two large meta-analyses suggested slightly different ranges of SpO_2 in critically ill patients. The first recommended that the SpO_2 value should not exceed 94%-96% [165], and the second indicated that the SpO_2 optimal range is between 94% 98% [166].

Nevertheless, Marn and co-workers [167] reported that in sepsis-induced ARDS, a DO_2 < 640 ml·min·m^2 was associated with 100% mortality, while a DO_2 > 686 ml·min·m^2 was linked with a 70% survival rate. On the other hand, Girardis and co-workers [168] found a mortality reduction by roughly 50% in patients who had a PaO_2 of 11.6 kPa, compared to a PaO_2 of 13.6 kPa. The highest mortality was observed in patients who had, on average, a PaO_2 ≥ 14.26 kPa.

3.7 The literature gap

Currently, there is no consensus for the optimal method to perform apnoeic oxygenation for all patient populations. Although apnoeic oxygenation has been shown to prolong the safe apnoea time during elective procedures [29, 46] even in mild [134], mild-to-moderate [135] and severe obesity [137], the effects of HFNO has not been extensively quantified in obesity. Further, it is unknown whether

HFNO provides additional benefits as compared to the classical apnoeic oxygenation, i.e. low-flow non-humidified.

The clinical implementation of prolonged apnoeic oxygenation may be limited by the significant rise in $PaCO_2$ and its subsequent falls in pH that may or may not jeopardise the patients' health conditions [46, 50, 51, 145]. Other limitations to using HFNO during apnoea include its high cost and unavailability at the clinical bedside.

An additional gap in the literature is the lack of studies that investigated the role of HBOT in ARDS. Reasons that may have prevented the use of the HBOT in ARDS include the fact that international HBOT societies have not classified ARDS as an approved indication for HBOT. Other factors include the cumbersome to use of HBOT, its high cost, lack of expertise, bulky, requires special equipment that is compatible with high pressure (e.g. ventilator, infusion pump) and the scarcity of Class I (i.e. that can support ICU patients) hyperbaric chambers. Additional factors are related to the severity of the targeted population for investigation, i.e. severe ARDS.

This is a very sick population, and establishing acceptable (or near acceptable) oxygenation in severe ARDS can be a challenging clinical task. Once achieved, clinicians would want to preserve it and minimise any interruption. I would argue that transporting severe ARDS patients and placing them on a different ventilator (HBOT-compatible ventilator) is a risky procedure that may hinder a trial of an HBOT session. HBOT is mainly limited by the O_2 toxicity affecting CNS and the pulmonary system. Even a slight elevation of pressure during prolonged sessions may produce a poisonous effect induced by O_2.

The conducted studies reported in Chapter 5 and 6 filled the gap pertaining to the efficacy of various apnoeic oxygenation strategies in

obesity. Chapter 8 addressed the gap related to the potential role of HBOT in ARDS with refractory hypoxaemia.

Chapter 4: Methodology

For the PhD thesis, I used the Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite, created and developed by the principal supervisor Prof Jonathan Hardman and his research group. It is a computational model of the pulmonary and cardiovascular systems, which details are reported in the second section of this chapter.

4.1 Overview

4.1.1 Terminology

4.1.1.1 Model

A model is the final product that is believed to represent a particular system or phenomenon, subject to various levels of approximation [169]. Some types of models are physical, mathematical and conceptional models. Few examples are cadavers, research animals, physical manikins, and computer models. A computer model is a set of ideas that are expressed mathematically using a series of equations in a particular order/fashion (e.g. iteration) to simulate the studied system or phenomenon. The accuracy of any given model is dependent on the knowledge base of the studied system or phenomenon, as well as the ability to precisely incorporate that knowledge in the model.

4.1.1.2 Modelling

Modelling refers to the construction process of a model [169]. In the case of a computer model, modelling involves a complete or near-complete understanding of the studied system or phenomenon as well as translating that understating to mathematical equations that best represent the process. This is particularly challenging when modelling constantly dynamic systems (e.g. human being), especially during

abnormal physiology that has predicted and unpredicted methods of compensatory mechanisms.

4.1.1.3 Simulation

Simulation is the process of performing the mathematical equations and running the pre-defined algorithms as set by the assigned researcher [169]. Simulation of complex systems is usually performed via computer software. The software may also output graphical illustration of different variables that interest the researcher.

4.1.2 Introduction

Modelling is as old as the civilizations of human. Historically, physical models were made for different reasons. For instance, architects used demo designs as models to illustrate and/or market their ideas. Ancient scholars used physical models to understand and portray the world. Computational modelling is a stand-alone research methodology [170]. Its purposes include investigating, predicting, and optimising certain behaviours of a system or phenomenon.

The first general-purpose computer was developed in 1946. It was able to execute 14 ten-digit multiplications in only 1 sec [171]. The increasing computing power, as well as the capacity to store a large amount of digital data, have played a critical role in advancing the use of computational modelling in diverse scientific fields like astrophysics, engineering, biology, and weather forecasting. In the modern era of technology, modelling and simulation have been expanded beyond research. It is widely used for training purposes in industries such as aviation and healthcare.

Simulation-based learning (SBL) is effective in hazardous industries such as aviation. It led to a 50% reduction in aircrafts accidents [172]. In healthcare, the third top cause of deaths in the

United States is preventable medical errors, resulting in more than 400,000 deaths annually [173]. A recent review highlighted that team training that included simulation has been shown to decrease mortality by 13% [174]. SBL offers a safe and controlled setting that is analogous to the real targeted environment. SBL could develop and enhance certain technical and non-technical skills by exposing trainees and allowing them to respond to challenging scenarios that are relevant to their work duties. Debriefing, feedback and reflection are vital to achieving learning [172].

Lung models have contributed to advance our understanding of the pulmonary system. For instance, West [175] lung model provided detailed quantification of the regional gas exchange (e.g. ventilation to perfusion match). Nine horizontal zones were identified with their associated regional parameters such as minute ventilation, perfusion, the pressure tension of O_2 and CO_2, which exhibited considerable variation. Hahn and Farmery [176] informed and critiqued the different types of lung models, along with their features and pitfalls. They advocated developing non-linear tidal-ventilation lung models rather than continuous-ventilation and steady-state models, as tidal-ventilation lung models reflect our natural way of breathing.

In the context of anaesthesia and critical care, comprehensive research work has been conducted using a computational model of the pulmonary and cardiovascular systems. In particular, Hardman and co-workers [142] examined hypoxaemia behaviour during several simulated conditions that may be encountered clinically. Examples of the factors that the authors studied include airway patency and obstruction, length of denitrogenation, FRC, and O_2 consumption. They individually quantified the impact of these factors on hypoxaemia. Moreover, McNamara and Hardman [143] evaluated the role of the O_2 concentration when applied during apnoea while

maintaining a patent airway. Interestingly, they observed a profound delay to reach life-threatening hypoxaemia when the O_2 concentration was increased from 90% to 100%. This finding has enriched the field's understanding of apnoeic oxygenation.

4.1.2.1 Strengths and limitations of computational modelling

There are many powerful features that distinct computational modelling methodology from other methodology types (e.g. laboratory and clinical investigation). First, computational modelling provides a safe research environment, as there are no real human nor animals involved in the investigations. Second, it enables high degrees of configurability of variables that may be of interest to researchers. The configurability of variables is performed independently hence controlling confounding and non-confounding factors, which leads to the homogeneity of subjects. Third, computational modelling offers a time-efficient and cost-effective method to conduct research as compared to clinical trials. Fourth, some models are highly integrated and incorporate important complex reactions that will improve the model outputs' accuracy, such as considering the effects of pH on the O_2 association dissociation curve and the hypoxic pulmonary vasoconstriction. Last but certainly not least, computational modelling can investigate conditions that are not ethically nor clinically possible due to its lethality, such as prolonged duration of apnoea or life-threatening hypoxaemia [170]. Despite these advantages, it is essential to recognise its shortcoming.

Just like any other methodologies, computational modelling presents some limitations. In biological research, where dynamic actions constantly exist, it is impossible to fully model a system due to the incomplete knowledge of human physiology or extreme scenarios. Therefore, computational modelling is based on an approximation of

the relevant physiological processes; thus, all the inherent complexity of the underlying pathophysiology cannot be represented.

Furthermore, the human being has different compensatory mechanisms to maintain normal body status. For example, during vigorous exercise, alteration in the breathing pattern and the cardiovascular system helps cope with the increased metabolic demand induced by exercise. Similarly, pathologies such as pulmonary oedema, pneumonia and metabolic acidosis can stimulate compensatory reactions, including increasing the minute ventilation and pulmonary vasoconstriction in hypoxic lung regions. However, not all compensatory mechanisms are completely understood, thus not incorporated in the computational models. Our model was configured to attenuate the confounding effects assuming that virtual subjects are fully sedated and paralysed; therefore, autonomic reflex modules were not utilised. Another limitation is that mathematical modelling relies on numerical data input; some of the required data may not be available in the literature. The researchers may enter data based on their knowledge that the entered values approximate the true values, according to their expertise.

4.2 The Interdisciplinary Collaboration in Systems Medicine

The Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite is a computational model, and it is the newer version of the model Nottingham Physiology Simulator (NPS). NPS was established more than two decades ago by Professor Jonathan Hardman at the University of Nottingham. The ICSM has been advanced remarkably throughout the years by Professor Hardman and his research group (ICSM), producing a world-renowned high-fidelity computational model of a number of organ systems, including

the heart, blood vessels (and blood) and the lungs. The ICSM is a dynamic model in which the outputs of the system will be fed back as inputs in an iterative fashion. Equilibrium in this context refers to the output variables being unchanged overtime.

The ICSM simulation suite has been widely validated in numerous research areas, including hypoxaemia during apnoea [142], pre-oxygenation [177] and apnoeic oxygenation in adults [143], children [178], obese [177, 179] and pregnant virtual (*in-silico*) subjects [49, 179-181], as well as in ARDS [182], and in chronic obstructive pulmonary disease (COPD) [183]. Recently, it has been utilised to investigate research areas such as the emergency rescue of airway obstruction [184], ventilator [185] and blast lung injuries [186]. The model integrates numerous complex physiological phenomena, such as the shift of the O_2 association dissociation curve and hypoxic pulmonary vasoconstriction.

As illustrated in Figure 4.1, the cardiopulmonary model contains a series deadspace (SD), 100 alveolar compartments and 19 in-series cardiovascular compartments that are independently configurable. The SD is located between the airway and the alveolar compartments. In the model, the SD is simulated as a series of stacked, rigid laminae ($N_{lam} = 50$) of equal volume. The static total volume of the SD is set by the user and each lamina, j, has a known fraction ($f\_((SD, j))\hat{}x$) of gas x. These gases comprise O_2, nitrogen, CO_2, water vapour and a 5th gas used to model additives. During each computational iteration of the model, the gases shift up or down the stacked laminae, driven by the pressure gradient between the alveoli and the environment.

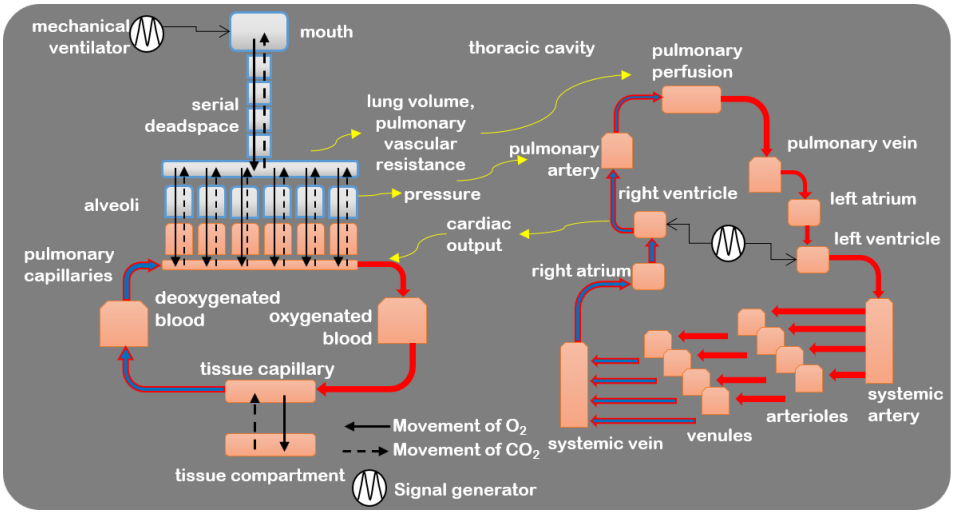

Figure 4.1. Schematic illustration of the cardiopulmonary system of the ICSM model.

The pressure of each alveolar compartment is described by a cubic function:

Equation 4.1

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

$$p_i = 0 \qquad otherwise$$

where

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

$p_i = S_i((10 \cdot v_i - 300)^3/6600) - P_{ext,i} \quad v_i > 0 \; for \; i = 0, \dots, N_{alv}$ determines the alveolar pressure p_i (as the pressure above atmospheric pressure in cm H_2O) for the i^{th} of N_{alv} alveolar compartments for the given volume of the alveolar compartment, v_i, in millilitres. $P_{ext,i}$ (per alveolar unit, in cm H_2O) represents the effective net pressure generated by the sum of the effects of factors outside each alveolus [187]. 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 coefficient that represent the stiffness of the alveolar compartments). The units of S_i are cm H_2O

ml^{-2}. Further details of the physiological principles and mathematical equations underpinning the model are described in [187, 188].

4.2.1 Apnoea Modules

Four modules have been recently developed and validated [189] to address known and hypothesised physiological mechanisms that influence gas exchange during apnoea. These mechanisms include cardiogenic oscillations of intrapulmonary gas, gas-mixing of the anatomical deadspace, and micro-ventilation induced by pharyngeal pressure oscillation during HFNO [189-192].

4.2.1.1 Cardiogenic oscillations module

The cardiogenic oscillations have been shown to influence the CO_2 clearance during breathing and apnoea [190, 191]. Other researchers suggested that the change in the gas flow is rather due to the change in the pulmonary blood flow [192]. Therefore, this module was established to incorporate the effects of the cardiogenic oscillations on the gas exchange during apnoea. The following equation describes their effect on alveolar compartments:

Equation 4.2

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

$P_{osc,i}$ represents the total pressure applied by the heart that acts on the alveolar compartment i. $K_{osc,i}$ is a constant, representing the strength of the effect of cardiogenic oscillations on alveolar ventilation due to the alveoli being physically compressed in a biphasic basis induced by, and synchronous with, the heartbeats and/or trans-alveolar blood volume. N_{osc} is the number of alveolar compartments that are affected by the cardiogenic oscillations. The function φ is the ventricle activation function. Thus, the alveolar pressure is given by:

Equation 4.3

$$p_i = S_i((10 \cdot v_i - 300)^3/6600) - P_{ext,i} - P_{osc,i} \quad v_i > 0 \; for \; i = 0, \dots, N_{alv}$$

$$p_i = 0 \qquad otherwise$$

4.2.1.2 Anatomical deadspace gas-mixing module

The anatomical deadspace gas mixing was represented by a newly developed parameter (σ) to enable various degrees of gas mixing. σ has a value that ranges between 1 to 0. A value of 1 indicates complete gas mixing between the laminas as a result of immense turbulent flow, where 0 reflects no gas mixing is occurring. Thus:

Equation 4.4

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

where $f^x_{SD,j}$ is the fraction of gas x in lamina j and $f^x_{SD,j+1}$is the fraction of gas x in the next lamina.

4.2.1.3 Tracheal insufflation module

Regarding tracheal insufflation, two parameters were configured, r_{insuff} and l_{insuff}. r_{insuff} is the amount of insufflated air flow L·min^{-1}. l_{insuff} represents the location of the insufflation. It can have a value from 1 to 5. Where l_{insuff} of 1 indicate that the insufflation location is at the glottis, while l_{insuff} of 5 represents the insufflation site at the carina. During the O_2 insufflation, $f^{O2}_{SD,k}$ at lamina k is given as follows:

Equation 4.5

$$\mathrm{f}^{\mathrm{O2}}_{\mathrm{SD,k}} = \frac{\left(\mathrm{v_k} * \mathrm{f}^{\mathrm{O2}}_{\mathrm{SD,k}}\right) + \left(\mathrm{F_{new}} * \mathrm{f_{insuff}}\right)}{\mathrm{v_k} + \mathrm{F_{new}}}$$

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

where f_{insuff} is the concentration of O_2 in the insufflated air (accounting for humidified air) and v_k is the volume of air in lamina k.

Following this, the fractions of the gases in all the layers are adjusted, taking into account the proportion of gas mixing between the laminas of the series deadspace.

4.2.1.4 Pharyngeal pressure

The delivery of high-flow nasal oxygen (HFNO) has been shown to generate positive pressure at the pharyngeal space [193, 194]. The oscillatory pharyngeal pressure (P_{phar}) has been added to the tracheal pressure (equal to the atmospheric pressure):

Equation 4.6

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

Where, A is the amplitude of the pressure in cmH_2O (values 0-2 cm H_2O) [195], and f is the frequency in Hz equal to 70. Currently, our modelling and simulation are performed using Matlab software version R2018a (MathWorks Inc., MA, USA). Initially, the ICSM's user configures *in-silico* subjects with particular pathophysiological characteristics to match the targeted condition/population that is intended to be investigated. The values used for configuring the subjects are based on human data that are published in the literature. Examples of the entered data include weight, height, FRC, cardiac output, venous admixture, O_2 consumption and some parameters of the mechanical ventilator such as the mode, P_{insp} or V_T, RR, inspiratory to expiratory ratio, FiO_2 and PEEP.

Example of protocols that have been used for the thesis includes pre-oxygenation, apnoeic oxygenation using various oxygenation strategies, and mechanical ventilation at the atmospheric and hyperbaric environment. Examples of simulations' endpoints include the duration of the simulation and/or when a certain level of hypoxaemia or hypercapnia is reached. The simulations output may

be exported as a spreadsheet or as plots of two or even three-axis graphs to observe certain behaviours. Then, a thorough analysis of the output is conducted.

Chapter 5: The impact of airway patency, oxygen concentration, and high-flow nasal oxygen on gas exchange during apnoea in obesity: a computational modelling investigation

5.1 Abstract

The prevalence of obesity is increasing worldwide. In the UK, almost a third of the adult population is obese. Obesity predisposes to rapid hypoxaemia during apnoea due to reduced functional residual capacity (FRC) and increased O_2 consumption. Using computational modelling, I configured eight *in-silico* subjects with body mass index (BMI) of 24 to 57 $kg \cdot m^{-2}$. Five conditions were simulated, which are: *(i)* complete obstruction of the upper airway, *(ii)* patent upper airway without supplemental O_2, *(iii)* patent upper airway with 0.25 $L \cdot min^{-1}$ of 100% O_2, *(iv)* patent upper airway with 5 $L \cdot min^{-1}$ 100% O_2 provided nasally, *(v)* patent upper airway with 70 $L \cdot min^{-1}$ humidified 100% O_2 delivered via the nose (HFNO). Apnoea continued for 30 minutes, and arterial O_2 saturation (SaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$) were recorded at 5 milliseconds intervals. Relieving the upper airway obstruction delays hypoxaemia by about one minute. HFNO was more effective than the other interventions in delaying the onset and progression of hypoxaemia in all obese subjects. HFNO delayed the occurrence of hypercapnia (i.e. $PaCO_2$ of 11 kPa) by 5 minutes and by less than a minute in non-obese and obese subjects, respectively. The results suggest that the provision of HFNO during apnoea delays the onset and slows the progression of hypoxaemia and hypercapnia, though with reduced benefits as BMI increases.

5.2 Introduction

Maintenance of adequate alveolar oxygenation is the principal task of airway managers. Appropriate pre-oxygenation, as well as apnoeic oxygenation (i.e. providing O_2 during apnoea), have been

demonstrated to be effective in delaying the onset of hypoxaemia [46, 122]. There are various methods to deliver apnoeic oxygenation, such as via a standard nasal cannulae, pharyngeal insufflation, intra-tracheal catheter and, more invasively, endobronchial insufflation. However, in recent years, HFNO appeared to gain considerable research and practical interest in the fields of anaesthesia, critical care and emergency medicine [130, 196]. Researchers have investigated the efficacy of HFNO during pre-oxygenation [197-200], airway management [50] and post-extubation [201].

5.2.1 What is HFNO?

HFNO is an O_2 therapy system that can independently provide an adjustable concentration of inspired O_2 up to 100%, airflow rate up to 120 $L \cdot min^{-1}$ and appropriate humidity and temperature of the delivered gas. HFNO is typically delivered via a specialised high-flow system that consists of a high flowmeter, O_2 blender and an active heating humidification system. Examples of some specialised and commercial HFNO devices are the POINT (Peri-Operative Insufflatory Nasal Therapy) system (Armstrong Medical, Coleraine, UK), Precision Flow (Vapotherm, Maryland, USA) and Optiflow (Fisher & Paykel, Auckland, New Zealand). However, some invasive and non-invasive mechanical ventilators have integrated high-flow O_2 therapy to deliver HFNO like the Drager babylog VN500, Savina 300 and the Philips V60 plus.

5.2.2 When did HFNO enter the practice of anaesthesia and critical care?

Although HFNO devices are commercially available since the early 2000s, their clinical application during apnoea was not utilised until 2013 [202]. As elaborated earlier, Patel and Nouraei [50] conducted the first study (in 2015) that investigated the use of HFNO

during prolonged apnoea in patients with difficult airways. The authors coined the term Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE). The multicentre PREOXYFLOW trial [197] followed suit, examining the use of HFNO, during apnoea, in acute hypoxaemic patients requiring emergency intubation.

5.2.3 What are the outcomes of HFNO in anaesthesia and critical care?

Provision of HFNO during apnoea has been shown to extend the period before dangerous hypoxaemia develops as well as decrease the $PaCO_2$ rate of increase in non-obese subjects undergoing elective procedures [50, 51, 125]. Nevertheless, during emergency intubations that take place outside the operating theatres, the literature demonstrates contradictory results of the efficiency of THRIVE. For instance, these RCTs [131, 197, 203] showed no difference in the lowest SpO_2 during intubation in the group that received HFNO and those who did not receive it. On the other hand, these trials [130, 204] found that the lowest SpO_2 during intubation was significantly higher in the group that received HFNO than those who did not receive it. Moreover, the effectiveness of THRIVE in some populations that are at risk for developing hypoxaemia, such as obesity, have not been quantified yet.

5.2.4 Why obesity?

The prevalence of obesity is dangerously rising. A study found no reduction in obesity rates in the screened 188 countries over 33 years, indicating a global crisis [205]. In the United States of America, the prevalence of obesity and severe obesity is 42.4% and 9.2%, respectively [206]. In the UK, approximately a third of the adult population is obese [2]. By 2030, an additional 11 million English adults are predicted to become obese [207].

Obesity imposes metabolic and anatomical deleterious implications on airway management. Obesity is considered a risk factor for diabetes, hiatus hernia and gastro-oesophageal reflux, which all increase the likelihood of developing regurgitation and aspiration [4]. Pulmonary aspiration is the leading cause of airway–related anaesthetic deaths [120]. Anatomically, upper body obesity, particularly around the neck, is believed to be the dominant risk factor for developing obstructive sleep apnoea (OSA) in adults [112]. Obesity is an independent risk factor for difficult face-mask ventilation, laryngeal-mask failure and difficult emergency surgical airway, while OSA is an independent predictor of impossible face-mask ventilation, difficult tracheal intubation and serious airway complications [4, 120, 208]. Furthermore, obesity predisposes an additional important risk factor, which is a remarkable short time to develop O_2 de-saturation after the anaesthesia induction and the subsequent apnoea.

Obese subjects are at risk to develop rapid hypoxaemia shortly after the anaesthesia induction due to the marked reduction of the FRC, i.e. O_2 reserve, caused by obesity [91] and anaesthesia induction (i.e. > 50%) [96], potentially increased closing capacity [95] and elevated O_2 consumption rate [94]. The concurrent occurrence of anatomical and physiological derangements may likely be responsible for the rapidly evolving hypoxaemia. The combination of low FRC and high closing capacity increases the probability of developing atelectasis (i.e. alveolar collapse), leading to pulmonary shunting, which may not be responsive to conventional O_2 therapy.

To sum up, obesity imposes airway-related difficulty that may increase the required time to secure an airway. On the other hand, hypoxaemia is developed much faster in obesity [24]. The combined consequences may seriously endanger these patients, especially that

severe hypoxia can rapidly cause cardiac arrest and/or irreversible brain damage [16].

5.3 Aim of the study

This study aims to investigate and quantify the effects of airway obstruction and patency, ambient O_2 concentration, and apnoeic oxygenation strategies, including HFNO, on gas exchange during apnoea in virtual obese subjects using computational modelling.

5.4 Methods

The ICSM suite used for this investigation is described in detail in Chapter 4.

5.4.1 Validation

Two published studies have been selected that investigated hypoxaemia and hypercapnia during apnoea. The first study conducted by Hardman and co-workers [142] was performed using a previous version of the ICSM (i.e. NPS). This study investigated the course of hypoxaemia under different conditions such as denitrogenation duration, minute ventilation, O_2 consumption, FRC, provision of O_2 during apnoea, and the airway state (patent or blocked) in a non-obese virtual subject. The study's endpoint was reaching a SaO_2 of 50%.

The second study was conducted by Heard and co-workers [135]. The authors evaluated apnoeic oxygenation using 10 $L{\cdot}min^{-1}$ of 100% O_2 in obese subjects. The endpoint of this study was once the SpO_2 reaches 95%.

To validate the current version of the model against Hardman and co-workers [142], I used values for the configuration of the non-obese virtual subject which included FRC of 2.5 $L{\cdot}min^{-1}$ and VO_2 of

250 ml·min^{-1}, while FRC of 1.3 L, VO_2 of 273 ml·min^{-1} was used for the configuration of the obese virtual subject to validate the model against Heard and co-workers [135]. Not all physiological values were reported in the study, so values were estimated according to the mean BMI**.** They were input based on other research studies [96, 118]. A two minutes pre-oxygenation was performed for both simulations.

Moreover, as described in Chapter 4, the anatomical deadspace gas mixing was represented by a newly developed parameter (σ) to enable various degrees of gas mixing. The parameter σ has a value that ranges between 1 to 0. A value of 1 indicates complete gas mixing between the laminas as a result of turbulent flow, where 0 reflects no gas mixing is occurring. The parameter σ was set 0.3 for all simulations except HFNO, which had a value of 0.6. Finally, the HFNO had an oropharyngeal pressure oscillation of 2 cmH_2O at 70 Hz, while all the other simulations had no pressure oscillation [189].

5.4.2 Virtual subjects and protocol

Eight virtual subjects with BMI 24, 27, 32, 37, 42, 47, 52 and 57 kg·m^{-2} were configured. The baseline physiological values used for their configuration are listed in Table 5.1. These values were extracted from previously published studies [31, 96, 101, 118, 209]. All virtual subjects received pulmonary denitrogenation (i.e. pre-oxygenation) by breathing 100% O_2 for two minutes. At simulated induction of general anaesthesia, the FRC was reduced by 20% in non-obese [31] and by 50% in obese subjects [96]. Subsequently, apnoea commenced and persisted for 30 minutes. From the onset of apnoea onwards, all virtual subjects underwent five different simulations:

1. 0 L·min^{-1} insufflation of 0% O_2 with closed glottis (simulating a complete blockage of the upper airway)

2. Patent upper airway, 0.25 L·min^{-1} of 21% O_2

3. Patent upper airway, 0.25 L·min^{-1} of 100% O_2
4. Patent upper airway, 5 L·min^{-1} of 100% O_2 delivered nasally (classical apnoeic oxygenation)
5. Patent upper airway, 70 L·min^{-1} of 100% O_2 delivered nasally (HFNO)

Table 5.1. The physiological characteristics used to configure the virtual subjects

Subjects	BMI	weight	V_T	RR	FRC*	VO_2	VCO_2
	kg/m^2	kg	ml	b/min	L	ml/min	ml/min
1	24	70.0	420	12.0	3.0	241	193
2	27	76.8	415	12.5	2.8	250	200
3	32	89.3	410	13.0	2.7	269	215
4	37	102.0	400	14.0	2.5	288	230
5	42	113.0	390	15.5	2.0	304	243
6	47	134.6	385	17.0	1.9	336	267
7	52	139.7	375	18.0	1.8	343	274
8	57	152.0	365	19.0	1.8	361	289

BMI, body mass index; V_T, tidal volume; RR, respiratory rate (breath·min^{-1}); FRC, functional residual capacity; VO_2, oxygen consumption; VCO_2, carbon dioxide production.
* FRC value prior to anaesthesia induction

The outcome data collected were: *(i)* the time from the start of apnoea until arterial O_2 saturation (SaO_2) reaches 90%, *(ii)* the rate of hypoxaemia progression from SaO_2 90% to 50%, *(iii)* the time from the start of apnoea until the CO_2 partial pressure in arterial blood ($PaCO_2$) reach 11 kPa, and *(iv)* the $PaCO_2$ rate of rise during the 30

minutes of apnoea. These parameters were collected every five milliseconds. The modelling and simulations were conducted using Matlab software version R2018a (MathWorks Inc., MA, USA).

5.5 Results

5.5.1 Validation results

Numerous simulations with various values of cardiogenic oscillations pressure and the number of alveoli affected by this pressure have been conducted. A cardiogenic oscillations pressure value of 2.5 cmH_2O affecting 60% of alveoli was found to best fit the oxyhemoglobin desaturation as well as the $PaCO_2$ rate of increase, as shown in Table 5.2 and Table 5.3. Therefore, all subsequent simulations were performed using a cardiogenic oscillation pressure value of 2.5 cmH_2O affecting 60% of alveoli. The output data from our current model displays notable comparability against the studies used for validation.

Table 5.2. Results of the current version model output in relation to the study of Hardman et al. [142]

	Airway	**Time to SaO_2 = 50% (min)**	**$PaCO_2$ increase ($kPa \cdot min^{-1}$)**
Hardman et al [142]	open	66.33	0.43
	close	8.22	
Model output	open	66.93	0.43*
	close	8.10	

SaO_2, arterial oxygen saturation; $PaCO_2$, partial pressure of CO_2 in arterial blood
*This is the mean value of the rate of increase

Table 5.3. Results of the current version model output in relation to the study of Heard et al. [135]

	FiO_2	insufflation	Time (min) to SpO_2 = 95%
Heard et al [135]	0.21	No	4.93
	1.0	10 $L \cdot min^{-1}$	12.50
Model output	0.21	No	4.43
	1.0	10 $L \cdot min^{-1}$	12.47

FiO_2, the fraction of inspired oxygen; SpO_2, pulse oximetry.

5.5.2 Hypoxaemia

All the simulated interventions have been shown to influence the timing in which the hypoxaemia occurs. The time from the start of apnoea until SaO_2 drop to 90% is summarised in Table 5.4.

With respect to airway obstruction, relieving the obstruction of the upper airway delays hypoxaemia by about one minute, while the airway is exposed to ambient air (i.e. 21% O_2). The provision of 100% O_2 demonstrated a substantial benefit to delaying hypoxaemia, especially in the non-obese subjects. Insufflating 5 $L \cdot min^{-1}$ of pure O_2 (i.e. classical apnoeic oxygenation) did not show to provide an additional delay in hypoxaemia onset in obesity, as compared with no insufflation. Compared to subjects receiving classical apnoeic oxygenation, HFNO provided additional delay to significant hypoxaemia (SaO_2 90%).

Although hypoxaemia did not occur in the virtual subject with BMI 24 $kg \cdot m^{-2}$ while receiving *(i)* 100% O_2, *(ii)* classical apnoeic oxygenation and *(iii)* HFNO within the apnoea period, at the end of apnoea (minute 30), his SaO_2 was 94%, 96% and 99% while receiving these interventions, respectively. In the same way, the virtual subject with BMI 27 $kg \cdot m^{-2}$ did not develop hypoxaemia; similarly, his SaO_2

was 93% and 99% while receiving classical apnoeic oxygenation and HFNO, respectively.

Table 5.4. The time (in minutes) from the start of apnoea until SaO_2 reached 90% in the eight virtual subjects undergoing all simulated interventions.

Subjects		Airway obstruction	21% oxygen	100% oxygen	classical apnoeic oxygenation	HFNO
#	BMI					
1	24	6.47	7.98	NR	NR	NR
2	27	6.21	7.61	30.00	NR	NR
3	32	4.08	5.11	13.36	13.45	20.36
4	37	3.67	4.77	12.55	12.50	17.19
5	42	3.53	4.26	11.76	11.75	13.41
6	47	3.09	3.88	10.78	10.77	12.02
7	52	3.01	3.75	10.55	10.55	11.58
8	57	2.88	3.56	10.03	10.03	10.86

SaO_2, arterial oxygen saturation; HFNO, high-flow nasal oxygen; NR, not reached during the 30 minutes of apnoea

The various interventions have demonstrated to affect also the acceleration of the O_2 desaturation after hypoxaemia has occurred. Table 5.5 summarises the mean rate of hypoxaemia progression expressed as a percentage drop from SaO_2 90% to 50%. Across all simulated interventions, the life-threatening hypoxaemia (i.e. SaO_2 50%) was reached faster as BMI increases. The fastest rate of hypoxaemia acceleration was observed during airway obstruction ranging approximately from 20 to 30 $\%\cdot min^{-1}$. Compared to airway obstruction, opening the airway to room air slowed the hypoxaemia acceleration by approximately 7 $\%\cdot min^{-1}$ in all subjects. The provision of 100% O_2 further slowed hypoxaemia by about 10 $\%\cdot min^{-1}$ in obesity.

Classical apnoeic oxygenation did not provide any further reduction in the hypoxaemia progression. As compared to classical apnoeic oxygenation, HFNO slowed the progression of hypoxaemia.

Table 5.5. The mean rate of hypoxaemia progression in (%·min^{-1}) from SaO_2 90% to 50%, in the eight virtual subjects undergoing all simulated interventions.

Subjects		Airway obstruction	21% oxygen	100% oxygen	classical apnoeic oxygenation	HFNO
#	BMI					
1	24	20.7	13.1	NR	NR	NR
2	27	21.7	13.8	NR	NR	NR
3	32	25.3	19.3	7.9	8.2	3.8
4	37	27.8	21.0	9.2	9.2	6.2
5	42	28.2	21.6	11.3	11.2	9.8
6	47	30.5	23.3	12.6	12.4	11.2
7	52	30.3	23.4	12.9	13.1	11.5
8	57	30.8	24.0	13.8	13.9	12.5

HFNO, high-flow nasal oxygen; NR, not reached during the 30 minutes of apnoea

5.5.3 Hypercapnia

The $PaCO_2$ mean rate of increase in the eight virtual subjects undergoing all simulated interventions is displayed in Table 5.6. The $PaCO_2$ rate of increase was observed to be proportionally related to BMI. This could be anticipated as the CO_2 production is increased as O_2 consumption increases, which is the case in obesity.

Compared to room air, the provision of pure O_2 increased the CO_2 mean rate of rise. However, in severe obesity (BMI ≥ 42 kg·m^{-2}), the 100% O_2 is observed to not increase the CO_2 rate of rise. The classical apnoeic oxygenation had minimal effect of the CO_2 rate of

rise in all subjects. Among all interventions, HFNO achieved the lowest $PaCO_2$ rate of increase in all subjects.

Table 5.6. The $PaCO_2$ mean rate of increase in ($kPa \cdot min^{-1}$) in the eight virtual subjects undergoing all simulated conditions.

Subjects		Airway obstruction	21% oxygen	100% oxygen	classical apnoeic oxygenation	HFNO
#	BMI					
1	24	0.76	0.45	0.60	0.56	0.27
2	27	0.80	0.44	0.63	0.60	0.28
3	32	1.18	0.66	0.85	0.84	0.80
4	37	1.55	0.71	0.89	0.88	0.85
5	42	1.57	0.94	0.93	0.92	0.90
6	47	1.90	1.06	1.05	1.02	0.94
7	52	1.93	1.10	1.07	1.07	0.95
8	57	1.98	1.19	1.14	1.13	0.96

HFNO, high-flow nasal oxygen

The time from the start of apnoea until the occurrence of significant hypercapnia (i.e. $PaCO_2$ 11 kPa) is presented in Table 5.7. As compared to classical apnoeic oxygenation, HFNO was observed to delay the occurrence of significant hypercapnia by 5.4 min and 4.9 min in the subjects with BMI 24 and 27 $kg \cdot m^{-2}$, respectively, while the time difference was less than 30 seconds in the obese subjects.

Interestingly, despite the similar values of CO_2 at the end of apnoea in obesity, the shape of the $PaCO_2$ curve of the severely obese subjects (i.e. BMI 47, 52 and 57 $kg \cdot m^{-2}$) is observed to behave differently. For instance, as compared to 21% O_2, the provision of pure O_2 delayed the sharp increase in the slope of the curve, as highlighted by red arrows in Figure 5.1. In the subject with BMI 42 $kg \cdot m^{-2}$, the

administration of pure O_2 prevented the appearance of this abrupt rise of the slope throughout the allocated apnoea time.

Table 5.7. The time (in minutes) from the start of apnoea until the arterial partial pressure of CO_2 ($PaCO_2$) reaches 11 kPa, in the eight virtual subjects undergoing all simulated interventions.

Subjects		Airway obstruction	21% oxygen	100% oxygen	classical apnoeic oxygenation	HFNO
#	BMI					
1	24	8.00	9.79	9.42	9.63	15.04
2	27	7.63	9.19	8.86	9.04	13.92
3	32	7.60	7.50	6.85	6.88	7.31
4	37	7.22	7.03	6.38	6.38	6.68
5	42	7.08	6.81	5.95	5.95	6.08
6	47	6.50	6.24	5.37	5.37	5.47
7	52	6.81	6.15	5.23	5.23	5.31
8	57	6.15	5.88	4.95	4.96	5.02

HFNO, high-flow nasal oxygen

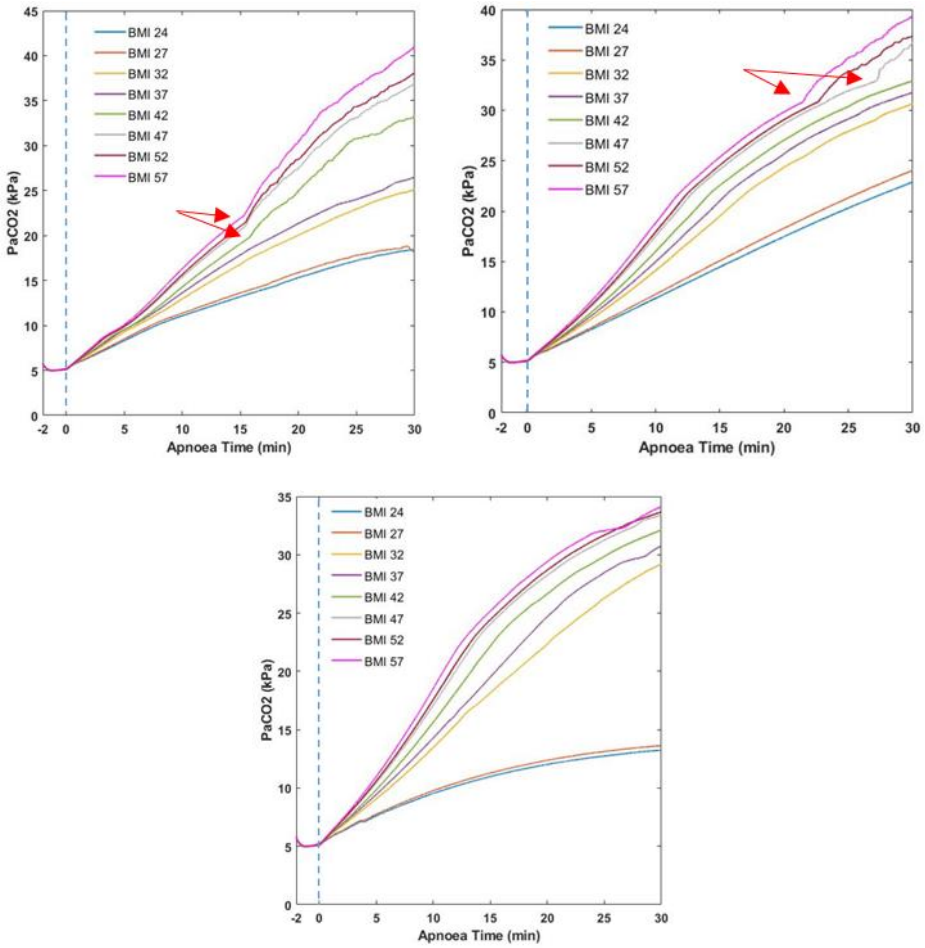

Figure 5.1. Time courses of $PaCO_2$ of all subjects while receiving 21% oxygen (left), 100% oxygen (right) and HFNO (bottom). The arrows indicate the increase in the slope. The vertical dashed line represents the start of apnoea.

5.6 Discussion

5.6.1 Main results

To my knowledge, this is the first study that thoroughly investigated apnoeic gas exchange during various interventions such as complete obstruction of the upper airway, patent airway that is exposed to room air and 100% O_2, classical apnoeic oxygenation and THRIVE, using computational modelling in virtual subjects with a wide spectrum of BMI (i.e. obesity). The results suggest that HFNO offers a significant delay before dangerous and life-threatening hypoxaemia and hypercapnia occurs, though with reduced benefits as BMI

increases. The finding demonstrated that relieving the upper airway obstruction delays hypoxaemia by about a minute. The provision of pure O_2 substantially extends the non-hypoxic apnoea time, especially in the non-obese subjects. Classical apnoeic oxygenation seems to not provide any additional gas exchange benefit compared to the sole provision of 100% O_2.

5.6.2 Relation to previous studies

Regarding obstructed-airway apnoea, the present study finding is in agreement with Cheun and Choi [147]. This study found a 6.5 min to reach SaO_2 of 90% (in the virtual subject with BMI 24 $kg{\cdot}m^{-2}$), while Cheun and Choi [147] found a 7.5 min to reach 90% in their subjects who had a mean BMI of 20 $kg{\cdot}m^{-2}$.

The safe apnoea time in the virtual subject with BMI 27 $kg{\cdot}m^{-2}$ (while receiving classical apnoeic oxygenation) is not consistent with Rajan et al. [124]. They found a 5.8 min to reach SpO_2 of 90% while the SaO_2, in the corresponding virtual subject, did not reach 90% throughout the 30 min of apnoea. The discrepancy may be due to the removal of the facemask (source of apnoeic oxygen) to evaluate the grade of the laryngeal view.

The clinical studies that examined HFNO in obesity are lacking. However, Gustafsson and co-workers [51] examined the effects of HFNO on gas exchange during apnoea in 18 subjects with normal BMI, eight overweight and four mildly obese subjects in their case series study. The findings of the current study are in partial agreement with their findings. For instance, all the lean subjects had a $SpO_2 \geq$ 98% during the entire apnoeic periods, which is consistent with the current study's finding. In the overweight population, two subjects with BMI 26 and 28 $kg{\cdot}m^{-2}$ had a SpO_2 of 99% at the end of their apnoea that lasted ≥25 minutes. The *in-silico* subject with BMI 27 $kg{\cdot}m^{-2}$ of this

study also had a SaO_2 of 99% at the end of the apnoea time. In the obese population, the authors reported that a subject with a BMI of 32.2 $kg \cdot m^{-2}$ had a SpO_2 of 91% after 21 minutes of apnoea. The *in-silico* subject with BMI 32 $kg \cdot m^{-2}$ here had a SaO_2 of 88% at the corresponding apnoea time (i.e. 21 min). A justification for this difference may be due to the longer pre-oxygenation time applied in their study (specified as at least 3 min) as compared to 2 minutes in the present study. Interestingly, the researchers also reported that another subject with identical BMI (i.e. 32.2 $kg \cdot m^{-2}$) had a longer apnoea time of 29 minutes (compared to 21 min) and a higher SpO_2 100% (compared to 91%).

These differences support the multifactorial causation and or association that may exist between obesity and hypoxaemia during apnoea. A few potential factors that may explain this discrepancy are the variation in the FRC, O_2 consumption and the degree of airway patency. Regarding the hypercapnia, in the study of Gustafsson and co-workers [51], a detailed analysis of their individual data revealed that the highest values of CO_2 rate of increase were mostly from non-obese subjects.

On the contrary, in the four obese subjects, their CO_2 rate of rise was actually less than the reported mean value (i.e. 0.24 $kPa \cdot min^{-1}$), except for one patient that had a rate of 0.29 $kPa \cdot min^{-1}$. This suggests that the CO_2 rate of increase may not be purely explained by the bodyweight, but other factors may play a role in the hypercapnia development during apnoea. The model data of this investigation for the CO_2 rate of rise are comparable with the lean and the overweight subjects, but not with the obese subjects.

The data reported by Gustafsson and co-workers [51] show that eight out of the eighteen (44%) lean subjects had a $PaCO_2$ rate of rise

that is equal to or higher than the overall mean rate (i.e. ≥0.24 kPa·min^{-1}) of the entire cohort, while only one out of the four (25%) obese subjects had that value. Furthermore, four of the lean subjects had a $PaCO_2$ rate of rise of ≥0.30 kPa·min^{-1}, where none of the obese subjects had a $PaCO_2$ rate of rise of ≥0.30 kPa·min^{-1}. Since the authors did not measure the metabolic status (e.g. CO_2 production) of the subjects, it is difficult to draw conclusions, but at least this observation may suggest that predicting the CO_2 clearance based on the bodyweight is not currently attainable.

This study's findings were also comparable to Lyons and Callaghan [125] case series. In their study, there was no incidence of hypoxaemia in the non-obese subjects with BMI ≤25 kg·m^{-2}, which is in agreement with this study's findings. Regarding obesity, the researchers recruited two mildly obese subjects with almost identical BMI (32.7 and 32.8 kg·m^{-2}) that had a non-consistent trend. The first subject had a SpO_2 of 93% at 30 min of apnoea, while the other subject had a SpO_2 of 87% only at 13 min of apnoea. The corresponding *in-silico* subject here with BMI 32 kg·m^{-2} had a 20 min of apnoea with a SaO_2 of 90%. The authors mentioned that O_2 de-saturation was reversed by opening the airway and increasing the flow rate from 80 to 120 L·min^{-1}. Therefore, this O_2 desaturation might be caused by some degree of airway obstruction rather than the inefficiency of the HFNO.

The present study also shows a partial agreement with the finding reported by Baraka and co-workers [137]. The authors randomised morbidly obese patients to 5 L·min^{-1} via nasopharyngeal insufflation or no insufflation. All the subjects in the study group completed the entire allocated apnoea period (i.e. 4 min) with SpO_2 of 100% except one patient whose BMI was 65 kg·m^{-2}, where the control group had a 2.4 min mean time to reach SpO_2 of 95%. The virtual

subject with BMI 42 $kg \cdot m^{-2}$ that correspond to the study group had 100% at the fourth minute of apnoea, but the virtual subject with BMI 42 $kg \cdot m^{-2}$ that correspond to the control group had 3.9 minutes to reach a SpO_2 of 95%.

5.6.3 Additions to the knowledge of the subject

This work provides a quantification of the time in which dangerous and life-threatening hypoxaemia and hypercapnia develop in diverse conditions that clinicians may encounter during an airway management crisis. Additionally, the effects of HFNO on gas exchange during apnoea in several obese populations were examined for the first time.

Furthermore, the finding of this study in which the classical apnoeic oxygenation provides no additional gas exchange benefit over the sole provision of 100% O_2 may support the current physiological understanding of the mechanism of apnoeic oxygenation. Unlike HFNO, insufflating low-flow O_2 would not affect the transairway pressure (P_{TA}), thus not influencing the mass inflow. I would argue that the superiority (in terms of oxygenation) of HFNO over classical apnoeic oxygenation may be due to a few reasons. Firstly, HFNO can increase the P_{TA} (the pressure gradient between the airway opening and the alveoli) via increasing the pharyngeal pressure [189, 193, 210], thus entraining a higher amount of gas (e.g. O_2) inflow to the alveoli. Secondly, HFNO may increase lung volume [211] hence pulmonary O_2 reservoir by the effect of the positive pressure associated with the high flow. Finally, HFNO washout the CO_2 in the anatomical deadspace [212] and replace it with 100% O_2 in which the mass inflow will carry and replenish continuously.

Regarding the superiority of HFNO over classical apnoeic oxygenation to achieve apnoeic ventilation (i.e. increase CO_2

clearance), our research group has investigated HFNO and suggested a few key responsible mechanisms. These mechanisms include the augmentation of gas mixing in the anatomical dead space, the micro-ventilation induced by cardiogenic oscillations and the pharyngeal pressure oscillation. Another research group [213] has shown that HFNO produces higher CO_2 clearance than classical apnoeic oxygenation, approximately from 25 to 55 ml·min^{-1}, that is induced by the same stroke volume (i.e. 40 ml) of cardiac oscillations.

5.6.4 Strengths and weakness of the study

Using the high-fidelity computational model allowed the investigation of gas exchange during fatal conditions (e.g. severe hypoxaemia) that maybe not feasible clinically nor ethically. On the other hand, a limitation of this study is that the model behaviour and outputs may not always be reliable during extreme situations, as it has not been validated in some of these scenarios (e.g. airway obstruction and obesity). Additionally, the study was limited by the lack of sufficient clinical and physiological data of obese subjects undergoing HFNO during apnoea. This has prevented the validation of the model in this area and warrant caution in generalising the preliminary results.

Part of the credibility of research findings is based on how representative is the sample to the studied population in terms of characteristics. Robust samples are large enough to represent the population but small enough to be measured easily and economically. The sample size of this study is small. However, it is worth mentioning that our model can individually configure the cardiopulmonary system, even the micromechanics, at the alveolar and capillary level [183]. It is quite reproducible and reliable [188]. Therefore small, yet, carefully-configured sample size might be as representative as a large randomly-selected sample.

5.6.5 Future studies

Hypercapnia and the subsequent acidemia remains a major limiting factor for the clinical use of prolonged apnoeic oxygenation. Although several mechanisms were suggested to be important [189, 213], the exact factors that affect the CO_2 clearance during apnoea are not completely understood.

Future physiological clinical research studies that examine the metabolic and the cardiopulmonary parameters during apnoeic oxygenation (e.g. THRIVE) may facilitate a better understanding and enable an analysis of the mechanisms involved and potentially establishing a relationship.

5.6.6 Conclusions

The results suggest that the patency of the upper airway, high O_2 concentration, and the use of HFNO during apnoea delays the onset and the progression rate of hypoxaemia. The HFNO was superior to the classical apnoeic oxygenation in terms of extending the safe apnoea time and increasing the CO_2 clearance, though with reduced benefits as BMI increases.

Chapter 6: High-flow nasal oxygen delays hypoxaemia during apnoea in virtual obese subjects

6.1 Abstract

Prolonging safe apnoea time is useful when anaesthetising patients at risk of rapid deoxygenation and patients who have increased difficulty with airway management. Obesity appears to be associated with both of these risk factors. This study quantified the effects of three treatments during apnoea *(i)* no supplemental O_2 (control), *(ii)* low-flow nasal O_2 (low-flow), *(iii)* high-flow nasal O_2 (HFNO) using a computer simulation of a bank of virtual obese subjects (n=90). Both forms of O_2 administration delayed hypoxaemia. HFNO outperformed low-flow O_2 in delaying hypoxaemia.

6.2 Introduction

As previously mentioned, the prevalence of obesity is continuing to increase worldwide. More than a quarter of the UK adult population are obese [2]. The combined effect of obesity [91], general anaesthesia [96], and supine position [32] on reducing the functional residual capacity (FRC), i.e. O_2 reserve in the lungs, is dramatic, causing a rapidly progressing hypoxaemia following the induction of general anaesthesia. Hypoxaemia can cause organ (e.g. brain) injury. Furthermore, obesity is linked with increased O_2 consumption [94] and is a risk factor for difficult face-mask ventilation, failure of supraglottic airways, and difficulty in establishing an emergency surgical airway [120]. Thus, obesity is associated with increased complexity in many aspects of airway management, while the time available for these interventions is shortened. Consequently, extending the non-hypoxaemic apnoea time in obese patients would be extremely valuable.

As previously stated, the use of HFNO has been shown to extend the safe apnoea time in non-obese subjects [50], but its effectiveness in obesity remains mostly unquantified.

In previous computational modelling research (described in Chapter 5), the values of physiological parameters of *in-silico* subjects were individually configured based on literature data. To enhance the model output, I configured a bank of obese *in-silico* subjects in which their physiological parameters' values were randomly selected by the ICSM model based on values extracted from the literature. This is claimed to better represent the variability that exists within the real-world targeted population.

6.2.1 Why extending safe apnoea time?

Prolonged safe apnoea time is not only useful when anaesthetising individuals at risk for rapid O_2 desaturation (e.g. severe obesity) but also during anaesthetising all individuals, as the vast majority of difficult airway incidences are unanticipated [214]. The difficult airway society 2015 guidelines recommend the use of apnoeic oxygenation in high-risk subjects [215]. Additionally, extending the safe apnoea time may minimise the repeated tracheal intubation attempts and increase the first-attempt intubation success [128]. A study collected data of more than 10,000 emergency tracheal intubations over ten years period has shown that more than two intubation attempts were positively correlated with significantly higher rates of complications such as hypoxaemia (70 vs 10.5 %), severe hypoxaemia (28 vs 1.9 %), aspiration (13 vs 0.8 %), and cardiac arrest (11 vs 0.7 %) [216].

Another critical reason to extend safe apnoea time is to decrease the likelihood of severe hypoxaemia because the incidence

of cardiac arrest has been strongly (83%) associated with severe hypoxaemia (SpO_2 < 70%) [16].

6.3 Aim of the study

This study aims to compare the effects of three O_2 treatments (HFNO, low-flow nasal O_2, and no supplemental O_2) during apnoea on gas exchange in a bank of obese virtual subjects.

6.4 Hypothesis

The delivery of O_2 during apnoea is hypothesised to delay safe apnoea time in obesity, and the use of HFNO is claimed to further increase the safe apnoea time with respect to classical apnoeic oxygenation.

6.5 Methods

In this study, the Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite was used, based upon the Nottingham Physiology Simulator [217]; it includes high-fidelity, integrated, computational models of several organ systems including respiratory and cardiovascular.

The ICSM is described in detail in Chapter 4. The design of this study is a crossover computational modelling experiment, where every *in-silico* subject undergoes all the simulated interventions. Conducting such a study on the clinical level is difficult and not ethical due to exposing real subjects to long durations of apnoea and life-threatening levels of hypoxaemia. Therefore, I chose to use this methodology because it allows a meticulous observation of the dynamic behaviour of the pulmonary gas exchange during apnoea.

6.5.1 Obesity data extraction from literature

Relevant parameters' values were required in order to configure the *in-silico* subjects appropriately. Therefore, a thorough literature search for clinical and physiological studies that examined obese individuals was performed. The targeted variables were mainly pulmonary and cardiovascular parameters such as respiratory rate, tidal volume, functional residual capacity, heart rate, cardiac output, O_2 consumption, anatomical shunt, and physiological deadspace. The search aimed to collect data only from obese subjects that are otherwise healthy.

A coding file has been scripted using Matlab software to create a bank of *in-silico* obese subjects. The values that were used to configure the physiological and metabolic parameters of the *in-silico* subjects were selected randomly by the computer simulator. However, the selected values are within pre-set ranges of values that are based on literature data.

6.5.2 Simulation of three different protocols

Part of the protocol used to conduct the study reported in Chapter 5 was implemented in this chapter. In particular, the gas-exchange efficiency of low-flow apnoeic oxygenation and high-flow nasal O_2 (HFNO) was compared in obesity during apnoea.

Three groups (i.e. obese I, II and III) of *in-silico* obese subjects were created, and each group consisted of 30 subjects. All groups received a pre-oxygenation of 100% O_2 for two minutes. The FRC was reduced by 50% to simulate the impact of the induction of general anaesthesia in obese individuals [96]. However, the baseline FRC values were variable.

Next, apnoea commenced and persisted until the SaO_2 reached 50%, while the upper airway remained patent. All the subjects (n=90) underwent the following interventions:

1. Control intervention: Ambient gas without supplemental O_2;
2. Low-flow intervention: 5 $L \cdot min^{-1}$ of cold (22° C) and dry O_2 delivered nasally;
3. HFNO intervention: 70 $L \cdot min^{-1}$ of heated (37° C) and humidified O_2 delivered via the nose with oropharyngeal pressure oscillations of 2 cmH_2O at 70 Hz.

In all interventions, the cardiac oscillations generated a pressure of 2.5 cmH_2O affecting 60% of the alveoli [189]. To predict O_2 consumption (VO_2) in obesity, I used White and co-workers [118] formula. The equation is $VO2 = 138 + (1.47 * body\ weight)$.

6.5.3 Outcome measures

The outcome variables were: *(i)* the time from the start of apnoea until SaO_2 reaches 90% (i.e. significant hypoxaemia) and 50% (i.e. life-threatening hypoxaemia), *(ii)* the rate of decrease of SaO_2 from 90% to 50%, *(iii)* the time from the start of apnoea until $PaCO_2$ reach 8 kPa (i.e. significant hypercapnia) and 16 kPa (i.e. severe hypercapnia), *(iv)* the rate of increase of $PaCO_2$ during apnoea. Variables such as PaO_2, SaO_2 and $PaCO_2$ were recorded at an interval of 5 milliseconds. Model simulations were run using a 64-bit Intel Core i3 3.7 GHz Windows 10 University of Nottingham computer, running Matlab version R2018a.v9 (MathWorks Inc. MA, USA).

6.6 Results

6.6.1 Data extraction from the literature and configuration of the bank

The consort flow diagram in Figure 6.1. highlight the number of subjects that were involved from the screening to the inclusion process. Out of 793 subjects, individual data of 115 obese subjects were used from eight clinical studies [89, 96, 101, 117-119, 218, 219]. The data were pooled all together in an excel spreadsheet then arranged according to the body weight. Next, the data were divided into three levels of obesity severities termed Obese I, II, and III. The bodyweight of Obese I is from 79 to 115 kg, Obese II is from 116 to 136 kg, and Obese III is from 137 to 205 kg. Table 6.1 summarises the actual values of the physiological parameters that were extracted from these clinical studies.

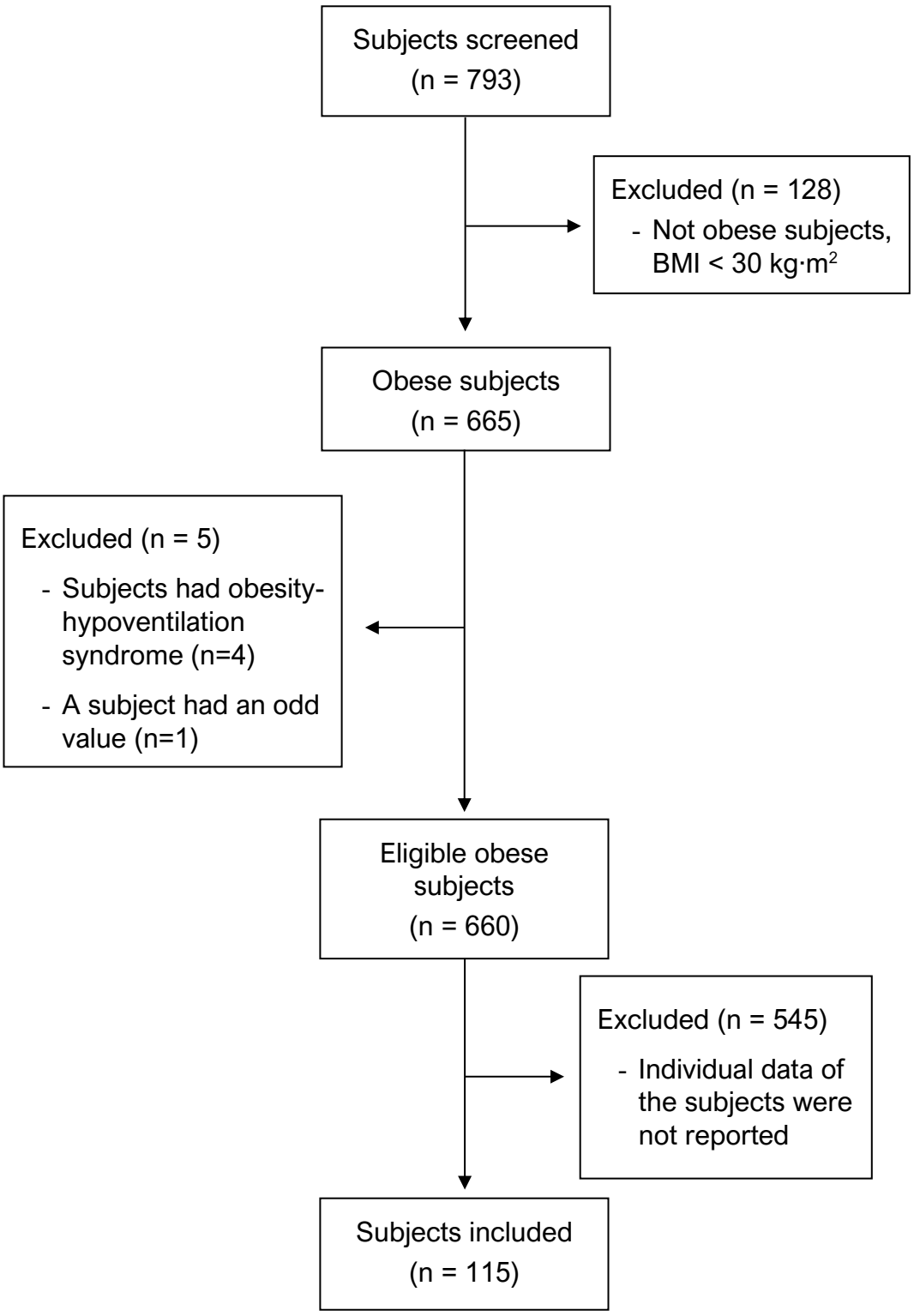

Figure 6.1. Consort flow diagram of the subjects from screening to inclusion.

Table 6.1. The baseline characteristics of the three levels of obesity obtained from eight clinical studies [89, 96, 101, 117-119, 218, 219].

		weight kg	**BMI** $kg \cdot m^{-2}$	**V_T** L	**RR** $breath \cdot min^{-1}$	**FRC*** L	**VO_2** $ml \cdot min^{-1}$	**HR** $beat \cdot min^{-1}$	**SV** ml	**CO*** $L \cdot min^{-1}$	**Q_S/Q_T Anat** %	**VD_{phys}** ml
Obese I n=37	mean (SD)	103 (11)	39 (5)	0.62 (0.17)	15.7 (6.3)	2.24 (0.9)	289 (16)	91 (14)	79 (17)	7 (1)	5.5 (2.0)	148 (73)
	(range)	(79-115)	(30-50)	(0.46-1.00)	(8.8-29.0)	(0.90-4.65)	(254-307)	(72-109)	(50-93)	(5-9)	(3.7-10.1)	(47-282)
	References	[96, 101, 218, 219]	**	[101]	[101]	[96, 101, 218]	[118]	[119]	[119]	[119]	[218]	[218, 219]
Obese II n=36	mean (SD)	125 (6)	44 (5)	0.65 (0.2)	17.6 (4)	2.39 (0.69)	322 (9)	75 (4)	75 (4)	7 (1)	5.2 (4.1)	189 (57)
	(range)	(116-136)	(36-57)	(0.42-1.05)	(9.0-22.0)	(1.00-3.75)	(309-336)	(72-78)	(72-78)	(6-7)	(1.0-12.7)	(103-270)
	References	[89, 96, 101, 218, 219]	**	[101, 117]	[101, 117]	[89, 96, 101, 117, 218]	[118]	[117, 119]	[119]	[119]	[218]	[218, 219]
Obese III n=42	mean (SD)	158 (18)	54 (8)	0.63 (0.2)	19.3 (7)	2.39 (0.72)	375 (28)	80 (12)	110 (10)	9 (1)	4.0 (1.9)	200 (103)
	(range)	(137-205)	(41-73)	(0.43-0.87)	(12.6-29.0)	(1.10-3.90)	(341-439)	(66-88)	(100-119)	(8-10)	(2.6-5.3)	(105-469)
	References	[89, 96, 101, 218, 219]	**	[101, 117]	[101, 117]	[89, 96, 101, 117, 218]	[118]	[117, 119]	[119]	[119]	[218]	[218, 219]

BMI, body mass index; V_T, tidal volume; RR, respiratory rate; FRC, functional residual capacity; VO_2, oxygen consumption; HR, heart rate; SV, stroke volume; CO, cardiac output; Q_S/Q_T Anat, anatomical shunt; VD_{phys}, physiological deadspace.
*values obtained during wakefulness
** BMI is a calculated variable

Due to the variability of the extracted data, the interquartile range was implemented as it appeared a better representation of the obesity level than the full range. Table 6.2 lists the values' ranges that were entered in the computer simulator to create the bank of the obese *in-silico* subjects.

Table 6.2. The parameters' values used to configure the bank

Parameter (unit)	**Obese I** [min-max]	**Obese II** [min-max]	**Obese III** [min-max]
weight (kg)	[79-115]	[116-136]	[137-205]
V_T (L)	[0.48-0.65]	[0.45-0.76]	[0.44-0.80]
RR (breath·min$^{-1)}$	[11.2-15.6]	[16.5-19.7]	[15.2-20.6]
FRC (L)	[1.1-3.7]	[1.3-3.4]	[1.3-3.3]
VO_2 (ml·min^{-1})	[254-307]	[308-337]	[339-439]
HR (beat·min^{-1})	[85-103]	[72-78]	[66-88]
Q_S/Q_T Anat (%)	[4-6]	[1-13]	[3-5]
VD_{phys} (ml)	[120-150]	[124-216]	[108-235]

V_T, tidal volume; RR, respiratory rate; FRC, functional residual capacity; VO_2, oxygen consumption; HR, heart rate; Q_S/Q_T Anat, anatomical shunt; $VD_{phys,}$ physiological deadspace.

The baseline characteristics of the 90 virtual obese subjects that were randomly configured by the computer simulator are presented in Table 6.3.

Table 6.3. The baseline characteristics of the three levels of obesity generated by the computer simulator

Parameter (unit)	Obese I n=30	Obese II n=30	Obese III n=30
Weight (kg)	97±10	126±5	171±20
Tallness (m)	1.63±0.1	1.67±0.1	1.63±0.1
BMI ($kg \cdot m^{-2}$)	37	45	64
PaO_2 (kPa)	12.5±0.7	12.0±2.0	12.1±1.2
$PaCO_2$ (kPa)	4.7±0.5	4.1±0.6	4.7±0.9
SaO_2 (%)	98±0.5	97±1.0	97±1.0
V_T (L)	0.59±0.44	0.65±0.08	0.65±0.11
RR ($breath \cdot min^{-1}$)	13.3±1.3	18.1±0.9	18.2±1.6
HR ($beat \cdot min^{-1}$)	94±6	75±2	76±6
CO ($L \cdot min^{-1}$)	7.4±0.9	7.5±0.3	9.1±0.5
FRC (L)	2.87±0.68	2.57±0.13	2.43±0.19
VO_2 ($ml \cdot min^{-1}$)	283±14	325±8	390±31
VD_{phys} (ml)	132±9	160±28	172±31
Q_S/Q_T Anat (%)	5±0.6	7±4	4±0.6

BMI, body mass index; V_T, tidal volume; RR, respiratory rate; FRC, functional residual capacity; CO, cardiac output; VO_2, oxygen consumption; HR, heart rate; Q_S/Q_T Anat, anatomical shunt; VD_{phys}, physiological deadspace.
Reported data is mean±SD

6.6.2 Simulations results

A total of 270 simulations have been performed. Their results are summarized in two tables, Table 6.4 (results related to hypoxaemia) and Table 6.5 (results related to hypercapnia). Compared to the control intervention, the provision of supplemental O_2 during apnoea substantially delayed hypoxaemia, more than tripling the duration of

safe apnoea in all groups. HFNO provided a further extension of the safe apnoea time.

Table 6.4. The onset and the progression of hypoxaemia of all the *in-silico* subjects in all the simulated interventions

		Time from the start of apnoea until SaO_2 reached		**SaO_2 rate of decrease from 90% to 50%**
		90%	**50%**	
Group	**Intervention**	min	min	$\%\cdot min^{-1}$
Obese I	Control	4.7 (0.4)	6.9 (0.5)	18.6 (1.6)
	Low-flow	16.3 (1.8)	21.0 (2.2)	8.6 (0.9)
	HFNO	19.1 (2.3)	25.3 (3.2)	6.6 (1.0)
Obese II	Control	4.5 (0.3)	6.4 (0.3)	21.3 (1.2)
	Low-flow	15.4 (2.1)	20.2 (2.2)	8.6 (1.1)
	HFNO	18.3 (2.6)	24.4 (3.2)	6.7 (1.1)
Obese III	Control	3.7 (0.4)	5.3 (0.5)	25.7 (2.4)
	Low-flow	13.6 (2.1)	17.4 (2.4)	10.6 (1.3)
	HFNO	15.2 (2.5)	19.8 (3.0)	9.0 (1.5)

Reported data is mean (SD). SaO_2, oxygen saturation in arterial blood, HFNO, high-flow nasal oxygen.

The control intervention was associated with the lowest $PaCO_2$ rate of increase, followed by HFNO and low-flow O_2, respectively, in all obesity severities. However, the time taken for hypercapnia to develop was similar in all interventions.

Table 6.5. The onset and the progression of hypercapnia of all the *in-silico* subjects in all the simulated interventions

		Time from the start of apnoea until $PaCO_2$ reached		$PaCO_2$ rate of increase
		8 kPa	16 kPa	
Group	**Intervention**	min	min	$kPa \cdot min^{-1}$
Obese I	Control	4.5 (0.7)	-	0.71 (0.07)
	Low-flow	4.4 (0.5)	12.6 (1.2)	0.99 (0.09)
	HFNO	4.5 (0.6)	13.1 (1.3)	0.92 (0.09)
Obese II	Control	4.8 (0.8)	-	0.75 (0.07)
	Low-flow	4.6 (0.6)	12.6 (1.1)	1.00 (0.08)
	HFNO	4.7 (0.7)	13.1 (1.2)	0.94 (0.08)
Obese III	Control	4.3 (0.7)	-	0.80 (0.08)
	Low-flow	4.2 (0.7)	11.4 (1.4)	1.09 (0.11)
	HFNO	4.2 (0.7)	11.7 (1.5)	1.05 (0.11)

Reported data is mean (SD). $PaCO_2$, partial pressure of carbon dioxide in arterial blood, HFNO, high-flow nasal oxygen.
- In the control intervention, the apnoea was terminated, and the $PaCO_2$ of 16 kPa was not reached due to meeting the study endpoint of SaO_2 of 50%.

6.7 Discussion

6.7.1 Main results

HFNO has been shown to be consistently more effective than low-flow nasal O_2 in terms of delaying significant and life-threatening hypoxaemia in all obesity severity levels. However, the impact of HFNO on extending the safe apnoea time was noticed to attenuate as obesity severity increases. The benefits of HFNO may be attributed to *(i)* higher mass inflow due to higher trans-airway pressure gradient induced by the flow-dependent positive pressure in the pharyngeal region, *(ii)* more lung volume induced by HFNO, and *(iii)* the enhanced CO_2 clearance allows O_2 to replace CO_2 molecules, which

may help maintain a positive gradient between PAO_2 and PaO_2 thus enabling longer duration of apnoeic O_2 diffusing into the bloodstream.

Although the time to reach $PaCO_2$ of 8 kPa was similar in all the interventions, the $PaCO_2$ rate of increase in the control intervention has been observed to be consistently lower relative to the classical apnoeic oxygenation and HFNO interventions. Compared to the classical apnoeic oxygenation, HFNO was always associated with a lower $PaCO_2$ rate of increase, leading to slight (subclinical) delays to develop severe hypercapnia (i.e. $PaCO_2$ of 16 kPa).

A possible explanation for the reduced efficiency of apnoeic ventilation during HFNO might be related to the visceral adipose tissues in obesity that may reduce the ability of cardiogenic oscillations to move gas within the respiratory system, which is a vital component of apnoeic ventilation [213]. An additional burden is that obesity is associated with noticeably increased CO_2 production.

6.7.2 Relation to previous studies

The present study's finding, which revealed that the use of HFNO extends the safe apnoea time more than low-flow apnoeic O_2 even in severely obese subjects, is in agreement with the finding's reported by a recent RCT [220]. The trial was conducted on 40 morbidly obese (BMI ≥ 40 $kg \cdot m^{-2}$) patients undergoing elective surgery. The authors found that the safe apnoea time (i.e. $SpO_2 \leq$ 95%) was 4.3 and 3.0 minutes in the groups that received HFNO (60 $L \cdot min^{-1}$) and the facemask O_2 (15 $L \cdot min^{-1}$), respectively. These values, however, are not consistent with the current study's data. The safe apnoea time observed in the current study is considerably higher than the cited study. The discrepancy may be related to *(i)* the efficacy of pre-oxygenation may have been suboptimal, *(ii)* the O_2 facemask has been removed (i.e. cessation of 100% O_2) to assess airway view, *(iii)*

a decreased degree of airway patency caused by either the reduced laryngoscopic force creating a grade III view, or nasopharyngeal/retropalatal reduced patency, and finally *(iv)* the development of early intrapulmonary shunt has not been integrated into the current study, which may have overestimated the effects of both HFNO and low-flow apnoeic O_2.

Another recent double-blinded RCT [221] has revealed that apnoeic oxygenation of 15 $L \cdot min^{-1}$ of O_2 resulted in a safe apnoea time of 4.4 minutes, which is higher than the safe apnoea time produced by the HFNO (60 $L \cdot min^{-1}$) reported by the previously described RCT [220]. This inconsistency could be attributed to methodological differences, such as the former trial [220] used a nasal cannulae to deliver O_2, while the latter [221] used a nasopharyngeal airway, which could theoretically guarantee that the O_2-rich gas reaches the pharynx. Secondly, the subjects who participated in the former study [220] are more obese (by about 10 $kg \cdot m^{-2}$ of BMI) than those who participated in the latter [221]. The authors [221] also reported that a total of ten obese patients have had reached the alternative endpoint of the study (i.e. 8 minutes of apnoea), while their SpO_2 values were more than 95%, which support the finding of the present study. An imperative implication that emerged from these studies confirms the crucial importance of maximising the patency of the upper airway, especially in obese subjects, as they are at a higher risk to develop airway obstruction (due to OSA) than lean subjects.

6.7.3 Additions to the knowledge of the subject

The findings of this study offer an in-depth quantitative analysis of the effects of three O_2 treatments (HFNO, low-flow O_2, and no supplemental O_2) on hypoxaemia and hypercapnia that occur during the apnoeic period in a bank of obese virtual subjects. HFNO has been

shown to be consistently more effective than low-flow O_2 in all obesity severity levels. However, the impact of HFNO on extending the safe apnoea time was noticed to decrease as obesity severity increases.

6.7.4 Strengths and weakness of the study

This study offers a novel and extensive investigation of apnoeic oxygenation interventions in a population that are at increased risk for rapid desaturation of O_2 (i.e. severe obesity). The course of gas exchange was tracked and meticulously inspected until the occurrence of life-threatening levels of hypoxaemia and hypercapnia during a simulated prolonged apnoea, which may not be feasible to perform clinically.

This study was limited by a few issues. First, the extracted data from the literature to create the bank did not specify the distribution of body fat, which is demonstrated to affect the magnitude of the alterations of the pulmonary and thoracic mechanics [97].

Secondly, although the influence of the induction of general anaesthesia on the FRC is assimilated in our model, the arising spontaneous development of ‘early’ intrapulmonary shunt as a result of the newly-formed atelectasis, that occur shortly post the general anaesthesia induction, is not yet incorporated, which may have overestimated the benefits of apnoeic oxygenation. Similarly, the development of absorption atelectasis due to receiving increased levels of inspired oxygen was not incorporated in the model, which may, in reality, affect the safe apnoea time.

6.7.5 Future studies

I would recommend that future PhD students investigate the role of HFNO use during extended apnoea periods in critically ill patients suffering from hypoxaemic respiratory failure using computational

modelling. The rationale behind this recommendation is because of the contradicting findings reported by the ICU and emergency department literature [130, 131, 197, 204]. Another reason is to evaluate whether HFNO still offers clinical benefits in the presence of pulmonary shunting.

Moreover, another interesting area to research is to determine the efficacy of CPAP as an apnoeic strategy. This may be relevant to neurocritical care and organ transplantation practice, where apnoea testing for the brain death assessment is regularly performed. The rationale for this recommendation is that a common method for oxygenation during this procedure (intra-tracheal insufflation O_2 at rates up to 15 $L \cdot min^{-1}$) has been reported unsafe and led to severe complications and fatality [222, 223]. Apnoeic CPAP may be more efficacious and safer than this method, though this would need to be confirmed by a thorough investigation.

6.7.6 Conclusions

The present computational modelling study was designed to compare the effects of three O_2 treatments (HFNO, low-flow O_2, and no supplemental O_2) on gas exchange in a bank of 90 obese virtual subjects. The findings indicate that the use of HFNO during apnoea is more effective than non-warmed, non-humidified, low-flow nasal O_2 in delaying life-threatening hypoxaemia in *in-silico* patients with all severity levels of obesity, though with reduced benefits as the severity of obesity increases. HFNO is likely to offer additional safe apnoea time during induction of general anaesthesia, with likely clinical benefit.

Chapter 7: High oxygen fraction during airway opening is key to effective airway rescue in obese subjects.

7.1 Disclosure

This study has been performed during my PhD by our multidisciplinary research group and has been published as an extended abstract in the IEEE Xplore and indexed in PubMed [224]. I was a co-author due to the scientific contribution that I offered, which included examining and amending the obese virtual subjects' configuration, as well as reviewing and editing the manuscript.

7.2 Abstract

Apnoea is common after induction of anaesthesia and may produce dangerous hypoxaemia, particularly in obese subjects. Optimal management of airway emergencies in obese, apnoeic subjects is complex and controversial, and clinical studies of rescue strategies are inherently difficult and ethically-challenging to perform. We investigated rescue strategies in various degrees of obesity, using a highly-integrated, computational model of the pulmonary and cardiovascular systems, configured against data from 8 virtual subjects (body mass index [BMI] 24-57 $kg \cdot m^{-2}$). Each subject received pre-oxygenation with 100% O_2 for 3 min, and then apnoea with an obstructed airway was simulated until SaO_2 reached 40%. At that time, airway rescue was simulated, opening of the airway with the provision of various patterns of tidal ventilation with 100% O_2. Rescue using tidal ventilation with 100% O_2 provided rapid re-oxygenation in all subjects, even with small tidal volumes in subjects with large BMI. Overall, subjects with larger BMI pre-oxygenated faster and, after airway obstruction, developed hypoxaemia more quickly. Our results indicate that attempts to achieve substantial tidal volumes during airway rescues are probably not worthwhile (and maybe counter-productive);

rather, it is the assurance of a high-inspired O_2 fraction that will prevent critical hypoxaemia.

7.3 Introduction

During anaesthesia, patients are often rendered apnoeic; the anaesthetist provides a patent airway through airway manipulation, facilitating pulmonary ventilation. Failure to manage the airway effectively may result in prolonged and potentially lethal apnoea. A worst-case scenario results in a "Can't intubate, can't oxygenate" situation. O_2 stores are depleted, and carbon dioxide accumulates during apnoea. However, our understanding of the factors affecting the progression of these pathophysiological abnormalities in various clinical contexts is incomplete.

Previous clinical investigations have highlighted obesity as an important risk factor that may radically change the progression of hypoxaemia during apnoea due to reduction of functional residual capacity (FRC) in obese patients [96, 225, 226] and higher metabolic O_2 consumption [227]. Equally, a high body mass index (BMI) and associated factors like a short, thick neck and obstructive sleep apnoea are recognized predictors for difficult mask ventilation and difficult laryngoscopy [228, 229]. However, the optimal management of airway emergencies is unclear even in healthy subjects, and the optimal management of obese, apnoeic subjects is complex and controversial. *In vivo* studies have been difficult and ethically-challenging to perform, and thus evidence to inform this issue is scarce.

This paper uses a high-integrated computational modelling of cardiovascular and pulmonary systems to evaluate different patterns of tidal ventilation achieving re-oxygenation following airway rescue (i.e. re-opening). We investigated different degrees of obesity,

examining the rate of progression of hypoxaemia and the impact on re-oxygenation following the opening of an obstructed airway and the application of various patterns of tidal ventilation.

7.4 Methods

7.4.1 Computational Model

We used the Interdisciplinary Collaboration in Systems Medicine (ICSM) suite of physiological simulations that consists of highly-integrated computational models of the pulmonary and cardiovascular systems [217, 230-233]. The model has been widely validated for the investigation of pre-oxygenation, apnoea and hypoxaemia in adults, [143, 177] parturients [179] and children [234].

The model includes a series deadspace volume, 100 independently-configurable alveolar compartments and 19 in-series cardiovascular compartments. The series deadspace (SD) is located between the airway and the alveolar compartments, and it is simulated as a series of stacked, rigid laminae of equal volume (N_{lam}). The static total volume of the series deadspace is set to 150 ml, and each lamina, *"j"*, has a known fraction ($f^{x}_{(SD,j)}$) of gas *"x"*. The pressure (above atmospheric) within each alveolar compartment is described by the following cubic function:

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

$$p_i = 0 \qquad \text{otherwise} \qquad \text{Equation 7.1}$$

In Equation 7.1, p_i is the alveolar 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. $P_{ext,i}$ (per alveolar unit, in cmH_2O) represents the effective net pressure generated by the sum of the effects of factors outside each alveolus.

We recently developed and validated additional modules in the ICSM simulation suite in order to include: *(i)* cardiogenic pulsation affecting intrathoracic gas spaces, *(ii)* augmented gas-mixing within the conducting respiratory deadspace, *(iii)* oxygen insufflation into the trachea, larynx or supraglottic space and *(iv)* pharyngeal pressure oscillation (e.g. occurring as a result of high-flow nasal oxygen administration) [189, 235]. For the purpose of this paper, we used the following modules:

7.4.1.1 Cardiogenic oscillations module

We described the effect of cardiac oscillations on alveolar compartments by the following equation:

$$P_{osc,i} = K_{osc} \cdot \varphi$$

$$\text{for } i = 0, .., N_{osc} \qquad \text{where } N_{osc} \leq N_{alv}$$

$$\text{In for } i = 0, .., N_{osc} \qquad \text{where } N_{osc} \leq N_{alv} \qquad \text{Equation 7.2}$$

$P_{osc,i}$ represents the pressure of the heart acting on the alveolar compartment i. This additional pressure, in combination with existing pressure values of the alveolar compartments, creates a pressure difference between the mouth and the alveolar compartments, across which the flow of gas can occur. The parameter $K_{osc,i}$ is a constant, representing the strength of the effect of cardiogenic oscillations on alveolar ventilation due to the alveoli being compressed by the heart and/or trans-alveolar blood volume. N_{osc} is the number of alveolar compartments that are affected by cardiogenic oscillations and N_{alv} represents the number of alveolar compartments. The function *"φ"*, described by a squared half-sine wave, is the ventricular activation function, equal to 1 at the peak of systolic contraction and 0 during maximal diastolic relaxation. Thus, the final equation (Equation 7.3) describing the pressure of each alveolar compartment is:

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

$$p_i = 0 \qquad \text{otherwise} \qquad \text{Equation 7.3}$$

7.4.1.2 Anatomical deadspace gas-mixing module

In order to represent the proportion of gas mixing between adjacent laminas of the anatomical deadspace, a variable parameter (*"σ"*) is introduced to the calculation of $f^{x}_{SD,j}$.

This new parameter allows various degrees of mixing: *"σ "* =1 would indicate a complete mixing of gases between layers, representing the effects of extreme turbulent flow of air, while *"σ"* = 0 would indicate no mixing of gases. Thus:

$$f^{x}_{(SD,j)} = \left((1 - \sigma) \cdot f^{x}_{SD,j}\right) + \sigma \cdot f^{x}_{(SD,j+1)} \text{ where } j < N_{lam} \qquad \text{Equation 7.4}$$

As it is presented in Equation 7.4, $f^{x}_{(SD,j)}$ is the fraction of gas *"x"* in lamina *j* and $f^{x}_{(SD,j+1)}$ is the fraction of gas x in the next lamina.

7.4.2 Virtual subjects, protocol and data

For this study, we created eight virtual (*in-silico*) subjects with BMI between 24 and 57 kg·m^{-2}, describing various degrees of obesity. Physiological variables relating to tidal ventilation, respiratory rate, FRC and oxygen consumption were calculated for each virtual subject using data from previously published papers [227, 236-238] and were used to configure the ICSM model to create a simulation of each patient. The physiological descriptors used are provided in Table 7.1.

Table 7.1. Physiological parameters of the virtual subjects

subject	BMI ($kg \cdot m^{-2}$)	weight (kg)	V_T (ml)	RR ($breaths \cdot min^{-1}$)	FRC (l)	VO_2 ($ml \cdot min^{-1}$)
BMI 24	24	70.0	420	12.0	3.00	250
BMI 27	27	76.8	415	12.5	2.87	251
BMI 32	32	89.3	410	13.0	2.73	269
BMI 37	37	102.0	400	14.5	2.57	288
BMI 42	42	113.0	390	15.5	2.06	304
BMI 47	47	134.6	385	16.5	1.99	336
BMI 52	52	139.7	375	18.0	1.89	343
BMI 57	57	152.0	365	19.0	1.80	361

BMI body mass index; V_T tidal volume; RR respiratory rate; VO_2 resting oxygen consumption; FRC function residual capacity before induction of anaesthesia

Resting tidal volume was configured as decreased in subjects with larger BMI; respiratory rate similarly increased with increasing BMI. Resting oxygen consumption (VO_2) was configured, as shown in Equation 7.5.

$$VO_2 = 138 + 1.47 \cdot \text{bodyweight} \qquad \text{Equation 7.5}$$

Where VO_2 is expressed in ml $min^{-1,}$ and body weight is expressed in kg [227]. During the induction of anaesthesia, the FRC was configured as decreasing by 20% in subjects with BMI<30 $kg \cdot m^{-2}$ and by 50% in subjects with BMI 32–57 $kg \cdot m^{-2}$ [237, 238].

Each virtual subject underwent pulmonary denitrogenation (i.e. pre-oxygenation) during resting, tidal breathing with an inspired oxygen fraction (FiO_2) of 100% for 3 min. Induction of general anaesthesia then occurred, and apnoea commenced. The upper airway became obstructed immediately upon loss of consciousness. Apnoea continued until the arterial oxygen saturation (SaO_2) reached 40%. At that time, for all virtual subjects, we simulated an airway

rescue manoeuvre that consisted of the opening of the airway and provision of various patterns of tidal ventilation with 100% oxygen. These ventilation patterns simulated varying degrees of success in re-instituting tidal ventilation; they were: 500 ml min^{-1} (50 ml x 10 min^{-1}), 2000 ml min^{-1} (200 ml x 10 min^{-1}) and 5000 ml min^{-1} (500 ml x 10 min^{-1}).

The following simulation outputs were recorded every 5 msec: arterial partial pressure of oxygen (PaO_2), the arterial partial pressure of carbon dioxide ($PaCO_2$) and SaO_2. Model simulations were run using a 64-bit Intel Core i7 3.7 GHz Windows 7 personal computer, running Matlab version R2018a.v9 (MathWorks Inc. MA, USA).

7.5 Results

Figure 7.1 shows the time courses of PaO_2 and $PaCO_2$ from the start of pre-oxygenation to the end of obstructed-airway apnoea (SaO_2 40%). All subjects showed a rapid increase in PaO_2 during pre-oxygenation; subjects with greater BMI pre-oxygenated more quickly. The progression of hypoxaemia during apnoea was consistently accelerated by increasing BMI, with the apnoea-time to reach SaO_2 40% in the BMI 57 kg m^{-2} subject being only 47% of that seen in subjects with BMI <30 kg m^{-2}. Carbon dioxide accumulation was effectively linear and was slightly slower with increasing BMI.

Figure 7.2 shows the effect of airway rescue involving airway opening and the application of various patterns of tidal ventilation using 100% oxygen. Rescuing apnoeic subjects with tidal ventilation provided rapid re-oxygenation for all subjects; increasing minute volume during rescue provided marginally faster re-oxygenation, but even very small volumes of 100% oxygen achieved effective (i.e. life-preserving) rescue. Post-intervention re-oxygenation was slightly slower in subjects with greater BMI.

The time from airway rescue to achieving PaO_2 8 kPa in the various configurations is reported in Table 7.2, representing the rapidity of rescue from critical hypoxaemia.

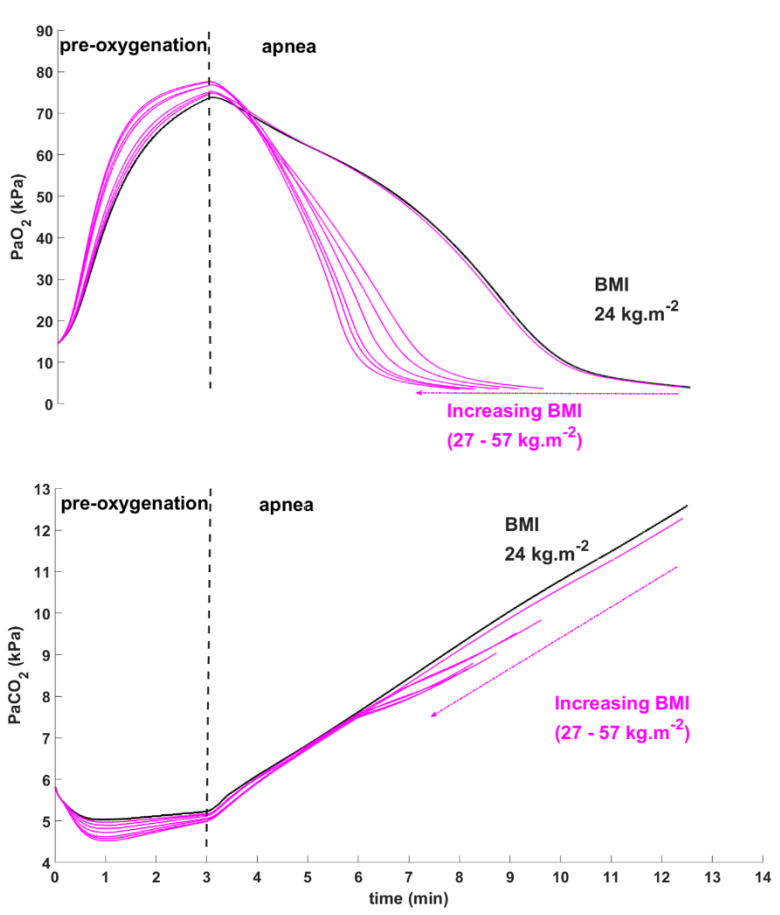

Figure 7.1. Time-course of PaO_2 (upper panel) and $PaCO_2$ (lower panel) during pre-oxygenation and apnoea with airway obstruction (black curve BMI 24 kg m^{-2}; magenta curves: BMI 27–57 kg m^{-2}). All curves end when SaO_2 reaches 40%. The vertical, black, dashed line marks the beginning of apnoea.

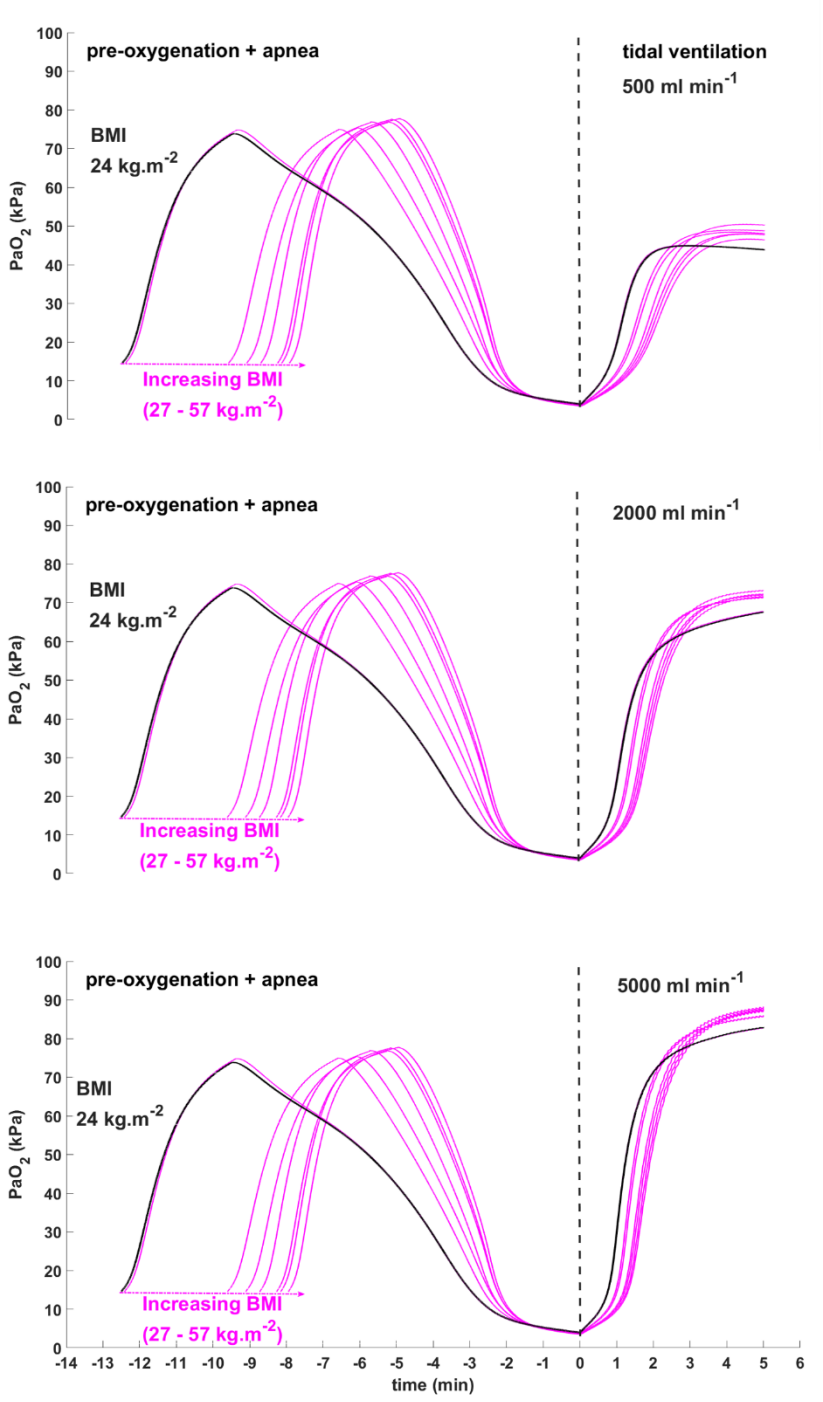

Figure 7.2. Time-course of PaO_2 during pre-oxygenation, apnoea with airway obstruction, and rescue with airway opening and tidal ventilation: minute ventilation of 500 ml min^{-1} (upper panel), 2000 ml min^{-1} (middle panel) and 5000 ml min^{-1} (lower panel) (black curve BMI 24 kg m^{-2}; magenta curves: BMI 27–57 kg m^{-2}). The vertical, black, dashed line marks airway-opening and rescue tidal ventilation.

Table 7.2. Time to reach PaO_2 8 kPa following tidal ventilation airway rescue

Subjects	Minute Ventilation ($ml \cdot min^{-1}$)		
	500	2000	5000
	Time (sec)		
BMI 24	25	25	25
BMI 27	25	25	25
BMI 32	35	35	35
BMI 37	37	36	36
BMI 42	45	44	44
BMI 47	47	46	46
BMI 52	49	48	48
BMI 57	51	50	49

BMI, body mass index

7.6 Discussion

We have performed a comprehensive modelling investigation into apnoea tolerance and rescue strategies in subjects with different degrees of obesity. We observed that de-oxygenation during obstructed-airway apnoea was significantly accelerated in subjects with greater BMI, and for each tidal ventilation pattern used, a degree of re-oxygenation was achieved.

We observed that re-oxygenation was slightly slower with increasing obesity, with a maximum delay of 26 sec to reach 8 kPa between the subjects with the highest and the lowest BMI. These findings are consistent with clinical experience, where it is often noted that rapid de-oxygenation may occur during apnoea in the obese patient, and that re-oxygenation may be slowed. [225, 238]

After simulated airway rescue, subjects did not re-oxygenate faster when receiving ventilation with larger tidal volumes compared to smaller ones. This has clear implications for clinical practice, in that

attempts to achieve substantial tidal volumes during airway rescues are probably not worthwhile and may be counter-productive. The extra effort required to deliver large tidal volumes may result in gastric distension, with consequent diaphragmatic splinting and regurgitation; rather, it is the assurance of a high-inspired oxygen fraction that will prevent critical hypoxaemia.

We chose to consider tidal ventilation with only one inspired oxygen fraction (i.e. 100%). The reason not to consider other inspired oxygen fractions was that, during airway rescue, if one can ventilate, then it will always be with 100% oxygen. However, in an airway crisis, most instances of airway *opening* are achieved with a local oxygen fraction of 21% (i.e. there is no provision of a high concentration of oxygen at the airway while it is manipulated). Thus, this study could inform clinical consideration for safe airway management in obese subjects undergoing anaesthesia.

Despite extensive validation and very good reproduction of normal physiology and pathology [217, 230, 231, 233], the modelled scenario must be viewed with a degree of caution since robust model validation is difficult due to the sparsity of clinical data describing scenarios of extreme physiological derangement. Prior validation of the model in less severe environments has been very encouraging, however, and given the lack of alternative methodologies to explore such crises, we believe that these results provide valuable insights into the management of apnoeic de-oxygenation and can usefully inform clinical practice and future research in such scenarios.

The next step will be that to investigate which combinations of tidal ventilation modalities assured safe intra-pulmonary pressures for airway resistances in small devices, while upper airway obstruction persists.

Chapter 8: The role of hyperbaric oxygen in rescuing severe acute respiratory distress syndrome with refractory hypoxaemia: a computational modelling investigation

8.1 Abstract

Introduction: The occurrence of refractory hypoxaemia in the context of acute respiratory distress syndrome (ARDS) is not uncommon and is associated with a substantial in-hospital mortality rate. Some mechanically-ventilated ARDS patients remain hypoxaemic despite the implementation of evidence-based techniques that significantly increase survival. Hyperbaric oxygen therapy (HBOT) is a powerful tool that increases systemic O_2 delivery to the tissues. However, the HBOT efficacy to reverse refractory hypoxaemia in severe ARDS patients has not been evaluated so far. This study aims to determine whether HBOT can achieve acceptable O_2 availability to the tissues in this population, using robust computer simulation.

Methods: A bank of 12 severe ARDS virtual patients with refractory hypoxaemia was configured using a high-fidelity, integrated computational simulator. The subjects received lung-protective mechanical ventilation at *(i)* atmospheric pressure, PEEP 18 cm H_2O and FiO_2 of 1.0 (high-PEEP intervention), and *(ii)* hyperbaric pressure (280 kPa), PEEP 5 cm H_2O and FiO_2, 0.40, 0.70, and 1.0 (HBOT intervention). Each simulation lasted for 30 minutes. The primary outcome is oxygen delivery (DO_2). The secondary outcomes are the arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), the arterial haemoglobin oxygen saturation (SaO_2), the arterial pH, and the Oxygenation Index (OI).

Results: The baseline characteristics of the 12 severe ARDS virtual patients are consistent with the Berlin definition severe

classification criteria, with a mean (standard deviation) PaO_2/FiO_2 ratio 39 (4) mmHg, SaO_2 72 (4) % and shunt fraction 55 (3) %. The DO_2 was 1071 (253), 1090 (255), 1196 (242) and 1221 (234) ml min^{-1} in the high-PEEP intervention and the HBOT intervention with FiO_2 of 0.40, 0.70 and 1.0, respectively. The HBOT significantly improved the other oxygenation indexes (i.e. PaO_2, SaO_2 and OI), while the $PaCO_2$ and pH values were similar in both interventions.

Conclusions: Our results suggest that hyperbaric oxygen significantly increases the oxygen delivery to tissues, even with a low FiO_2 in severe ARDS patients. HBOT could be sufficient to rescue severely hypoxaemic respiratory failure patients who failed maximal lung-protective mechanical ventilation. However, the effectiveness of the HBOT needs to be confirmed by an RCT.

8.2 Introduction

Acute respiratory distress syndrome (ARDS) is prevalent, affecting 10% of all patients admitted to intensive care units (ICU) [57]. ARDS causes profound hypoxaemia that is usually responsive to moderate-to-high levels of positive end-expiratory pressure (PEEP) [239]. However, a minority of ARDS patients remain hypoxaemic despite the implementation of adequate levels of PEEP, high fractions of inspired oxygen (FiO_2), restricted tidal-volume and plateau-pressure, i.e. lung-protective ventilation, and prone-position ventilation, as recommended by ARDS management guidelines [240, 241]. Refractory hypoxaemia causes up to 15% of the ARDS total deaths [242]. A multicentre observational study found a 21% incidence rate of refractory hypoxaemia (i.e. PaO_2/FiO_2 < 60 mmHg on FiO_2 of 1.0) in a moderate-to-severe ARDS cohort and was associated with a substantial in-hospital mortality rate of 64% [243].

Although many of the ventilatory and non-ventilatory rescue therapies (e.g. recruitment manoeuvres [244], high-frequency oscillatory ventilation [245], inhaled nitric oxide [246], and neuromuscular blockade [247]) improve the oxygenation via various mechanisms, none of the therapies demonstrated favourable patient-important outcomes (e.g. mortality), which may contribute to the inconsistent frequency to offer these adjunctive therapies [243, 248]. Nevertheless, a recent network meta-analysis [249] showed that the use of venovenous extracorporeal membrane oxygenation is likely to offer a survival benefit for severely hypoxaemic ARDS patients. Hyperbaric oxygen therapy (HBOT) has been recommended for conditions that cause hypoxia, e.g. carbon monoxide poisoning and severe anaemia [250, 251].

HBOT is referred to as the breathing of a high concentration of oxygen (O_2) at an increased ambient pressure environment. HBOT substantially increases the amount of O_2 diffused into plasma as well as fully saturating the haemoglobin, leading to increased systemic O_2 delivery to the tissues. The amount of the O_2 dissolved in the plasma at 3 atmospheres absolute (ATA) with 100% O_2 can theoretically exceed the total O_2 consumption of a healthy subject at rest, as supported by an animal model experiment [67].

Despite the powerful capability of the HBOT to increase oxygenation, it has not been assessed to reverse the life-threatening refractory hypoxaemia in ARDS patients. Conflicting anecdotal views exist on the potential benefit of HBOT in patients with significant shunt fraction [252, 253].

The aim of this study was to determine the efficacy of HBOT, with respect to maximal lung-protective mechanical ventilation, to achieve and maintain acceptable O_2 availability to the tissues in severe

ARDS virtual patients with refractory hypoxaemia, using robust computer simulation.

8.3 Research question

Can hyperbaric oxygen therapy (HBOT) (i.e. increased ambient pressure in combination with mechanical ventilation) achieve and maintain acceptable O_2 availability to tissues in severe ARDS virtual patients who remain hypoxaemic despite maximum lung-protective mechanical ventilation?

8.4 Hypothesis

Hyperbaric oxygen therapy may provide acceptable tissue oxygenation hence may serve as an appropriate alternative to ECMO in severe ARDS patients that failed mechanical ventilation.

8.5 Methods

The Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite, used in this study, is a rapidly deployed, agile and robust computational model of several organ systems, including the respiratory and the cardiovascular, originally developed in 1998 [217]. The simulator has been validated in numerous pathologies, including ARDS [182, 185, 254, 255]. Recently, it has been utilised to investigate the Coronavirus disease 2019 (COVID-19) [256] responsible for the current pandemic. ICSM simulation suite was used in all my previous studies. The ICSM is described in detail in Chapter 4. I chose this methodology (computational modelling) because the nature of this investigation may be considered as high risk and is likely to be challenging to perform clinically. Our high-fidelity model offers a suitable, efficient, and ethical-free platform to conduct this study.

8.5.1 Virtual subjects and protocol

A bank of severe ARDS virtual patients with refractory hypoxaemia was configured based on values partially extracted from Nirmalan and co-workers [257]. The other pulmonary and cardiovascular values were obtained from Chikhani and co-workers [187]. Table 8.1 shows the ranges of values used to configure the ARDS bank.

Table 8.1. Parameters' ranges used to configure the severe ARDS bank

Parameter (unit)	Minimum	Maximum
Weight (kg)	60	80
RR (breath·min^{-1})	24	30
V_T (ml)	320	560
HR (beat·min^{-1})	80	120
Q_S/Q_T (%)	50	60
VD_{phys} (ml)	195	235
VO_2 (ml·min^{-1})	200	260
CO (L·min^{-1})	6.5	9.4
Hb (g·L^{-1})	99	123

RR, respiratory rate; V_T, tidal volume; Q_S/Q_T, shunt fraction; CO, cardiac output; Vd_{phys}, physiological deadspace; CO, cardiac output, Hb, haemoglobin concentration.

The severe ARDS virtual patients (n=12) received a time-cycled pressure-limited controlled mechanical ventilation at:

1) high-PEEP intervention: atmospheric pressure (101.3 kPa) with PEEP of 18 cm H_2O and FiO_2 of 1.0;

2) HBOT intervention: hyperbaric pressure of 280 kPa with PEEP of 5 cm H_2O and three FiO_2, 0.40, 0.70, and 1.0.

The duration of each simulated intervention was 30 minutes. The inspiratory pressure (P_{insp}) level was initially adjusted to achieve lung-protective ventilation strategy defined in this study as *(i)* tidal volume ≤ 8 ml kg^{-1} of predicted body weight [155], *(ii)* inspiratory plateau pressure (P_{plat}) ≤ 30 cm H_2O [155], and *(iii)* driving pressure (∆P) ≤ 15 cm H_2O - i.e. calculated as P_{plat} minus total PEEP [156]. The virtual subjects had variable baseline cardiac output (CO) and shunt fraction, but they remained unchanged while undergoing the simulated interventions to assess the sole effect of the HBOT.

8.5.2 Outcome measures

The primary outcome measure is the oxygen delivery (DO_2), which was calculated using this formula: DO_2 (ml min^{-1}) = CO (L min^{-1}) * [1.39 * Hb (g L^{-1}) * SaO_2] + [PaO_2 (kPa) * 0.02]. The secondary outcome measures are the arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), the arterial haemoglobin oxygen saturation (SaO_2), the arterial pH, and the Oxygenation Index (OI) corrected for ambient pressure. OI reflects the severity of the oxygenation impairment (i.e. PaO_2) while considering the intensity of the ventilatory support (i.e. FiO_2 and mean airway pressure). Refractory hypoxaemia was defined as OI > 30 [258]. OI was calculated as [ambient pressure (ATA) * FiO_2 * mean airway pressure (cmH_2O) * 100] / PaO_2 (mmHg).

All parameters were recorded at 5 milliseconds interval. Model simulations were run using a 64-bit Intel Core i5 3.20 GHz Windows 10 personal computer, running Matlab version R2018a.v9 (MathWorks Inc. MA, USA).

8.6 Results

Table 8.2 summarises the characteristics of the ARDS virtual patients randomly configured by the computer simulator. Their

baseline values are consistent with the Berlin definition severe classification criteria [55].

Table 8.3. The baseline characteristics of the ARDS virtual patients (n=12) generated randomly by the computer simulator.

Parameter (unit)	**Mean (SD)**
Weight (kg)	69 (6)
HR (beat min^{-1})	98 (11)
VF (breath min^{-1})	28 (1)
V_T (ml)	450 (81)
V_E (L min^{-1})	12.8 (2.3)
PaO_2 (kPa)	4.6 (0.3)
FiO_2	0.89 (0.07)
PF ratio (mmHg)	39 (4)
SaO_2 (%)	72 (4)
PEEP (cm H_2O)	6.7 (1.1)
CO (L min^{-1})	7.9 (1.1)
Q_S/Q_T (%)	55 (3)
VO_2 (ml)	228 (15)
VD_{phys} (ml)	215 (9)
Hb (g L^{-1})	109 (8)

HR, heart rate; VF, ventilatory frequency; V_T, tidal volume; V_E, minute ventilation; PaO_2, the arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PF ratio, PaO_2 to FiO_2 ratio; SaO_2, the arterial oxygen saturation; PEEP, positive end-expiratory pressure; CO, cardiac output; Q_S/Q_T, shunt fraction, VO_2, oxygen consumption; VD_{phys}, physiological deadspace; Hb, haemoglobin concentration.

Table 8.4 presents the mechanical ventilator settings that achieved a lung-protective ventilation strategy and, consequently, used in the present investigation. Compared to the HBOT intervention, the increased PEEP level used in the high-PEEP intervention resulted in a higher functional residual capacity, a lower ΔP, and, therefore, generated a lower V_T and minute ventilation.

Table 8.4. Settings and parameters of the mechanical ventilator in the two simulated interventions

Parameter (unit)	High-PEEP intervention	HBOT intervention
P_{insp} (above PEEP) (cm H_2O)	13 (0)	18 (0)
PIP (cm H_2O)	31 (0.2)	23 (0.3)
P_{plat} (cm H_2O)	29 (0.2)	18 (0.3)
ΔP (cm H_2O)	9 (0.2)	11 (0.3)
V_T (ml) [ml kg^{-1} PBW]	311 (7) [4.4 (0.1)]	480 (15) [6.9 (0.2)]
VF (breath min^{-1})	28 (1)	28 (1)
V_E (L min^{-1})	8.8 (0.2)	13.6 (0.2)
FRC (L)	0.85 (0.07)	0.33 (0.06)

Reported data is mean (SD). P_{insp}, inspiratory pressure; PEEP, positive end-expiratory pressure; HBOT, hyperbaric oxygen therapy; PIP, peak inspiratory pressure; V_T, tidal volume; P_{plat}, inspiratory plateau pressure; ΔP, driving pressure calculated as P_{plat} minus total PEEP; PBW, predicted body weight; VF, ventilatory frequency; V_E, minute ventilation; FRC, functional residual capacity.

Table 8.5 shows the primary and secondary outcome measures. Compared to the high-PEEP intervention, the HBOT intervention provided higher O_2 delivery even when using a FiO_2 of 0.40. The HBOT intervention significantly improved the other oxygenation

indexes (i.e. PaO_2, SaO_2 and OI), while the $PaCO_2$ and pH were similar in both interventions.

Table 8.5. The primary and secondary outcome measures at the end of the simulated interventions.

	High-PEEP	HBOT		
	FiO_2 1.0	**FiO_2 0.40**	**FiO_2 0.70**	**FiO_2 1.0**
DO_2 (ml min^{-1})	1071 (253)	1090 (255)	1196 (242)	1221 (234)
PaO_2 (kPa)	8.4 (1.4)	9.0 (1.6)	35.9 (21.0)	111.0 (30.3)
SaO_2 (%)	88 (5)	90 (5)	99 (2)	100 (0)
$PaCO_2$ (kPa)	7.1 (0.2)	7.2 (0.2)	7.3 (0.2)	7.3 (0.2)
pH	7.33 (0.01)	7.32 (0.01)	7.32 (0.01)	7.32 (0.01)
OI	35.6	18.0	7.9	3.6

Data is presented as mean (standard deviation). PEEP, positive end-expiratory pressure; HBOT, hyperbaric oxygen therapy; DO_2, oxygen delivery; PaO_2, the arterial partial pressure of oxygen; PF, PaO_2 to FiO_2; SaO_2, the arterial oxygen saturation; $PaCO_2$, the arterial partial pressure of CO_2, pH, the arterial pH; OI, oxygenation index corrected for ambient pressure.

8.7 Discussion

8.7.1 Main findings

In severe ARDS virtual patients, the hyperbaric oxygen increased the tissue and arterial oxygenation remarkably with respect to the high-PEEP conventional ventilation. The OI was significantly lower in the HBOT intervention even after the correction for the ambient pressure. OI has been found as an accurate prognostic indicator for mortality [259]. No difference was detected in hypercapnia and acid-base balance. However, the HBOT had higher minute ventilation than the high-PEEP intervention.

8.7.2 Relation to previous studies

Studies that explored the use of HBOT to treat severe ARDS are sparse. However, the present study's finding is in agreement with a recent unpublished case series [260], which demonstrated that HBOT was effective in improving the hypoxaemia of five (two critically ill and three severe) patients suffering from COVID-19. The authors showed that the oxygenation of all the patients had consistently improved after each HBOT session. A six-year prospective observational study [75] reported data of 150 mechanically-ventilated (MV) patients, which included 35 ARDS patients that underwent a single session of HBOT. The most common indication that led these patients to receive MV and HBOT was severe carbon monoxide poisoning. The reported mortality rate in these moderate-to-severe ARDS cohort was 23%, which is substantially lower than the reported 32% and 45% for the moderate and severe ARDS, respectively [55].

The use of HBOT in critical illness is supported by an animal model experiment [261]. The authors showed that, in severe sepsis, the early administration of a single HBOT session (98% O_2 at 2.4 ATA for 60 minutes) significantly increased survival from 13% to 52% (in the group that received HBOT after 1 hour from the sepsis induction). Additional repeated sessions of HBOT at (1 and 6 hours) and (1, 6, and 21 hours) further increased survival to 58% and 60%, respectively. The authors suggested that survival benefit is attributed to the reduction of the host systemic inflammatory response induced by the HBOT.

8.7.2.1 What are the benefits, risks and challenges of HBOT?

HBOT presents several benefits, risks and challenges. Firstly, HBOT is an effective non-invasive procedure to increase tissue oxygenation, even during severe anaemia [67]. This benefit would

allow the FiO_2 and PEEP to be tapered off. Decreasing the FiO_2 minimises the absorption atelectasis [23], thus gaining more alveolar surface area for gas exchange. Decreasing the PEEP level may potentially *(i)* enhance the cardiac output hence tissue oxygenation [187], *(ii)* improve the pulmonary lymphatic circulation, therefore, increase the rate of pulmonary oedema elimination, and *(iii)* minimise the risk for the static strain lung injury [262]. Additionally, HBOT offers anti-inflammatory [261] and antimicrobial [263] effects. In the context of ARDS, both defensive mechanisms would be theoretically helpful since ARDS results in an intense inflammatory response, and is most commonly caused by infection, e.g. pneumonia and sepsis [264].

As discussed earlier, O_2 toxicity is a well-recognised risk of HBOT. Unit Pulmonary Toxic Dose (UPTD) was established [83] to quantify the pulmonary O_2 toxicity. One UPTD is equal to breathing 100% O_2 at 1 ATA for 1 minute. The upper cut-off is 1440 UPTD (equivalent to breathing pure O_2 for 24 hours at sea level). The O_2 toxicity of the central nervous system requires higher PiO_2 than the pulmonary system. The threshold, however, could not be precisely defined due to the wide variation of O_2 tolerance even within the same subject at different times [76]. Therefore, it is recommended that the PiO_2 does not exceed 2.8 bar absolute to minimise the occurrence of the CNS O_2 toxicity, which our methods considered.

Appropriate oxygenation level should be targeted to avoid hypoxaemia and hyperoxia, potential lung injury and O_2 toxicity (i.e. high PiO_2). High-quality evidence indicated that liberal use of O_2 increases mortality in critically ill patients [165]. Girardis and co-workers [168] found approximately 50% mortality reduction in patients who had a lower PaO_2 (11.6 vs 13.6 kPa). In our study, the HBOT using FiO_2 of 0.40 nearly achieved the oxygenation goal, where the other interventions resulted in either hyperoxia or hypoxaemia.

Interestingly, the incidence rate of seizures was less in ARDS patients than non-ARDS patients that underwent HBOT [75]. This may be explained by the decreased PaO_2, eventually delivered to the brain, caused by the ARDS-induced intrapulmonary shunt.

The use of mechanical ventilation per se has been deemed safe in hyperbaric chambers [75]. Critically ill patients should only be admitted into a Class 1 chamber, defined as a hyperbaric facility capable of supporting ICU patients. However, in the event of an emergency, it is likely that rapid decompression will be needed, risking decompression sickness, which would be dangerous in this vulnerable population.

If HBOT were to be implemented at a large scale, substantial financial expenses are expected for purchasing and installing ICU hyperbaric rooms and hyperbaric-compatible devices (e.g. cardiac monitors, ventilators, infusion pumps and defibrillators). Additionally, medical practitioners involved in this procedure must be well-trained in both disciplines (critical care and hyperbaric medicine) [265]. This procedure is semi labour-intensive, especially on multi-place chambers [265], where close monitoring from various professionals (e.g. chamber operator, ICU nurse and doctor) is required. Therefore, an adequate number of qualified staff should be available. Depending on the duration of the prescribed HBOT session and the available staff, the ongoing ICU care (e.g. nursing) is a challenging task. However, it may be feasible with sound planning and appropriate resources.

Preparation of environment, equipment, patient and staff are paramount. Intensive care monitoring and support can be safely provided via mono- and multi-place hyperbaric chambers [266, 267]. Each chamber type has its advantages and disadvantages [268]. The

decision to prescribe HBO should be based on a deliberate risk/benefit evaluation. As fire is considered one of the most significant hazards of hyperbaric oxygen, particularly during the mono-place chamber [268], the clinicians must be aware of and adhere to the safety guidelines meticulously. An additional issue to consider is that if the national medical device regulatory system requires that all devices be CE-marked, that will impose a limitation for the devices' usage [266].

Traditionally, hyperbaric chambers are small, circular and located far-away from ICU, which increases transportation risks [265]. However, advancements in industry and technology have facilitated the utilisation of this modality to critically ill patients. For instance, it led to the production of purpose-built large, rectangular, hyperbaric rooms located within ICU or in its immediate vicinity. Moreover, the availability of a modern closed-loop ventilator (Servo-i HBO, Maquet, Bridgewater, NJ), a CE-marked ventilator for hyperbaric use, enabled automatic ventilatory adjustments necessary to maintain consistent tidal volume delivery irrespective of ambient pressure, which can be a challenge when using a ventilator that does not have this feature where clinicians rely on manual measurements and adjustments [269].

Nevertheless, I would claim that HBOT presents a number of benefits that may counterbalance the benefits offered by ECMO and trades of the known risks. Firstly, unlike ECMO, *(i)* HBOT is a non-invasive procedure that does not jeopardises patients to bleeding or hematologic disorders. Secondly, *(ii)* HBOT possesses a higher capability than ECMO to increase O_2 tissue and does not require an adequate amount of haemoglobin to provide sufficient tissue oxygenation. Thirdly, *(iii)* HBOT offers anti-inflammatory [261] and anti-microbial [263] effects.

8.7.3 Additions to the knowledge of the subject

This study has added to the body of knowledge that a 30-minute session of HBOT at 280 kPa is capable of providing adequate tissue oxygenation in severe ARDS (with a mean shunt fraction of 55%) virtual patients, which has been previously challenged by Haddon [253]. Additionally, it offered a quantitative insight into the impact of the FiO_2 at hyperbaric pressure on the oxygenation indexes.

8.7.4 Strengths and weakness of the study

This is the first study that investigated and quantified the effects of HBOT in severe ARDS virtual patients. Our high-fidelity computational model allowed the investigation of HBOT in this extremely sick population, which is very challenging to conduct clinically for ethical, logistical, and medical reasons.

This study, however, had a number of limitations. Firstly, it is true that our model has been validated in ARDS [182] but was not validated under increased ambient pressure with a high concentration of O_2. This environment may cause variations in systemic vascular resistance and hemodynamic. Secondly, although the influence of the positive end-expiratory pressure (PEEP) on the FRC is integrated into our model, the PEEP impact on the degree of the intra-pulmonary shunt is not yet incorporated, which may affect the research output accuracy. Thirdly, it would have been interesting to study the role of the HBOT-induced anti-inflammatory when treating ARDS, especially in the hyperinflammatory phenotype. This effect has not been integrated into our model, which in reality may expand the HBOT benefits beyond the oxygenation advantage to perhaps a survival benefit.

Further, several assumptions were made. First, some physiological and anatomical parameters of the virtual subjects

remained constant despite being exposed to influential factors. For instance, the response of cardiovascular (e.g. cardiac output and systemic vascular resistance) to hypoxia and lung volume (i.e. FRC) alteration to FiO_2 exposure due to absorption atelectasis. Secondly, the virtual subjects were assumed fully sedated and paralysed and received controlled ventilation entirely determined by the ventilator. Moreover, the physiological ramifications resulting from the ARDS-induced increased cytokine in the systemic circulation are not incorporated in the model.

8.7.5 Future studies

It would be helpful to evaluate the HBOT in critical illness (e.g. COVID-19) that leads to hypoxia. In particular, sepsis with or without ARDS appears as a good choice. Sepsis and septic shock occur commonly affecting more than 50 million individuals worldwide, leading to more than 5 million deaths annually [270].

Considering the beneficial effects of HBOT, sepsis is ideally situated due to *(i)* caused by infection, *(ii)* produces an aggressive inflammatory cascade, and *(iii)* results in hypotension and hypoperfusion. It would be helpful to consider answering the following question: will HBOT be effective in terms of providing adequate tissue O_2 delivery and restoring adequate blood pressure due to the HBOT-induced systemic vasoconstriction in septic shock despite the presence of hypotension and hypoperfusion in virtual patients?

The present study focussed on evaluating hyperbaric oxygen therapy's efficacy from a gas-exchange perspective, mainly on its ability to reverse refractory hypoxaemia. However, future research should assess other endpoints, such as alveolar stability, especially in ARDS, whereas alveolar micromechanics and their response to positive-pressure ventilatory strategies (e.g., mode, PEEP level) can

be quite variable, at the global and regional level, due to the syndrome heterogeneity [271, 272].

Since the ICSM simulation suite is computational in nature, it does not provide any imaging (e.g. microscopy) of alveolar perimeters while being under a certain dynamic condition, which is how relevant research assess alveolar stability [272]. However, our model can record static and dynamic alveolar strains, which dynamic strain has been reported as a reliable surrogate for lung injury [273]. Finally, it must be recognised that the level of PEEP contributes to the prevention or minimisation of lung injury [273, 274], particularly atelectrauma, if it is set optimally. Therefore, caution is warranted when interpreting this study's findings.

8.7.6 Conclusions

The findings of this study suggest that HBOT can achieve and maintain acceptable O_2 availability to the tissues in refractory hypoxaemic ARDS virtual patients and may be considered as an appropriate rescue option. Despite the significant shunt fraction, low levels of FiO_2 and PEEP at hyperbaric pressure improved oxygenation status more than high FiO_2 and PEEP settings at atmospheric pressure. However, the HBOT effectiveness needs to be confirmed by an RCT, and whether the HBOT results in a favourable patient-important outcome.

Chapter 9: Thesis summary, contributions, and conclusion

9.1 Summary of the thesis

The thesis evaluated the efficacy of interventions applied during three dangerous situations, namely *(i)* extended duration of apnoea in obesity, *(ii)* emergency rescue of airway obstruction, and *(iii)* hyperbaric oxygen therapy in severe ARDS virtual patients using computer simulation. The thesis aimed to establish and quantify credible strategies that improve the oxygenation and ventilation of high-risk populations during anaesthesia and critical care settings using a series of computational modelling studies. These studies have fulfilled their aims and answered their research questions.

The first modelling study (**Chapter 5**) aimed to compare the effects of airway obstruction and patency, O_2 concentration, classical apnoeic oxygenation and high-flow nasal O_2 on the pulmonary gas exchange during apnoea in eight virtual subjects with BMI between 24 to 57 kg $\cdot m^{-2}$. The results revealed that airway patency, high O_2 concentration and HFNO delayed the occurrence of hypoxaemia. However, HFNO achieved the longest safe apnoea time as well as the lowest $PaCO_2$ rate of increase, though with reduced benefits as obesity severity increases.

Based on the promising findings of the HFNO in obesity obtained from Chapter 5, the next study (**Chapter 6**) expanded the investigation on a bank (n=90) of virtual obese subjects. It aimed to assess the effects of three different interventions rendered during apnoea with an open airway: *(i)* no supplemental O_2, *(ii)* low-flow nasal O_2 (classical apnoeic oxygenation), and *(iii)* high-flow nasal oxygen (HFNO). The findings indicated that, in obesity, the use of HFNO during apnoea is more effective than classical apnoeic oxygenation in

delaying significant and life-threatening hypoxaemia but without significant delay to hypercapnia.

The third modelling study (**Chapter 7**) explored the role of various patterns of tidal ventilation, following the opening of an obstructed airway, on the re-oxygenation period to a safe level in obese virtual subjects. This study aimed to examine the rate of progression of hypoxaemia and the re-oxygenation to a safe level in eight virtual subjects with BMI between 24 to 57 kg $\cdot m^{-2}$. The results showed that during obstructed-airway apnoea, hypoxaemia progressed faster in subjects with higher BMI. Also, after the airway opening, their re-oxygenation rate was slower than subjects with lower BMIs. Moreover, larger tidal volumes compared to smaller ones did not produce faster re-oxygenation to a safe level.

The fourth and final study (**Chapter 8**) evaluated the use of HBOT in virtual patients suffering from severe ARDS who remain hypoxaemic despite maximum lung-protective ventilation strategy. This study aimed to quantify the O_2 delivery to tissues in a bank of virtual ARDS patients with refractory hypoxaemia. Subjects underwent two interventions: *(i)* high-PEEP protective lung strategy at atmospheric pressure, and *(ii)* low-PEEP protective lung strategy in a simulated hyperbaric environment with three levels of inspired O_2 concentration - FiO_2 (i.e. 0.40, 0.70 and 1.0). The results demonstrated that hyperbaric oxygen was able to deliver higher O_2 delivery to tissues even with lower FiO_2 in 12 severe ARDS virtual patients.

9.2 The thesis original contributions to the field

The results obtained from **Chapter 5** and **6** offered a valuable quantitative perspective that describes the course in which hypoxaemia and hypercapnia evolve during prolonged periods of apnoea in obesity. The presented data are unique and are not likely

to be obtained from human trials as the nature of these investigations is lethal, thus unethical to conduct. The findings of these studies featured the impact of the patency of the upper airway, high O_2 concentration and HFNO, during apnoea, on delaying the onset of significant and life-threatening hypoxaemia and hypercapnia in the obese population.

The implications of the results attained by these studies highlight the effectiveness levels of various apnoeic oxygenation strategies. It recommends to healthcare practitioners, who are involved in airway management, the use of HFNO during apnoea as it showed to provide longer safe apnoea time in obesity, respect to classical apnoeic oxygenation. In case of the unavailability of HFNO, it is recommended to provide classical apnoeic oxygenation (e.g. via low-flow nasal oxygen) during the apnoeic period as it has shown to be significantly superior compared to not providing O_2.

The study reported in **Chapter 7** contributes to the field by demonstrating the unnecessity of providing large tidal ventilation following the rescue attempt of airway obstruction, as it was not associated with a faster re-oxygenation rate. The implication of this research work could inform clinicians to prioritise the provision of a high concentration of O_2 during this scenario. Additionally, in this context, massive tidal ventilation is not recommended as it has shown not to be beneficial in terms of oxygenation and might risk patients for untoward complications (e.g. pulmonary aspiration and lung injury).

Finally, the last study (**Chapter 8**) added to the body of knowledge that HBOT could be sufficient to rescue severely hypoxaemic respiratory failure patients who failed maximum lung-protective mechanical ventilation. However, the effectiveness of the HBOT needs to be confirmed by an RCT. The implication of this

finding should encourage researchers to consider and utilise this powerful modality that we possess within our armamentarium for ARDS future trials.

9.3 Limitations of this research

There are a few limitations that are related to the methodology used, i.e. computational modelling. First, it is impossible to model the full aspects of the human organ system due to the incomplete knowledge of human physiology during extreme scenarios. Moreover, there are physiological compensatory mechanisms to maintain normal body homeostasis, and not all compensatory mechanisms are entirely understood and applicable, thus not incorporated in the computational model. Second, several assumptions were considered. For instance, it was assumed that the FRC and O_2 consumption were constant during apnoea and at different levels of hypoxaemia, which may not represent the actual physiology. In the reported modelling studies, the autonomic reflex modules were not enabled to minimise the effects of confounding factors.

Additionally, mathematical modelling requires numerical data input. So the sparsity of particular literature prevented the calibration of the model against human data in specific areas such as in obese subjects receiving HFNO during prolonged apnoea and in severe ARDS patients receiving mechanical ventilation in a hyperbaric environment. Finally, the ICSM model has not incorporated a few mechanisms that may play a role in the investigations, such as *(i)* the development of the 'early' intrapulmonary shunt occurring after the induction of general anaesthesia, *(ii)* the impact of PEEP on the intrapulmonary shunt, *(iii)* the anti-inflammatory effects and systemic vascular constriction induced by the HBOT and hyperoxia.

Nevertheless, the latter two mechanisms are not relevant to the investigations' outcome measures.

9.4 Recommendations for future studies

It would be encouraging to see more engagement and collaborative research work between interdisciplinary professionals from the fields of medicine, engineering and computer science. The joint efforts would help advance the research by answering multi-faceted questions in a quality and efficient manner.

I recommend that future computational modelling studies consider examing the following areas: the impact of the early implementation of HBOT in COVID-19 patients to decrease the intensity of hypoxaemia, thus minimise the need for ICU admission and the role of HFNO during apnoea in obstetrics undergoing rapid sequence induction since they are considered a high-risk population for developing rapid O_2 desaturation.

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Appendix

The appendix presents several tables that summarise the studies that investigated apnoeic oxygenation and ventilation while undergoing various strategies at different settings.

Table 0.1. Summary of the studies that investigated apnoeic oxygenation during elective procedures.

Author	Year	# Subjects	Type	Methods	Results
Frumin et al. [46]	1959	8	Observational	- Apn-oxy: 100% O_2 via endotracheal tube. - Subjects were pre-oxygenated with 100% O_2 for ≥ 30 min.	- 7 patients had SaO_2 ≥ 98% throughout 30-55 min of apnoea.
Lee [123]	1998	46	RCT	- Apn-oxy: 5 L·min^{-1} O_2 via nasal prongs. - Control: no Apn-oxy	- The PaO_2 dropped steeply in the control group, from 63.8 to 34.1 kPa, as compared to 65.1 to 45.9 kPa, in the Apn-oxy group.
Taha et al. [275]	2006	30	RCT	- Apn-oxy: 5 L·min^{-1} O_2 via a nasal pharyngeal catheter. - The cut-off either: SpO_2 fall to ≤ 95% or 6 min of apnoea has occurred.	- SpO_2 was 100% throughout the full 6 min of apnoea in the Apn-oxy group, while the SAT was 3.65 min in the control group.
Rudlof and Hohenhorst [29]	2013	47	Retrospective	- Apn-oxy: 0.5 L·min^{-1} O_2 via an intratracheal catheter placed proximal to the carina.	- SpO_2 was maintained ≥ 93% up to 45 min of apnoea except in 3 patients due to O_2 desaturation, which was due to obesity, inadequate pre-oxygenation and spontaneous breathing.
Christodoulou et al. [276]	2013	41	RCT	3 groups: (Apn-oxy via nasal prongs) - control no Apn-oxy - Apn-oxy 5 L·min^{-1} - Apn-oxy 10 L·min^{-1} O_2	- Apn-oxy of 10 L·min^{-1} group sustained higher PaO_2 compared to 5 L·min^{-1} group and the control group, 33.7, 22.3 and 17.8 kPa, respectively.
Rajan et al. [124]	2018	20	RCT	- 1st group: CPAP of 20 cm H_2O, 10 L·min^{-1} of O_2. - 2^{ed} group: 6 L·min^{-1} O_2 via face mask. - The cut-off was either SpO_2 ≤90% or 14 min of apnoea.	- CPAP group had significantly longer SAT than non-CPAP group (13.6 vs 5.8 min) respectively.

RCT, randomized control trial; Apn-oxy, apnoeic oxygenation; SAT, safe apnoea time; NC, nasal cannulae; SpO_2, oxygen saturation; CPAP, continuous positive airway pressure.

Table 0.2. Summary of the studies that investigated THRIVE during elective procedures in the adult population

Author	Year	# Subjects	Type	Methods	Results
Patel and Nouraei [50]	2015	25	case series	- Pre-oxy: 10 min, 70 L·min^{-1}, FiO_2 1.0 - Apn-oxy: 70 L·min^{-1}, FiO_2 1.0.	- All patients maintained SpO_2 ≥90% throughout the apnoea period, ranged from 5-35 min, except 1 patient had a 65 min of apnoea with O_2 saturation of 95%
Gustafsson et al. [51]	2017	30	case series	- Pre-oxy: ≥3 min, 40 L·min^{-1}, FiO_2 1.0 - Apn-oxy: 70 L·min^{-1}, FiO_2 1.0	- All patients maintained SpO_2 ≥91% throughout apnoea period, ranged from 11-30 min, mean 22.5 min
Lyons and Callaghan [125]	2017	28	case series	- Pre-oxy: 3 min, 80 L·min^{-1}, FiO_2 1.0 - Apn-oxy: 80 L·min^{-1}, FiO_2 1.0	- The median apnoea time was 19 ranged from 9–37 min - All patients maintained SpO_2 ≥92% except 4 patients who had hypoxaemia with lowest SpO_2 of 85%
Joseph et al. [126]	2018	20	RCT	<u>HFNO group:</u> - Pre-oxy: 3 min, 30 L·min^{-1}, FiO_2 1.0 - Apn-oxy: 60 L·min^{-1}, FiO_2 1.0 <u>CPAP group:</u> - Pre-oxy: 3 min, CPAP 15 cmH_2O, 6 L·min^{-1}, FiO_2 1.0 - Apn-oxy: CPAP 15 cmH_2O, 10 L·min^{-1}, FiO_2 1.0	- Both groups completed the allocated 12 min of apnoea without hypoxaemia - CPAP group had significantly higher PaO_2 (at the end of apnoea) 54.6 kPa as compared to 28.1 kPa in the HFNO group.

RCT, randomized control trial; Pre-oxy, pre-oxygenation; Apn-oxy, apnoeic oxygenation; HFNO, high flow nasal oxygen; SpO_2, oxygen saturation; CPAP, continuous positive airway pressure.

Table 0.3. Summary of apnoeic oxygenation studies during emergency intubation.

Author	Year	# Subject	Type	Population	Methods	Results
Wimalasena et al. [127]	2015	728	experimental pre-post	RSI, majority trauma	- Study group: Apn-oxy - 15 L·min^{-1} O_2 via NC - Control group: no Apn-oxy	- Hypoxaemia incidence (SpO_2< 93%) was 16.5% and 22.6% in the group that received Apn-oxy and not received Apn-oxy, respectively. - Hypoxaemia duration was shorter in the Apn-oxy group 92.5 vs 169.8 sec.

Dyett et al. [15]	2015	129	prospective observational	different pathologies, (respiratory failure 34.5%*)	- Study group: Apn-oxy
					  - NC 15 L·min^{-1} (31.7%*)
					  - BVM (15.1%*)
					  - BVM + NC 15 L·min^{-1} (2.2%*)
					  - NIV (5.8%*)
					- Control group: no Apn-oxy
						- Hypoxaemia incidence in the non-respiratory failure patients who received Apn-oxy was 0.0% as compared to 16.7% who did not receive Apn-oxy.
						- Apn-oxy did not prevent hypoxaemia in the respiratory failure patients.
						- Hypoxaemia was the most common complication at 17.3%.

Sakles et al. [128]	2016	635	observational	emergency intubation mainly for airway protection (54% obese*)	- Study group: Apn-oxy via NC:
					  - 5 L·min^{-1}
					  - 10 L·min^{-1}
					  - 15 L·min^{-1}
					  - >15 L·min^{-1}
					- Control group: no Apn-oxy
						- Hypoxaemia incidence was 12.6% and 20% in the Apn-oxy and no Apn-oxy respectively.
						- First-time intubation success without hypoxaemia was 82% in Apn-oxy cohort, compared to 69% in no Apn-oxy cohort.

Sakles et al. [129]	2016	127	observational	intracranial hemorrhage mainly intubated for airway protection	- Study group: Apn-oxy via NC:
					  - 5 L·min^{-1} (14%*)
					  - 10 L·min^{-1} (18%*)
					  - 15 L·min^{-1} (35%*)
					  - >15 L·min^{-1} (33%*)
					- Control group: no Apn-oxy
						- Mild, moderate and severe hypoxaemia incidence was significantly lower in the Apn-oxy group than the no Apn-oxy: 7% vs 29%, 4% vs 18% and 3% vs 9% respectively.

Apn-oxy, apnoeic oxygenation; NC, nasal cannulae; BVM, bag valve mask; NIV, non-invasive ventilation; SpO_2, oxygen saturation. *percentage of the group

Table 0.4. Summary of the studies that investigated THRIVE during emergency procedures in the adult population.

Author	Year	# Subject	Type	Methods	Results
Miguel-Montanes et al. [130]	2014	101	quasi-experimental pre-post	- HFNO group: Pre-oxy, 3 min, 60 L·min^{-1}, FiO_2 1.0 and remained during apnoea - Nasopharyngeal catheter group: Pre-oxy for ≥3 min via 15 L·min^{-1} NRM then 6 L·min^{-1} via a nasopharyngeal catheter during apnoea	- The median SpO_2 was 100% in the HFNO group while 94% in the NRM group - Hypoxaemia incidence (SpO_2 < 80%) was 2 % in the HFNO group and 14% in the NRM group
Vourc'h et al. [197]	2015	118	RCT	- HFNC group: Pre-oxy, 4 min, 60 L·min^{-1}, FiO_2 1.0 and remained during apnoea - Facemask group: Pre-oxy for 4 min with 15 L·min^{-1} then no Apn-oxy	- No difference in the median lowest SpO_2 during intubation 91.5% in the HFNO group and 89.5% in the facemask group - Both groups had the same median apnoea duration of 1 minute
Semler et al. [131]	2016	150	RCT	- HFNC group: 15 L·min^{-1}, FiO_2 1.0 during apnoea - Control group: no Apn-oxy	- No statistical difference in the median lowest SpO_2 in between the Apn-oxy and the control group.
Jaber et al. [133]	2016	49	RCT	- Study group: Pre-oxy, 4 min, HFNO (60 L·min^{-1}, FiO_2 1.0) combined with NIV (PS 10, PEEP 5 cm H_2O, FiO_2 1.0), and HFNO remained during apnoea - Control group: NIV (same setting) during 4 min of Pre-oxy, no Apn-oxy	- The lowest SpO_2 values were significantly higher in the intervention group than in the control group, 100 % vs 96 % despite the double median apnoea time (120 vs 60 sec) - Zero % of patients in the study group and 21 % of patients in the control group had SpO_2 below 80 %
Simon et al. [203]	2016	40	RCT	- Study group: Pre-oxy, 4 min, HFNO 60 L·min^{-1}, FiO_2 1.0 and remained during apnoea - Control group: Pre-oxy, 4 min, BVM 10 L·min^{-1} then no Apn-oxy	- No difference in the mean lowest SpO_2 during intubation 89% in the HFNO group and 86% in the control group - Both groups had similar mean apnoea duration of about half a minute

RCT, randomized control trial; Apn-oxy, apnoeic oxygenation; Pre-oxy, pre-oxygenation; HFNO, high flow nasal oxygen; NRM, non-rebreathing mask; NC, nasal cannulae; SpO_2, oxygen saturation; NIV, non-invasive ventilation; PS, pressure support; PEEP, positive end-expiratory pressure; BVM, bag valve mask.

Table 0.5. Summary of apnoeic oxygenation studies during elective procedures on obese patients.

Author	Year	# Subjects	Type	Population	Method	Cut-off	Results
Baraka et al. [137]	2007	34	RCT	Morbid obesity	- Study group: 5 L·min^{-1} O_2 via pharyngeal catheter insufflation - Control group: no Apn-oxy	- SpO_2≤95 %, or - 4 min of apnoea.	- All Apn-oxy group completed the 4 min of apnoea with SpO_2 of 100%, while the control group had a mean SAT of 2.4 min. - A significant negative linear correlation between SAT and BMI was observed.
Ramachandran et al. [134]	2009	30	RCT	Mild obesity	- Study group: 5 L·min^{-1} O_2 via NP - Control group: no Apn-oxy	- SpO_2≤95 %, or - 6 min of apnoea.	- The Apn-oxy group had a significantly longer time to desaturate to 95% (5.29 min vs 3.49 min).
Heard et al. [135]	2017	40	RCT	Mild/moderate obesity	- Study group: 10 L·min^{-1} O_2 via a 3.5 ETT in the buccal area - Control group: no Apn-oxy	- SpO_2≤95%, or - 12.5 min of apnoea.	- The median SAT was 12.5 min in the Apn-oxy group compared to 4.9 min in the control group.
Moon et al. [221]	2019	135	RCT	Moderate/morbid obesity	- O_2 group: 15 L·min^{-1} O_2 via NP - Air group: 15 L·min^{-1} air via NP - Control group: no Apn-oxy	- SpO_2≤95%, or - 8 min of apnoea.	- The median safe apnoea time was 4.4, 2.5, and 2.7 min in the O_2, air, and the control group, respectively. - 10 subjects in the O_2 group completed the entire allocated apnoea time with SpO_2 >95 %.

RCT, randomized control trial; Apn-oxy, apnoeic oxygenation; NP, nasal prongs; SAT, safe apnoea time; SpO_2, oxygen saturation.

Table 0.6. Summary of studies that investigated the CO_2 rate of rise during apnoea.

Author	Year	# Subjects	Measurement	Apnoea duration (min)	Methods ($L \cdot min^{-1}$)	CO_2 rate of rise ($kPa \cdot min^{-1}$)
Holmdahl et al. [48]	1956	9	Arterial	6 (total)	O_2 via ETT	0.68
Frumin et al. [46]	1959	8	Arterial	41 (mean)	O_2 via ETT	0.45
Eger and Severinghaus [145]	1961	5	Alveolar	- 9.6 (mean) (normoventilation) - 16.4 (mean) (hyperventilation)	O_2 via ETT	- 0.56 (normoventilation) - 0.40 (hyperventilation) - 0.3 (hypothermia) after 1st min of apnoea
Lee [123]	1998	46	Arterial	3-4 (total)	5 via NP	0.5
Rudlof and Hohenhorst [29]	2013	47	End-tidal	24.7 (mean)	0.5 via IC	0.24
Patel and Nouraei [50]	2015	25	End-tidal	14±5 (median)	70 via HFNO	0.15
Gustafsson et al. [51]	2017	31	Arterial End-tidal	22.5±4 (mean)	70 via HFNO	0.24 0.12
Joseph et al. [126]	2018	20	Arterial	12 (total)	15 cm H_2O via CPAP	0.3
Babinski et al. [148]	1985	5	Arterial	30 (total)	24-28 via EI	0.08
Watson et al. [146]	1992	11	Arterial	~22 (mean)	45 via EI	- 0.32 (1st 5 min of apnoea) then remained relatively unchanged
Stock et al. [150]	1989	14	Arterial	~3.5 (mean)	Airway obstruction	- 1.6 (1st min) - 0.45 (thereafter)
Cheun and Choi [147]	1992	16	Arterial	- 7.5 (mean) (non-pregnant) - 3.6 (mean) (pregnant)	Airway obstruction	- 0.37 (non-pregnant) - 0.90 (pregnant)

ETT, endotracheal tube; NP, nasal prongs; IC, intratracheal catheter; EI, endobronchial insufflation.

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