

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

Quantifying the Severity of Respiratory Critical Illness

Taha Ismaeil

30 September 2016

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy in Anaesthesia and critical care

Abstract

Clinicians use several oxygen-based indices in intensive care units as surrogates to determine the condition of the patient's lung and verify monitoring progress. Examples of these oxygen indices include the ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2 ratio); arterial/alveolar oxygen tension ratio (PaO_2/PAO_2); alveolar–arterial oxygen tension difference ($PA\text{-}aO_2$); respiratory index (RI= ($PA\text{-}aO_2$)/PaO_2), and content-based venous admixture (Qs/Qt). One of the issues with this approach is that these indices fail to take into consideration several additional external pulmonary physiological factors and, as such, these indices could potentially mislead clinicians. This thesis explores the nature of the oxygen-tension-based indices response and examined the effect that varying certain external pulmonary factors, such as FiO_2, $PaCO_2$, Hb, respiratory rate, oxygen consumption, cardiac output, and respiratory quotient, had on PaO_2 using virtual subjects and patients' data to quantify oxygenation defect through a combination of mathematics, different diseases, and pathophysiology. There were one or two approaches that could lead us to the answer, and many dead end routes. Eventually, the research produced a new index that was compared and validated using two approaches. First, on virtual subjects with lung pathologies that were commonly seen in the intensive care unit and then on real clinical data that was obtained from the intensive care unit. The results of these validation investigations indicated that the proposed index

is more robust and resistant to variations in certain external pulmonary factors than the PaO_2/FiO_2 ratio. As such, there is a strong indication that it may help to improve the quality of patient care provided. The feasibility of manually calculating and applying this newly proposed index in the ICU is an issue that merits further exploration. Theoretically, if the newly proposed index was found to be practicable, it could improve the healthcare provided; reduce the cost of unnecessary blood work, and save time and effort. However, due to the time it takes to calculate crPaO2 manually, the use of medical technology and computer applications is desirable.

Acknowledgements

‘All praise is due to Allah lord of the worlds the Beneficent, the Merciful’

My sincerest thanks go to my supervisor Professor Jonathan G. Hardman; I thank him for his excellent support, encouragement, and guidance; and without whose support this thesis could never have been completed. I look forward to working with him in the near future. In addition, I thank Professor Ravi P. Mahajan for similar help and support through the process of this PhD.

I thankfully acknowledge my sponsor the government of Saudi Arabia in funding this work in the form of a scholarship from the King Saud bin Abdul-Aziz University for Health Sciences.

I express my deepest gratitude to my parents whom I owe my life for their constant love, encouragement, and blessing. I would like to thank my wife, Fatmah, who has provided me with tireless love and enthusiasm.

Finally, I express my sincere thanks to PhD colleagues and all numerous staff, administrative, academic within the University of Nottingham in the School of Medicine within the Anaesthesia and Critical Care Section, who provided help to me and have made my study time enjoyable and productive.

Publications and presentations from this thesis

Ismaeil, T., Alotaibi, A., Alahmad, A., Naeem, U., Bates, D., Das, A., & Hardman, J. (2015). Development of a New Index to Assess Pulmonary Oxygenation. Poster presented at the American Association for Respiratory Care Congress, Tampa, USA. http://rc.rcjournal.com/site/open_forum/2015_OF.pdf

Ismaeil, T., Alotaibi, A., Bates, D., Das, A., & Hardman, J. (2015). Variation of Pulmonary oxygenation indices using a computational modelling. Poster presented at the American Association for Respiratory Care Congress, Tampa, USA. http://rc.rcjournal.com/site/open_forum/2015_OF.pdf

Ismaeil, T. Hardman, J., Differences of pulmonary oxygen indices using a computational modelling Postgraduate research student oral presentation event. 22 May 2014, Nottingham, United Kingdom.

List of Abbreviations

ABG	Arterial blood gases
ACPC	Pressure Control Ventilation
ACVC	Volume control ventilation
AECC	American-European Consensus conference
ALI	Acute lung injury
ARDS	Adult respiratory distress syndrome
BE	Extracellular base excess
$C(a\text{-}v)O_2$	Arterial-mixed venous oxygen content difference
CaO_2	Arterial oxygen content
CcO_2	Pulmonary capillary oxygen content
CCU	Critical care unit
CF	Correction factor
CO	Cardiac output
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
$crFiO_2$	Correction factor for fraction of inspired oxygen
crHb	Correction factor for haemoglobin
$crPaO_2$	Corrected arterial partial pressure of oxygen
$crPCO_2$	Correction factor for arterial partial pressure of CO_2
crRR	Correction factor for respiratory rate
$crVO_2$	Correction factor for oxygen consumption
CV	Coefficient of variation
CvO_2	Mixed venous oxygen content
DO_2	oxygen delivery
EPF	Extra-pulmonary factor
$ETCO_2$	End tidal carbon dioxide
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
Hb	Haemoglobin level
HCO_3^-	Bicarbonate
HPV	Hypoxic pulmonary vasoconstriction
I:E ratio	Inspiratory to expiratory time ratio
ICU	Intensive care unit
KAMC	King Abdul-Aziz Medical City
LA95%	95% limit of agreement
MPP	Mean predicted partial pressure of arterial oxygen
MV	Mechanical ventilator
NPS	Nottingham physiology simulator
O_2	Oxygen
ODC	Oxyhaemoglobin dissociation curve
$P(A\text{-}a)O_2$	Difference between alveolar partial pressure of oxygen and arterial
PAC	Pulmonary artery catheter
$PaCO_2$	Arterial partial pressure of carbon dioxide

$PACO_2$	Alveolar partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PAO_2	Alveolar partial pressure of oxygen
PaO_2/FiO_2	The ratio of the arterial partial pressure of oxygen to the inspired oxygen
PaO_2/PAO_2	The ratio of arterial to alveolar partial pressure of oxygen
Patm	Barometric pressure
PEEP	Positive end expiratory pressure
PFc	Corrected PF ratio
pH	the negative logarithm of the hydrogen ion concentration
PIP	Peak inspiratory pressure
PRVC	Pressure regulated volume control
PSV	Pressure support ventilation
PvO_2	Partial pressure of venous oxygen tension
QC	Quality control
$\dot{Q}s/\dot{Q}t$	Intrapulmonary shunt
R_b	Bronchiolar resistances
RI	Respiratory index
RQ	Respiratory quotient
RR	Respiratory rate
RSD	Relative standard deviation
RT	Respiratory therapist
R_v	Vascular resistances
SaO_2	Arterial oxygen saturation
ScO_2	Capillary oxygen saturation
SD	Standard deviation
SIMV	Synchronized intermittent mandatory ventilation
SpO_2	Pulse oximetry
SvO_2	Venous oxygen saturation
UoN	University of Nottingham
$\dot{V}/\dot{Q}$	Ventilation to perfusion
VC+	volume control plus ventilation
VCO_2	metabolic production of carbon dioxide
VD/VT	Physiological dead space fraction
VE	Minute ventilation
VO_2	Oxygen consumption
Vt	Tidal volume
WHO	World Health Organization

Table of Contents

ABSTRACT ..... **I**

ACKNOWLEDGEMENTS ..... **III**

PUBLICATIONS AND PRESENTATIONS FROM THIS THESIS ..... **V**

LIST OF ABBREVIATIONS ..... **VII**

1. CHAPTER ONE - INTRODUCTION **1**

2. CHAPTER TWO - OUTLINE AND AIMS OF THESIS **4**

2.1. OUTLINE OF THESIS 7

2.2. AIMS OF THESIS 8

3. CHAPTER THREE - LITERATURE REVIEW **9**

3.1. OXYGEN INDEX 11

3.2. COMPUTER SIMULATOR 33

4. CHAPTER FOUR - DEVELOPING AND IMPROVING MPP WITH NPS **49**

4.1. INTRODUCTION TO MPP 51

4.2. COMPARING MPP WITH OTHER OXYGEN INDICES USING 6 SIMULATED PATIENTS 58

4.3. HYPOTHESIS AND AIMS 58

4.4. METHODS AND MATERIALS 59

4.5. RESULTS 67

4.6. DISCUSSION 69

4.7. CONCLUSION 72

5. CHAPTER FIVE- DEVELOPING CRPO$_2$ AND VALIDATING IT WITH NPS **73**

5.1. INTRODUCTION TO CRPAO$_2$ 75

5.2. METHODS 78

5.3. EXPERIMENTS REPORT 89

5.4. CONCLUSION 162

6. CHAPTER SIX - VALIDATING $CRPO_2$ WITH PATIENTS DATA 163

6.1. INTRODUCTION 165

6.2. METHODS 166

6.3. RESULTS 170

6.4. DISCUSSION AND CONCLUSION 180

7. CHAPTER SEVEN - CONCLUSION AND IMPLICATION OF THE WORK 185

7.1. SUMMARY OF THE MAIN FINDINGS 187

7.2. OTHER RELEVANT RESEARCH GROUPS 189

7.3. CLINICAL IMPLICATION AND SUGGESTIONS FOR FURTHER RESEARCH 191

8. REFERENCES 195

LIST OF FIGURES 209

LIST OF TABLES 214

9. APPENDIX 216

9.1. CONFIGURATION AND CHARACTERISTIC OF NINETY VIRTUAL NPS PATIENTS 216

9.2. DETAILED RESULTS FOR (FIO_2, HB, VO_2, RQ, CO) VARIATION 220

9.3. DETAILED RESULTS FOR OXYGEN INDICES AND VARIATION IN THE CLINICAL DATA 253

CHAPTER 1

Introduction

Lung diseases are among the leading causes of death worldwide. Data that were produced by the World Health Organization (WHO) in 2014 reported that the morbidity and mortality related to respiratory diseases are increasing (1). Lower respiratory infections were ranked fourth among the leading causes of death in 2010, followed by cancer and chronic obstructive lung disease (COPD), respectively. In addition, according to The British Thoracic Society (2), pulmonary disease is the most common cause of admissions into the emergency department. The primary admission diagnoses within the Intensive Care Unit (ICU) in the UK are respiratory and cardiac diagnoses (3), and COPD represents about 2.9 percent of all ICU admissions in the UK (4). Furthermore, an epidemiological survey that was conducted by the European multi-centre found that acute lung injury (5) is responsible for 7 percent of all ICU admissions, and accounts for 15 percent of the patients who require mechanical ventilation for 24 hours or more (6, 7).

Despite radical improvements in healthcare and advancements in the technologies that enhance patient monitoring, respiratory disease remains an important cause of death and disability globally (8). The complexity of the physiology of the respiratory system and the dynamics of the human body make managing this condition very difficult (8). Early identification and correction of the underlying cause, therefore, are fundamental to the management of patients with respiratory illness.

Clinicians who manage respiratory diseases use patients' blood gas tensions to understand the severity of gas exchange impairment. They

combine some values from the patients' blood gas results with mathematical equations that are commonly known as oxygen indices. The respiratory therapist, nurse, and physician typically use these indices as a tool to assess pulmonary oxygenation in critically ill patients. Many clinical decisions are based on the value and interpretation of theses indices.

Despite the use of oxygen indices in critical care settings, numerous studies have questioned the accuracy and/or precision of these indices on the basis that they fail to take into consideration additional external pulmonary physiological factors that may have an impact on pulmonary oxygenation; as such, the indices may be misleading clinicians.

Therefore, it is vital to understand the nature, indication, and limitation of the oxygen indices that are currently utilised in critical care settings. Moreover, there is a need to develop a new mathematical index that takes into consideration external pulmonary physiological factors such that it can be used in the critical care setting to more accurately assess pulmonary oxygenation.

CHAPTER 2

Outline and aims of thesis

2.1. Outline of thesis

This thesis investigates the nature of the oxygen indices that are currently utilised in critical care settings. Chapter 3-4 describes the use and limitations of the indices that are currently in use through considering both the computer simulation of patients (*in silico*), and real clinical patients (*in vivo*). Chapter 5 describes a new index by which pulmonary oxygenation can be assessed. The concepts underpinning this new index were explored using external pulmonary factors to quantify oxygenation defects through a combination of mathematics, different diseases, and pathophysiology. Ultimately, this produced an equation that was more robust than the PaO_2/FiO_2 ratio in so much that it resulted in less variation. As such, it may help to improve the quality of patient care provided. Since we hypothesised that the newly proposed index that was developed in Chapter 5 is less affected by any variation in the external pulmonary factors than existing oxygen-tension-based indices, we validated the indices using a validated computer model of virtual simulated subjects. Finally, Chapter 6 and 7 describes how the application of the index was validated through testing the index on a wide-scale sample of critically ill patient's data and the clinical implication.

2.2. Aims of thesis

- To investigate the variation of current oxygen indices on a variety of lung defects using a validated computational model (the Nottingham Physiology Simulator: NPS)
- To investigate the variation of the new oxygenation index (mean predicted PO_2 [MPP]) across a variety of lung statuses with various external factors including FiO_2 change, oxygen consumption, haemoglobin concentration and respiratory exchange ratio by using the Nottingham Physiology Simulator (NPS).
- To develop a robust index of oxygenation that can compensate for the effect of non-pulmonary-factors, including fraction of inspired oxygen (FiO_2), haemoglobin (Hb), partial pressure of arterial carbon dioxide ($PaCO_2$), respiratory rate (RR), cardiac output (CO), and respiratory quotient (RQ), and, therefore, more accurately represent the condition of a lung.
- To evaluate the newly proposed index $crPaO_2$ against FiO_2, Hb, and $PacO_2$ variations on a large-scale sample of critically ill patient's data.

CHAPTER 3

Literature review

This section of the literature review is divided into two parts. The first part of the literature review examines oxygen indices. It assesses the relative importance of employing different types of oxygen indices, it explains why indices are required, and the pros and cons of each index. The second part describes a medical computer simulator, why such a simulator can be of use, the type of simulator that was employed in this thesis research, and the use of an oxygen index in combination with a simulator.

3.1. Oxygen Index

This section begins by exploring the physiological concepts of oxygen transport in the body. It will then progress to link these concepts with different stages of the pulmonary disease in critically ill patients and consider the reasons why there is a need for an oxygenation index.

Continuous oxygen transport and supply to body tissue is vital to normal cellular functioning and maintaining aerobic metabolism (9). The global oxygen delivery (DO_2) is the total amount of oxygen delivered to the body tissue per minute, regardless of the distribution of blood flow (9, 10). While a normal subject is at rest, the distribution of cardiac output is adequate to maintain aerobic metabolism and meet the total oxygen requirements of the tissue (9). Global oxygen consumption (VO_2) measures the amount of oxygen consumed by body tissues per minute(10) , while the cellular metabolic rate determines the rate of VO_2 (8). For instance, the metabolic rate of breathing in a normal individual can reach less than 5 percent of the total VO_2, while the rate may

increase to 30 percent in critically ill patients who are in respiratory distress (8).

Oxygen transport from capillary blood to the body tissue correlates with following factors (9): the position of the oxygen and haemoglobin dissociation relationship, the rate of DO_2, issues that affect capillary diffusion, and the rate of VO_2 (10). For example, the diffusion between capillary and cell can be impaired by tissue oedema as a result of excessive fluid loading or increased vascular permeability, which leads to cellular hypoxemia (8).

The oxygen-haemoglobin dissociation curve (ODC) defines the relationship between O_2 content and the partial pressure of oxygen PO_2 (11). The ODC has a sigmoid shape that influenced by various physiochemical factors. The partial pressure of oxygen required to produce a 50 percent saturation of haemoglobin is defined as P50 (11). An increase in the P50 causes a right shift of the ODC, which reduces haemoglobin saturation and, thereby, increases the oxygen that is available to the tissues. Numerous factors affect the position of the curve including pyrexia, acidosis and an increase in 2,3-diphosphoglycerate (2,3-DPG) (12, 13).

Over the past two decades, an increasing amount of research studies have focused on the association between VO_2 and DO_2 in critically ill patients (9, 14-19). In the early stages of the disease, it is difficult to recognise inadequate DO_2 due to the non-specific clinical features of most

cases. DO_2 relies on oxygen saturation rather than partial pressure. Accordingly, the DO_2 could be compromised by oxygen desaturation, low haemoglobin levels, and a reduction in cardiac output (8, 9). Several epidemiological studies have reported reductions in mortality rates in critically ill patients as a result of maximising DO_2 and VO_2 as well as a cardiac index (14, 20). These studies concluded that postoperative patients potentially benefit from therapeutic interventions that are designed to achieve the supraphysiologic goals of cardiac index, DO_2 and VO_2 (14).

However, in critically ill patients with a complex problem, many controlled trials have yielded inconsistent results regarding the impact such a strategy can have on clinical outcomes (21). The controversial results of these clinical trials could be attributed to methodological factors such as failure to adequately define the disease and issues with the sample population (21). However, in general, a perfusion pressure and the minimum level of DO_2 must be maintained in critically ill patients, while controlling other factors that influence oxygenation, in order to improve outcomes (8).

Therefore, the primary aim of any treatment for critically ill patients should be to maintain adequate oxygenation. The oxygenation of blood occurs during a gas exchange in which oxygen (O_2) is delivered from the alveoli to the capillary bed, and carbon dioxide (CO_2) is eliminated from the bloodstream (10). Arterial oxygen tension (PaO_2) reflects this transport process, and insufficient oxygenation leads to hypoxemia.

Hypoxemia is a common clinical problem that leads to hypoxic organ damage. Several pathological mechanisms lead to hypoxemia including diffusion impairment, right-to-left shunting, ventilation-perfusion mismatch, hypoventilation, and reduced inspired oxygen tension.

Alveolar hypoventilation is defined as insufficient ventilation leading to an elevation in alveolar CO_2 tension ($PaCO_2$). The etiology of hypoventilation includes central nervous system impairment (encephalitis, trauma), neuromuscular disorders (Guillain-Barre syndrome, myasthenia gravis), chest wall deformities, or other conditions such as obesity hypoventilation syndrome, COPD, and drug overdoses. Ventilation is influenced and regulated by impulses from the chemoreceptor (for $PaCO_2$, PaO_2, and PH), which is located in the brain stem; and the stretch receptor, which is located in the lung and the cerebral cortex (22). Therefore, failure of any of these mechanisms will lead to hypoventilation and the state of hypercapnia. This is better explained in the context of the relationship between ventilation and $PaCO_2$. This relationship is expressed as follows:

$$PaCO_2 = (k)\ (VCO_2) / VA$$

VCO_2 = metabolic production of carbon dioxide,

k is a constant,

VA is alveolar ventilation.

Therefore, as can be seen in the equation above, as the $PaCO_2$ increases, the VA decreases, which is explained by the limited space of the alveolus.

Ventilation-perfusion (V/Q) mismatch is an imbalance between alveolar ventilation and pulmonary capillary blood flow (10). Physiologically, the V/Q ratio varies relatively throughout the lung. For instance, the V/Q ratio decreases in the apex of the lung. This standard distribution accounts for around 2/3 of the normal $P(A\text{-}a)O_2$ seen in healthy subjects and does not present any gas exchange problems. A low V/Q ratio results in an impairment in pulmonary gas exchange, causing low levels of arterial PO_2 and high PCO_2. This can be seen in cases such as asthma, chronic bronchitis, and acute pulmonary oedema. On the other hand, a high V/Q ratio implies there is ventilation but no perfusion. This ratio is typically associated with pulmonary embolism.

Diffusion impairment occurs when the lung's capacity for diffusion is reduced because of changes in the respiratory unit across the alveolar capillary membrane. This means there is an increase in the thickness that separates the alveolar gas and the pulmonary capillary blood. Consequently, this will lead to a reduction in pulmonary transit time. This is commonly the case in interstitial lung disease and pulmonary fibrosis (10). Measured variables, such as atrial oxygen saturation ($\%SaO_2$) and arterial oxygen tension (PaO_2), reflect oxygen impairment. However, these measured values depend on various physiological factors. These factors can be internal or external. The internal factors result from the non-linear nature of the relationship between PaO_2 and Hb saturation in

the ODC, changing blood flow, and the acid-base status of the blood (23, 24). The external factors result from issues such as minute ventilation, inspired oxygen fraction (FiO_2), and oxygen consumption (25). In other words, both SaO_2 and PaO_2 are still not reliable enough indicators of oxygenation due to their poor correlation with changes in clinical circumstance (24, 26).

In order to improve tissue oxygenation, an index is necessary to define the nature of the impairment that clarifies the oxygenation defect. This index must be a non-invasive tool that guides clinicians and helps them to better manage patient conditions, assess the severity of the disease, select the most effective treatment strategy, monitor the progress of the disease and determine the cost balance of more expensive treatments (24). In addition, the index should consider the complexity of the lung physiology, measure the oxygenation independent of FiO_2, assess whether the breathing process is dynamic, and determine the non-linear relationship between oxygen tension and content (27, 28).

Over the past 50 years, many oxygen indices have been proposed that can accurately measure pulmonary oxygenation status. However, developing indices should be straightforward, accurate, informative, feasible and cost-effective (27, 29). Gould (28) highlighted the characteristics that are important to the development of a perfect oxygenation index:

a) The index must be reliable under constant conditions; therefore, it should present the same value with repetition.

b) The index must work for what it purports to measure.

c) The index must respond to physiological changes with an acceptable sensitivity.

d) The index should present valuable clinical progress or diagnosis.

Common indices of oxygenation have historically consisted of content-based venous admixture (Qs/Qt) or tension-based indices. The four most common tension-based indices of oxygenation are arterial oxygen tension to a fraction of inspired oxygen ratio (PaO_2/FiO_2)(30, 31); the respiratory index ($P(A–a)O_2/PaO_2$)(32, 33); the arterial/alveolar oxygen tension ratio (PaO_2/PAO_2)(34-36); and the alveolar–arterial oxygen tension difference ratio ($P(A–a)O_2$)(28, 37, 38). Generally, content-based indexes are considered the gold standard and more reliable than tension-based indices. This point will be reviewed in more depth later in the thesis (26, 39-44).

3.1.1 The content-based index

Many researchers have claimed that using a content-based index that measures venous admixture Qs/Qt represents the gold standard for assessing the pulmonary and extra-pulmonary variables that influence gas exchange (25, 28, 41, 42). Venous admixture Qs/Qt is defined as the amount of mixed venous blood that needs to be added to the blood at the

pulmonary end capillary (PcO_2) to produce the observed difference between the arterial oxygen PaO_2 and PcO_2 that is observed in the systemic arteries (10, 45).

However, the clinical method that is employed to calculate the Qs/Qt requires an invasive procedure through which samples of mixed venous blood are collected. This method requires pulmonary artery catheterisation (PAC), which may not be feasible for all patients. In addition, some research studies have reported that there are many risks and complications associated with the use of PAC, such as cardiac arrhythmias, thrombosis, infection and bacterial colonisation, vascular injury, perforation of pulmonary artery, and occlusion and infarction (5, 46-50). The PAC placement decision must be balanced against the risks and the extent to which the information collated via the process is of value (5, 24). The possible information gained from the PAC generates an equation for theoretical intra-pulmonary shunt fraction as follows:

$$\boldsymbol{Qs/Qt = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}}$$

Where:

Qs/Qt: Intra-pulmonary Shunt Fraction

CcO_2: Capillary Oxygen Content

CaO_2: Arterial Oxygen Content

CvO_2: Mixed Venous Oxygen Content

This equation is considered to represent a useful indicator through which pulmonary oxygenation gas impairment can be assessed. Moreover, if the patient is breathing 100% oxygen, it would be the most accurate means of assessing the degree of a true shunt because it could vary in accordance with decreased ventilation/perfusion levels or changes of inspired oxygen FiO_2(24, 41, 51-53).

This inter-patient variation in physiology was demonstrated by Gowda and Klocke (41), who found that measured venous admixture may vary with changes in FiO_2 and the degree of this variation is proportional to the degree of V/Q imbalance. Originally, this equation was considered to be stable when employed with a healthy subject or patients with hypoxemia resulting from secondary to true shunt (24, 28, 41). However, numerous researchers and investigators have since criticised the reliability of calculating Qs/Qt (53). For example, some studies have shown that there is an increase in intra-pulmonary shunting when the subject breathes 100% FiO_2 (54-56). Another study found a reduction in Qs/Qt (57, 58), and others present almost no changes in Qs/Qt with changes in FiO_2 (25, 42, 59). These inconsistent Qs/Qt variations could be the result of severe, underlying lung disease (55, 57, 58, 60). Alternatively, the increase in Qs/Qt could be due to measurement errors when determining the contents of the blood oxygenation (61, 62).

Quan and colleague(52) elaborated on the variation of Qs/Qt with FiO_2 1.00 with two mechanisms. First, due to lung atelectasis or reabsorption atelectasis resulting from the nitrogen washed out in poorly

ventilated alveolar units. They found that this reduction in the quantity of nitrogen caused a reduction in functional residual capacity (FRC) and large shunt fractions. The authors described how the increased Qs/Qt might also be due to the dilatation of pulmonary arterioles constricted by alveolar hypoxia. This vasoconstriction will increase the blood flow in the pulmonary circulation to the non-ventilated alveoli, a phenomenon that is known as a hypoxic pulmonary vasoconstriction (HPV). To elaborate further, when the alveolar ventilation decreases in the lung, HPV occurs and causes the redistribution of the pulmonary blood flow in the pulmonary circulation. The authors attributed this phenomenon to an increase in PAO_2 or an increase in mixed venous oxygen tension, which could ease the effect of pulmonary arteriolar vasoconstriction. Therefore, it is possible that, with increased FiO_2, the alveoli will increase blood flow circulation, which will increase the Qs/Qt with no effect on functional residual capacity (23, 52, 53).

Quan and colleague (52) examined subjects who experienced a decrease in Qs/Qt when FiO_2 increased and were subject to a drop in "shunt-like effects" caused by V/Q mismatch and poorly ventilated alveoli. As such, it can be argued that an increase in PAO_2 tends to improve the oxygen diffusion gradient across the alveolar-capillary membrane, which ultimately increases oxygenation and minimises the induction of V/Q mismatch. Another explanation for Qs/Qt variation could be emphasised by the severity of lung disease and pulmonary vasoregulatory mechanism PAO_2 level (52). As such, it is feasible to argue that, in the case of

patients with mild lung diseases, the pulmonary vasoregulatory mechanism may contribute to a redistribution of pulmonary blood flow from the poorly ventilated alveoli to a well-ventilated region. This mechanism and redistribution of blood flow may decrease (63) with FiO_2 at a high level, creating an increase in Qs/Qt (52). There is a risk that this mechanism will be impaired in patients who have a severe pulmonary disease. In addition, PAO_2 will not affect vascular tone because a large region of pulmonary is not ventilated; consequently, Qs/Qt will decrease.

In conclusion, due to the absence of a strong valid and robust index, clinical doctors and investigators still consider the Qs/Qt equation to represent the best method of assessing gas impairment, even though it has some inherent limitations.

3.1.2 The tension-based indices

Oxygen tension-based indices employ equations that use PaO_2, PAO_2, and FiO_2 in a variety of combinations. These indices are the alveolar to arterial oxygen tension differences ($P(A\text{-}a)O_2$), arterial oxygen tension to alveolar oxygen tension ratio (PaO_2/PAO_2), PaO_2 to FiO_2 ratio (PaO_2/FiO_2) and the respiratory index (RI).

The advantage of tension-based indices is that they do not necessitate the use of invasive methods to obtain measurements because they employ inspired gas measurement and ABG sampling. On the other hand, the disadvantages of these indices include the following (24):

a) They operate on the assumption that the $C(a\text{-}v)O_2$ level is constant.

b) They are intrinsically affected by different FiO_2 levels.

c) They hold further assumption, specifically for indices that use PAO_2:

   - $PACO_2 = PaCO_2$
   - RQ = 0.8
   - PAH_2O = 6.3 kpa
   - $PaCO_2$ is in a steady state.

In addition, PAO_2 is initially utilized for other calculations; for example, $P(A\text{-}a)O_2$, PaO_2/PAO_2 and RI. PAO_2 is directly proportional to FiO_2. As such, a higher FiO_2 increases PaO_2 under normal

conditions (64). However, all these previous assumptions vary according to disease status. Therefore, there is a possibility that the results will be inaccurate and the reliability of the value generated by these indices is questionable.

3.1.2.1 $P(A–a)O_2$

The alveolar-arterial oxygen tension gradient $\boxed{P(A-a)O_2}$ has been proposed as a first oxygen index for gas exchange impairment (65). Since the $P(A\text{-}a)O_2$ equation is simple to use (by measuring PaO_2 from the arterial blood gas tension and calculating the alveolar tension), it has become more popular (54, 55). According to Lumb (45), the $P(A\text{-}a)O_2$ should not be greater than 2-5 kPa in a healthy young subject breathing air. However, it may increase as a result of a pulmonary disease that causes shunting or V/Q mismatching.

In addition, $P(A\text{-}a)O_2$ would theoretically increase as the alveolar oxygen tension PAO_2 increases in a normal subject. Yet, when the PAO_2 reaches 20 KPa, it will remain constant, even with a further increase in PAO_2 (66). As indicated by established theory (37, 67, 68) the three most significant explanations for $P(A\text{-}a)O_2$ difference are as follows: venous admixture, diffusion limitation, and a distribution element related to the presence of alveoli with various ventilation-perfusion ratios. Rahn and colleagues (68) took this hypothesis into account to configure curves that could predict the contributions that these three factors would make to the total P(A-

a)O_2 at different levels of alveolar PAO_2. For this configuration, they expected a typical diffusing capacity, a lognormal distribution of V/Q around a mean value of 0.85, and a consistent venous admixture of 2% of the total cardiac output. The configuration predicts three things that are as follows:

a) Diffusion limitation will be huge just when PAO_2 is not exactly around 70 mmHg,

b) The impact of V/Q distribution will be maximal over a scope of PAO_2 from 70 to 100 mm Hg, and will reduce as PAO_2 is further increased,

c) The total P(A-a)O_2 and the venous admixture component will increase suddenly between PAO_2 values of 100-200 mm Hg and will stay basically steady at a larger level of PAO_2, in spite of the fact that the predicted curve for P(A-a)O_2 is generally consistent with widely scattered data (37, 68).

Further, P(A-a)O_2 could estimate the calculation of Qs/Qt measurement at 100% of FiO_2, which will eliminate the influence of FiO_2 dependency (54). On the other hand, according to Oliven and colleague (51) and Douglas and colleague (53, 69), the calculated Qs/Qt value at 100% of FiO_2 did not replicate the correct rate of Qs/Qt. Likewise, Van De Water et al. (70) showed that even in a normal subject, P(A-a)O_2 may vary at 100% FiO_2.

Theoretically, the $P(A\text{-}a)O_2$ difference in reaction to the FiO_2 changes is a function of pulmonary configuration (35). For instance, the $P(A\text{-}a)O_2$ increases as FiO_2 increases in subjects with true shunt (rich defect), and a constant V/Q mismatch. Therefore, this sharp increase in $P(A\text{-}a)O_2$ is actually influenced by the variation in Qs/Qt, and it is more obvious in patients with high shunt degrees. In contrast, subjects with true shunt (poor defect) where the Qs/Qt is constant, the interaction of $P(A\text{-}a)O_2$ and increases in FiO_2 is different. To explain further, initially, when the FiO_2 increases, the $P(A\text{-}a)O_2$ also increases. After a while, when the FiO_2 reaches 0.70, it sharply decreases in response to FiO_2 increases. This result is probably attributed to V/Q mismatch variation (35).

Cane and colleague (40) and Zetterstrom (43) argued that P(A-a)O2 had less correlation with Qs/Qt; therefore, it may be considered to be less reliable than the oxygen index. Moreover, P(A-a)O2 varies according to other factors; for example, changes in C(a-v)O2 (26, 42), cardiac output, and haemoglobin concentration (45, 71).

3.1.2.2 PaO_2/FiO_2

The ratio of arterial oxygen tension to inspired oxygen fraction was introduced by Lecky and Alan as the simple oxygenation index in 1972, and was calculated as $\boxed{PaO_2/FIO_2}$ (72). Initially, this index was known as the oxygenation ratio, and the preliminary purposes

of this index were to quantify the sufficiency of pulmonary oxygen exchange by relating PaO_2 to FiO_2, and to assist critical care physicians with the process by which they weaned patients from mechanical ventilators where the initial scale rated from 1 to 5. For instance, PaO_2= 500 torr on FiO_2=100% the PaO_2/FiO_2 = five indicated an excellent-oxygenation, while a ratio of one denoted a poor-oxygenation (PaO_2 100 torr/ FiO_2 100%). In addition, the PaO_2/FiO_2 was used as objective evidence of further fluid overload (72). Then, the PaO_2/FiO_2 ratio was adjusted to estimate the degree of gas exchange impairment by considering the range 47-67 kpa of a PaO_2/FiO_2 ratio as normal and less than 40 kpa, as associated with significant pulmonary dysfunction (30). Since then, PaO_2/FiO_2 has been commonly used to assess respiratory status and responses to different therapies (73, 74).

Consequently, the PaO_2/FiO_2 ratio was used to diagnose patients with acute respiratory distress syndrome (ARDS) and acute lung injury (5, 12, 75-80). Initially, in 1967, Ashbaugh and colleagues described the manifestation of adult respiratory distress syndrome by acute onset of tachypnoea, hypoxaemia, and loss of compliance, and this syndrome was difficult to treat by ordinary methods of respiratory medicine (81). Since then, there have been a number of different definitions and studies for ARDS (82-88). For Example, in 1988, Murray and colleagues (84) extended the definition of ARDS that operationally measured the physiologic

impairment using a four scoring framework (lung injury score) including the degree of infiltration on chest X-ray, the static lung compliance, a level of PEEP, and PaO_2/FiO_2 value.

However, a wide agreement was accomplished in 1994 when the American-European Consensus Conference (AECC) group published a new definition (75). First, they replaced the word "adult" with "acute" and characterized ARDS as bilateral infiltrates on chest X-ray, acute onset of hypoxemia with $PaO_2/ FiO_2 < 200$, consistent with edema in the absence of left atrial hypertension. Additionally, they also added an extensive term, acute lung injury (ALI). This utilised the same definition as ARDS but with less hypoxemia $PaO_2/FiO_2 \leq 300$ (75, 76, 80, 89). Therefore, it is probable that the PaO_2/FiO_2 ratio is the most common oxygen tension-based index used by clinicians, as the AECC included this index in their definition of ARDS and ALI (75). According to the AECC, ARDS is associated with a PaO_2/FiO_2 ratio less than or equal to 27 kpa, while ALI is associated with a PaO_2/FiO_2 ratio less than or equal to 40 kpa (89).

Nevertheless, various issues in regards to the reliability and validity of the different criteria associated with the AECC definition have developed after 18 years of applied research (90, 91). These issues (91) include the following: no clear definition is yet available for the word 'acute', inconsistency between PaO_2/FiO_2 and different mechanical ventilator settings (92, 93), interobserver variation in

interpreting the chest X-ray (94, 95), and hydrostatic edema is difficult to distinguish in some cases (96-98). For these reasons, and in addition to the periodical review for diseases, a panel of experts formed in 2011 and used the international consensus process to develop the Berlin Definition. This approach was endorsed by professional societies with an empirical evaluation that focused on validity, reliability, feasibility, and objective evaluation of its performance (99). The Berlin Definition of ARDS resulted in different modifications. The category of ALI was eliminated, and ARDS was split into three categories of severity based on the PaO_2/FiO_2. For example, in the case of mild ARDS, the PaO_2/FiO_2 ratio ranged from 201 to 300 mmHg, the moderate from 101 to 200 mmHg, and severe less than 100 mmHg (99).

The reliability of the PaO_2/FiO_2 ratio as an indicator for measuring venous admixture Qs/Qt in critically ill patients is controversial. Two studies have considered PaO_2/FiO_2 ratio as a reliable tool for assessing pulmonary gas exchange status (43, 100). Study results (100) have shown that there is a correlation ($r = 0.9$) between PaO_2/FiO_2 ratio and Qs/Qt, and the PaO_2/FiO_2 ratio explains about 80 percent of the variation in Qs/Qt ($R^2 = 0.81$). However, the authors stated that this relation acceptably reflects the pulmonary gas exchange only when $Qs/Qt > 0.2$ and the extra-pulmonary factors, such as cardiac index and $C(a\text{-}v)O_2$, are within

normal limits (100). Similarly, the study (43) found a correlation between PaO_2/FiO_2 ratio and Qs/Qt to be equal to r =0.88.

On the other hand, in 1988 a study found that oxygen tension-based indices are not as reliable indications of Qs/Qt as the oxygen content-based index (40). Another study found that PaO_2/FiO_2 ratio is the least sensitive to changes in Qs/Qt (101). In addition, an alternative study suggested that PaO_2/FiO_2 ratio loses its sensitivity to extreme changes in Qs/Qt (102).

However, recent studies have questioned the validity of using PaO_2/FiO_2 ratio as part of ARDS diagnosis (24). Thus, recent studies used complex computer modelling to simulate ARDS patients with metabolic instability or haemodynamic such as increased shunt, V/Q mismatch, and low haemoglobin levels. This computer modelling showed variations in accordance with changes in FiO_2 (42). Therefore, when adjusting FiO_2 to 0.4, a PaO_2/FiO_2 ratio of around 18 kpa was formed, which classified the patient as ARDS (42). However, when the FiO_2 fell to 0.21, the PaO_2/FiO_2 ratio increased to 29 kpa (42). This resulted in the misclassification of patients and entailed that the results of previous studies that supported the use of PaO_2/FiO_2 for the purposes of oxygenation assessment (24) was questionable. Moreover, one study examined the relationship between PaO_2/FiO_2 and FiO_2 (103). This study demonstrated that PaO_2/FiO_2 exhibits an initial decrease as FiO_2 increases, and a substantial increase as FiO_2 increases further (103). In addition, a

recent investigation employed computational modelling to evaluate variations in the PaO_2/FiO_2 ratio in response to changes in FiO_2, $PaCO_2$, and Hb concentration (104). This investigation found that PaO_2/FiO_2 varied by 77 percent through the range of FiO_2.

Therefore, based on previous studies, PaO_2/FiO_2 ratio is a flawed indicator of oxygenation, and the factors that affect its reliability should be taken into consideration in particular variations of FiO_2.

3.1.2.3 PaO_2/PAO_2

In the early 1970s, researchers claimed that the $\boxed{PaO_2/PAO_2}$ ratio can be accurately employed to assess pulmonary gas exchange impairment (34) after it was introduced in 1965 (105). Researchers initially considered the PaO_2/PAO_2 ratio to represent an accurate and valid tool for two reasons. First, because of its stability, even in the case of FiO_2 variations in healthy subjects and patients on mechanical ventilators or with pulmonary diseases (34). Secondly, because there is a significant correlation between the PaO_2/PAO_2 ratio and the Qs/Qt ratio (73).

Other investigators reported that PaO_2/PAO_2 ratio differs when FiO_2 changes and that this could result in an early conclusion. For instance, (103) claimed that the PaO_2/PAO_2 ratio decreases when the FiO_2 is between 0.21 and 0.40, then it stays relatively stable when the FiO_2 ranges between 0.40 and 0.55, and increases with additional increases in FiO_2. Moreover, (35) claimed that PaO_2/PAO_2

ratio varies as FiO_2 changes. For example, in virtual patients, the PaO_2/PAO_2 ratio decreased as the FiO_2 increased in subjects that had a true shunt (rich defect) and constant V/Q mismatch. After that, the PaO_2/PAO_2 ratio gradually increased as the FiO_2 increased. This sudden increase in the PaO_2/PAO_2 ratio was actually influenced by the Qs/Qt variation, and was more obvious in patients with high shunt degrees. On the other hand, in subjects with true shunt (poor defect), where the Qs/Qt was constant, the interaction of PaO_2/PAO_2 ratio with FiO_2 was different. To explain further, at the outset, when the FiO_2 increased from 0.21 to 0.30, the PaO_2/PAO_2 ratio decreased and remained relatively constant until PaO_2 = 13.3 kPa. At this point, the PaO_2/PAO_2 ratio increased in response to the FiO_2 increase (35). In addition, the PaO_2/PAO_2 ratio exhibited a linear relationship with Qs/Qt at a low level of Qs/Qt (36, 106). As such, this linear relationship turned curvilinear if the Qs/Qt increased (26, 43).

3.1.2.4 RI

The respiratory index (RI) was first introduced in 1973 (24). This index simply depends on the alveolar to arterial oxygen tension differences divided by the arterial oxygen tension: $\boxed{P(A-a)O_2/PaO_2}$ (32). Goldfarb and colleagues (32) conducted a retrospective study on 177 mechanically intubated patients through which they investigated the respiratory index (RI). They set an RI of two or

greater to intubate patients. They found that the probability of survival increased by 12 per cent with patients who reached an RI≥ 6.

Additionally, the RI reveals pulmonary shunt in different situations such as pulmonary emboli, atelectasis, and pulmonary contusion. Moreover, Covelli and his colleagues (100) found that there was a positive correlation between RI and pulmonary shunt when they conducted a study on 33 ARDS patients using invasive and non-invasive methods to monitor the oxygen derived. In addition, Sganga and colleague (39) investigated the relation between RI and shunt (Qs/Qt) with different types of diseases (e.g., patients with liver disease, pulmonary or extra-pulmonary sepsis and cardiac failure). They concluded that RI could be used as an indicator of pulmonary status, and that RI varies with disease types.

However, some scholars have argued that whenever there is an increase in FiO_2, measured changes in RI were opposite to the corresponding variations in the pulmonary shunt (40, 43, 107). For example, Herrick and colleague (107) reported that significant changes (67%) of RI are magnitudes of the opposite changes to the physiological shunt. Therefore, they concluded that using RI on a clinical basis is not a reliable indication of pulmonary gas exchange impairment and could be misleading. As such, RI behaviour in response to changes in FiO_2 is unpredictable because shunt varies.

3.2. Computer Simulator

The use of simulators to practice skills, solve problems, make decisions, teach, and conduct research is widespread. Certain practical skills, such as those employed in medicine or other fields (e.g., military training), take a significant amount of time to master and may be required to handle life-threatening situations (108). For instance, in military training, the pilot needs to practice the skills required to handle an engine fire, land a plane in an emergency, or perform a given manoeuvre while flying at a low level. Trainees can practice these skills and gain experience of dealing with a critical situation easily, less expensively, and safely using a flight simulator. In reality, the pilot may could spend many hours of flight time before encountering or being forced to deal with the experiences he or she could easily practice in such a simulator (108, 109).

According to (109), there are many advantages associated with the use of a flight simulator. For example, training simulators provide trainees with the opportunity to develop skills to the highest level, they advance the efficiency of training through the repetition of routine procedures, they help learners to develop the skills they need to handle emergencies safely and cost-effectively, and they can be used to evaluate applicants and/or assess their ability to perform a specific task (110). In addition, digital computer models or simulators can be very useful for teaching research. For instance, in the medical field, processes such as pulmonary

ventilation, gas exchange, carriage of gases in the blood, and blood circulation in the body can be measured accurately enough to use simulators to explore some of the key interactions that take place in the human body (111).

3.2.1 The concept of modelling

Many of the physiological terms that have previously described in this paper would not have been clinically significant unless they had been applied in medicine. All clinical practitioners trust their own mental calculations and intuition when making important medical decisions. These practitioners typically have general expectations of the clinical outcomes they will observe on a patient in accordance with the brain models that have been built over time and as a result of their own diverse clinical experiences. As such, a model simply represents a process by which a set of rules and concepts can be employed to make a decision.

Likewise, applied medicine relies on indices or the formulation of models. These models are constructed as a means of developing a simple view of a complex physiological process in order to encourage learning, improve decision-making abilities, and help clinicians to understand the physiological consequences of a certain action. Over the course of the last decade, varieties of techniques have been employed via computer physiological modelling to achieve different purposes. Members of the public, clinicians, medical students and researchers have all used modelling. For example, in the research field, modelling has been used to

explore the best methods by which difficult clinical decisions can be made in clinical situations without conducting experiments that may pose a risk to patients or animals (112-122). In addition, modelling allows the researcher to explore concepts in more depth and to apply experiments on a body system that would impractical to perform on a real subject (123-131). Modelling has also been used as a means of training medical students without putting patients at risk (115-119) and to enhance the effectiveness of practical training (132-136). Clinicians commonly use modelling to predict the physiological consequences of any clinical intervention (137-142), or to estimate clinical data and values (143-146). Furthermore, modelling facilitates clinical management (147, 148) and helps clinicians to plan for patient care and the appropriate allocation of resources (149, 150).

3.2.2 Medical Simulator

Simulator training can be employed to help answer the questions of practitioners who feel they lack the training or expertise to deal with the challenges they encounter in the clinical setting. This training can also improve their clinical performance (151). Some authors have differentiated between simulators and training devices (109, 133, 152, 153). According to these researchers, medical simulators mimic the environment and phenomena as it is in reality. Therefore, a surgical simulator must deliver a teaching experience that imitates the real operating room, as it would be with patients. However, while simulators

may be useful for providing students with an opportunity to practice expert practical skills, they are not necessarily effective for systematically teaching new methods or skills (109).

Training devices differ from simulators in that they are designed to teach certain procedures. For example, training aids, such as intubation or resuscitation manikins or fibre optic laryngo bronchoscopy, systematically provide the trainee with training feedback, reinforcement and practice opportunities (109). Gaba described different classifications of simulations, which include the hands-on simulator, computer screen simulator, and the virtual reality simulator.

Digital simulation models, computer models, mathematical or pathophysiological models have been validated as practical, accurate and reliable in different clinical situations (109, 111, 154-158).

The Advantages of Simulators (109)

- No risk to the patient.
- Scenarios can be presented that involve uncommon but serious problems.
- The same scenario can be presented to many different trainees.
- Scenarios can be repeated.
- The student can make mistakes without putting the patient at risk.

- Simulation can be stopped and restarted for teaching purposes.

3.2.3 Why Use a Pathophysiological Modelling Simulator?

Knowledge expansion in medical science is vital, as too is the development of an understanding of disease progression and treatments. To this end, more research studies are required. However, applying research in-vivo has many drawbacks. Some of these are as follows:

- The requirement to gain ethical approval to use human or animal subjects
- Costs
- Labour
- Time intensity
- Questionable usefulness
- Population representation

Computer modelling has been used in many aspects of scientific research, including clinical research models. However, the outputs of these studies are not always well recognised. For example, several of the studies that have examined the correlation between a surrogate and clinical outcomes have depended on an underlying model. Similarly, many statistical analyses have concluded that the results of these studies depend on statistical models of data relationships (159).

Computer modelling involves imitating the real-life shapes, functions or forms related to mental, physical, computational, mathematical, animal or laboratory phenomena (159-161).

Modelling can provide patient surrogates for investigations. Such surrogates are free from ethical concerns and may repeatedly be used to generate incredibly detailed and uniform data. So how is such modelling research performed?

The first step in modelling research involves defining the research question(s). After that, the researcher must develop the model and prove it is reliable. The researcher must subsequently validate the model before investigating it in depth. Finally, the researcher will design the protocol conducted on the model constructed to match a specific patient or disease of interest.

However, questions that suit modelling research must address any issues that are unsuitable for clinical research. Thus, it is unethical and impractical to investigate patients because some patients may be critically ill or the measurement cannot be taken frequently because it could put the patient's health at risk. In addition, researchers should decide whether a modelling approach could provide valid and reliable answers to the research question.

Therefore, establishing the validity of the model is the most important and difficult part of the research process. In the case of research into gas exchange, the virtual model should perfectly represent

the respiratory physiological ideas and predict gas exchange values along with the values that have been experimentally demonstrated in the literature (162).

In essence, the accurate replication of a biological process via a model is impossible. However, credibility represents an alternative approach through which trust can be established in the mind of the modelling researcher so that the model can adequately replicate the process with specific consideration. Thus, such credibility may be proven through comparisons with new patient data, old patient data, accepted theory, and clear and open descriptions of the model as a means of generating a sympathetic confidence.

3.2.4 The Nottingham Physiology Simulator

The Nottingham Physiology Simulator (NPS) is a simulation of several originals. The respiratory computational model integrates the mechanical ventilator affect with respiratory physiological datasets to produce stable clinical scenarios (157).

The NPS allows the user to adjust more than 40 variables. For example, the user can change the myriad of ventilation settings. In fact, this model has been used effectively to characterise deterioration in tissue oxygenation through apnoea episodes (163).

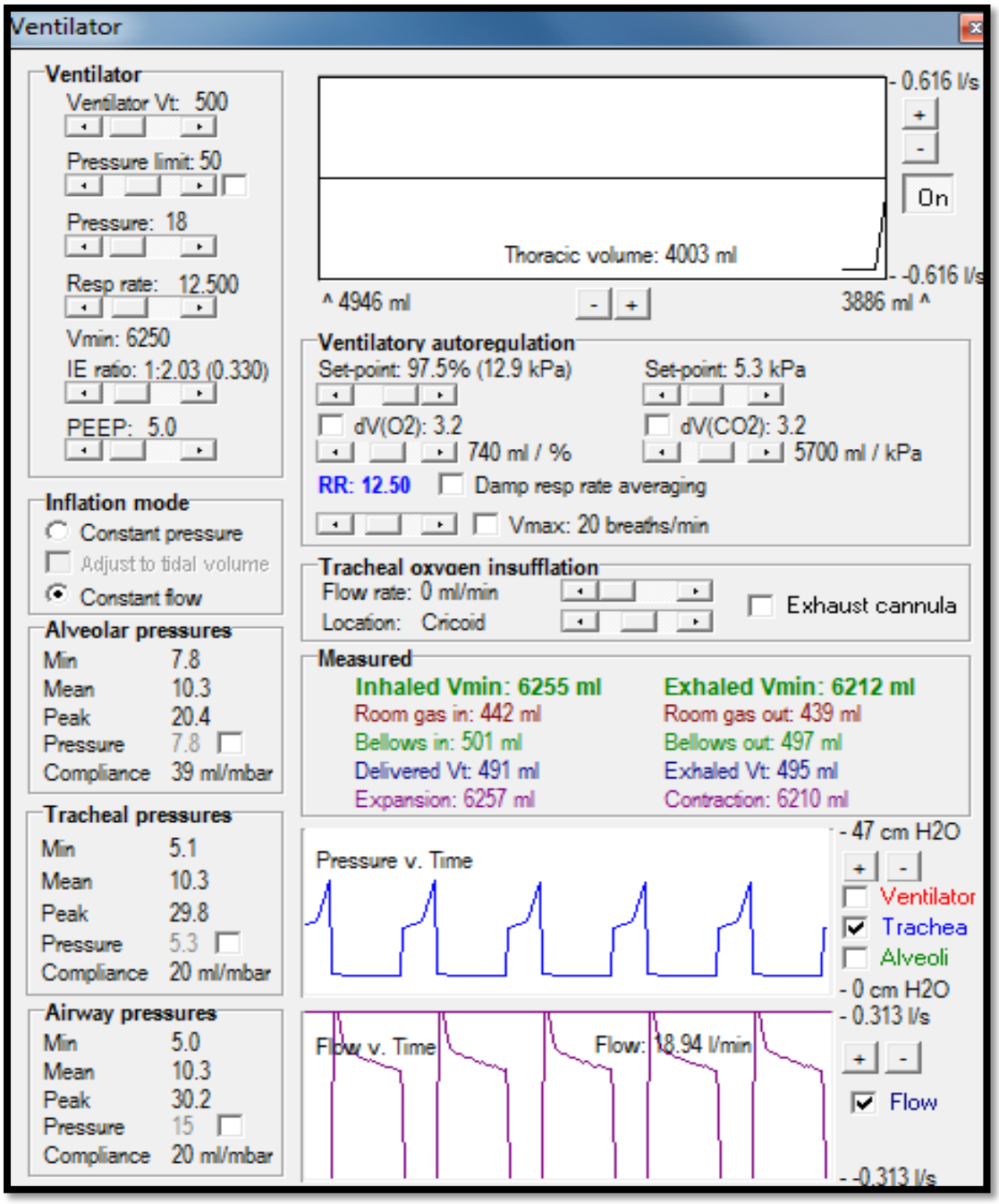


Figure 1 NPS mechanical ventilator control panel.

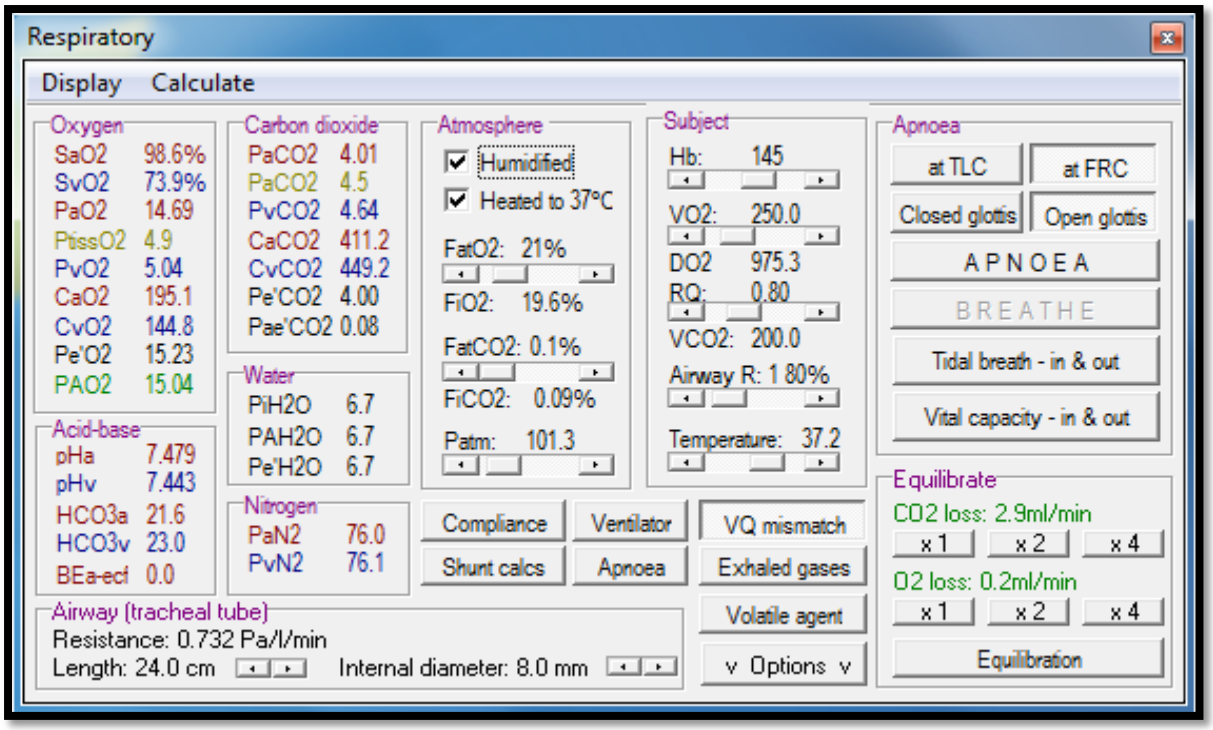


Figure 2 NPS respiratory physiological variable control panel

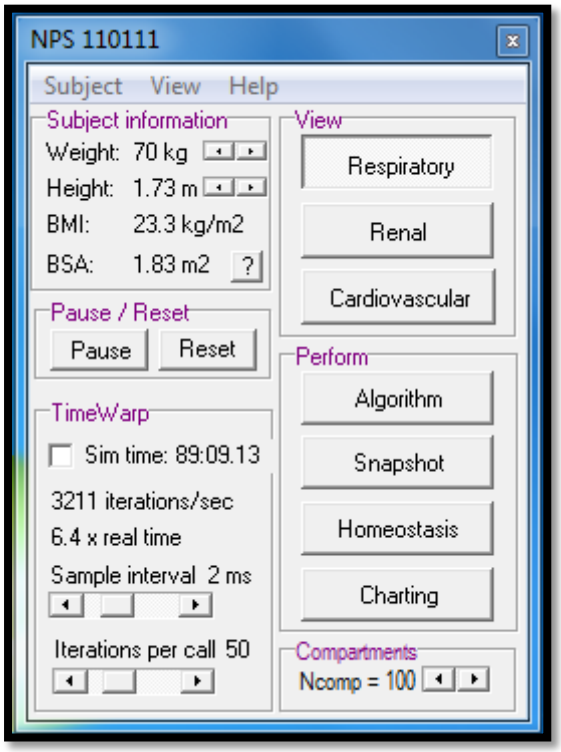


Figure 3 NPS patient information

3.2.5 How Simulator Works

The process of modelling and applying the model as a computer simulation is complex, and it depends on several repeated build-up calculations and the complex interaction of many arithmetic models of micro-processes that require significant computer power to execute. The program starts with a pre-set algorithm progress with a multi-scalar view. These pre-set algorithms depend on mathematical processes, laws of physics, and an established pathophysiological theory. Ultimately, these algorithms are coded using a computer programming language, such as C++ or by the modelling toolkit MATLAB software. MATLAB is simple to control, can develop returnable model building blocks, and is suitable for widespread use.

The Nottingham physiology simulator is made up of three major sections: 1) Pulmonary, 2) transport, and 3) tissue (see Figure 4).

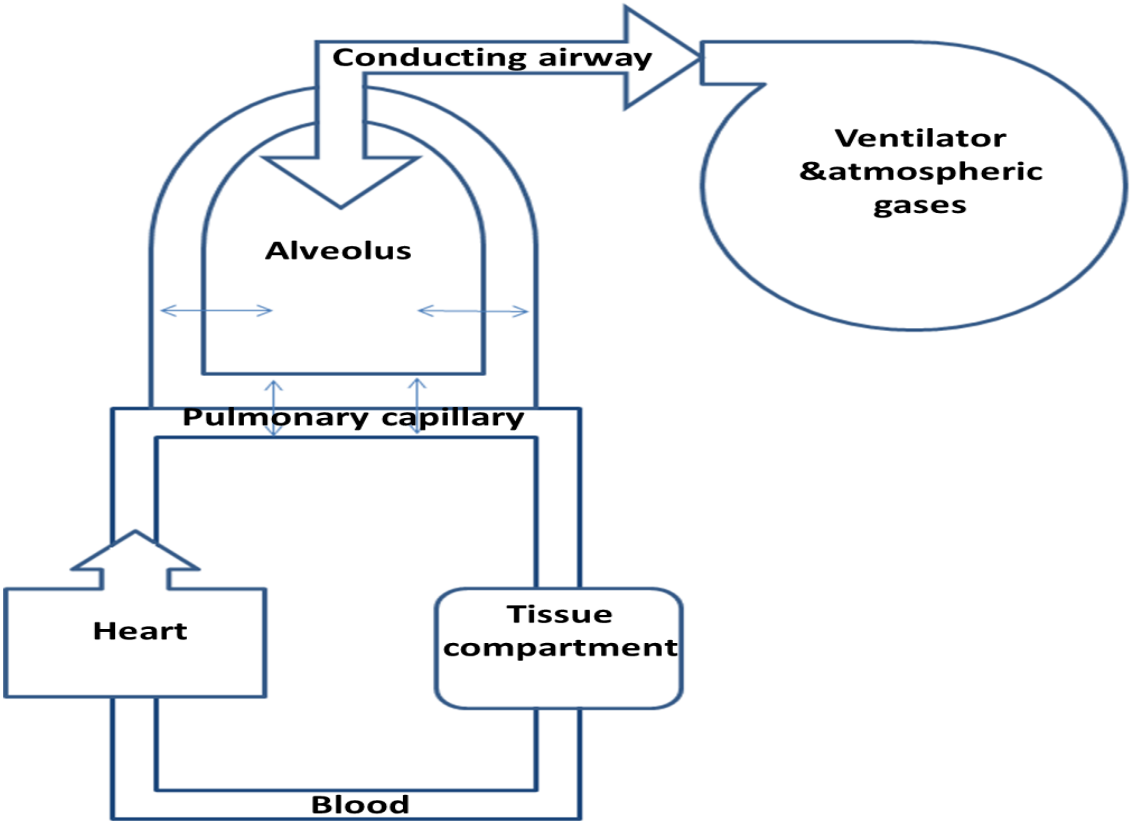


Figure 4 NPS illustration

NPS ventilator generates a constant flow of a complex interaction of multiple resistors and alveolar compartments with independent compliance curves. Conducting airways (non-compliant, containing stacked plates of mixing gas). Alveolus (compliant air-sac, constantly equilibrating with blood flow and constantly changing volume, usually use 500 alveolar compartments). Pulmonary capillary (compliant vessel driven by heart, contains blood that equilibrates with alveolar gas). Blood (fluid containing with complex mutually dependent solubility, also regulation of pH and buffering). Tissue compartment (production of carbon dioxide and consumption of oxygen occurs inside this compartment, generating gas tensions that equilibrate with passing arterial blood). Heart (circulating the blood around all section)

The pulmonary part of the system is modelled as consisting of equipment that includes ventilated perfused alveoli and alveolar and anatomical dead spaces in which the entire gas exchange inside the alveoli is presumed. In addition, the lung-modelling element of the

simulator considers the variations in the lung volume and residual gas concentration that result from oxygen extraction and carbon dioxide excretion. The transportation aspect of the system, which represents blood circulation inside the lung, is categorised in the model in two parts: non-shunted and shunted blood (111, 154, 156, 157, 164). In the model, the blood circulation that passes the alveoli unit is "time sliced," which produces a distinct packet of blood that is used in the modelling process.

Thus, the equilibration steps generated through an iterative process that includes gas exchange between the capillary compartments and the alveolar unit is precisely simulated. This is accomplished through the use of standard formulae of blood CO_2 consternation content and blood oxygenation after the equilibration is calculated. This also considers the metabolic effects of base excess (BE), plasma pH, and body temperature (157, 165, 166). The PaO_2 is calculated from content and is required to estimate the combination of pulmonary capillary blood with shunted mixed venous blood oxygen calculation partial pressure from content that was used within Thomas's equation (157, 166). The tissue compartment is modelled as a peripheral metabolism that involves simple carbon dioxide production and extraction of pre-set VO_2. VO_2, RQ, and cardiac output (CO) determines the resulting mixed venous gas content. In addition, the plasma pH is defined in accordance with the BE temperature and plasma CO_2 content.

3.2.6 Oxygen indices and simulator

Oxygen indices have been extensively used as research tools to examine reliability and reflect lung status. Computerised models aim to create conditions that simulate lung diseases through the incorporation of variables that represent actual dynamic systems in the respiratory system. To this end, a number of modern modelling systems have been developed to examine changes in oxygen indices in a variety of lung statuses in response to changes in physiological parameters such as FiO_2 and haemoglobin concentration. In addition, these simulators have been used to compare oxygen indices with one other.

In terms of the Qs/Qt content base index, Kathirgamanathan and colleagues (104) pointed out that the Qs/Qt decreases more linearly in cases of true shunt and poor defect when the FiO_2 increases than it does in cases of true shunt and rich defects. McCahon and colleagues (25) noted small changes in the Qs/Qt ratio is response to a variation in FiO_2 from 0.30-1.00. Yet, McCahon's findings were limited to a single case of a virtual computational ARDS model. Elsewhere, Nirmalan and colleagues (42) conducted a study on a computational model of ARDS patients and reported minimal changes in the Qs/Qt ratio in response to FiO_2 variation. The authors claimed this minimal change could be the result of the effect of hypoxic pulmonary vasoconstriction pneumonia (HPV), or the alveolar partial pressure of oxygen on pulmonary vascular tone on their computational model. HPV is a further possible underlying cause of Qs/Qt

variation that could result when alveolar ventilation decreases in the lung and the HPV occurs, resulting in a redistribution of the pulmonary blood flow (23, 52).

In terms of alveolar-arterial oxygen tension gradient, Granger and colleagues (103) reported a variation of $P(A\text{-}a)O_2$ with FiO_2 and Qs/Qt changes with three virtual subjects on a computer model. With those virtual subjects the $P(A\text{-}a)O_2$ increased accordingly. However, the $P(A\text{-}a)O_2$ amplitude increased according to the Qs/Qt degree. For instance, if the Qs/Qt was at a high level, the $P(A\text{-}a)O_2$ increased. In alternative research, Nirmalan and colleagues (42) and McCahon and colleagues (25) conducted research with a virtual computational ARDS model and reported a linear relationship between $P(A\text{-}a)O_2$ and FiO_2. However, Kathirgamanathan and colleagues (104) claimed that there was a linear relationship between $P(A\text{-}a)O_2$ and FiO_2 between 0.30 to 0.6, and that this would continue to increase in response to an increase in FiO_2 in subjects with true shunt and rich defect. However, they argued that the $P(A\text{-}a)O_2$ in subjects with true shunt and poor defect would remain unchanged as the FiO_2 increased.

In terms of tension-based oxygen indices, recent studies that have employed computer modelling have revealed that there is a substantial variation in PaO_2/FiO_2 in accordance with changes in FiO_2. This variation tends to be exhibited in patients with ARDS and patients with hemodynamic and metabolic instability (42). In addition, the validity of using PaO_2/FiO_2 as part of ARDS diagnosis was studied using a computer-

modelling simulation. This study concluded that the variation in this index results in the misclassification of ARDS patients (42).

In terms of the PaO_2/PAO_2 index, recent modelling has indicated that this index demonstrates a higher degree of stability in healthy lungs than it does in lungs that exhibit a high degree of V/Q mismatch (41).

CHAPTER 4

Developing and improving MPP with NPS

4.1. Introduction to MPP

Prof. Jonathan Hardman and his Ph.D. students introduced the mean predicted PaO_2 (MPP) recently(167).

The following data in this investigation were collected and analysed jointly by Adil Alotibi (another PhD student in the division) and myself. This data and results had been shared between us but were utilised in different experiments and outcome measures.

One of the significant challenges in intensive care units is adjusting mechanical ventilator to optimize a safe level of oxygenation and ventilation (168, 169). Therefore, the mechanical ventilator must be adjusted to maintain appropriate oxygenation supply and carbon dioxide clearance. These adjustments are based on several factors one of them is to assess atrial blood gas test (ABG), which is one of the methods that been used as routine in ICU. The study was done by Merlani and colleagues (170) shows that nearly half of the ABG tests in ICU been carelessly drawn. In addition, unnecessarily ABG sampling increases the risk of a potential hazard (171), and it considers one of the most expensive of ancillary practice in ICU (172).

Consequently, to minimize the attempt of use needlessly ABG sampling, there has been a different methods suggested to predict PaO_2(107). Andrews and Waterman (173) reports the value of PO_2 had a consistent correlation with a frequency of ABG sampling. Furthermore,

these frequent ABG samples were drawn to track oxygenation after adjusting FiO_2 despite of the existence of devices that continually monitor oxygenation such as pulse oximetry SaO_2. In ICU setting, predicting PaO_2 after adjusting FiO_2 had been used with different mathematical formulas that been made in the past (107). One of the gold stander methods that been used to estimate PaO_2 is by isoshunt virtual lines which rely on several factors that relate FiO_2 to PaO_2(174). However, the isoshunt method is a burden in terms of its practical and frequent used in ICU(174). Gross and Israel (105) reports the use of a nomogram methods to predict a new PaO_2 after FiO_2 changes that depend on the PaO_2/PAO_2 ratio and the severity of the gas exchange defect. They found that the overall sensitivity of a nomogram method to predict PaO_2 was 85% only when the predicted PaO_2 within 1.3kPa of the measured value.

Nevertheless, Herrick and his colleagues (107) states that half of the changes in PaO_2/PAO_2 ratio were inaccurate and behaved differently to those patients with low Qs/Qt with negative correlation. In addition, Hess (175) integrated the PaO_2/PAO_2 into a mathematical formula to predict PaO_2. The author found a positive correlation between PaO_2 (measured and predicted) values after evaluating its accuracy and reliability on 35 mechanically ventilated patients' data. Another study done by Abidance and Lopez (176) also used the PaO_2/PAO_2 ratio to predict PaO_2. The author used data retrieved from 17 hemodynamically stable subjects to validate their new formula. 13 subjects were mechanically ventilated, and the rest were on oxygen therapy devices.

The author reports a great correlation between predicted PaO_2 values and measured. The author recommends to use it with a patient who are receiving FiO_2 more that 30% and hemodynamically stable.

Therefore, the current oxygen indices been varied with changes of FiO_2. There is a need to develop an oxygen index that are resisting any changes in FiO_2 and compare its accessibility and reliability with other current oxygen indices. A new index developed (MPP) and been validated in vivo and in-silico and our aim is to have an index that is robust any reliable even with FiO_2 changes.

To generate an MPP the clinician need to use three ABG at three different level of FiO_2 for example (21%, 60% and 100%). Moreover, by the three value of PaO_2 from ABG we can predict the PaO_2 behaviour. There are two main possibilities that PaO_2 may interact with FiO_2 changes using either a linear approach (Equation B) or the second polynomial order(Equation A). Therefore, PaO_2 was modelled with these two algorithm equations:

Equation A: $PaO_2 = FiO_2 \times Y \times (FiO_2 \times Z + 1)$

Equation B: $PaO_2 = FiO_2 \times W + S$

(Y, Z, W and S) are coefficients were derived as follows

$$Y = \frac{\left(1^{st}lowPaO_2 - \left(\left((2^{nd}high\ PaO_2 - 2) \times 1^{st}lowFiO_2 \times 1^{st}lowFIO_2\right)/(2^{nd}highFiO_2 \times 2^{nd}highFiO_2)\right)\right)}{\left(1^{st}lowFiO_2 - \left((1^{st}lowFiO_2 \times 1^{st}\ lowFiO_2)/2^{nd}highFiO_2\right)\right)}$$

$$Z = \frac{\left((2^{nd}highPaO_2 - 2) - (Y \times 2^{nd}highFiO_2)\right)}{(Y \times 2^{nd}highFiO_2 \times 2^{nd}highFiO_2)}$$

$$W = \frac{(2^{nd}highPaO_2 - 1^{st}lowPaO_2)}{(2^{nd}highFIO_2 - 1^{st}lowFIO_2)}$$

$$S = (2^{nd}highPaO_2 - W \times 2^{nd}highFiO_2\ )$$

If (Y x Z > 0) then we use the (second order polynomial Equation A), but if the product of (Y x Z < 0) then we use the (linear Equation B). Then the MPP will be the average of PaO_2 at three levels of FiO_2.

Initially, MPP was validated using the Nottingham physiology simulator. Ninety simulated patients were configured with unique lung characteristics that depend mainly on the V/Q mismatch and different degree of shunt. The pulmonary shunt present was ranging from 3%-30% (please see appendix A for more details about the lung configurations of the 90 virtual patients).

Each PaO_2 value for virtual patient measured at three different level of FiO_2 (21%, 60% and 100%). Subsequently, from three PaO_2's MPP and PaO_2/FiO_2 ratio were calculated. We have used the PaO_2/FiO_2 ratio to check its stability with FiO_2 changes against the MPP index.

Other mechanical ventilator parameters were remained similar and constant during the test (for examples respiratory rate, tidal volume, PEEP, I:E ratio, Inspiratory flow rate, the minute ventilation, cardiac output, haemoglobin, oxygen consumption, respiratory exchange ratio, body temperature and inspiratory pressure) were constant during the test the only changes is FiO_2. The general results show that the MPP was less varied and more stable than the PaO_2/FiO_2 ratio see Table 1 and Figure 5

Table 1 comparison of CV% for MPP and PaO_2/FiO_2 ratio using NPS data

	N	Mean of Variation	SD	min	max	df	p-value	95% Confidence Interval of the Difference	
								Lower	Upper
MPP	90	26.6%	19%	0%	80%	89	<0.005	23%	31%
PaO_2/FiO_2	90	76.1%	35%	21%	156%			69%	83%

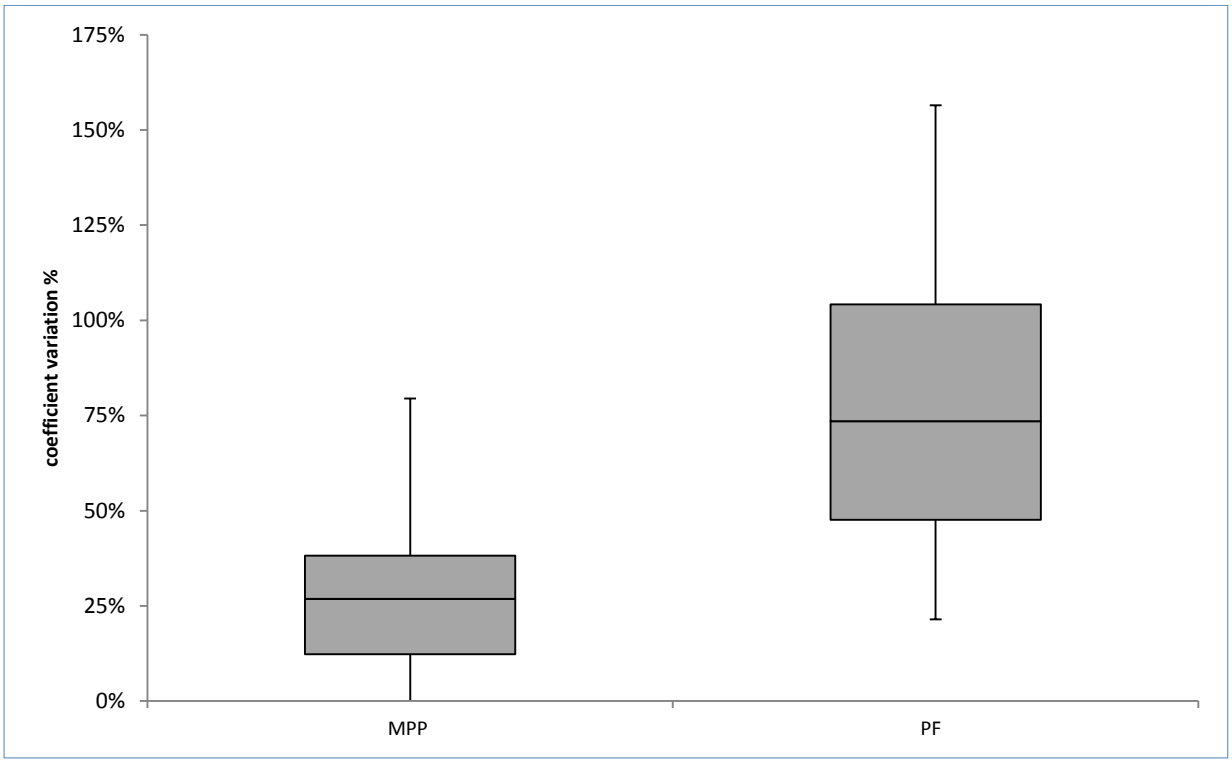


Figure 5 MPP and PaO_2/FiO_2 ratio variation using NPS subjects

After the MPP was compared with PaO_2/FiO_2 ratio using NPS lung module, another trial was done using a real patient data that were collected from a local hospital in Saudi Arabia (after having ethical approval IRB to start the investigations). The investigation methods are first to do three ABGs 20 minutes after each time the clinicians decide to change the FiO_2 as routine managements, and that is only if the patient fit the inclusion criteria. Consequently, 140 patients data were collected from

Intensive care units, those are adult, on mechanical ventilator and hemodinaclly stable (mean arterial pressure < 60 or > 110 (mm Hg), or heart rate <50 or > 120 (beats/min) or not significantly anaemic (Hb < 8 g/dl)), 53 patients were excluded due to different reasons (missing data, patients been extubated from mechanical ventilator, death, changes in hemodynamic status, changes in mechanical ventilator setting that could affect the PaO_2 rather than FiO_2 (PEEP, inspiratory time, I:E ratio, changes in mean airway pressure). After applying inclusion and exclusion criteria, 87 patient's data were obtained in this study.

The results show below (Table 2 and Figure 6) that the MPP mean variation percent still less than the mean variation present for the PF ratio. This result is a good indicator that shows the MPP index is less affected by FiO_2 changes, unlike the PF ratio.

However, comparing MPP with PF ratio alone does not necessary mean that MPP is better than other oxygenation indices (Qs/Qt, RI, $P(A-a)O_2$ and PaO_2/PAO_2). In fact, another investigation is required to compare MPP with other oxygenation indices.

Table 2 comparison of CV% for MPP and PaO_2/FiO_2 ratio using patient's data

	N	Mean of Variation	SD	min	max	p-value	95% Confidence Interval of the Difference	
							Lower	Upper
MPP	87	13.1%	16%	0%	76%	<0.0006	9%	16%
PaO_2/FiO_2	87	20.4%	19%	2%	97%		16%	25%

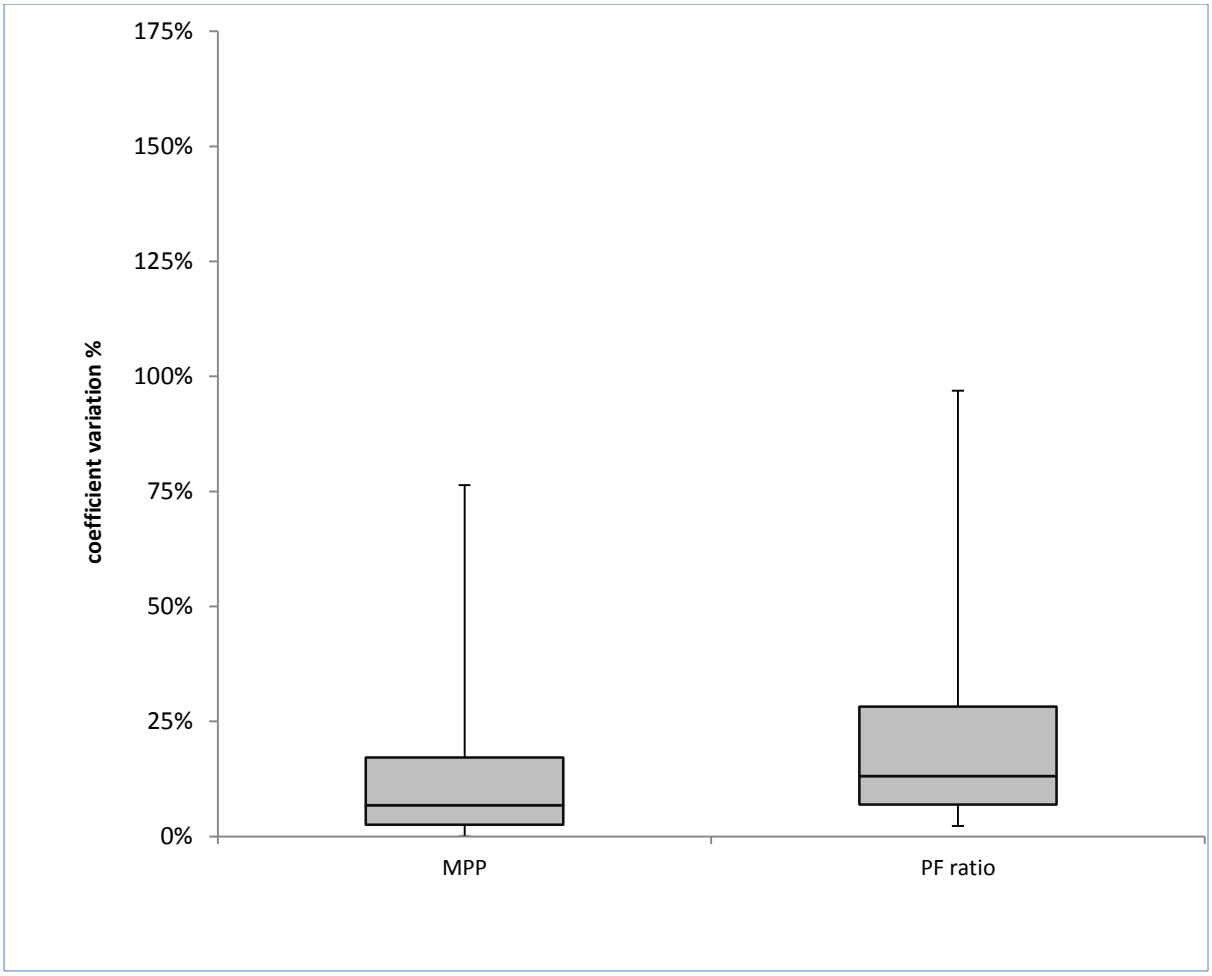


Figure 6 MPP and PaO_2/FiO_2 ratio variation using clinical patients data

4.2. Comparing MPP with other Oxygen indices using 6 simulated patients

4.3. Hypothesis and Aims

Previous literature suggested that some indices are reliable in specific scenarios such as ARDS, while they may be unreliable in other lung defects. Thus, as mentioned in chapter three, studies suggested that existing oxygen indices vary with external physiological factors such as the fraction of inspired oxygen (FiO_2), haemoglobin concentration (Hb), Respiratory exchange ratio (RQ), and oxygen consumption (VO_2). However, investigating oxygen indices variation with these physiological factors in real patients with lung diseases is challenging and impractical.

Further research, therefore, is necessary to determine the pattern of variability of existing common oxygen indices among a variety of lung diseases.

In this chapter, we hypothesised that the current indices of pulmonary gas-exchange are misleading in indicating the changes in gas-exchanging ability during non-pulmonary variation, despite the stability of lung status. The main aim of the present chapter is to investigate the variation of current oxygen indices and the new oxygenation index (mean predicted

PO_2 (MPP)) in a variety of lung defects using a validated computational model (the Nottingham Physiology Simulator: NPS). This includes FiO_2 change, VO_2, Hb, and RQ exchange ratio.

4.4. Methods and Materials

4.3.1 The Nottingham Physiology Simulator

The computational simulator that been used in this study is extended from MATLAB® implementation of several pathophysiological models initially established within the Nottingham Physiology Simulator (NPS). The Nottingham Physiology Simulator has been validated in different situations with many lung configurations (25, 157, 163, 177-179). This research used the Nottingham Physiology Simulator (NPS version 110111). The models in the simulator rely on several repeated build-up calculations and a complex interaction of much arithmetic modelling of micro-processes that designed to represent a dynamic in vivo cardio-vasculo-pulmonary state. These build-up calculations are based on a pathophysiological principles that been published in previous studies (25, 157, 163, 177-179). The pulmonary simulator consists of 100 compartments that simulate the alveoli, and each one is corresponding to set parameters and reflect the lung compliance, vascular and airway resistances.

4.3.2 Configuration of Subjects

Six virtual ARDS patients were configured. All virtual patients were identical in respect to their physiological e.g. (weight, height, body mass index, body temperature) and mechanical ventilator settings such as (endotracheal tube size, respiratory rate, tidal volume, PEEP, Inspiratory pressure ...etc.). The source code and a Windows™-executable and this computer simulation are available upon request from Prof. JG Hardman (Anaesthesia & Critical Care Research Group, Division of Clinical Neuroscience, School of Medicine, University of Nottingham). Table 3 shows the configuration for the virtual ARDS patients in this investigation.

Table 3 Physiological and mechanical ventilator sittings for virtual patients used in this investigation

Weight	70 kg
Height	1.70 meter
Body service area	1.83
body mass index	23.3
Inspired gas	Warmed and humidified to 37C
Inspiratory flow pattern	Constant flow
Tidal volume	6 ml kg^{-1}
Inspiratory pressure	15 cm H_2O
Respiratory rate	12 bpm
PEEP	5 cm H_2O
Inspiratory to expiratory ratio	1:2
Base excess	0 mmol $litre^{-1}$
Endotracheal tube information Length/ internal diameter	24 cm/ 8.0 mm

Air way resistance	0.732 Pa/L/min	
Atmospheric pressure	101	a

Each virtual patient had a unique lung defect consisting of a true shunt and ventilation and perfusion V/Q mismatch. The modelled virtual patients were obtained from Anup and colleges (180) simulated data that were configured and validated based on ARDS patients (Table 4). Furthermore, Anup gathered some data from Nirmalan and colleagues (42) the data contain arterial and venous blood gas values, cardiac output (CO), shunt fraction (Qs/Qt), fraction of inspired oxygen (FiO_2) and haemoglobin (Hb). Then the author fixed initial values (Hb, CO, FiO_2) while he simulates each virtual patients. Subsequently, in order to find the model configuration, the author generate data from simulated patient that is very close the clinical data that were extracted by using optimization-based methodology.

Table 4 Configuration for the six ARDS virtual patients

	Parameters obtained from data			Parameters obtained through optimization				Comparison of model outputs and patient data							
	Hb (g dl^{-1})	CO l min^{-1}	FiO_2	RR b/min	IE	RQ	VO_2ml min^{-1}	PvO_2 mm Hg		$PvCO_2$ mm Hg		Qs/Qt%		PaO_2 mm Hg	
								Data	Model	Data	Model	Data	Model	Data	Model
Patient 1	10.5	11.1	0.8	12.25	0.28	0.6	294	47.3	49.5	44.4	46.2	28.6	31.8	153	149
Patient 2	10.8	7.2	0.9	12.14	0.25	0.6	300	38.3	39.4	55.5	54.4	31.7	33.9	85	87
Patient 3	11.5	5.6	0.5	16.04	0.38	0.9	200	48.0	45.4	47.6	49.9	22.6	19.4	130	129
Patient 4	9.8	7.7	0.8	17.68	0.38	0.7	257	42.8	42.2	51.0	48.8	32.3	31.4	110	109
Patient 5	9	5.9	1	17.10	0.43	0.6	246	34.5	30.3	33.8	36.1	43.1	39.1	64	64
Patient 6	12.2	8.4	1	22.01	0.38	0.7	257	39.1	41.7	38	40.5	38.2	41.7	84	85

Definition of Abbreviations: Hb = Haemoglobin, CO = Cardiac Output, FiO_2 = Fraction of Inhaled Oxygen, RR = Respiratory Rate, IE: Inspiratory to Expiratory Ratio, RQ = Respiratory Quotient, VO_2 = Oxygen Consumption, PvO_2 = partial pressure of oxygen in the venous blood, $PvCO_2$ = partial pressure of carbon dioxide in the venous blood, Qs/Qt = Shunt Fraction, PaO_2 = partial pressure of oxygen in the arterial blood.

4.3.3 Evaluation of Oxygen Indices

This investigation examined the following oxygen indices; alveolar–arterial oxygen tension gradient $P(A–a)O_2$, respiratory index ($PA–aO_2/PaO_2$), Mean predicted arterial oxygen tension (MPP), PF ratio (PaO_2/FiO_2) and calculated shunt fraction (Qs/Qt).

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$$

The capillary oxygen content (CcO_2) and the capillary oxygen saturation (ScO_2) were calculated from calculated PAO_2 as follows:

$CcO_2 = 1.34 \times Hb \times ScO_2 + 0.225 \times PaO_2$ [All units use litres (not decilitre) and kPa (not mmHg)]

$ScO_2 = 1/\left(1 + 23400/\left(n \times (n \times n + 150)\right)\right)$ [This assumes normal pH, BE & temperature, which is reasonable]

$n = 7.5 \times PAO_2$ [Convert mmHg to kPa]

Arterial oxygen tension (PaO_2), mixed venous oxygen tension (PvO_2), arterial oxygen saturation (SaO_2), venous oxygen saturation (SvO_2), arterial oxygen content (CaO_2), and venous oxygen content (CvO_2) were recorded. Yet, the alveolar oxygen tension (PAO_2) was calculated using the alveolar gas equation:

$$PAO_2 = (Patm - PH_2O) \times FiO_2 - \left(PaCO_2 \times \left(1 - \left(FiO_2 \times (1 - RQ)\right)\right)/RQ\right)$$

Where the PAO_2 is alveolar partial pressure of oxygen (kPa), Patm is the barometric pressure (101.3 kPa), PH_2O is the saturated vapour pressure

of water at 37^{c} (6.7 kPa), FiO_2 is the fraction of inspired oxygen, and $PaCO_2$ is the partial pressure of carbon dioxide (kPa) Respiratory exchange ratio (RQ) (45).

During the investigation, oxygen indices were examined for each virtual patient as (the fraction of inspired oxygen (FiO_2), haemoglobin concentration (Hb), Respiratory exchange ratio (RQ), and oxygen consumption (VO_2) were varied in isolation (Table 5). The FiO_2 ranged from 30% to 100% in 10% increments, Hb ranged from 60 grams per decilitre to 160 grams per decilitre, RQ ranged from 0.40 to 1.20, VO_2 ranged from 150 ml min^{-1} to 350 ml min^{-1}.

Mechanical ventilator settings (tidal volume, respiratory rate, PEEP, inspiratory time) were kept constant during the investigation to maintain a constant lung state (Table 3).

Table 5 The four variables that adjusted during examination of the indices of oxygenation.

	Baseline	Examined range	Increment
FiO_2 (%)	30	30–100	10
Haemoglobin (grams per litter)	145	60–160	20
Respiratory exchange ratio	0.8	0.40-1.20	0.20
Oxygen consumption VO_2 (ml min^{-1})	250	150-350	50

4.3.4 Statistical Analysis

To calculate the variation in oxygen indices (Qs/Qt, PaO_2/FiO_2, $P(A–a)O_2$, MPP and $P(A–a)O_2/PaO_2$) induced by changes in each external

physiological factor in isolation (FiO_2, Hb, RQ, and VO_2), the mean of the repeated measurements for each oxygen indices on one subject was estimated. Then, the mean percentage of coefficient of variation (CV%) was utilised to evaluate the stability of oxygen indices.

Thus, in our method we were merely seeking a way to quantify the "scatteredness" of the data; therefore, the data distribution were not statistically important in our case as range & IQR ignore much of the dataset, and focused on two values each; in other words, the distribution of the central portion of the data is ignored using these measures . CV% was used to assess the variation by dividing standard deviation (SD) to the mean, expressed as a percentage, this is also known as the relative standard deviation (RSD) (181, 182). The CV% was utilised for two reasons; first, the values that were used in this study were in different scale unit; therefore, it was difficult to compare them together. Thus, the exact value of CV% was independent of the unit in which the measurements were taken i.e. it was a dimensionless number. Second, the SD of a data continually understood in the context of the mean of the data(182). The SD is expressed as an absolute value, specifically; it is an average of the distance of all data points from the mean. It is reasonable to use average and SD in continuous datasets to represent the data. However, it would not be accurate if the data were non-continuous (e.g. categorical, such as scoring systems). To make the "scatteredness" comparable between datasets (e.g. comparing index variability in a

hypoxic vs a hyperoxic patient) we need to divide by the mean (average). Example:

- Hypoxic patient's MPP variability is shown as SD 14, mean 7
- Normal patient's MPP variability is SD 21, mean 14

Using plain SD makes the normal patient appears to have more scatter in MPP, but that is an artefact caused by the normal patients PaO_2 being larger. When corrected, we have hypoxic patient CV% 2 and normal patient 1.5 - normal patient has lower variability. Thus, we treated the MPP as being normally distributed, and CV% is a good metric of "scatteredness" for our purposes. Data processing and charting were conducted using Microsoft Excel (2010).

4.5. Results

Figure 7 presents the mean variations in oxygen indices (PaO_2/FiO_2, Qs/Qt, $P(A–a)O_2$, $PA–aO_2/PaO_2$, and MPP) induced by changing the following factors (FiO_2, Hb, RQ, and VO_2).

Each oxygen index was affected mainly with the variation of FiO_2. The calculated Qs/Qt index and MPP index behave relatively similar and they had the smallest mean variation with FiO_2 10-13%. While the $P(A-a)O_2$ index shows the largest mean variation of 127% , the mean variation percent for the rest of other indices (PaO_2/FiO_2, PaO_2/PAO_2 and RI) rage between 70% and 90%.

Qs/Qt was the index with the lowest mean variation with Hb (9%). Whereas, the PaO_2/PAO_2 index had a mean variation of (12%). In contrast, RI index had the largest mean variation with Hb (44%). The rest of other indices (PaO_2/FiO_2, $P(A-a)O_2$ and MPP) had the same mean variation percent (30%).

RQ difference caused minimal changes to all oxygen indices. The calculated Qs/Qt index considered the lowest index with mean variation (5%), while RI index had the largest variation (45%). The rest of other indices (PaO_2/FiO_2, $P(A-a)O_2$, PaO_2/PAO_2, and MPP) had mean variation percent range between (21-30%).

With VO_2 changes, the MPP index had the largest mean variation (52%). The Qs/Qt index considered the lowest mean variation in VO_2

changes (22%). Whereas, the P(A-a)O_2 index behaved relatively similar to Qs/Qt index which had a mean variation of 23%. The rest of other indices (PaO_2/FiO_2, PaO_2/PAO_2, and RI) had mean variation percent range between (25-34%). Moreover, there is a detailed discussion of the effect of each factor variations FiO_2, Hb, VO_2, RQ, CO in (appendix 9.2.)

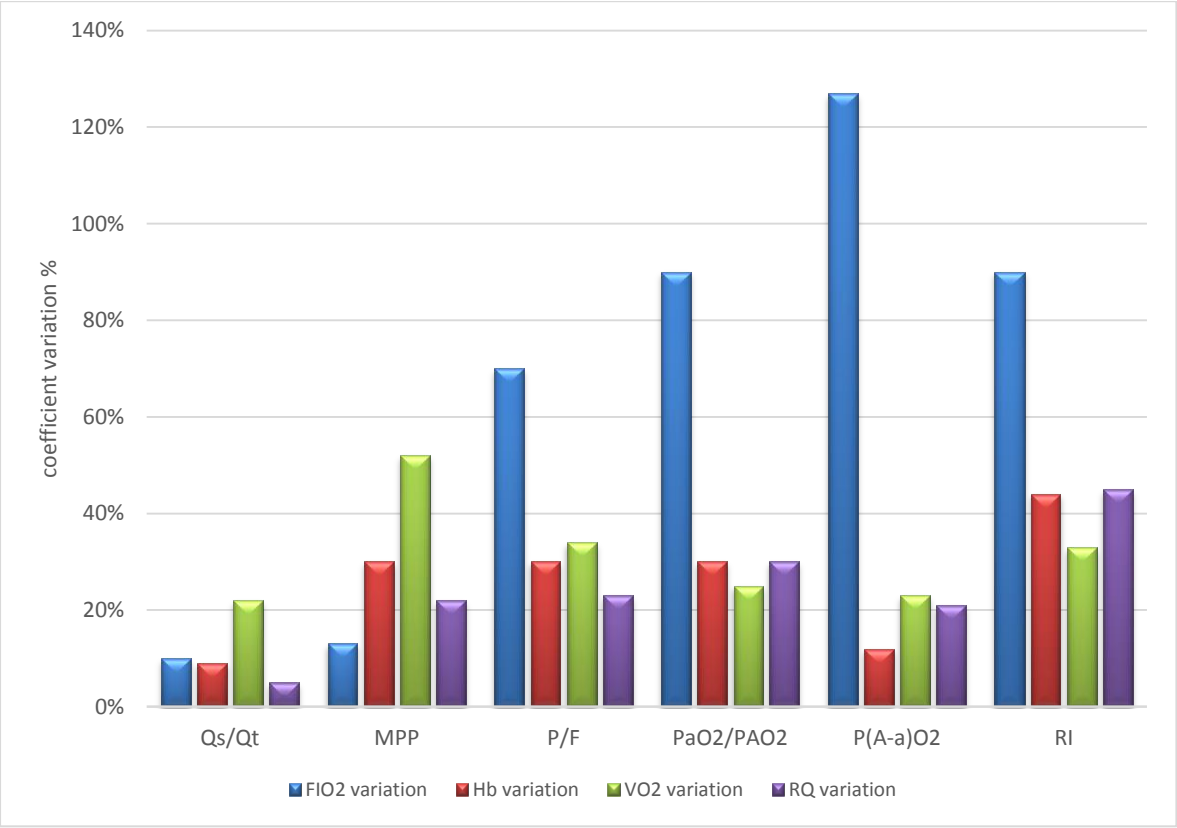


Figure 7 The variation of the utilised indices with EFPs changes.

4.6. Discussion

In this study, we examined the current pulmonary oxygenation indices variation under the effect of different external physiological factors (FiO_2, Hb, RQ, and VO_2) on validated NPS ARDS simulated patients. The findings of this study indicated a substantial variation in oxygen indices with changes in external physiological factors even without changing the pulmonary configuration status of the ARDS simulated patients. This study demonstrates that FiO_2 induced a remarkable variation in comparing to other oxygen indices (PaO_2/FiO_2 ratio, RI, P (A-a) O_2, and PaO_2/PAO_2). On the other hand, (Qs/Qt) and (MPP) were less varied with changing in external physiological factors; thereby, they could be used as indicators to represent the pulmonary oxygenation defect.

The findings of the current study are in agreement with the outcomes from previous studies which indicated that Qs/Qt was considered as a reliable indicator to quantify pulmonary oxygenation defect (25, 40, 73, 107). Gowda et al used sixteen computer modelled ARDS patients where they examined the effect of varying FiO_2 (21%-100%) on the following oxygen indices (PaO_2/FiO_2 ratio, PaO_2/PAO_2, P (A-a)O_2, RI, and Qs/Qt). They reported that oxygen indices varied with changes of FiO_2 especially for those patients with ventilation perfusion abnormalities (41). However, they reported that PaO_2/FiO_2 ratio was less varied and could be used as a useful indicator to monitor patients receiving FiO_2 equal or greater than 50% under usual clinical conditions (41). Nirmalan et al studied the effect

of within-subject variations in $C(a-\bar{v})O_2$ and FiO_2 on five oxygen indices (PaO_2/FiO_2 ratio, PaO_2/PAO_2, $C(a-v)O_2$, $P(A-a)O_2$, and Qs/Qt) using validated ARSD lung models. They concluded that all oxygen indices showed a substantial variation with FiO_2 and $C(a-\bar{v})O_2$ except for Qs/Qt where the change was <2% (42). Despite of previous studies that showed that Qs/Qt was the most reliable index to assess the pulmonary oxygenation than PaO_2/FiO_2 ratio, it required direct sampling of mixed venous blood which carries some risk, especially for critically ill patients(25).

Furthermore, Kathirgamanathan et al (104) conducted a study using nine NPS ARDS simulated patients where they divided the simulated patients into two groups; true-shunt-rich and true-shunt-poor lung configurations. They studied the variation of four oxygen indices (Qs/Qt, RI, PaO_2/FiO_2 ratio, and A-a gradient) with changing on (FiO_2, PCO_2, and HB). They concluded that all four indices varied with all factors except the Qs/Qt, which had a small variation by 30% during FiO_2 changes. Likewise, another study was conducted by McCahon et al (25), using NPS computer model, examined four oxygen indices susceptibility (Qs/Qt, RI, PaO_2/FiO_2, and A-a gradient) to the variation induced by independent factors (Hb, FiO_2, VO_2 and $PaCO_2$) without changing lung configurations. Results showed that the smallest index variation was Qs/Qt =5.1%, in contrast, and the largest variation was 77% with PaO_2/FiO_2 ratio. The results from both Kathirgamanathan et al and McCahon et al suggested a further effort

to be done to determine the robustness of these indices with a variety population and different pulmonary disease

Qs/Qt still considered the best indicator to determine lung condition; nonetheless, it may be impractical due to its inflexibility to place a pulmonary artery catheter in order for clinicians to draw a blood sample to calculate Qs/Qt. Generally, based on our results MPP is considered one of the best non-invasive index to assess lung condition.

It works very well and it shows a small variation with other physiological factors. However, in order to calculate MPP it required two points of PaO_2 at two different FiO_2 levels. In addition, in terms of its clinical application, clinician may suffer from the extra effort to collect additional ABG results in different FiO_2 levels in order to have better indicator to the lung condition.

Despite the aforementioned beneficial affects, our study has several limitations. Unlike real patients, we had the assumption that the baseline for the lung status was kept constant irrespective of changes to external physiological factors. For instance, increasing FiO_2 level in real clinical settings could lead to absorption atelectasis. Likewise, substantial changes in Hb and $PaCO_2$ may have an affect on metabolic rate at cellular level.

Another limitation was sample size, as we only modelled six patients in our study that was relatively small. However, despite a small sample size we modelled these patients carefully in a way that represented a real

spectrum of disease. This method was better than a random selection of real patients who might have confounding factors that might be either unmeasured or difficult to control. For instance, the VQ mismatch in some cases in ICU cannot be determined while oxygen indices are used to diagnose, monitor and treat ARDS patients. This means that the chance of having improper results from oxygen indices is more with ARDS patients. By using modelled virtual patients, it is possible to count for those factors even though with small sample size.

4.7. Conclusion

In conclusion, the clinician should be aware to use the best index according to patient's status. According to our results if the patients hypoxic and required high FiO_2 levels and the clinician want to assess the lung status the best oxygenation index are Qs/Qt and MPP. For patients with haemoglobin differences or with high Oxygen consumption the best oxygen indices to choose are Qs/Qt and $P(A\text{-}a)O_2$. For a patient with hypercapnia, the Qs/Qt index is the best one that represents lung condition. Accordingly, having different index corresponding to patient status is not clinically applicable. Although our new MPP index showed a small change as Qs/Qt index with FiO_2 variations. Yet, the need to develop a new independent oxygen index and to consider isolating the external independent factors (Hb, FiO_2, VO_2 and $PaCO_2$) mathematically to represent a real lung condition even if there are an external lung factors.

CHAPTER 5

Developing $crPO_2$ and validating it with NPS

5.1. Introduction to crPaO$_2$

One of the most significant measurements that are currently used in intensive care units is the measurement of partial pressure of gases in the blood via an arterial blood gas (ABG) test. The partial pressure of oxygen (PaO_2) is an important component of ABG analysis and plays a key role in assessing lung oxygenation. However, when used in isolation, PaO_2 by itself is not a good representative of the lung condition, because other factors, besides lung defects, can affect this metric. With a simple mathematical example, we can demonstrate that an increase in PaO_2 does not necessarily result in an improvement in a patient's lung condition; for example, such an improvement may be due to an increase in FiO_2 or other physiological factors. As such, it is difficult to judge the condition of a patient with PaO_2 alone. There is a growing body of literature that recognises the importance of creating pulmonary oxygen transfer indices that clinicians can use to determine the nature of gas impairment, correct PaO_2 or reduce the inaccuracy that results from assumptions relating to the application of the alveolar gas equation (24, 27).

Oxygen indices-such as the ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2 ratio); arterial/alveolar oxygen tension ratio (PaO_2/PAO_2); alveolar–arterial oxygen tension difference $P(A\text{-}a)O_2$; respiratory index (RI= ($PA\text{-}aO_2$)/PaO_2), and content-based venous admixture (Qs/Qt); provide clinicians with an indication of the condition of a patient's lung. However, additional external pulmonary physiological

factors are missing in these oxygen indices and the absence of these may have an impact on the PaO_2 value, thus misleading clinicians (24, 25, 42, 104).

To illustrate the concept further, let us consider the example of a subject who exhibits the following: PaO_2 12.78 kPa, FiO_2 21%, Hb 145 g/l, $PaCO_2$ 5.3 kPa. His PF ratio can be calculated as 61 kPa and, according to this ratio, the subject is "healthy". However, if the subject suddenly started to bleed, his lung condition remains unchanged and the ABG results change to PaO_2=8.40 kPa, FiO_2 21%, Hb 60 g/l and $PaCO_2$ 5.1 kPa, the calculated PF ratio would drop to 40 kPa. This would imply that the gas exchange defect has worsened; in fact, the problem is that the subject is losing the oxygen carrier (Hb), which accentuates the venous admixture, and consequently reduces the PaO_2. This example demonstrates the need for a better index that can adequately take into consideration the effect that factors that are independent of the pulmonary configuration have on PaO_2 values in order to ensure that the condition of a patient's lung is more adequately represented and thus a more accurate treatment plan is developed.

In this study, we hypothesised that we could calculate a "corrected" PaO_2 value (i.e., at standard values of physiological parameters). This is a similar concept to that of the ABG machine that gives us blood gas results corrected to a pre-set temperature and pressure. Therefore, our goal in this investigation was to mathematically "correct" or "standardise" the

PaO_2, making it independent of variations in physiological factors that operate independently of lung configuration. For example, in the case described above, if we have an anaemic patient, we could calculate a corrected PaO_2 – where we estimate the value of PaO_2 if the anaemia was not present in that patient. This study aimed, to create a robust index of oxygenation that can compensate for the effect of non-pulmonary-factors, including fraction of inspired oxygen (FiO_2), haemoglobin (Hb), partial pressure of arterial carbon dioxide ($PaCO_2$), respiratory rate (RR), cardiac output (CO), and respiratory quotient (RQ), and, therefore, more accurately represent the condition of a lung.

5.2. Methods

This chapter describes a series of mathematical interventions that were tested as part of the research. This methods section describes the simulated subjects' configuration, the generation of corrected PaO_2 equation ($crPaO_2$), the numerical analysis employed, and finally the experiment report.

5.2.1. Subject Configuration

A validated computer model ("The Nottingham Physiology simulator" - NPS), was used in this study to configure a population of simulated subjects. The NPS is a computer simulation that employ original multi-compartmental cardiovascular, pulmonary and cerebrovascular physiological models (183). The NPS has been used and validated across a spectrum of pulmonary diseases (25, 157, 163, 177-179). The present investigation used version NPS-110111. The source code and a Windows™-executable and this computer simulation are available upon request from Prof. JG Hardman (Anaesthesia & Critical Care Research Group, Division of Clinical Neuroscience, School of Medicine, University of Nottingham).

The first step in the model configuration involved the creation of six virtual subjects. These modelled virtual subjects were validated using data obtained from acute respiratory distress syndrome (ARDS) patients (180). The clinical data against which the subjects were generated included

arterial and venous blood gas values and cardiac output. To simulate an individual patient, one set of data were selected and the values of Hb, CO and FiO_2 were fixed as given. An optimization-based methodology was used to identify the model configuration that would generate outputs that represented a close match with the clinical patient data.

Initially, six simulated subjects were generated. The characteristics of the six simulated subjects are described in Chapter 4. The data pertaining to these simulated subjects was employed in Trials 2 - 6. Following the creation of these six virtual subjects, the effects of increasing $PaCO_2$ on PF ratio without changing the FiO_2 level were examined. To illustrate, in NPS, different techniques can be used to increase $PaCO_2$, one of which involves changing respiratory quotient (RQ). Subsequently, after the RQ was changed, a source of error was observed. The error was that the PaO_2 values increased suddenly without changing the FiO_2 level. The justification for this error was presented in Trial 6. This finding was unexpected and suggested that, using the same six virtual subjects would not be useful for further experiments. As such, there was a requirement to create new simulated subjects.

In Trial 7, ten new virtual subjects were configured, and another five random test subjects were created to test them using the $crPaO_2$. The new virtual subjects were identical in respect to their physiology and mechanical ventilator settings (weight: 75 kg, height: 1.75 m, body mass index: 23.3, supine posture, body temperature: 37.0^C, inspired oxygen

fraction: 30%, inspired gas warmed and humidified to 37^{C}, oxygen consumption: 250 mL/min, respiratory rate: 12 b/min, respiratory quotient: 0.8, haemoglobin: 145 g/L, anatomical pulmonary shunt: 1% of cardiac output, tidal volume: 500 mL). However, each virtual subject had a unique lung defect that consisted of a degree of calculated pulmonary shunt fraction, dead space and ventilation perfusion (VQ) mismatch. Each VQ mismatch was generated by varying the slider for the compartmental bronchiolar (Rb) and vascular (Rv) resistances. A summary of the configuration for the 10 simulated subject's characteristics is presented Table 16. The variation between Rb and Rv was performed in different directions to generate a realistic ventilation-perfusion scatter and to create asynchronous alveolar ventilation (184).

From Trial 8 to Trial 11 the VQ ratio for the eleven virtual subjects was varied. These virtual subjects were divided into two groups according to their VQ mismatch ratio: the first group (A) had high shunt and lower deadspace, and the other group (B) had a low shunt and higher deadspace, a comparison between these groups is provided in Table 18 .

5.2.2. Derivation of new oxygenation index: $crPaO_2$

Firstly, our investigation started by using hypothetical values for PaO_2 with different levels of FiO_2, as per Trial 1. Then, the PF ratio values were calculated and plotted on a scatter chart see Figure 8. The chart displayed

the interaction between the PF ratio and FiO_2, and a trendline was fitted to the PF ratio curve using the polynomial trendline. The fitted trendline describes the experiment data as a mathematical equation. This equation can be represented as follows:

$$y = (ax^n) + (bx^{n-1}) + \ldots + cx + z$$

Where y is the dependent variable (PF ratio) and x is the independent variable (FiO_2), a, b, c and z are coefficient factors (185). The polynomial formula was a regression equation that calculated the future value of the predicted variables and connected it with the past values (186). Following this, the corrected PF ratio (PFc) was calculated by dividing the PF ratio by the polynomial line equation with different FiO_2 levels. Figure 8 shows the original PF ratio and PFc, which demonstrates how the new PFc corrected the lack of "flatness" and present the PF ratio with minimal effect of FiO_2.

Subsequently, using the initial results, the accuracy of the new corrected PF ratio was compared with the original PF ratio. The results of Trial 1 revealed that the mean variability percentage of the cPF ratio was less varied than the PF ratio (see Table 6). The results were acceptable and the corrected ratio was deemed suitable for further testing on simulated subjects.

In Trial two, the cPF was examined on six (ARDS) patients that were simulated using simulated using subject data (180) that varied in FiO_2 only. A new cPF was generated was generated according to the changes that resulted from the polynomial trendline

polynomial trendline formula. The preliminary results for the PFc indicated less variation indicated less variation in response to FiO_2 changes (

Table 8). The entailed that we were able to create a correction factor that corrects for variations in FiO_2. The next step in the process involved generating another correction factor that had the capability to correct for other external pulmonary factors (EPF).

The third and fourth trials sought to examine potential methods of describing a new corrected PF ratio using other physiological factors. Six extra-pulmonary factors were initially investigated;(fraction of inspired oxygen (FiO_2), haemoglobin (Hb), the partial pressure of arterial carbon dioxide ($PaCO_2$), respiratory rate (RR), cardiac output (CO), and respiratory quotient (RQ). These aspects were varied independently to examine the effect they had on the most common oxygen index (PaO_2/FiO_2 ratio) and the new corrected PaO_2 ($crPaO_2$). The EPF were adjusted according to the results of each trial and the outcome of the previous trial. As such, some of the EPF we initially identified were omitted.

In Trial 4, it emerged that there was an issue when the corrected PF ratio was used as an indicator to assess the pulmonary gas exchange impairment: FiO_2 already corrected the PF ratio index the PaO2. In fact, our attempt to correct the PF ratio involved correcting the PaO_2 by FiO_2 over the FiO_2 again. Therefore, the replication of the correction for FiO_2 was not correct. Thus, after Trial 4, the PaO_2 was used as an alternative

to the PF ratio. A linear equation was used to correct for the FiO_2. However, due to the large variation between the new $crPaO_2$ and the PF ratio, different polynomial model equations were used. The $crPaO_2$ equation was changed according to its variation as compared with the PF ratio. Therefore, we tried to find the best equation that fit our EPF and minimised variation. In fact, a trial and error technique was used to select and modify the best fit and the polynomial equation. If the corrected curve showed a lack of flatness line of data, then a higher order equation was attempted. Thus, the polynomial equation, then the 3^{rd} order polynomial, 4^{th} order polynomial, 5^{th} order polynomial, and 10^{th} polynomial equations were employed. Figure 22 shows the difference between the $crPaO_2$ when different polynomial equation orders were utilised. We concluded that it was preferable for the $crPaO_2$ to be approximated by the 5^{th} order polynomial rather than by a straight line or other polynomial equations curve.

In Trial 5, we attempted to correct for the PaO_2 and generate a new correction factor before comparing the new equation variability with the PF ratio. The derivation of the new $crPaO_2$ was also described in detail in this trial. We varied each extra-pulmonary factor (EPF) one at a time (e.g., varying FiO_2 and keeping Hb, VO_2 and $PacO_2$ constant).Each EPF had a set of PaO_2 averages that were plotted on a scatter chart (PaO_2 in y-axis VS EPF in X-axis). To correct for EPF, we initially used a PaO_2 averages chart to generate a linear trendline curve for Hb, VO_2 and $PaCO_2$. We then displayed the equations in charts, and used these

equations to calculate the best fit to predict PaO_2 values for the given values of EPF (Fit PaO_2 = EPF X b + a), where Fit PaO_2 was the dependent variable and EPF was the independent variable, and a, b were coefficient factors. We then corrected PaO_2 for each EPF calculated by dividing the PaO_2 by the fit PaO_2 for each EPF. Each EPF had an equation, and these equations were combined to create a correction factor equation (CF).

The stability and validity of the CF were tested with ten different test simulated subjects that were programmed with different external pulmonary factor values. NPS was used to generate data for the ten simulated patients, and some patient data were obtained from (104). Following this, the corrected PaO_2 ($crPaO_2$) was calculated by dividing the PaO_2 by the correction factors as follows:

$$\boldsymbol{crPaO_2 = PaO_2/CF}$$

The correction factor CF was calculated from each four individual equations for (FiO_2, Hb, VO_2, $PaCO_2$) as follows:

$$\boldsymbol{CF = crFIO_2 \times crHb \times crVO_2 \times crPaCO_2}$$

Many issues need to be considered when exploring the possibility of using different external physiological factors (FiO_2, Hb, CO, RQ, VO_2, $PaCO_2$, and RR) to correct a PF ratio and PaO_2. For example, Oxygen consumption (VO_2) was employed in all trials up to Trial Eight; however, due to the difficulty of measuring and estimating VO_2 in the critical ventilated subject, it was removed from further trials at this point In

addition, in Trial Four we tried to correct for the cardiac output (CO), yet we noticed that varying the CO resulted in uncontrolled changes in the lung characteristics by affecting the shunt % and V/Q mismatch in the sick lung (Figure 13).

Another issue that emerged during Trial 4 involved the varied use of respiratory quotient (RQ) in the equation. It was difficult to measure the RQ in a clinical setting; however, it was used in Trial 5 and Trial 6 to generate a $PaCO_2$. Interestingly, when the $PaCO_2$ increased as a result of the RQ being increased, the PaO_2 also increased on the same FiO_2 level. According to the alveolar gas equation (PAO_2), whenever the $PaCO_2$ increases the PaO_2 drops; however, in our case, both $PaCO_2$ and PaO_2 increased (187). Therefore, changing RQ to get $PaCO_2$ could lead to an error in the PAO_2. For instance, the calculated PAO_2 would be the same for a subject who exhibited RQ=0.4 and $PaCO_2$=4.6 as it would be for another who had RQ=1.2 and $PaCO_2$ 13.9. Thus, varying RQ to produce a $PaCO_2$ value was deemed to be not inappropriate due to the impact such action would have on the PAO_2. Consequently, respiratory rate (RR) variation was used to study the effect RR had on PaO_2. Then, due to the RR large variation, as in Trial 7, RR was used to produce $PaCO_2$ values.

In Trial 8, the $PaCO_2$ values were used as a corrected factor and the effect this had on PaO_2 was assessed. After adding RR to the correction factors, in general, when the RR value increased, the PaO_2 also increased

but the $crPaO_2$ decreased. The use of a linear equation to correct for RR resulted in negative results for all patient groups (Figure 20).

Therefore, in Trial 9, the alveolar gas equation PAO_2 was used to calculate the corrected $PaCO_2$ for PaO_2 instead of correcting RR for PaO_2. The results of Trial 9 indicated that the PF ratio was less varied than our $crPaO_2$ see (Table 19). Hence, in trial 9, the equation did not work well because we first corrected for $PaCO_2$ then multiplied it again by other correction factors ($CrFiO_2$ and CrHb). However, these corrected factors were based on the curve that we generated and our correction factor with $PaCO_2$ was generated by using the alveolar gas equation. The results indicated what the PaO_2 value would be if the $PaCO_2$ were within a certain range. However, it was not mathematically acceptable to multiply the corrected $PaCO_2$ with other correction factors because the $crPaO_2$ is the actual corrected value for PaO_2 after adjusting $PaCO_2$. Therefore, to correct for $PaCO_2$ it was necessary to add it after correcting for the FiO_2 and Hb. Following the $PaCO_2$ correction, the results indicated that the PaO_2 in the heavy shunted patients did not increase following hyperventilation.

In Trial 10, the new $crPaO_2$ was used again without adding $PaCO_2$. This resulted in a good outcome and indicated that the $crPaO_2$ was nearly three times better than the PF ratio (Table 20). Therefore, by using the alveolar gas equation correctly, and adding it after calculating the correction factors, in Trial 11 we were able to fix the new $crPaO_2$. The

overall results revealed that the PF ratio was two times more varied than the new $crPaO_2$. Yet, the $crPaO_2$ values for Group A subjects were more varied for the PF ratio (Table 21).

We aimed to get some information about the patient; i.e., FiO_2, Hb, and $PaCO_2$, and we tried to standardise system employed to measure a patient's ability to oxygenate while we ignored other useful information. We assumed that reducing the $PaCO_2$ in any patient would always increase the PaO_2; however, we did not consider the fact that alveolar gas tension is not reflected very well in the arterial blood of heavy shunted patients because it mainly reflects the venous blood.

As such, we were unable to classify patients according to the PF ratio or rely on the degree of hypoxemia; although this may be more straightforward with V/Q mismatch, it is difficult to calculate in the clinical setting. Consequently, one of the solutions was to remove the $PaCO_2$ correction and rely on Trial 10. Then, we could conclude that, for blind matching, the best correction process to apply is to use an equation, as per Trial 10.

The next step involved disease classification using the $PaCO_2$. If, for example, we informed the clinician we would use 'A' equation for ARDS and 'B' equation for COPD or pneumonia, this would not be accurate. The equations are not comparable because if there is a mistake in the diagnosis, the values could change. Thus, we sought a reproducible approach that could accurately define a patient's ability to oxygenate. As

such, we may end up with dual points of ABG on the curve and from there we can direct the selection of our equation, which could be better than using the patient classification. Then, for example, if we find that a patient is not oxygen responsive, we will not use the correction for $PaCO_2$.

5.2.3. Statistical Analysis

The basic descriptions of the continuous variables were expressed as standard deviations divided by mean (SD/mean), which is usually referred to as the coefficient of variation (CV). If expressed as a percentage, this is regarded as the relative standard deviation (RSD or CV %).

The coefficient of variation or the relative standard deviation is useful because the standard deviation of data must always be understood in the context of the mean of the data. In contrast, the actual value of the CV% is independent of the unit in which the measurement has been taken; as such, it is dimensionless. To develop a comparison between data sets with different units, or vastly different means, one should use the coefficient of variation instead of the standard deviation. All data were processed and charted using Microsoft Excel (2010) and Graph-Pad Prism v6 (2014).

5.3. Experiments Report

Each trial will be described separately in details, and the progress of the methodology outlined.

5.3.1. Trial (1) Initial mathematical correction for PF ratio with FiO_2 variation

5.3.1.1. Name of excel file

23.05.14

5.3.1.2. Introduction and Aims

To construct a mathematical correction factor for the PF ratio that is reliable and stable in a wide variety of pulmonary configurations, despite FiO_2 variation.

5.3.1.3. Methods

Hypothetical values for PaO_2 were used with FiO_2 values that ranged from 30-100%. PF ratios were then calculated.

The PF ratio values were plotted on a scatter chart. A best-fit polynomial trendline was then calculated for the PF ratio curve.

Subsequently, by using the polynomial trendline equation the following equation was generated:

(Polynomial line equation $PaO_2 = 0.0003 \times FiO_2^2 - 0.052 \times FiO_2 + 3.9208$)

The corrected PF ratio (PFc) was calculated by dividing the PF ratio by the polynomial line equation using different FiO_2 levels. The PFc was then plotted on a scatter chart using the original PF ratio see Figure 8.

$$\boldsymbol{PF_c = PF\ ratio / 0.0003 \times FIO_2^2 - 0.052 \times FIO_2 + 3.9208}$$

The PF ratio and PFc were compared visually and variations in CV% were calculated (see Table 6, Figure 8)

5.3.1.4. Results

- The average CV % for the PF ratio was 32%, while for the PFc it was 6%
- Figure 8 depicts variations in PF ratio (blue) and corrected PFc ratio (orange) according to changes in FiO_2. PFc was less varied and exhibited a slightly straighter line than the PF ratio.

5.3.1.5. Conclusion

- The results indicated that there were a small variation between PF ratio and PFc when the new PFc was applied. As such, future research was required to investigate the simulated subjects' data in more depth using the same methods to calculate the PFc.

Table 6 correcting of PaO_2/FiO_2 ratio with FiO_2 %

FiO_2 %	$PaO_{2\ mmgh}$	P/F ratio	PFc
30	80.0	2.67	2.10
40	93.0	2.33	2.0
50	103.0	2.06	2.0
60	115.2	1.92	2.0
70	125.7	1.80	1.9
80	143.6	1.80	2.0
90	160.0	1.78	2.0
100	180.0	1.80	2.0
	C.V% Variation	**32%**	**6%**

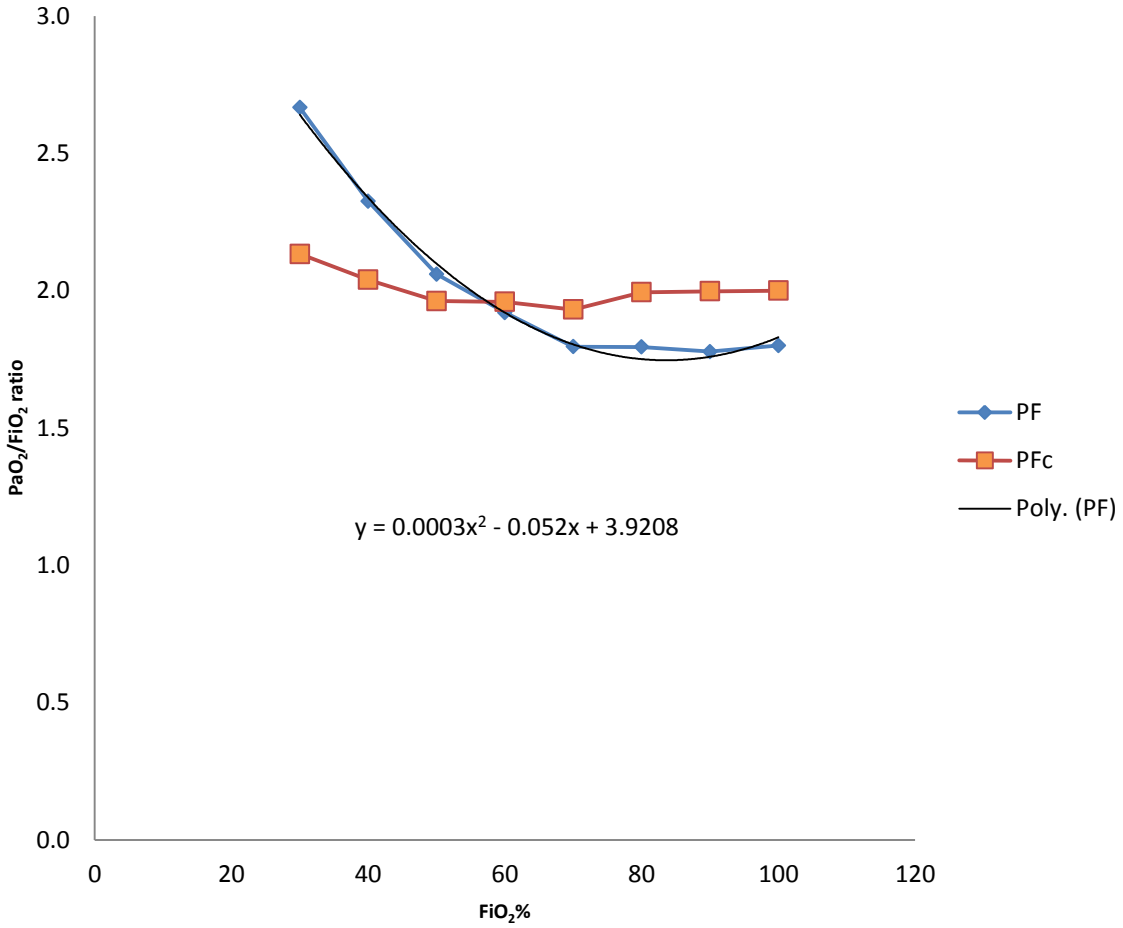


Figure 8 The PaO_2/FiO_2 ratio (PF) and the corrected PaO_2/FiO_2 ratio (PFc) with FiO_2 variation and the polynomial trend line equation.

5.3.2. Trial (2) the correct PF ratio with FiO_2 variation using simulated subject

5.3.2.1. Name of excel file

09.06.14

5.3.2.2. Introduction and aims

To use the data from simulated subjects with PF ratio and corrected PF ratio to examine the effects variations in FiO_2 had on CV%.

5.3.2.3. Methods

- Data were obtained from six ARDS simulated subjects that were based on real ARDS patient data(180). PaO_2 values were measured at different levels of FiO_2 (30% -100%) for each simulated subject and the PF ratios were calculated and (see Table 7 and Figure 9).
- The behaviour of the average PF ratio in response to FiO_2 changes were evaluated and plotted on scatter chart (see Figure 10). The best-fit polynomial trendline formula was generated
  ($y = 60.726 \times FiO_2^{\ 2} - 86.55 \times FiO_2 + 48.815$).
- The PF ratio was normalized. On average, the value of y was 1 through values of FiO_2 of 30 - 100; and divided by the average PF value in this average curve i.e. 21.4 (see Table 7
- Table 8).
- The calculated PF ratios were subsequently, divided by the normalised equation (
- Table 8)

$$PF_c = PF\ ratio / \left({}^{60.726}/_{21.4} \times FIO_2^2 - {}^{86.55}/_{21.4} \times FIO_2 + {}^{48.815}/_{21.4} \right)$$

- Variations in CV% were calculated and compared for the PF and PFc ratios. Visual comparisons were also produced (see Figure 11)

5.3.2.4. Results

- The total average CV% for the PF ratio was 24% while for the PFc ratio it was 13% (see Table 7 and
- Table 8). This indicated that variations in EPF have less of on an impact on the PFc in terms of CV% than they do on the PF ratio.

5.3.2.5. Conclusion

- Since the preliminary results for the PFc indicated a lower variation in CV% in response to FiO_2 changes, future studies were required to examine how PFc behaves in response to variations in other extra-pulmonary factors e.g. (Hb, VO_2, RQ, and CO) and there was a required to generate a correction factor for each of these aspects.

Table 7 PaO_2/FiO_2 ratio (kPa)for 6 simulated patients during FiO_2 % variation

FiO_2	PaO_2/FiO_2 pt1	$PaO2/FiO_2$ pt2	PaO_2/FiO_2 pt3	PaO_2/FiO_2 pt4	PaO_2/FiO_2 pt5	PaO_2/FiO_2 pt6	Average
30%	28.63	28.43	22.42	25.69	31.04	36.76	28.83
40%	23.30	23.18	17.25	19.52	25.51	31.76	23.42
50%	20.16	19.60	14.29	16.22	22.45	29.32	20.34
60%	18.28	17.17	12.33	13.78	20.91	29.30	18.63
70%	17.29	16.13	10.96	12.45	20.64	31.85	18.22
80%	17.18	15.83	9.96	11.56	21.85	36.66	18.84
90%	18.23	16.38	9.23	11.00	25.00	42.22	20.34
100%	20.76	18.19	8.69	10.73	29.89	47.34	22.60
CV%	19%	23%	36%	34%	16%	18%	**24%**

Table 8 corrected PaO_2/FiO_2 ratio PFc (kPa) for 6 simulated patients during FiO_2 % variation

FiO_2	PFc_1	PFc_2	PFc_3	PFc_4	PFc_5	PFc_6	PFc Ave.
30%	21.8	21.6	17.1	19.6	23.6	28.0	28.8
40%	21.2	21.1	15.7	17.8	23.3	28.9	23.4
50%	21.6	21.0	15.3	17.4	24.0	31.4	20.3
60%	22.1	20.8	14.9	16.7	25.3	35.5	18.6
70%	22.4	20.9	14.2	16.1	26.7	41.3	18.2
80%	22.2	20.5	12.9	15.0	28.3	47.5	18.8

90%	22.1	19.8	11.2	13.3	30.3	51.1	20.3
100%	22.2	19.5	9.3	11.5	32.0	50.7	22.6
CV%	2%	3%	19%	16%	12%	25%	**13%**

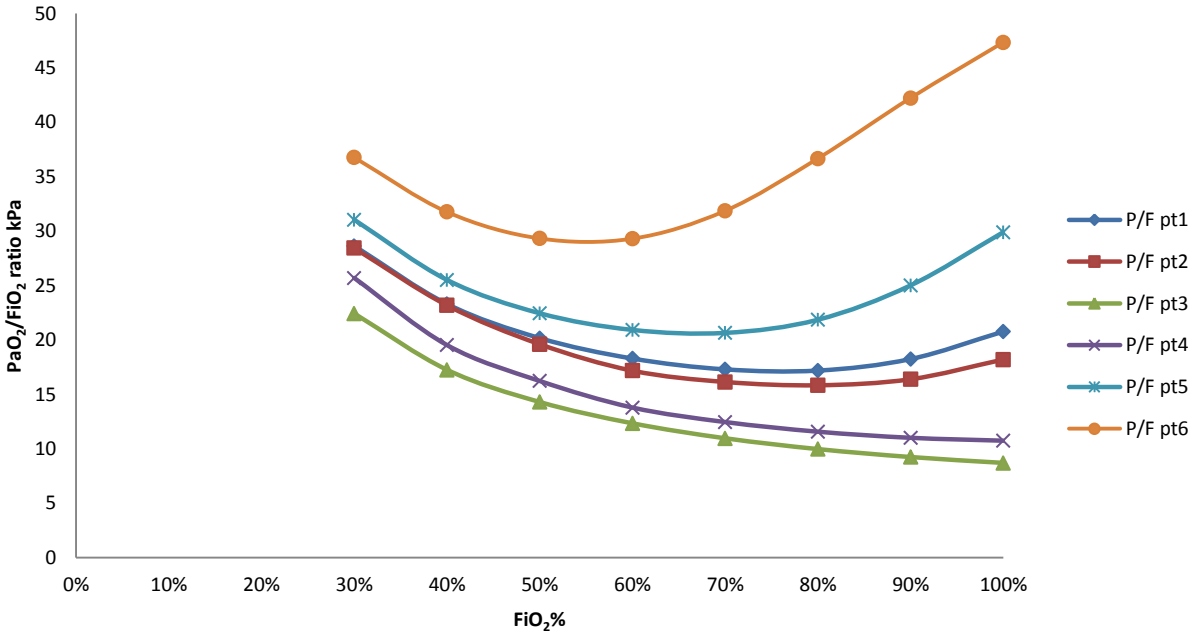


Figure 9 PaO_2/FiO_2 ratio (kPa) for six ARDS simulated patients

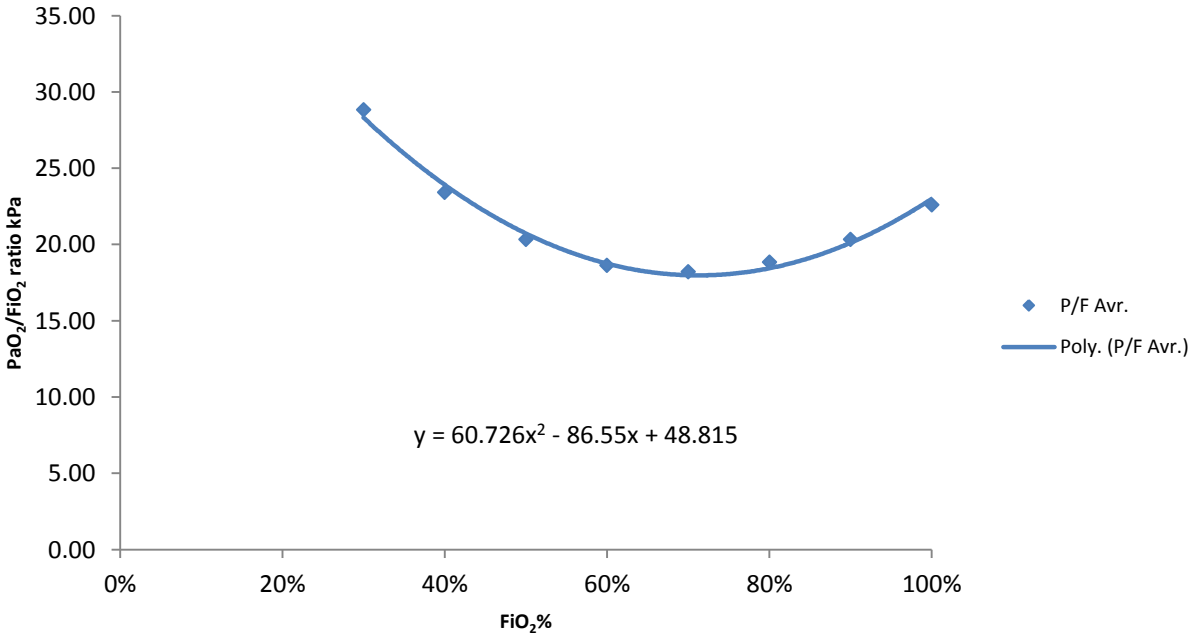


Figure 10 the average PaO_2/FiO_2 ratio (kPa) with polynomial equation

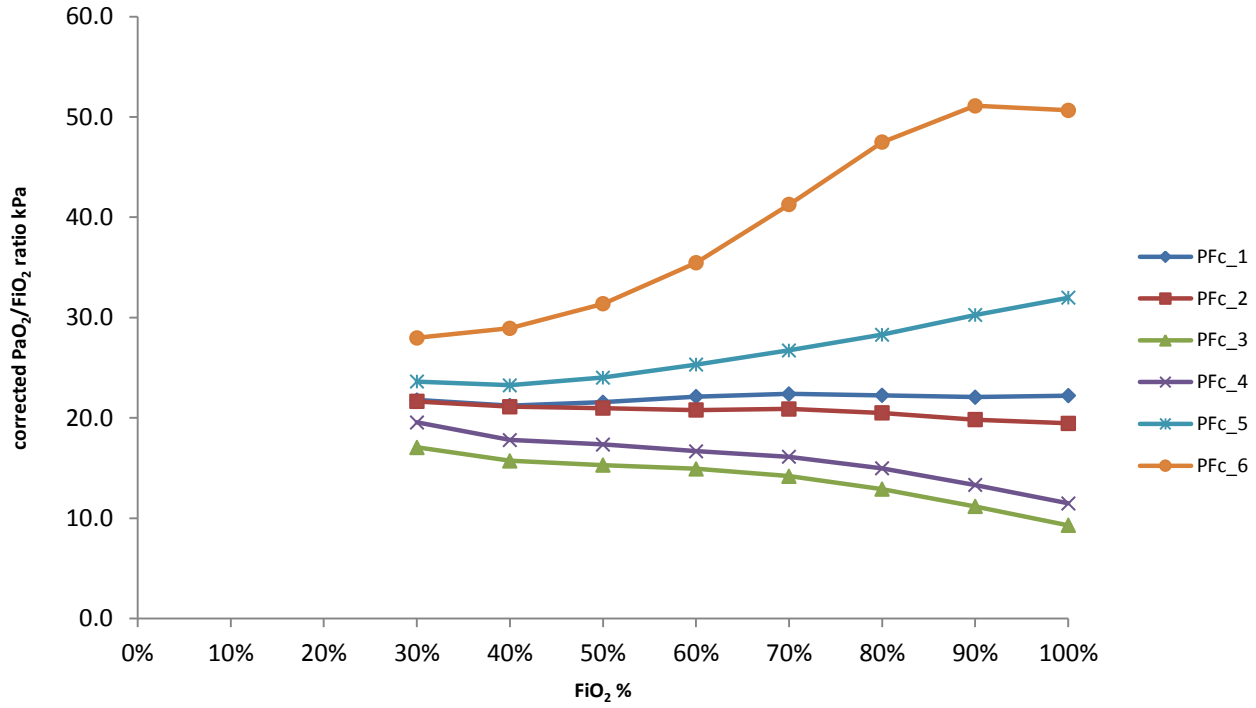


Figure 11 The corrected PaO_2/FiO_2 ratio kPa (PFc) for six simulated patients

5.3.3. Trial (3) Testing the correct PF ratio with other extra-pulmonary factors variation with one equation

5.3.3.1. Name of excel file

12.06.14

5.3.3.2. Introduction and aims

To examine how PFc behaves in response to variations in other extra-pulmonary factors; e.g., Hb, VO_2, RQ, and CO, and to generate a correction factor for each of these aspects.

5.3.3.3. Methods

- The same data from the six simulated subjects employed in Trial 2 were used.
- The PFc ratio formula was calculated using the same equation that was used in Trial 2.
- In addition to measuring FiO_2 variations in additional extra-pulmonary factors (EPF) were calculated; haemoglobin concentration (Hb), respiratory exchange ratio (RQ), cardiac output (CO), and oxygen consumption (VO_2). Therefore, after changing the EPF, the new PF ratio was calculated and employed in the equation.

$$\boldsymbol{PF_c = PF\,ratio / \left({}^{60.726}/_{21.4} \times FIO_2^2 - {}^{86.55}/_{21.4} \times FIO_2 + {}^{48.815}/_{21.4} \right)}$$

5.3.3.4. Results

- The results indicated that there was no difference between the total average variability percentage for PF ratio and PFc when Hb was varied (see Figure 12).

5.3.3.5. Conclusion

- The PFc ratio formula depends on FiO_2 changes. In this experiment, FiO_2 was constant. As such, varying any other extra-pulmonary factors did not affect the new PFc ratio. It was concluded that the next step in the process should involve creating correction factors for each extra-pulmonary factors variations.

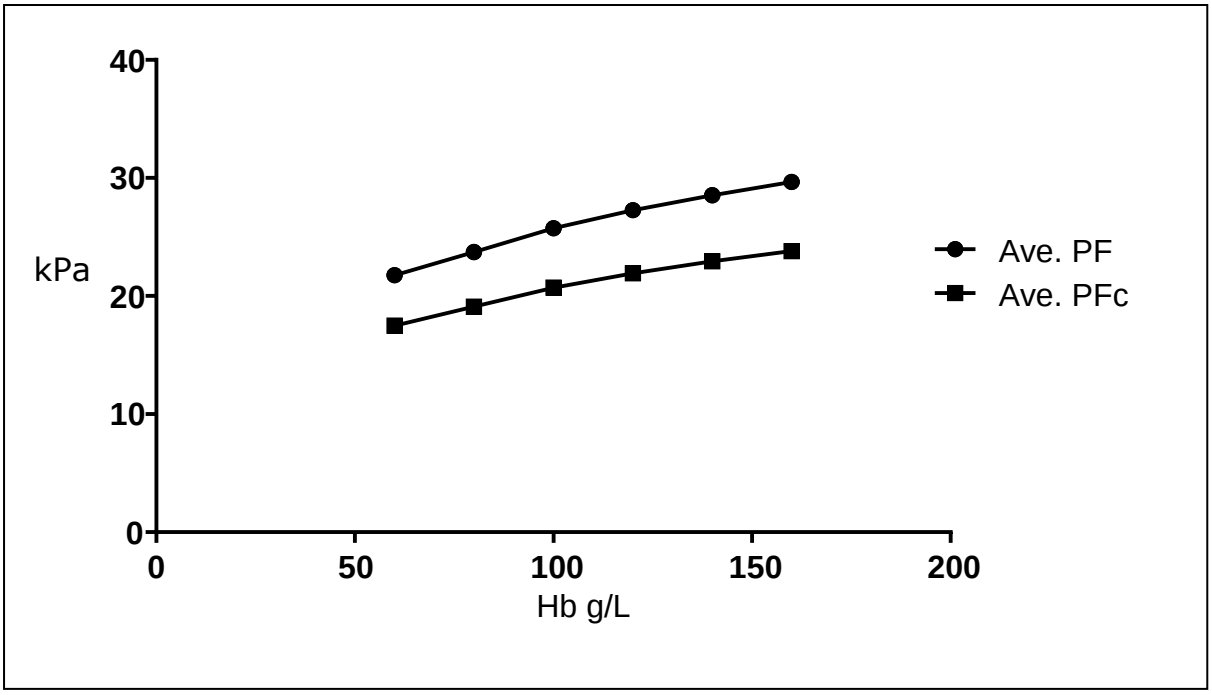


Figure 12 The average PaO_2/FiO_2 ratio in kPa (Ave.PF) and the corrected PaO_2/FiO_2 ratio (Ave.PFc) for all six NPS subjects with Hb g/L variation

5.3.4. Trial (4) Creating a multiple PFc ratio equations with extra-pulmonary factors (Hb, VO_2, RQ, CO)

5.3.4.1. Name of excel file

10 07 14

5.3.4.2. Introduction and aims

To correct the PF ratio using multiple equations derived from variations in EPFs.

5.3.4.3. Methods

- The same data from the six simulated subjects employed in Trial 2 were used.
- The average PF ratio was plotted on a scatter chart and the best-fit polynomial trendline for the averaged curve was calculated for each EPFs (Hb, VO_2, RQ and CO). These were as follows:
    - For HB correction

      $(\boldsymbol{PFc_HB})\ \boldsymbol{y} = \boldsymbol{P/F\ Ave.Hb}/(((-\mathbf{0.0003/26.12})\ \boldsymbol{X\ Hb2} + (\mathbf{0.1368/26.12})\ \boldsymbol{X\ Hb} + (\mathbf{14.517}))/\mathbf{26.12})$.

    - For VO_2 correction

      $(\boldsymbol{PFc_VO2})\ \boldsymbol{y} = \boldsymbol{P/F\ Ave.VO2}/(((\mathbf{7E-05/29.27})\ \boldsymbol{X\ VO22} - (\mathbf{0.0592/29.27})\ \boldsymbol{X\ VO2} + (\mathbf{39.593}))/\mathbf{29.27})$.

    - For RQ correction

      $(\boldsymbol{PFc_RQ})\ \boldsymbol{y} = \boldsymbol{P/F\ Ave.RQ}\ /(((-\mathbf{4.2115/28.52})\ \boldsymbol{X\ RQ2} + (\mathbf{14.646/}$

$\mathbf{28.52}) \boldsymbol{X\ RQ} + (\mathbf{19.833}))/\mathbf{28.52})$.

- For CO correction

  $(\boldsymbol{PFc_CO})\ \boldsymbol{y} = \boldsymbol{P/F\ Ave.CO}\ /(((-\mathbf{0.0373/33.03})\ \boldsymbol{X\ CO2} + (\mathbf{1.1976/33.03})\ \boldsymbol{X\ CO} + (\mathbf{5.9885}))/\mathbf{33.03})$.

5.3.4.4. Results

- After correcting for each extra-pulmonary factor individually, it was observed that the average CV% for the PF ratio (before and after correction) was the nearly the same, (see Table 9).
- Figure 13 presents multiple graphs that depict PFc versus PF ratio according to different extra-pulmonary factors. In general, the curve line for the PFc was not stable and, demonstrated a lack of flat curve. In fact, most of PFc curves behaved in much the same way as the PF ratio curves.

5.3.4.5. Conclusion

- The PFc should correct for the extra-pulmonary factors with less variation and a flat curve.
- Correcting for PF ratio may not be the best index to detect gas exchange impairment. In the equation used to calculate the PF ratio, PaO_2 is divided by FiO_2, which indicates that the PaO_2 is already corrected by FiO_2.
- Therefore, our attempt to correct for PF ratio was, in fact, correcting the PaO_2 by FiO_2 over the FiO_2 again.
- Using the PaO_2 and correcting it for other extra-pulmonary factors is more reasonable.

- In addition, when we corrected the PF ratio by cardiac output (CO) variation, a remarkable variation in PFc than the average PF ratio was observed (see Figure 13). Changing CO creates changes in the lung characteristics by affecting the shunt% and V/Q mismatch in a sick lung, thus, examination in variations of CO can be excluded (188, 189).
- In future research, the PF ratio should be dismissed and replaced with $PaO_{2,}$ before the equations are recalculated using the average PaO_2 as opposed to the PF ratio and CO should be excluded.
- Due to the difficulties associated with measuring RQ in clinical settings, future studies should generate a $PaCO_2$ by varying RQ.

Table 9 the CV% for average PF ratio and PFc (kPa)with external factors variations

Hb	PaO_2/FiO_2 **Ave.Hb**	**PFc_Hb**
60	21.76	38.43
80	23.74	41.72
100	25.73	45.02
120	27.28	47.57
140	28.55	49.62
160	29.66	51.44
Average	26.12	45.63
CV%	11%	11%
VO_2	PaO_2/FiO_2 **Ave.VO_2**	**PFC_VO_2**
150	32.40	24.10
200	30.18	22.49
250	28.83	21.51
300	27.85	20.80
350	27.07	20.22
Average	29.27	21.82
CV%	7%	7%
RQ	PaO_2/FiO_2 **Ave.RQ**	**PFC_RQ**
0.4	25.01	35.63
0.6	27.13	38.52
0.8	28.83	40.81
1	30.25	42.71
1.2	31.37	44.20
Average	28.52	40.38
CV%	9%	8%
CO	PaO_2/FiO_2 **Ave.CO**	**PFC_CO**
2	20.62	112.43
4	26.64	143.86
6	30.70	164.49
8	33.68	179.22
10	36.09	191.07
12	38.07	200.86
Average	30.97	165.32
CV%	21%	20%

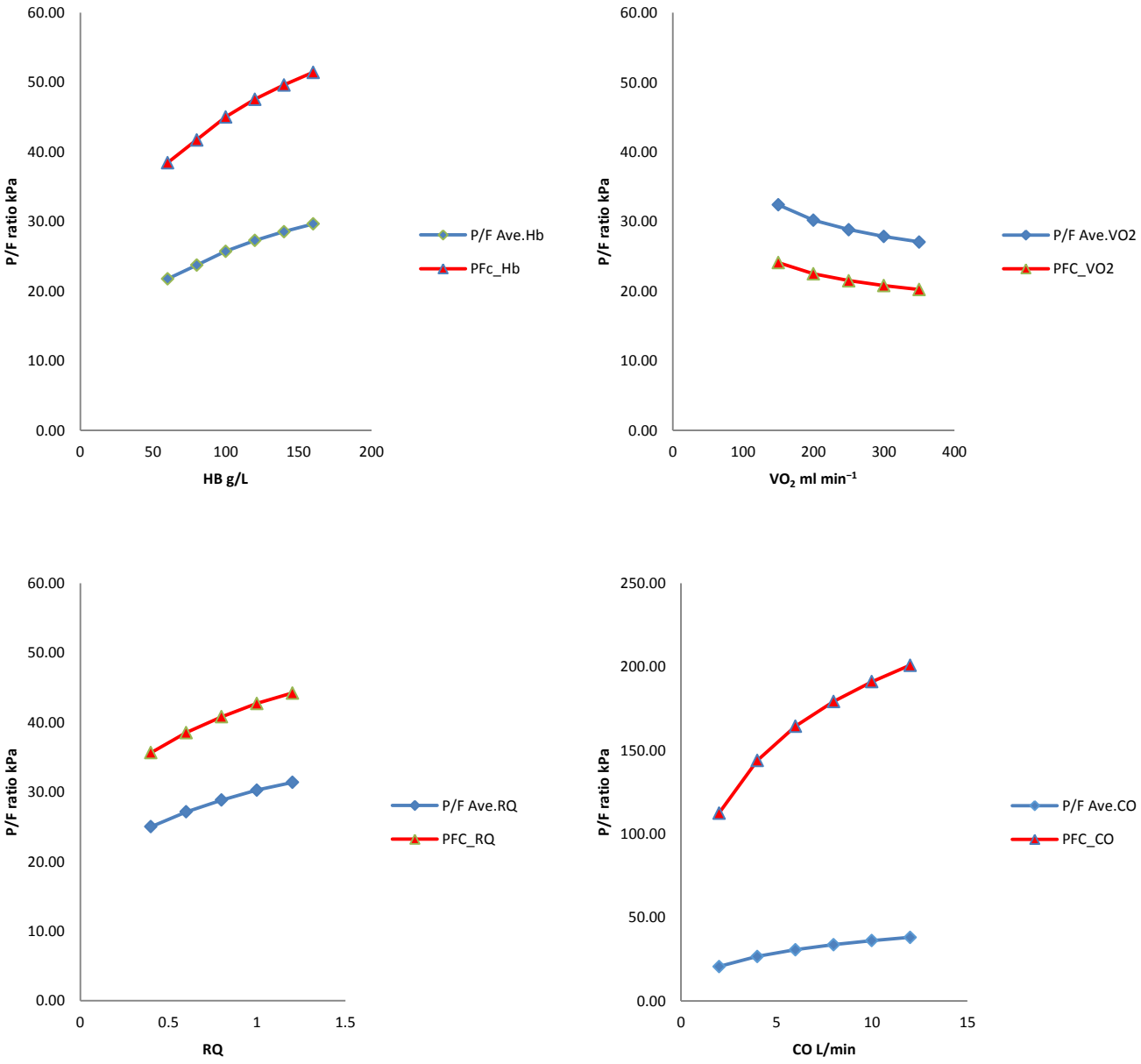


Figure 13 Four charts for the average PaO_2/FiO_2 ratio in kPa (Ave.PF) and the corrected PaO_2/FiO_2 ratio (Ave.PFc) with EPFs variation

5.3.5. Trial (5) Testing the correct PaO_2 with extra-pulmonary factors variation (FO_2, Hb, VO_2, $PaCO_2$) with multiple equations on 10 random NPS subjects.

5.3.5.1. Name of excel files

15.07.2014,
17-07-2014,
02-08-2014,
26-08-2014,
27-08-2014,
15-09-2014,
11.12.2014,
22-09-2014 B

5.3.5.2. Introduction and aims

To correct the PaO_2 using multiple equations derived from variations in extra- pulmonary factors.

5.3.5.3. Methods

The same data from the six simulated subjects employed in Trial 2 were used as configuration subjects with the exception of Patient 6, whose values were excluded because the values for this subject were less severe than those of the other simulated subjects.

Ten additional simulated subjects were configured as test subjects, to examine the new $crPaO_2$.

A correction factor (CF) was created for each EPF by varying each EPF one at a time.

Each EPF had a set of PaO_2 averages that were plotted on a scatter chart (PaO_2 in y-axis VS EPF in X-axis) as described in Figure 14-17.

Next, to correct for Hb, VO_2 and $PaCO_2$, the first PaO_2 / mean PaO_2 were calculated and plotted on the chart to generate a linear trendline curve. The linear equations were displayed on the charts (see Figure 15-17).

The previous equations were used to calculate the best fit to predict PaO_2 values for the given values of EPF (Fit PaO_2 = EPF X b + a), where Fit PaO_2 was the dependent variable and EPF was the independent variable (Hb, VO_2 and $PaCO_2$), and a, b were coefficient factors.

PaO_2 was corrected for each Hb, VO_2 and $PaCO_2$ by dividing the PaO_2 by the fit PaO_2 for each factor. An equation was developed for each corrected Hb, VO_2 and $PaCO_2$, and these equations were combined to create a CF equation.

The $PaCO_2$ value was generated by changing RQ from (0.40 - 1.20).

Table 10 to 14 depict the correction process that was for the Hb, VO_2 and $PaCO_2$.

A linear equation was initially used to correct for FiO_2. However, due to the large variation between the new $crPaO_2$ and the PF ratio, different polynomial model equations were employed. If the corrected curve showed a lack of flatness, a higher order of polynomial equation was tested. Thus, we used the polynomial equation, and then the 3rd order polynomial equations were employed. The results indicated that it was preferable for the $crPaO_2$ to be approximated by the 3^{th} order polynomial as opposed to using a straight-line equation. Figure 14 depicts the 3^{rd}

polynomial equation generated by Microsoft Excel using either the regression (LINEST function) or by Regression Statistics summary output tables (190).The corrected PaO_2 ($crPaO_2$) was calculated by dividing the PaO_2 by the CF

$$\boldsymbol{CrPaO_2 = PaO_2/CF}$$

The CF was calculated using each of the four equations for (FiO_2, Hb, VO_2, and $PaCO_2$) as follows:

$$\boldsymbol{CF = CrFIO_2 \times CrHb \times CrVO_2 \times CrPaCO_2}$$

$$\boldsymbol{CrFIO_2 = \left(\left(FIO_2{}^3 \times 0.0000032\right) + \left(FIO_2{}^2 \times -0.00044187\right) + \left(FIO_2{}^1 \times 0.02454222\right) + 0.288865\right)}$$

$$\boldsymbol{CrHb = (Hb \times 0.00319363 + 0.6487003)}$$

$$\boldsymbol{CrVO_2 = (VO_2 \times -0.00088736 + 1.2218424)}$$

$$\boldsymbol{CrPaCO_2 = (PaCO_2 \times 0.0396 + 0.75741)}$$

Next, the average variability for the simulated patients was compared according to CV%.

Consequently, a headline figure was formed to compare how many times the $crPaO_2$ was better than the PF ratio during FiO_2, HB, VO_2, and RR variation. The headline figure was calculated first, after which the average CV% for both $crPaO_2$ and PF ratio were calculated before the ratio between them was determined by dividing the CV% for $crPaO_2$ by the PF ratio and the reciprocal (1/ratio) was identified.

5.3.5.4. Results

When FiO_2, HB, $PaCO_2$ and VO_2 were varied in the ten-modelled subjects, the mean CV% for $crPaO_2$ was 20% and the PF ratio was 22%. As such, CV% was one times better than that calculated for PF ratio in the same subjects under the same conditions (see Table 14). However, this indicated that, in some cases (Pt.4, Pt.5, Pt.6, and Pt.10), the PF ratio was much better than $crPaO_2$.

A comparison of the total averages for all simulated patients indicated that the mean absolute difference in variation percentages was 6% lower in PF ratio than it was for $crPaO_2$, with an average ratio of 1.1 times that in $crPaO_2$. Furthermore, the mean percentage difference was 26% lower in the PF ratio than it was in the $crPaO_2$.

5.3.5.5. Conclusion

Examining the new CF stability on ten random subjects may have been misleading, because the test subjects may not be from the same group within the configuration groups. This entails that not all subjects were necessarily healthy subjects or the subjects may have represented an extreme sample of patients who were not included in the configuration groups.

Future studies should test the CF on the same configuration subjects that were used to generate the CF equation and consideration should be given to excluding extreme example patients.

Table 10 correction for FiO_2 %

FiO_2	ave.PaO_2	PaO_2/mean	fit PaO_2	crPaO_2
30	8.17	0.718	0.7144	11.440
40	8.70	0.764	0.7698	11.303
50	9.27	0.814	0.8141	11.390
60	9.90	0.869	0.8667	11.420
70	10.84	0.952	0.9469	11.453
80	12.22	1.073	1.0740	11.376
90	14.37	1.262	1.2675	11.339
100	17.65	1.550	1.5466	11.414
Average	**11.39**	**1.000**	**1.000**	**11.392**
Variability:	28.4%	28.4%	28.4%	0.4%

coefficients factors C3	**0.000003222**
coefficients factors C2	**-0.000441871**
coefficients factors C1	**0.024542220**
intercept (a)	**0.288865140**

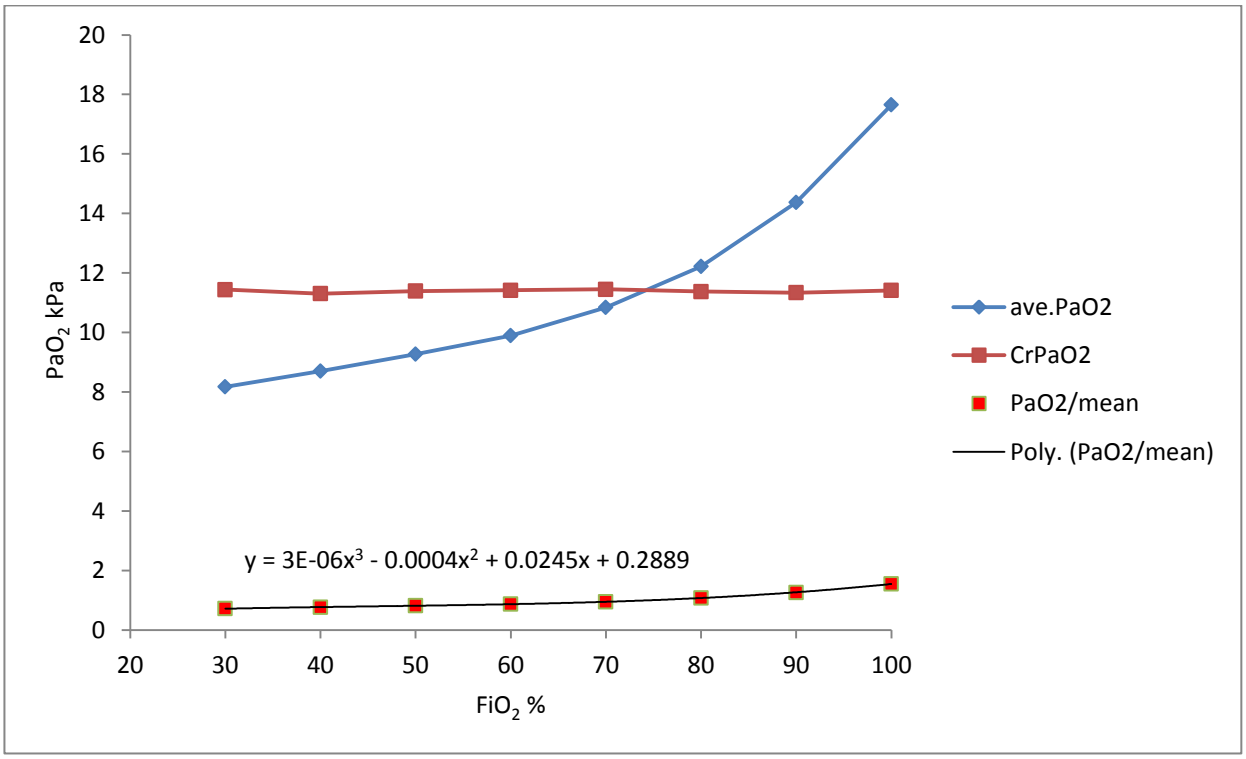


Figure 14 The average PaO_2 (kPa)and the corrected crPaO_2 (kPa) with FiO_2% variation and the polynomial equation

Table 11 correction for HB g/l

Hb g/L	ave.PaO_2 kPa	PaO_2/mean	fit PaO_2	crPaO_2 kPa
60	6.07	0.82	0.84	7.224
80	6.67	0.90	0.90	7.373
100	7.26	0.98	0.97	7.498
120	7.71	1.05	1.03	7.473
140	8.09	1.10	1.10	7.382
160	8.42	1.14	1.16	7.262
Average	**7.37**	**1.00**	**1.00**	**7.37**
Variability:	12.0%	12.0%	11.9%	1.5%
slope (b)	**0.0031**			
intercept (a)	**0.6663**			

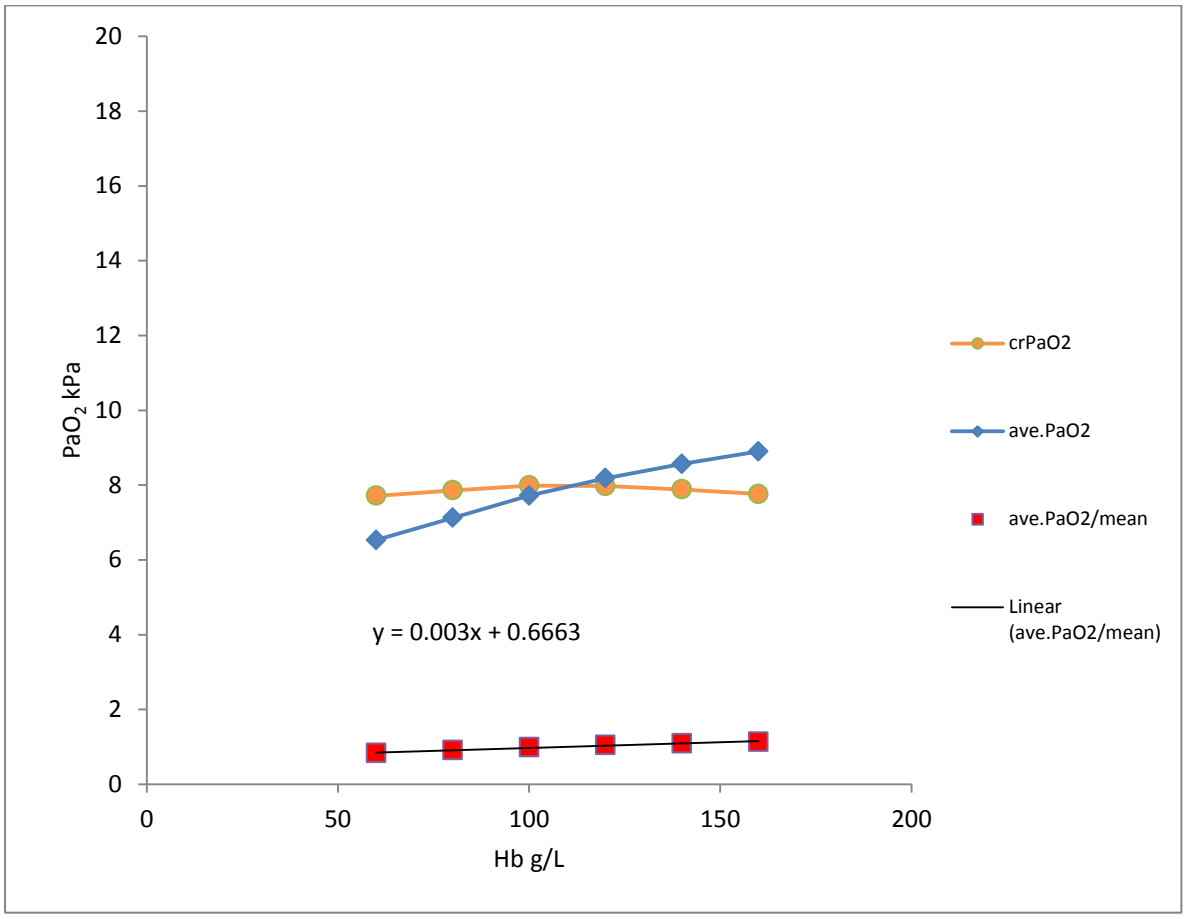


Figure 15 the average PaO_2 (kPa) and the corrected crPaO_2 (kPa) with Hb (g/L) variation and a liner equation.

Table 12 Correction for VO_2 ml min^{-1}

$VO_{2\ ml\ min}^{-1}$	ave.PaO_2 kpa	PaO_2/mean	fit PaO_2	crPaO_2 kPa
150	9.72	1.11	1.09	8.93
200	9.05	1.03	1.04	8.67
250	8.65	0.99	1.00	8.65
300	8.36	0.95	0.96	8.74
350	8.12	0.92	0.91	8.91
Average	**8.78**	**1.00**	**1.00**	**8.78**
Variability:	7.2%	7.2%	7.0%	1.5%
slope (b)	**-0.0008874**			
intercept (a)	**1.2218424**			

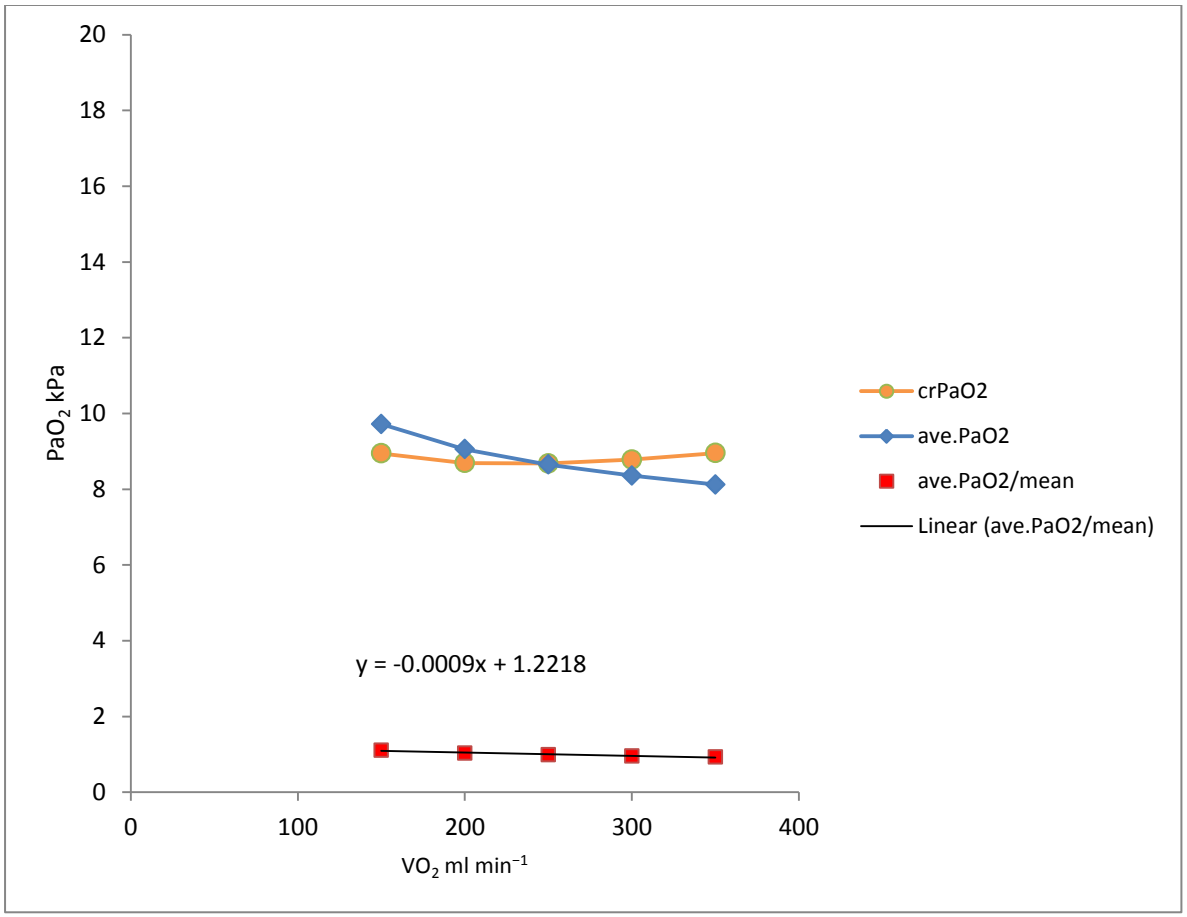


Figure 16 the average PaO_2 (kPa) and the corrected crPaO_2 (kPa) with VO_2 (ml min^{-1}) variation and a linear equation.

Table 13 correction for $PaCO_2$ (kPa)

$PaCO_2$ kPa	ave.PaO_2 kPa	PaO_2/mean	Fit PaO_2	crPaO_2 kPa
3.2	7.05	0.87	0.88	7.976
4.6	7.67	0.95	0.94	8.149
6.1	8.17	1.01	1.00	8.174
7.6	8.60	1.06	1.06	8.122
9.0	8.94	1.11	1.12	8.008
Average	**8.09**	**1.00**	**1.00**	**8.09**
Variability:	9.3%	9.3%	9.2%	1.1%
slope (b)	**0.0396904543**			
intercept (a)	**0.7574147189**			

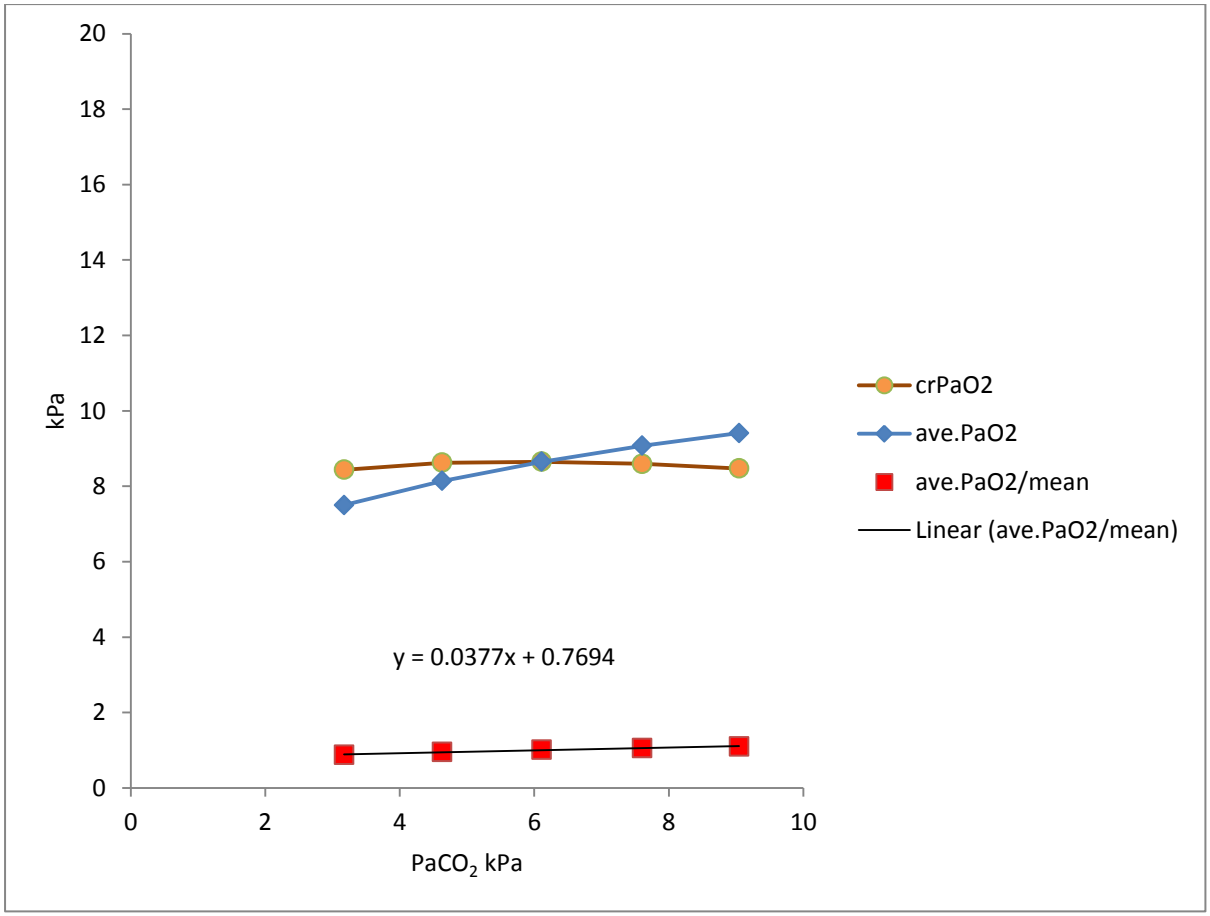


Figure 17 the average PaO_2 (kPa) and the corrected crPaO_2 (kPa) with with $PaCO_2$ variation kPa and a linear equation.

Table 14 summary measures of association between PF ratio and $crPaO_2$ using 10 simulated patients

Simulated patient number	The average variability CV% for PF ratio	The average variability CV% for $crPaO_2$	Absolute difference	Ratio	Percentage Difference
Pt.1	5%	4%	1%	1.0	4%
Pt.2	43%	25%	18%	1.7	75%
Pt.3	28%	19%	9%	1.5	49%
Pt.4	26%	27%	1%	0.9	5%
Pt.5	10%	11%	1%	0.9	6%
Pt.6	36%	51%	15%	0.7	29%
Pt.7	17%	10%	7%	1.6	59%
Pt.8	20%	19%	1%	1.0	5%
Pt.9	9%	8%	1%	1.1	14%
Pt.10	22%	25%	3%	0.9	12%
Average	22%	20%	6%	1.1	26%

5.3.6. Trial (6) Testing the correct PaO_2 with other extra-pulmonary factors variation with multiple equations with same configuration subjects.

5.3.6.1. Name of excel file

06.10.2014 A,
13.10.2014,
14.10.2014,
16.10.2014,
17.10.2014,
20.10.2014,
23 10 14,
24.10.2014,
23 10 14 A,
29.10.2014,
30.10.2014,
30.10.2014 A,
30.10.2014 B,
31.10.2014,
231014 edit 14.01.2015

5.3.6.2. Introduction and aims

To test the CF from Trial 5 on the same configuration subjects that were employed to create the CF equation before considering excluding the extreme example patients

5.3.6.3. Methods

- The same data from the six simulated subjects employed in Trial 5 were used as configuration subjects. Each external pulmonary factor (EPF) was then varied in isolation and the PaO_2 was recorded each time.
- The $crPaO_2$ and PF ratio was then calculated, and the average variability across each simulated patient was identified according to CV%.

- The ratios were then calculated by dividing the average variation per cent for $crPaO_2$ by the average variation per cent for the Pf ratio.

5.3.6.4. Results

- Table 15 shows the average variation of each EPF for each five-modelled subject. The mean CV% was 4% for $crPaO_2$ and 13% for the PF ratio. This was 3.5 times better than that calculated for the PF ratio in the same subjects under the same conditions.
- Table 15Figure 18 shows series of scatter charts that compared PaO_2 and $crPaO_2$ according to FiO_2 variations for the five simulated patients. Simulated patient numbers 3 and 4 were in the negative direction, and it was noted that further investigation would be needed to correct this.

5.3.6.5. Conclusion

- RQ was manipulated to generate a $PaCO_2$. Therefore, in order to produce values for $PaCO_2$, a series of increasing RQ was performed and a source of error was observed. The simultaneous changes of RQ and $PaCO_2$ affected the PaO_2 value although the FiO_2 level did not change. Thus, the PF ratio was less varied and more stable than the $crPaO_2$. A according to the alveolar gas equation (PAO_2) whenever the $PaCO_2$ increases the PaO_2 decreases; however, in this trial, when the $PaCO_2$ increased, the PaO_2 also increased (187).
- The source of uncertainty was in the method used to calculate $PaCO_2$. By increasing RQ, it was observed that if one subject with a result of (RQ =0.4 and $PaCO_2$=4.6) and another with a result of (RQ=1.2 and

$PaCO_2$ 13.9) the calculated PAO_2 for both examples would be the same; (i.e. the PAO_2 for both would be 38).

- Consequently, it was noted that as opposed to RQ, the respiratory rate (RR) and its effect on PaO_2 variation should be employed to the correction factor.
- Therefore, it was noted that the current data were not suitable for any further investigation and that the correction of a new simulated patient using NPS was preferable

Table 15 summary results of trial six average variations for all simulated patients

The average variation of the physiological factors	**$crPaO_2$ CV%**	**PF ratio CV%**
FiO_2	10%	26%
HB	2%	12%
VO_2	2%	6%
$PaCO_2$	1%	9%
Average	4%	13%
$crPaO_2$/PF ratio	0.29	
the reciprocal	3.5	

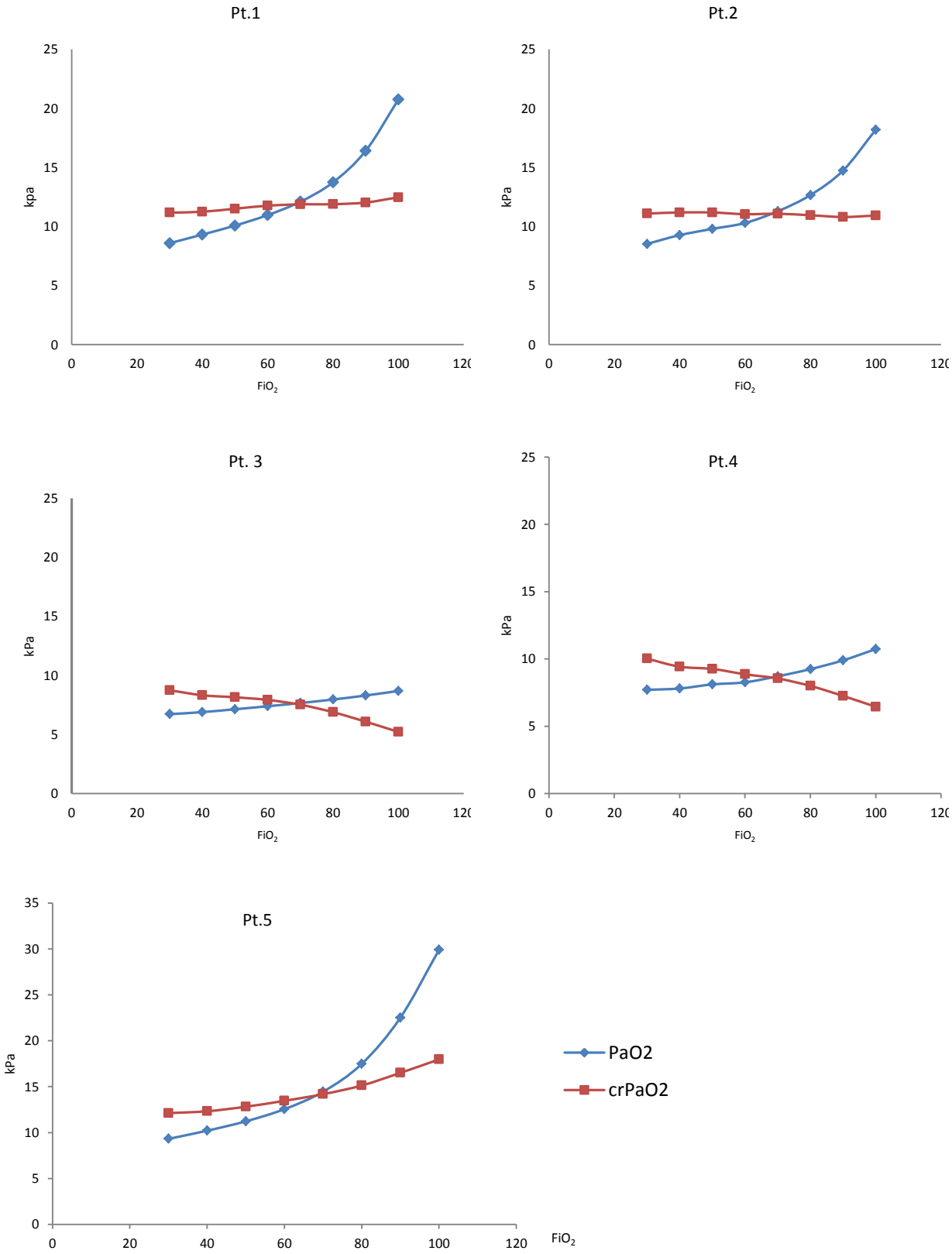


Figure 18 comparing PaO_2 (kPa) with $crPaO_2$ (kPa) during FiO_2 % variation for 5 simulated patients

5.3.7. Trial (7) Testing crPaO_2 with the extra-pulmonary factors (FiO_2, Hb, VO_2, RR) on a new ten NPS subjects

5.3.7.1. Name of excel file

07 11 2014 A

5.3.7.2. Introduction and aims

New NPS configuration subjects were created and tested against other test subjects.

5.3.7.3. Methods

- Ten simulated patients were configured using NPS. Each simulated subject had a unique pulmonary configuration with a degree of calculated pulmonary shunt fraction, deadspace and ventilation perfusion mismatch, yet had identical level of FiO_2 (0.3), Hb (145 g/l), VO_2 (250) For further information about and in respect to their physiology and mechanical ventilator settings, see Table 16.
- Five new simulated subjects were configured as test subjects for the purpose of examining the new crPaO_2.
- Each EPF (FiO_2, Hb, VO_2, and RR) was varied in isolation and the PaO_2 was recorded each time.
- Following this, a correction factor (CF) was created for each EPF by using the average PaO_2 values that were obtained from the 10 simulated patients. To establish the FiO_2 variation, the crPaO_2 was first calculated using the 3rd polynomial equation; however, the scattered chart for the crPaO_2 was not as straight and flat as expected. Therefore,

the 4th polynomial equation was used to correct the average PaO_2 values.

- A linear equation was used to correct for PaO_2 with the other extra-pulmonary factors variation (HB, VO_2, and RR). As such, the new $crPaO_2$ equation was:

$$\boldsymbol{CrPaO_2 = PaO_2 / CF}$$

$$\boldsymbol{CF = CrFIO_2\ X\ CrHB\ X\ CrVO_2\ X\ CrRR}$$

$$\boldsymbol{CrFIO_2} = \left(\left(\boldsymbol{FIO_2}^{\boldsymbol{4}} \times \boldsymbol{-0.000000221}\right) + \left(\boldsymbol{FIO_2}^{\boldsymbol{3}} \times \boldsymbol{0.000050576}\right) + \left(\boldsymbol{FIO_2}^{\boldsymbol{2}} \times \boldsymbol{-0.003624573}\right) + \left(\boldsymbol{FIO_2}^{\boldsymbol{1}} \times \boldsymbol{0.110188282}\right) + (\boldsymbol{-1.017289013})\right)$$

$$\boldsymbol{CrHb} = (\boldsymbol{Hb} \times \boldsymbol{0.00319363} + \boldsymbol{0.7731689})$$

$$\boldsymbol{CrVO_2} = (\boldsymbol{VO_2} \times \boldsymbol{-0.0027701} + \boldsymbol{1.6925182})$$

$$\boldsymbol{CrRR} = (\boldsymbol{RR} \times \boldsymbol{0.0429636} + \boldsymbol{0.5531782})$$

- Next, the average PaO_2 was assessed and compared with the average new $crPaO_2$ in terms of the FiO_2, Hb, RR, and VO_2 variation for each of the 10 simulated patients (see Figure 19).

- Following that, another five test subjects were configured to test the reliability of the new $crPaO_2$ with the PF ratio.

- Consequently, a headline figure was formed to compare how many times $crPaO_2$ was better than the PF ratio during FiO_2, HB, VO_2, and RR variations. The headline figure was calculated first, after which the average CV% for both $crPaO_2$ and PF ratio were calculated before the ratio between them was determined by dividing the CV% for $crPaO_2$ by the PF ratio and the reciprocal (1/ratio) was identified.

5.3.7.4. Results

- Table 17 presents the average headline figure for 15 simulated subjects. The results indicated that, in general, the $crPaO_2$ was 1.23 times better than the PF ratio within the configuration patients (Pt.1-Pt.10). Similarly, $crPaO_2$ increased two times more than the PF ratio when the data from the five test subjects were combined.

5.3.7.5. Conclusion

- For some patients (Pt.1-4), the headline figure indicated that the PF ratio was less variable than the $crPaO_2$. This requires further investigation (see Table 17). Separating, these patients into two different categories may improve the headline figure.

Table 16 configuring for 10 simulated patients using NPS

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.7	Pt.8	Pt.9	Pt.10
BR	1004.9-1/2460.2-20/	1253.2-1/1176.5-20/	998.6-1/876.2-20/	1049.8-1/888.0-20/	566.4-1/231.0-20/	151.3-1/50.4-20/	100.0-1/25.0-20	39.7-1/25.0-20/	39.7-1/25.0-20/	86.5-1/28.1-20/
VR	/1.7-80/1.4-100	/2.3-80/1.7-100	/2.3-80/3.2-100	/4.0-80/4.8-100	/7.3-80/18.5-100	/20.3-80/100.0-100	/20.3-80/100.0-100	/39.7-80/118.8-100	/70.6-80/182.3-100	/43.6-80/313.3-100
shunt%	29	31	32	41	47	50	33	36	42	48
Mean VQ	0.78	0.81	0.90	1.10	2.00	6.70	8.50	9.67	14.64	16.14
SD of VQ	0.76	0.80	0.94	1.18	2.62	10.80	13.70	13.70	20.20	28.70
SaO%	90	89	88	82	76	75	87	82	77	73

PaO_2 Kpa	8.11	7.82	7.61	6.58	6.01	6.24	8.39	7.62	7.27	6.37
pH	7.40	7.39	7.38	7.36	7.32	7.26	7.25	7.22	7.19	7.20
$PaCO_2$ Kpa	5.52	5.85	5.88	6.2	7.33	9.56	9.49	10.67	11.81	11.42
HCO_3	24.40	25.70	25.7	26.1	27.80	30.90	30.70	31.80	33.40	33.00
Hb	145	145	145	145	145	145	145	145	145	145
VO_2	250	250	250	250	250	250	250	250	250	250
RR b/min	12	12	12	12	12	12	12	12	12	12
PEEP cmH_2O	0	0	0	0	0	0	0	0	0	0
PAO_2 Kpa	21.00	19.79	21.65	20.82	19.76	17.41	17.39	15.53	14.13	15
PaO_2/FiO_2	27	26	25	22	20	21	28	25	24	21
$P(A\text{-}a)O_2$	13	12	14	14	14	3	2	8	7	9

Table 17 the headline figure for NPS patients

NPS patient Number	($crPaO_2$/PF ratio) ratio	
	All subjects	**Configuration subjects**
Pt 1	0.32	0.32
Pt 2	0.28	0.28
Pt 3	0.24	0.24
Pt 4	0.33	0.33
Pt 5	1.32	1.32
Pt 6	3.04	3.04
Pt 7	1.32	1.32
Pt 8	1.17	1.17
Pt 9	1.75	1.75
Pt 10	2.53	2.53
Pt.11	3.54	-
Pt 12	2.47	-
Pt 13	4.12	-
Pt 14	3.87	-
Pt 15	3.29	-
Total ($crPaO_2$/PF ratio) ratio averages	**1.97**	**1.23**

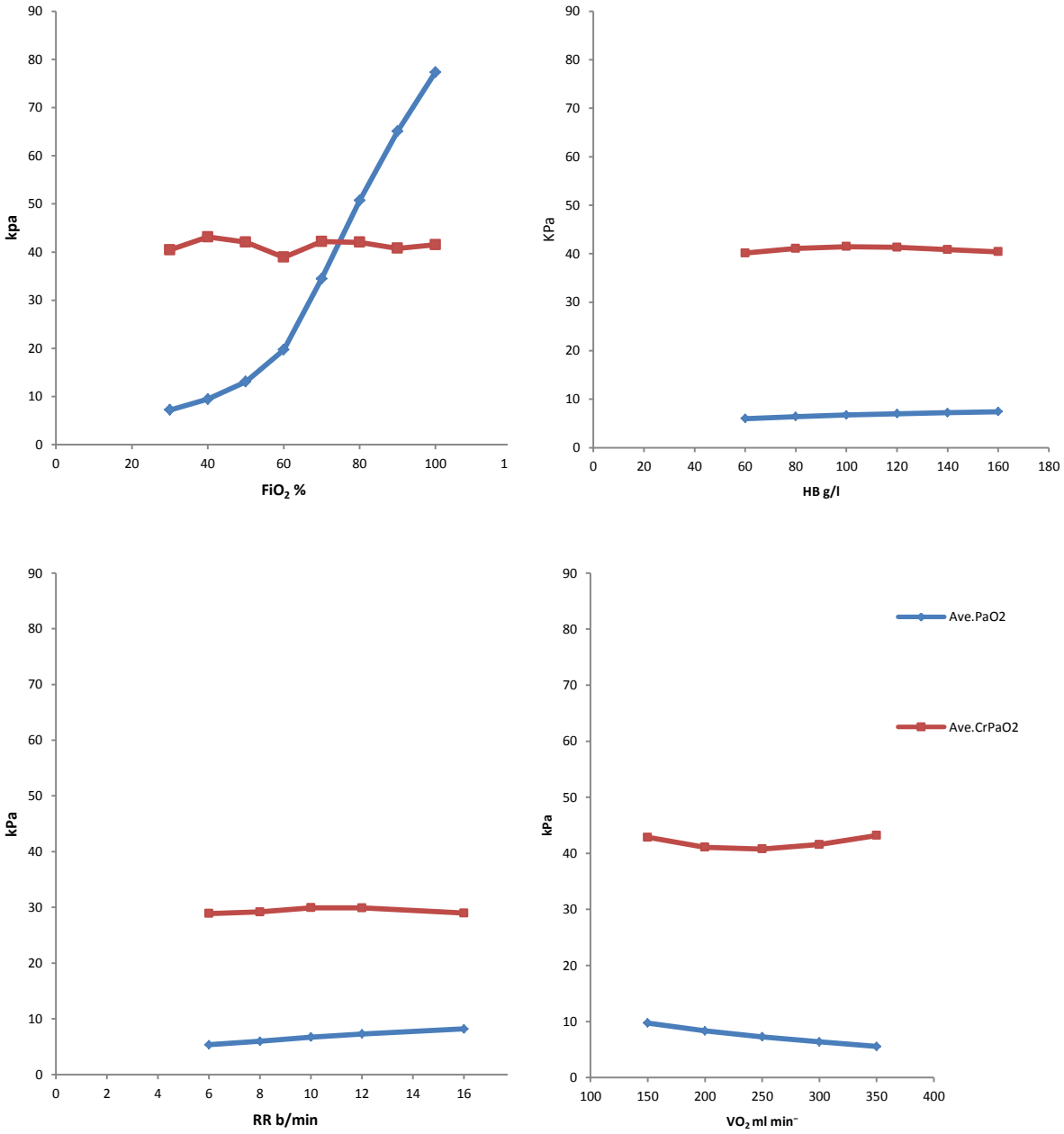


Figure 19 comparing the average PaO_2 (kPa) with average $crPaO_2$ (kPa) with four EPFs variation for 10 simulated patients

5.3.8. Trial (8) Testing $crPaO_2$ in two groups

5.3.8.1. Name of excel file

18 11 2014,
19 11 2014,
20 11 2014,
21 11 2014,
25 11 2014,
26 11 2014,
12.12.2014.

5.3.8.2. Introduction and aims

To improve the headline figure from the previous trial and the scatter charts. Due to vast pathophysiological differences among the configuration subjects, it was difficult to place all the data under one CF curve, and the headline figure was low. In fact, the results obtained for some subjects indicated that the PF ratio was much better in terms of less variation than it was for the new $crPaO_2$. Therefore, Trial 8 aimed to categorise subjects into one of two groups according to pathophysiological characteristics.

5.3.8.3. Methods

- The same data from the ten simulated subjects employed in Trial 7 were used.
- These virtual subjects were divided into two groups according to their VQ mismatch ratio: the first group (A) Pt. 1-5 had a high shunt and lower deadspace, and the second group (B) Pt. 6-10 had a low shunt and higher deadspace.

- Table 18**Error! Reference source not found.** presents the mean and the range of the initial configuration values for both groups at the same FiO_2, Hb, VO_2, RR and PEEP values:
    a. The mean VQ was 1.14 in Group A, which was much smaller than that of Group B (13.13).
    b. The mean variability% and sat% were higher for Group A than they were for Group B.
    c. The mean VQ and shunt % were higher in Group B than they were for Group A.
    d. Both groups shared the same mean of PaO_2/FiO_2 ratio and PaO_2.
- Figure 20 depicts the following results:
    a. With FiO_2 between 30-60%, the average PaO_2 in Group A were slightly increased; however, at 61-100% it increased remarkably with Group B.
    b. The mean PaO_2 in Group A was decreased as VO_2 increased.
    c. Finally, the average PaO_2 in Group B increased as respiratory rate increased, while it remained largely constant in Group A.
- Next, two CFs were generated, one using the Group A data and another using the Group B data.
- The mathematical stability and variation of the $crPaO_2$ was tested by changing the correction factor equation. In other words, to examine the effect of changing the correction factor according to

FiO_2 variation, 3rd, 4th, 5th and 10th polynomial equations were used.

5.3.8.4. Results

- When the $crPaO_2$ curves that were generated using the Group B data were compared using different polynomial equations (using the 3rd, 4th, 5th, and 10th order), across multiple modelled subjects, the 5th order polynomial equation curve was better than the calculated $crPaO_2$ curves that were generated using the Group A data under the same conditions (see Figure 21 and Figure 22).
- Attempts were made to make the $crPaO_2$ curve for the Group A data more flat by using the 3rd, 4th, 5th, 6th and 10th order polynomial equations (see Figure 22). Despite the fact that a flat line was achieved on the scatter chart through the application of the 10th order polynomial equation, the line was not straight and exhibited more variation than the equation derived from the Group B data.

5.3.8.5. Conclusion

- Since the 5th order polynomial equation that was generated using the data from Group B was less varied and more stable than the one generated using the Group A data, it was noted that this 5th order polynomial equation should be employed in further trials.

- Due to the difficulties associated with measuring the oxygen consumption V_{O2} in a clinical setting and the researcher's inability to accurately estimate it, no corrections for V_{O2} were developed.
- After increasing RR in the correction factors, the PaO_2 increased, but the $crPaO_2$ decreased (see Figure 20).
- Using the linear equation to correct for RR produced negative results in all patient groups. The researchers noted that it would be interesting to examine a different method of correction; for example, through using the alveolar gas equation PAO_2. Using the PAO_2, it may be possible to calculate the corrected $PaCO_2$ for PaO_2 instead of correcting RR for PaO_2.

Table 18 comparison of initial configuration values between group A and B

Group of subjects	A (Pt. 1-5)			B (Pt. 6-10)		
	Min	Mean	Max	Min	Mean	Max
variability %	81	88	100	65	72	81
Shunt %	29	36	47	33	41	50
Mean VQ	0.78	1.14	2.11	6.70	13.13	23.14
SD of VQ	0.76	1.29	2.76	10.80	22.75	49.40
Sat%	76	85	90	73	78	87
PaO_2	6.01	7.23	8.11	6.24	7.23	8.39
pH	7.32	7.37	7.40	7.19	7.23	7.26
$PaCO_2$	5.52	6.16	7.33	9.20	10.36	11.81
HCO_3	24.40	25.94	27.80	30.20	31.67	33.40
PaO_2/FiO_2	20.03	24.09	27.03	20.80	24.09	27.97

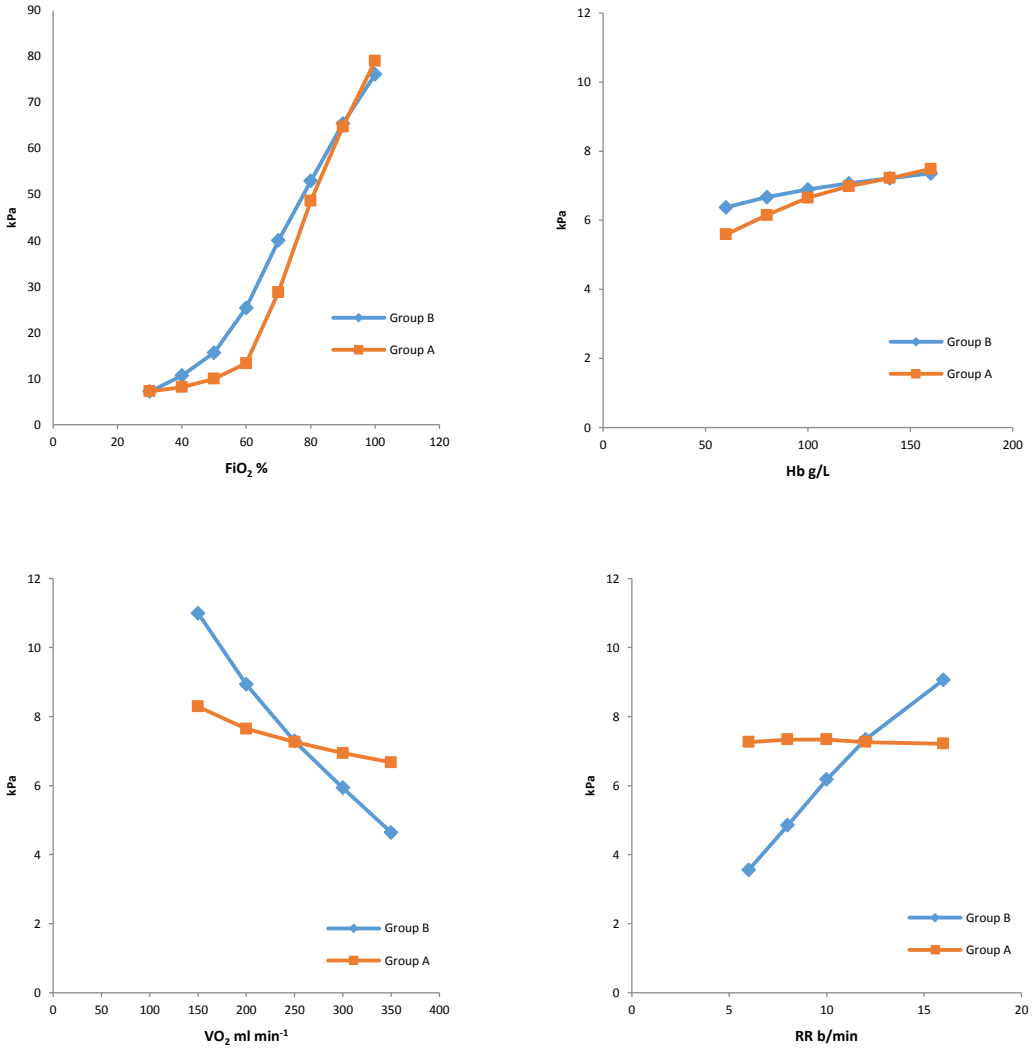


Figure 20 average PaO_2 (kPa) for group A and B with EPF variations.

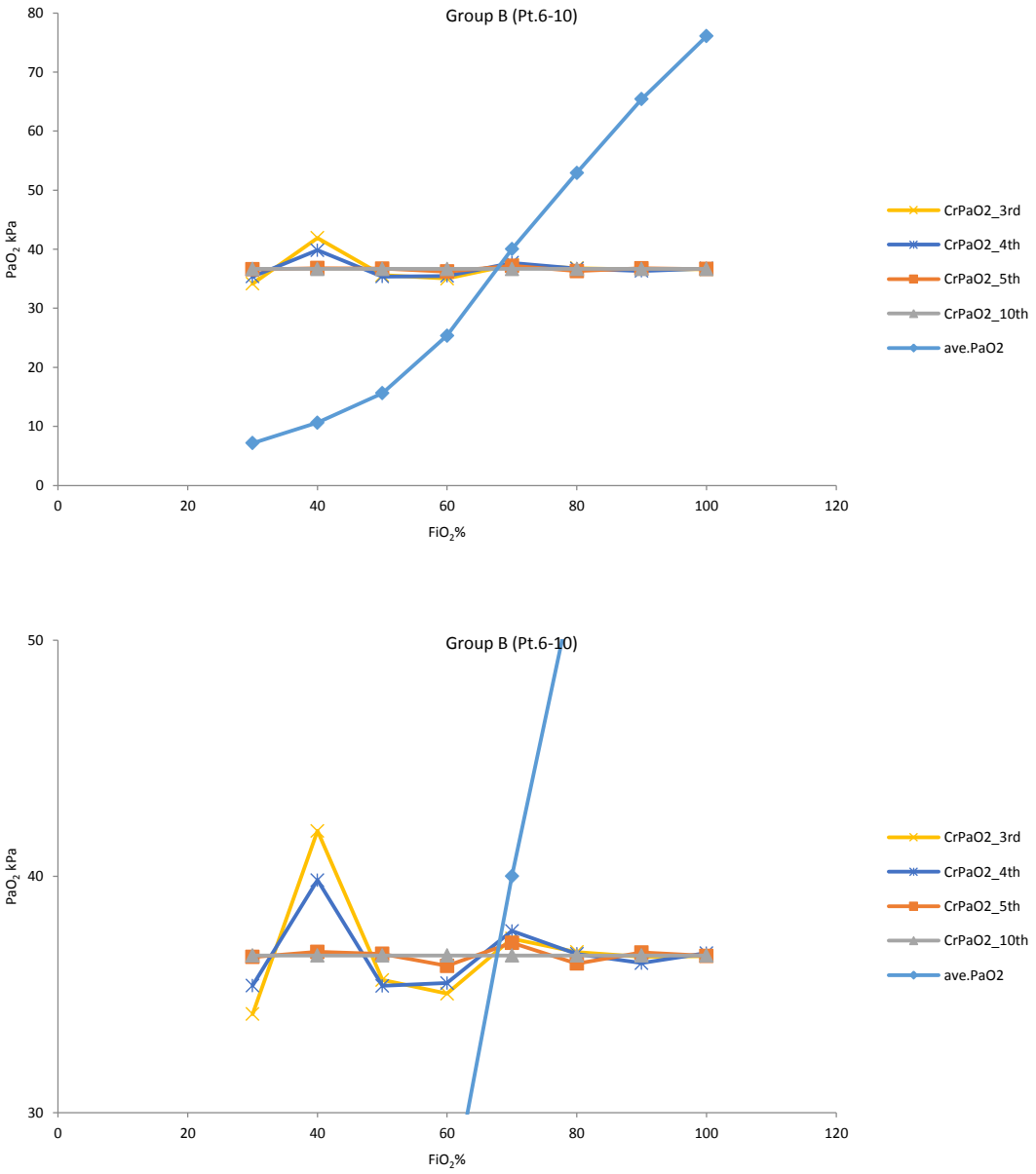


Figure 21 different crPaO$_2$ (kPa)curves using equation from group B with FiO$_2$ variation

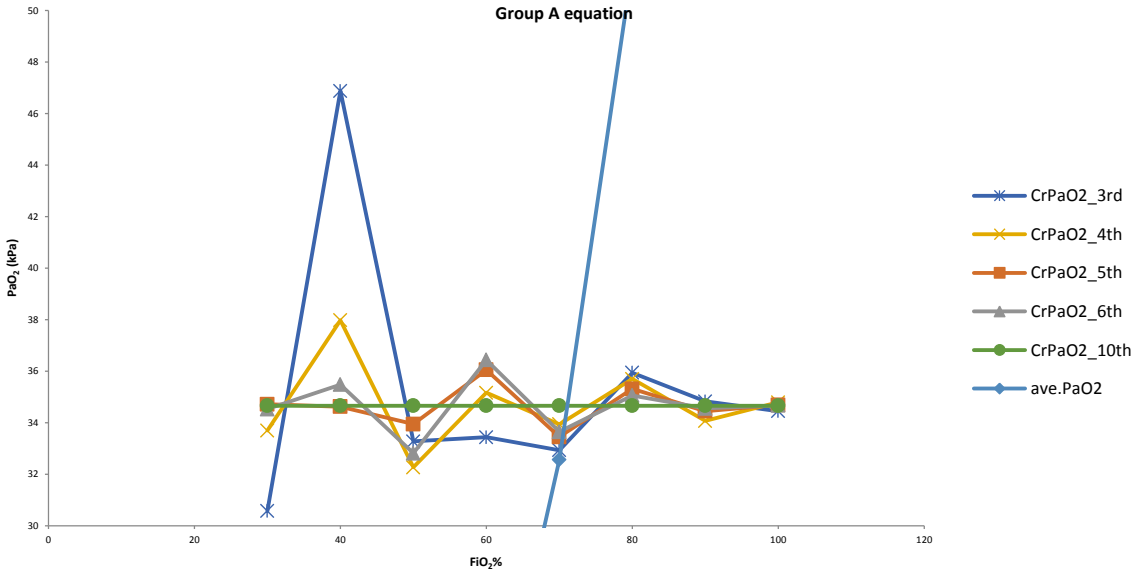


Figure 22 different crPaO$_2$ (kPa) using Group A equation with FiO$_2$ variation

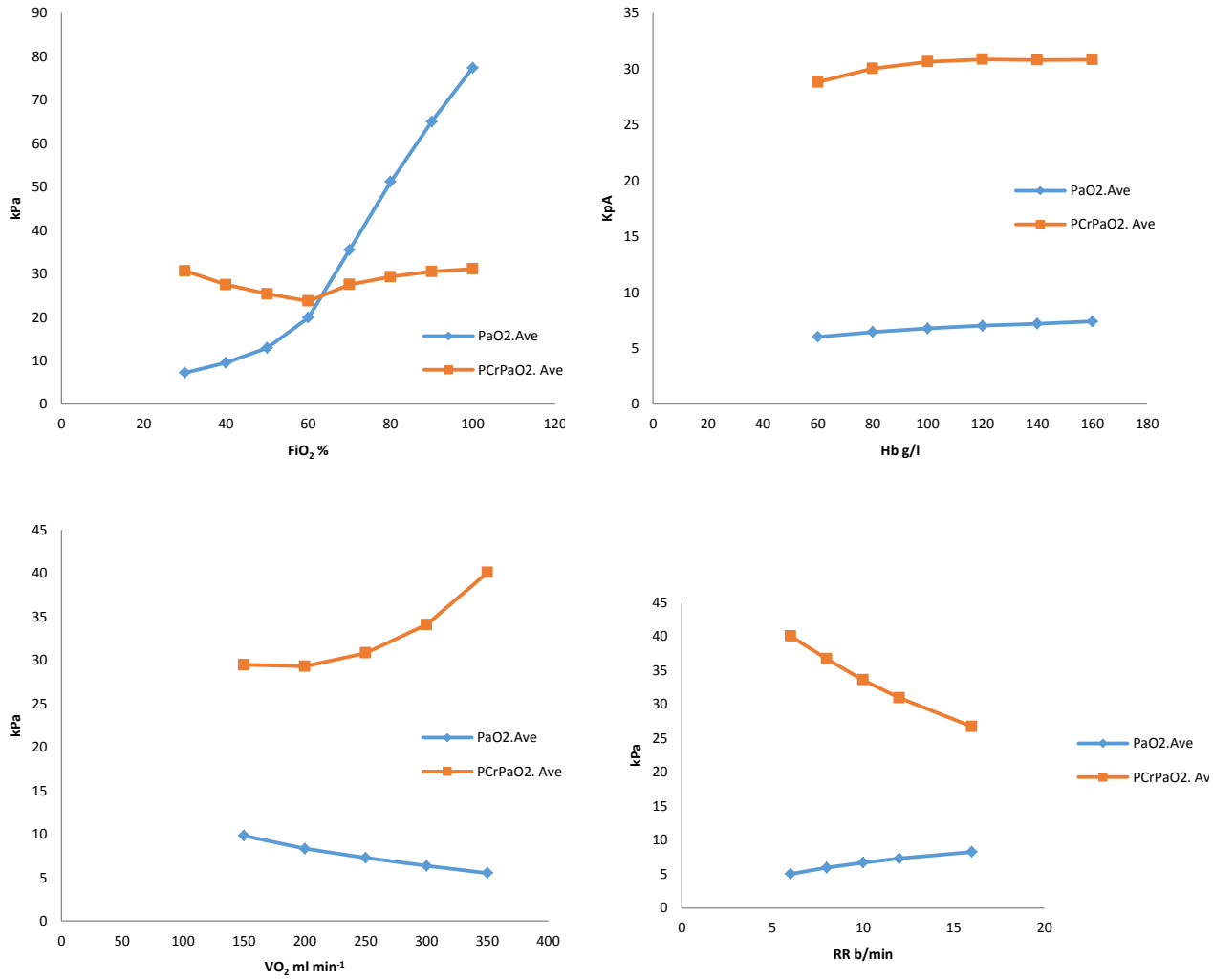


Figure 23 comparing average PaO_2 (kPa) and $crPaO_2$ (kPa) for all simulated subjects with variation of EFP(FiO_2, HB, VO_2,and RR)

5.3.9. Trial (9) Testing crPaO_2 with (FiO_2, Hb, and PaCO_2) variation

5.3.9.1. Name of excel file

14.01.2015

5.3.9.2. Introduction and aims

To correct for PaCO_2 using the alveolar gas equation (PaO_2).

5.3.9.3. Methods

- The same ten test simulated subjects' data from Trial 7 were used and then another five test subjects were configured to test the reliability of the new crPaO_2 with PF ratio.
- The PaCO_2 was corrected using the PaO_2 equation:

  PaO_2=PIO_2-PaCO_2/RQ

  crPaO_2= PaO_2 + (PaCO_2-5.3)/0.8

  PaO_2 and PaCO_2 were measured before the PaCO_2 was subtracted from the normal level; for example, 5.3. In a given subject, if the PaCO_2=6 KPa and PaO_2=10 Kpa, the corrected crPaO_2 would be:

  = 10+ (6-5.3)/0.8

  =11 Kpa

- Then, the new crPaO_2 for PaCO_2 would be:
  - $\boldsymbol{CrPaO_2 = PaO_2 / CF}$
  - $\boldsymbol{CF = CrFIO_2\ X\ CrHB\ X\ CrPaCO_2}$

- $\boldsymbol{CrFIO_2 = \left(\left(FIO_2{}^5 \times 0.0000000067\right) + \left(FIO_2{}^4 \times -0.0000022381\right) + \left(FIO_2{}^3 \times 0.0002814522\right) + \left(FIO_2{}^2 \times -0.0162723936\right) + \left(FIO_2{}^1 \times 0.4463108631\right) + (-4.4971618467)\right)}$
- $\boldsymbol{CrHb = (Hb \times 0.0013887 + 0.8472483)}$
- $\boldsymbol{CrPaCO_2 = (mPaO_2 + (PaCO_2 - 5.3)/0.8)}$
- Consequently, the headline figures were compared for different subject groups.

5.3.9.4. Results

- The headline figures for all patients group are described in Table 19. The outputs indicate that, when FiO_2, Hb, and $PaCO_2$ were varied in multiple modelled subjects, the headline figures for the new $crPaO_2$ were more varied than the variation of PF ratio.

5.3.9.5. Conclusion

- Examining the stability of the new CF after adding $PaCO_2$ may require mathematical intervention. Therefore, it was noted that further consultation with a mathematician was required. However, further studies could experiment with correcting FiO_2 and HB and only. This would potentially improve the results because previous trials indicated that correcting for variables like $PaCO_2$, RR and VO_2 does not improve the new $crPaO_2$.
- Another justification for having higher variation with $crPaO_2$ was that the subjects with a large deadspace might not respond physiologically

in the same way as subjects with less deadspace. Regardless, the effort applied on ventilation that will not affect the gases as much as we have a large deadspace.

Table 19 headline figure with different groups using equation generated from trial nine

Patient number	Group A	Group B	test subjects	Group A+B	All Patients
Pt 1	0.20	-	-	0.20	0.20
Pt 2	0.18	-	-	0.18	0.18
Pt 3	0.24	-	-	0.24	0.24
Pt 4	0.22	-	-	0.22	0.22
Pt 5	0.49	-	-	0.49	0.49
Pt 6	-	0.96	-	0.96	0.96
Pt 7	-	0.68	-	0.68	0.68
Pt 8	-	0.69	-	0.69	0.69
Pt 9	-	0.96	-	0.96	0.96
Pt 10	-	1.12	-	1.12	1.12
Pt.11	-	-	0.78		0.78
Pt 12	-	-	0.76	-	0.76
Pt 13	-	-	0.67	-	0.67
Pt 14	-	-	0.84	-	0.84
Pt 15	-	-	0.85	-	0.85
Average	0.27	0.86	0.78	0.59	0.64

5.3.10. Trial (10) Testing crPaO$_2$ with (FiO$_2$ and Hb) only

5.3.10.1. Name of excel file

14.01.2015 B

5.3.10.2. Introduction and aims

Examine the variation of FiO$_2$ and Hb only

5.3.10.3. Methods

- The same ten test simulated subjects' data from Trial 7 were used and then another five test subjects were configured to test the reliability of the new crPaO$_2$ with PF ratio.
- The new crPaO$_2$ equation was:
- $\boldsymbol{CrPaO_2 = PaO_2 / CF}$
- $\boldsymbol{CF = CrFIO_2 \, X \, CrHB}$
- $\boldsymbol{CrFIO_2 = \left(\left({FIO_2}^5 \times 0.0000000067 \right) + \left({FIO_2}^4 \times -0.0000022381 \right) + \left({FIO_2}^3 \times 0.0002814522 \right) + \left({FIO_2}^2 \times -0.0162723936 \right) + \left({FIO_2}^1 \times 0.4463108631 \right) + (-4.4971618467) \right)}$
- $\boldsymbol{CrHb = (Hb \times 0.0013887 + 0.8472483)}$

5.3.10.4. Results

- The headline figures for all patients group are described in Table 20, when FiO$_2$ and Hb were varied, in multiple modelled subjects, the mean CV% for crPaO$_2$ was less varied than PF ratio which was almost 2.8 times better than that calculated for PF ratio in the same subjects under the same conditions

- Figure 24-25 compare the average PaO_2 and average $crPaO_2$ according to variations in FiO_2 and Hb. .

5.3.10.5. Conclusion

- Instead of configuring a curve that corrected for $PaCO_2$ by adjusting respiratory rate, it was ascertained that, if the deadspace changed a lot in the patient lung, this would result in a huge difference in the lung characteristic that would make the prediction of $crPaO_2$ less accurate.
- Previous investigations established that different lung disease types behave differently in terms of external physiological factors. This research attempted to correct them all at the same time, and this approach was not useful. While the correction factor performed well in terms of the FiO_2 and HB variations, the $crPaO_2$ did not improve with other physiological factors (CO, RQ, VO_2, RR, and $PaCO_2$). Therefore, there is a need to use PAO_2 and test it again after mathematical consultation.

Table 20 headline figure with different groups using equation generated from trial ten

Patient number	Group A	Group B	test subjects	Group A+B	All Patients
Pt 1	2.4	-	-	2.4	2.4
Pt 2	2.2	-	-	2.2	2.2
Pt 3	3.6	-	-	3.6	3.6
Pt 4	1.8	-	-	1.8	1.8
Pt 5	1.8	-	-	1.8	1.8
Pt 6	-	2.6	-	2.6	2.6
Pt 7	-	1.7	-	1.7	1.7
Pt 8	-	1.7	-	1.7	1.7
Pt 9	-	3.3	-	3.3	3.3
Pt 10	-	4.8	-	4.8	4.8
Pt.11	-	-	4.1	-	4.1
Pt 12	-	-	5.4	-	5.4
Pt 13	-	-	2.5	-	2.5
Pt 14	-	-	1.4	-	1.4
Pt 15	-	-	2.6	-	2.6
Average	2.4	3.0	3.0	2.7	2.8

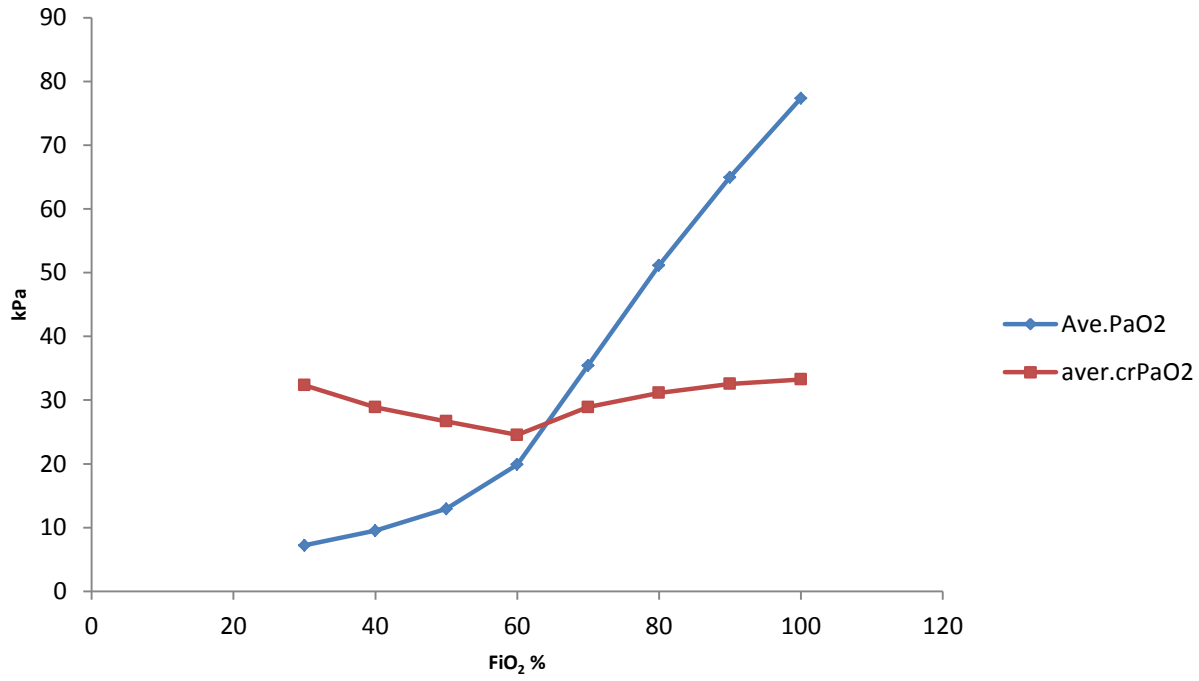


Figure 24 comparing the average PaO_2 and average $crPaO_2$ with FiO_2 variation

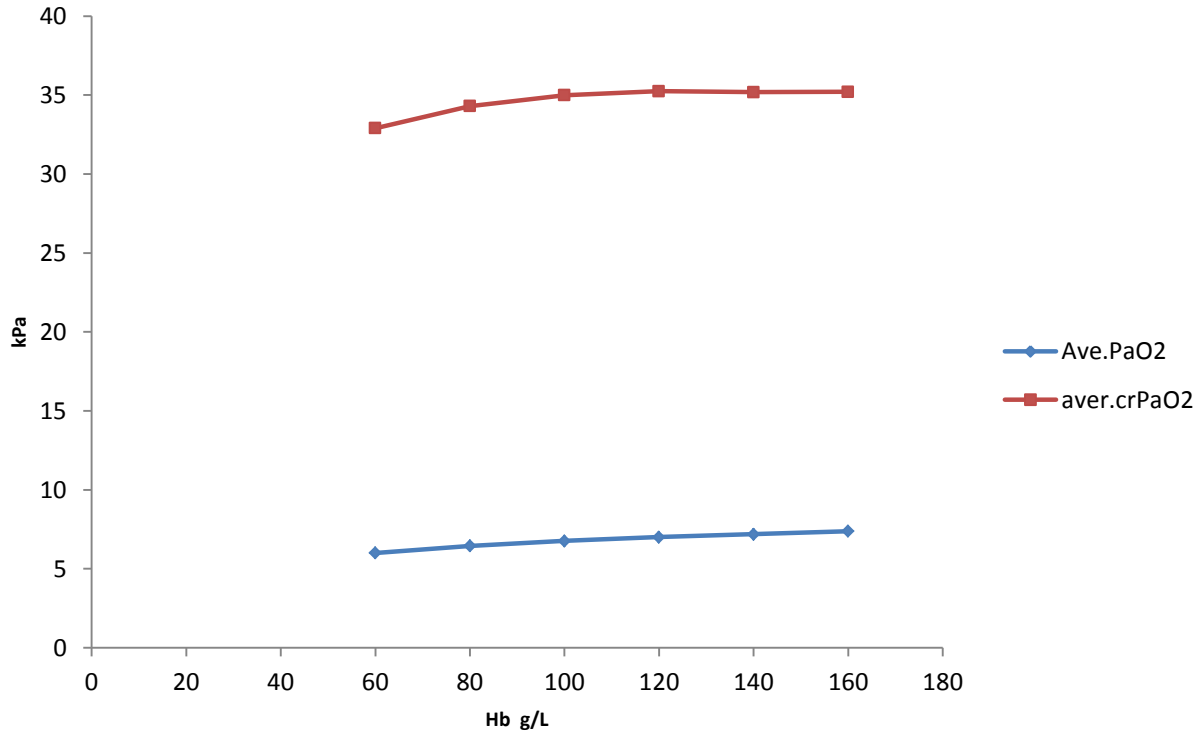


Figure 25 comparing the average PaO_2 (kPa) and average $crPaO_2$ (kPa)with Hb g/L variation

5.3.11. Trial (11) Testing crPaO_2 with variation of FiO_2 and Hb then corrected PaCO_2

5.3.11.1. Name of excel file

29.01.2015

5.3.11.2. Introduction and aims

Examine the variation of FiO_2, Hb then add to the corrected PaCO_2

5.3.11.3. Methods

- The same ten test simulated subjects' data from Trial 7 were used and then another five test subjects were configured to test the reliability of the new crPaO_2 with PF ratio.
- The new crPaO_2 equation was:

$$\boldsymbol{crPaO_2} = (\boldsymbol{PaO_2}/\boldsymbol{CF}) + (\boldsymbol{PaCO_2} - \mathbf{5.3}/\mathbf{0.8})$$

- $\boldsymbol{CF} = \boldsymbol{crFIO_2}\ \boldsymbol{X}\ \boldsymbol{crHB}$
- $\boldsymbol{crFIO_2} = \left(\left(\boldsymbol{FIO_2}^{\mathbf{5}} \times \mathbf{0.0000000067}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{4}} \times -\mathbf{0.0000022381}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{3}} \times \mathbf{0.0002814522}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{2}} \times -\mathbf{0.0162723936}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{1}} \times \mathbf{0.4463108631}\right) + (-\mathbf{4.4971618467})\right)$
- $\boldsymbol{crHb} = (\boldsymbol{Hb} \times \mathbf{0.0013887} + \mathbf{0.8472483})$

5.3.11.4. Results

- The headline figures for all patients group are presented in Table 21.

5.3.11.5. Conclusion

- In Trial 11, the new $crPaO_2$ results indicated that the data for the Group A subjects (who had high shunt and lower deadspace) exhibited more variation than the PF ratio. However, in Group B (people with a low shunt and higher deadspace), the $crPaO_2$ results exhibited less variation than the PF ratio. However, when the equation developed in Trial 10 was applied, the overall results indicated that the $crPaO_2$ was nearly three times better than the PF ratio.
- Therefore, the alveolar gas equation showed no correction for the $PaCO_2$ in Group A. In addition, the PaO_2 in Group A did not respond to respiratory rate variation in the same way that it responded to variations in FiO_2.
- Furthermore, the researchers were aware that this group was not oxygen responding and were, therefore, not very hyperventilation responsive. As such, it was not possible to correct for the same group.
- Therefore, the possibility of including the $PaCO_2$ correction was explored. This revealed that the PaO_2 in the heavy shunted subjects did increase as a result of hyperventilation in the same way as that observed in the group B subjects.
- The research concluded that we were able to create one equation that can fit different patients' disease and this topic was explored with other external factors to quantify oxygenation defect through a maze of maths, different diseases, and pathophysiology. There was properly one or two ways that could lead to us to the answer and many dead end

routes. Ultimately, the research produced an equation that was three times better than PF the ratio in terms of less variation.

- The $crPaO_2$ that was generated from the data on a group of simulated subjects involved patients with a low shunt and higher deadspace. As such, it may not be suitable for use on subjects with high shunt and lower deadspace.

- The researchers concluded that the next Trial should involve the creation of a further $crPaO_2$ equation for simulated subjects that have high shunt and lower deadspace, and should then identify new methods of classifying the subjects accordingly

Table 21 headline figure with different groups using equation generated from trial eleven

Patient number	Group A	Group B	test subjects	Group A+B	All Patients
Pt 1	0.63	-	-	0.63	0.63
Pt 2	0.54	-	-	0.54	0.54
Pt 3	0.73	-	-	0.73	0.73
Pt 4	0.59	-	-	0.59	0.59
Pt 5	0.62	-	-	0.62	0.62
Pt 6	-	2.78	-	2.78	2.78
Pt 7	-	1.72	-	1.72	1.72
Pt 8	-	1.77	-	1.77	1.77
Pt 9	-	2.24	-	2.24	2.24
Pt 10	-	3.29	-	3.29	3.29
Pt.11	-	-	3.67	-	3.67
Pt 12	-	-	3.40	-	3.40
Pt 13	-	-	3.29	-	3.29
Pt 14	-	-	2.95	-	2.95
Pt 15	-	-	3.04	-	3.04
Average	0.62	2.58	3.17	1.69	2.08

5.3.12. Trial (12) categorizing NPS subjects according to oxygen indices

5.3.12.1. Name of excel file

17.04.2015 B

5.3.12.2. Introduction and aims

- Trial aimed to find new methods of categorizing the simulated subjects into two groups (Group A subjects who had high shunt and lower deadspace and Group B with a low shunt and higher deadspace) using different approaches.
- Previous investigations revealed that $PaCO_2$ is a key factor that may aid this classification. As such two methods were hypothesized:
    a) Introduce a minimum of two $crPaO_2$ points in the curve and use these to estimate the direction of the subject's pathology. However, having two points of PaO_2 and $PaCO_2$ requires the clinician to draw two ABGs at different times in order to classify the subjects. This may result in risks and complications of ABG and reduce the cost effectiveness of the system. As such, the use of two points was not deemed clinically acceptable.

    b) The second method involved using an oxygenation indices (PaO_2/FiO_2, $P(A\text{-}a)O_2$, PaO_2/PAO_2, and RI) as a monitoring indicator.

5.3.12.3. Methods

- Each oxygen index (PaO_2/FiO_2, $P(A\text{-}a)O_2$, PaO_2/PAO_2, and RI) was calculated for each group and plotted against variations in FiO_2.
- The calculated mean PF ratio for Group A and Group B were plotted. Figure 26 shows that, for both groups, the start and end points for the PF ratio on FiO_2 of 30% and 90% was the same. This indicated that the PF ratio did not represent an accurate means of identifying the types of each subject category.
- The average RI (Figure 27) and PaO_2/PAO_2 (Figure 28) described the behaviour of these indices in response to FiO_2 variation for both groups. The results revealed that there was a very close gap between the groups when the FiO_2 was more than 80%. This also makes it difficult to distinguish subject category.
- On the other hand, Figure 29 shows that the average $P(A\text{-}a)O_2$ interaction with FiO_2 variation in the two groups were not similar. As such, this measurement may act as a useful indicator that can be used to categorize the subjects.

5.3.12.4. Results

- Based on the average $P(A\text{-}a)O_2$, the subjects were categorized according to the following conditions (see the flowchart in Figure 30).

a) First, if the FiO_2 was between 30-40% and the $P(A\text{-}a)O_2$ was equal or less than 13 kPa, the subject belonged to Group B, otherwise the subject was from Group A.
b) Second, if the FiO_2 was between 41-80% and the $P(A\text{-}a)O_2$ was equal or less than 17 kPa, the subject belonged to Group B, otherwise the subject was from Group A.
c) Third, if the FiO_2 was more than 81% and the P $(A\text{-}a)O_2$ was equal or less than 9 kPa, the subject belonged to Group B; otherwise the subject was from Group A.

5.3.12.5. Conclusion

- Separating Group A and B was explored and different oxygenation indices were employed to represent the shunt and deadspace group. Because some of the oxygenation indices methods incorporated outliers, some groups behaved differently; as such, there may be a requirement to make mathematical adjustments and incorporate some form of representation of deadspace. Fortunately, it was possible to classify the patient group using $P(A\text{-}a)O_2$.
- An unexpected problem was discovered when the average $P(A\text{-}a)O_2$ measurement was employed on the box-and-whisker plot for both groups. Figure 31 shows that, after 80% of FiO_2, the groups overlapped.
- However, if we incorporate $P(A\text{-}a)O_2$ mathematically into the equation rather than employing it in the decision process, it may be possible to use one general equation. If we have a subject that is on the border of

Group A or B with one number, the results can vary. As such, the $CrPaO_2$ result may change dramatically, and this renders the approach invalid.

- The solution would be more elegant if we can generate one single equation that can be employed to identify a group that they did not progress well and then correct for the factor that appeared to be the issue.
-

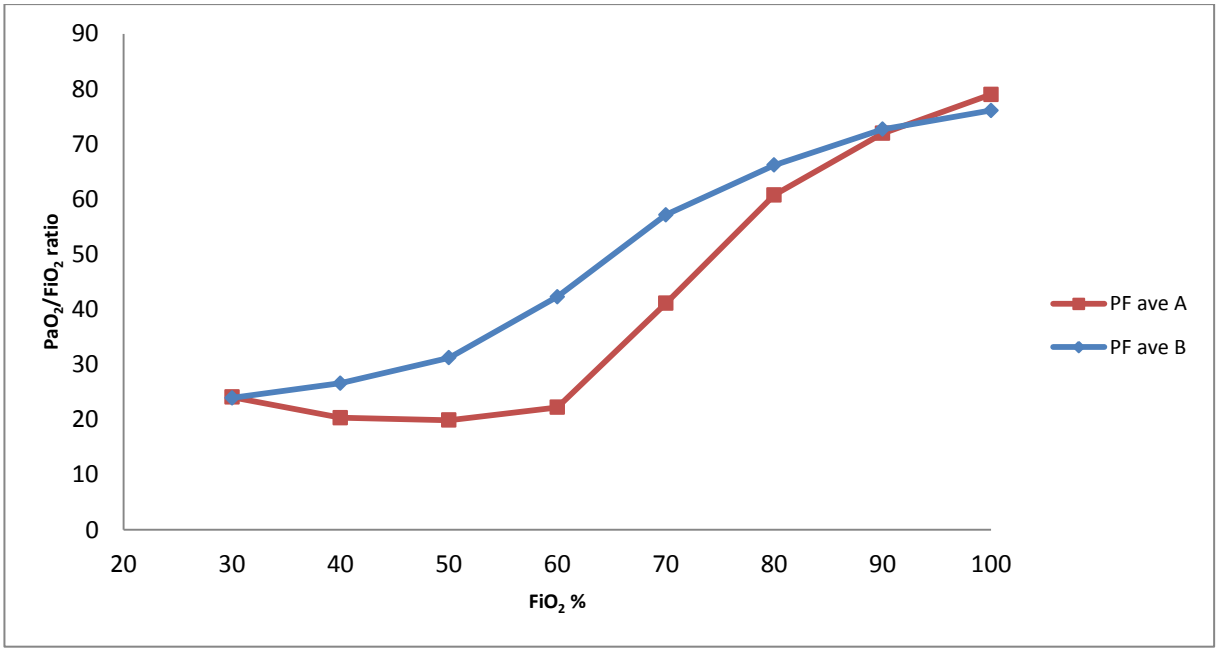


Figure 26 comparing the average PaO_2/FiO_2 ratio (kPa) for group A and B with FiO_2% variation.

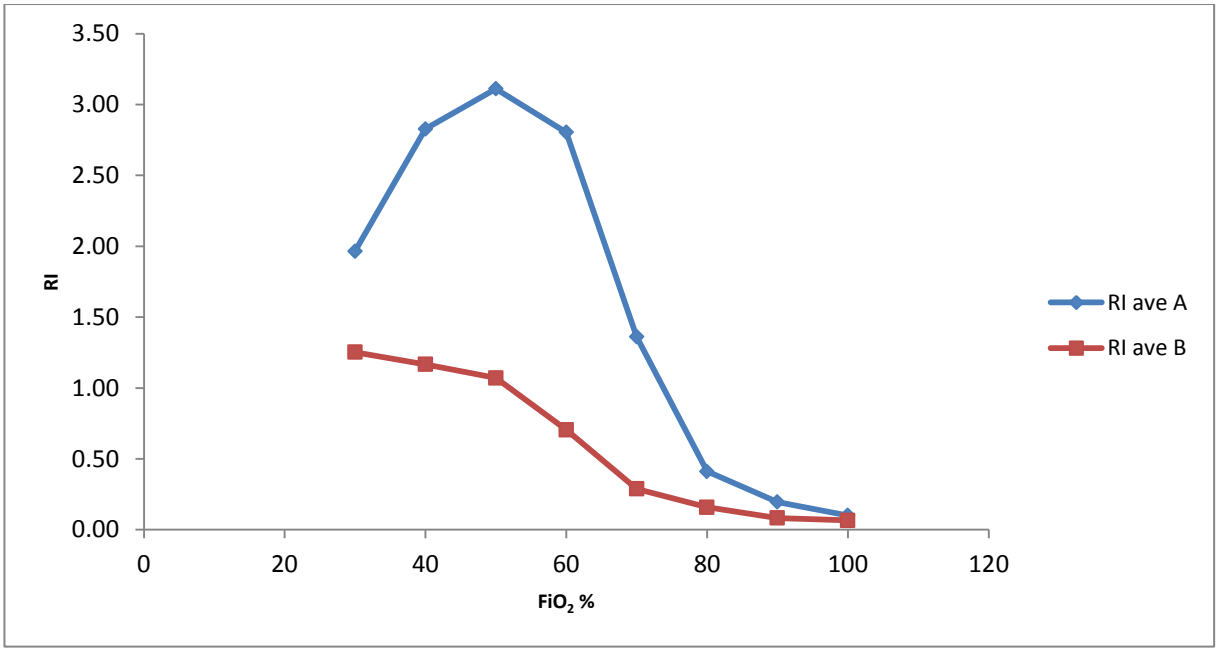


Figure 27 comparing the average RI for group A and B with FiO_2 % variation

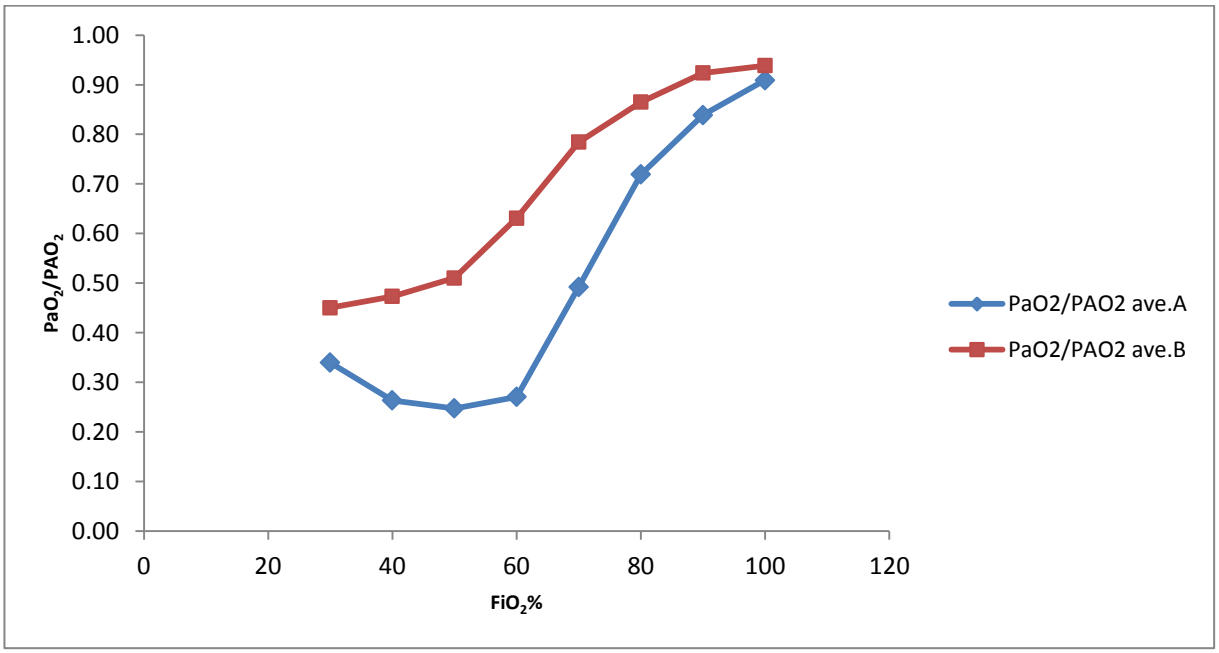


Figure 28 comparing the average PaO_2/PAO_2 for group A and B

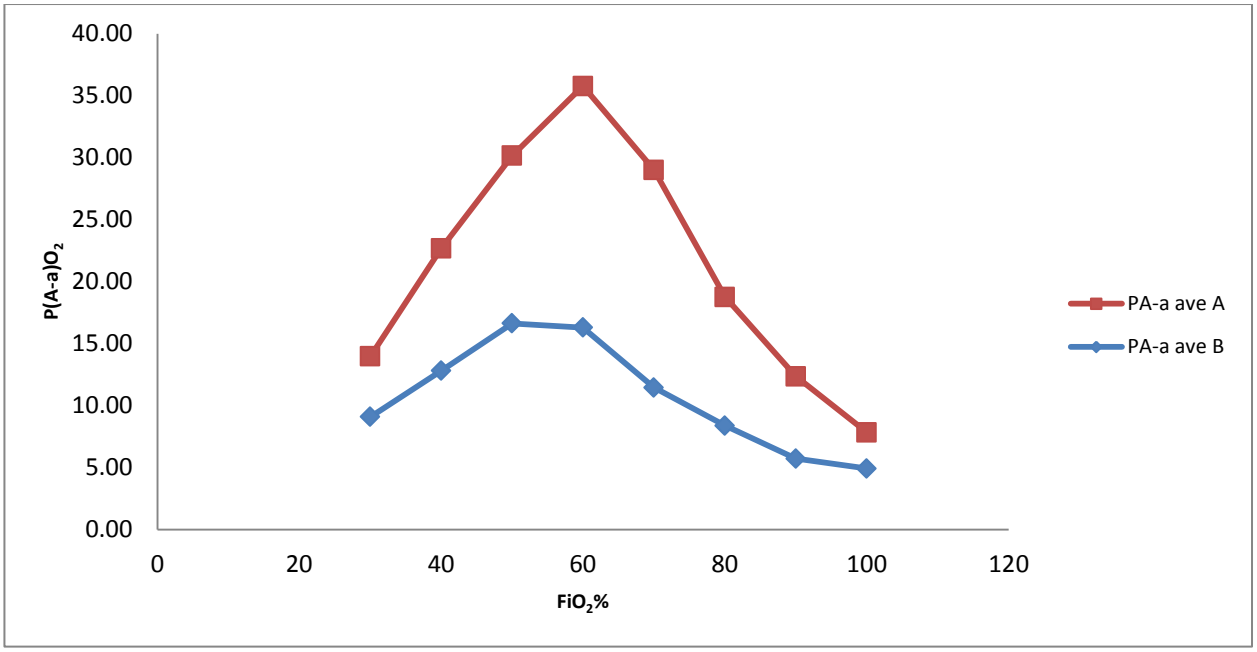


Figure 29 comparing the average $P(A\text{-}a)O_2$ for group A and B

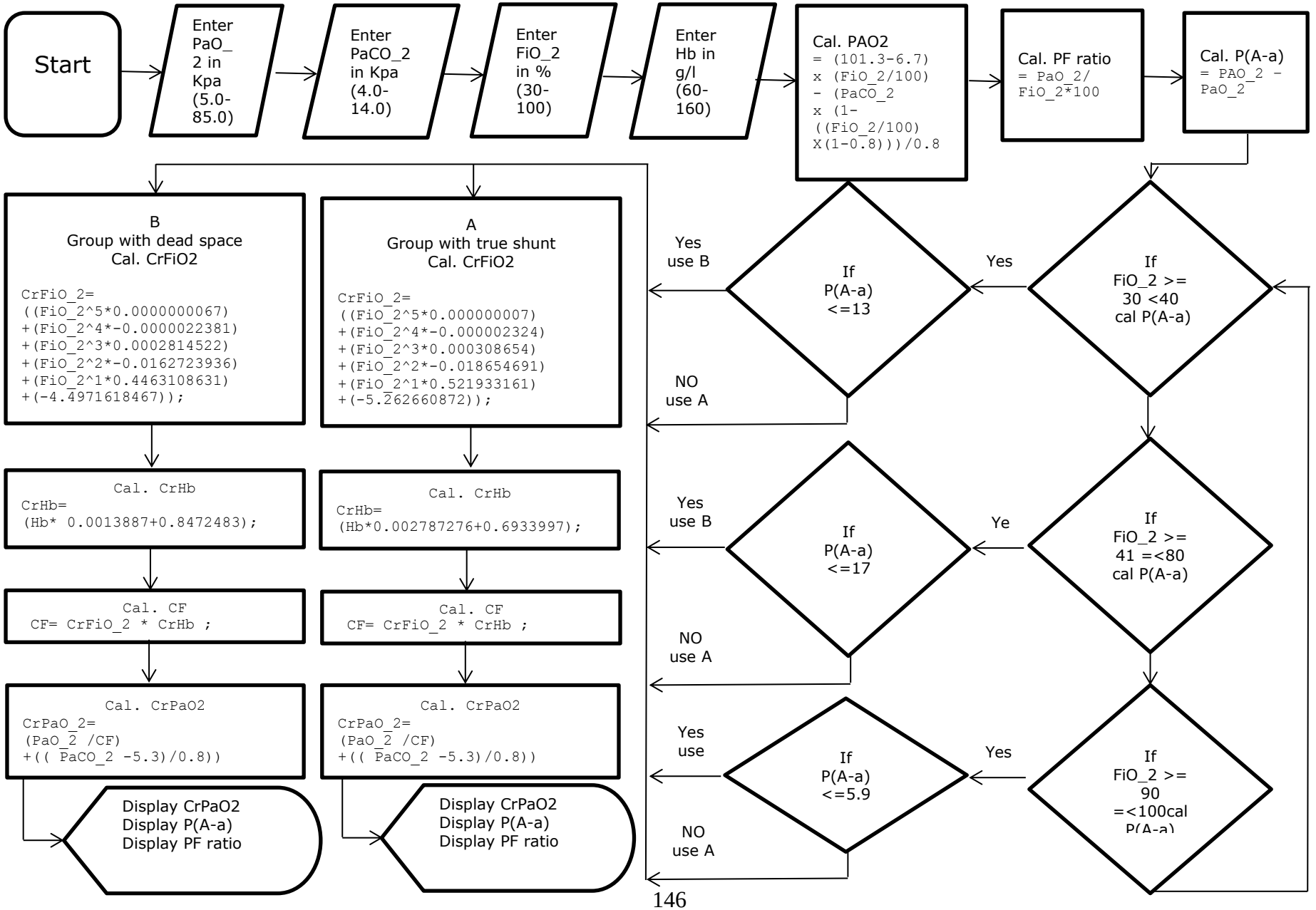


Figure 30 flowchart

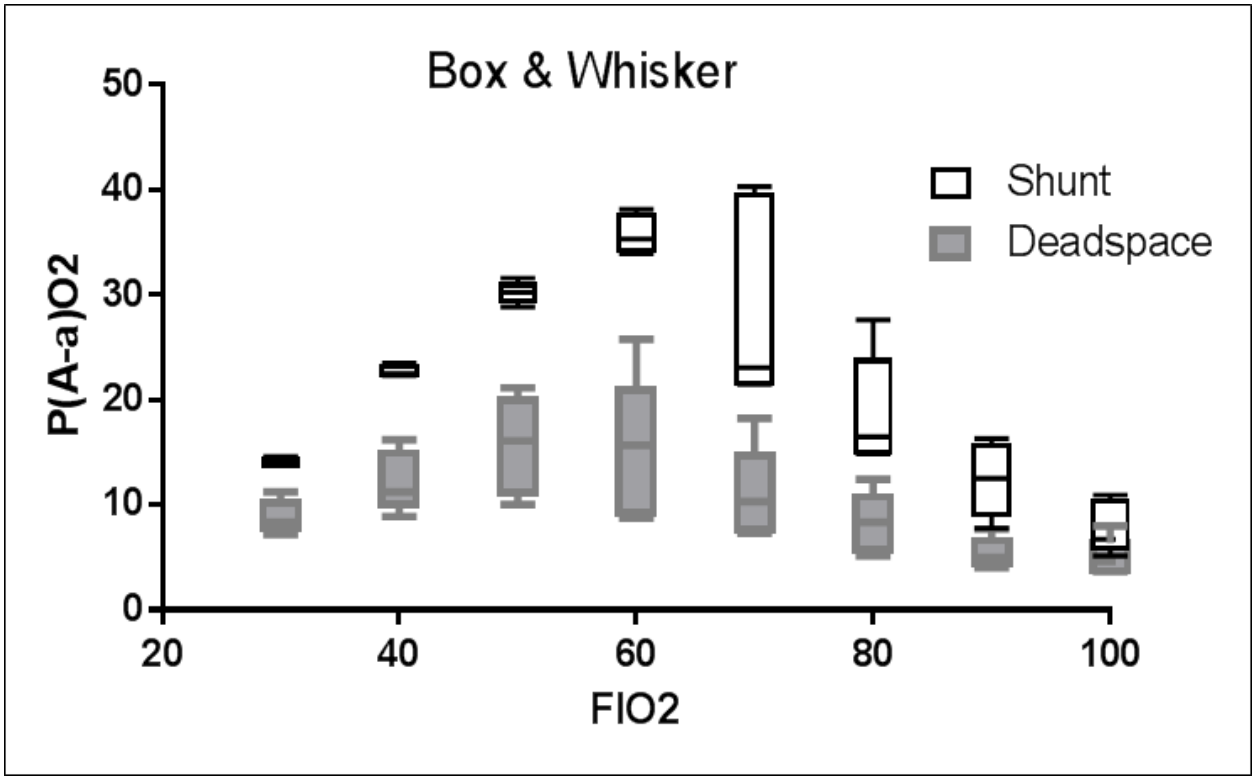


Figure 31 Box & whisker plot for P(A-a)O_2 with different groups during FiO_2%.

5.3.13. Trial (13) Generating a new $crPaO_2$ with $PAaO_2$ correction

5.3.13.1. Name of excel file

28.05.2015

5.3.13.2. Introduction and aims

- Our aim was to generate one single $crPaO_2$ equation to quantify oxygen impairment. By observation, when we developed $crPaO_2$ previously from Trial 10, the $crPaO_2$ was generated based on group B results (which were the subjects who had low shunt and higher deadspace). However, with the $P(A\text{-}a)O_2$, we were able to detect the different groups by looking at the deadspace, which could be roughly considered as a shunt assessment.

- $P(A\text{-}a)O_2$ was useful with the (Shunt) group because it increases with FiO_2 and it mirrors that of the $CrPaO_2$ for the same group (see Figure 32). Therefore, we predicted that we might be able to use the $PA\text{-}aO_2$ as a mathematical correction factor. Yet, our problem for these two groups was that the correction factor (CF) was less reliable in one group than it was in the other; however, if we were able to make the CF work for both groups it would be reasonable.
- All that we were willing to do was to make Group A and B the same. If we were to use the "if condition", the potential problem would be high and, as soon as we introduced a different way to treat a patient's data, we would not have a single value. In other words, with our complicated

"if condition" we may achieve a result of $CrPaO_2$ of 40 and, with a tiny change in our PaO_2, the $CrPaO_2$ may suddenly rise to 80, rendering the equation invalid. Therefore, if we employed a different equation that triggered small changes, it would be difficult to believe and trust these values. Thus, the previous logical flowchart could work; however, we needed to apply a lot of mathematical effort to show that the boundaries where we flicked between these two groups did not suddenly have major different values. Therefore, the aim of this trial was to correct the new $crPaO_2$ mathematically to fit both groups.

5.3.13.3. Methods

- By using the $P(A\text{-}a)O_2$ chart for Group A, "more shunt", we could lower the curves because it would lower the curve close to Group B.
- If we drop the Group A curve close to Group B, a minimal effect on Group B will be occur, because the $P(A\text{-}a)O_2$ range for Group B was between 15 and 10 and. For example, if we used $P(A\text{-}a)O_2$ of 10, the $CrPaO_2$ would not change = CF /1.
- Next, we attempted the following equation: $\sqrt{P(A\text{-}a)O_2}/10$ and drew a graph to allow us to try different subjects.
- Therefore the new $crPaO_2$ is
- $\frac{PaO_2}{CF} \times \sqrt{\frac{P(A-a)O_2}{10}}$
  - $CF = crFIO_2 \; X \; crHB$

- $\boldsymbol{crFIO_2} =$

  $\left(\left(\boldsymbol{FIO_2}^{\mathbf{5}} \times \mathbf{0.0000000067}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{4}} \times \mathbf{-0.0000022381}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{3}} \times \mathbf{0.0002814522}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{2}} \times \mathbf{-0.0162723936}\right) + \left(\boldsymbol{FIO_2}^{\mathbf{1}} \times \mathbf{0.4463108631}\right) + (\mathbf{-4.4971618467})\right)$

- $\boldsymbol{crHb} = (\boldsymbol{Hb} \times \mathbf{0.0013887} + \mathbf{0.8472483})$

- After creating a new crPaO_2 from the ten simulated subjects, the flatness of the curves was visually compared.
- Following that, to test the new approach, additional random simulated subjects were generated as four subjects with high shunt and another four subjects with high deadspace.
- Consequently, the headline figure was formed to compare how many times the new crPaO_2 and the old crPaO_2 performed better than the PF ratio.

5.3.13.4. Results

- When FiO_2 and Hb were varied, in eight modelled subjects, the mean headline figures for the new crPaO_2 (crPaO_2X PA-aO_2 corrected) were 3.3 times better than those calculated for the PF ratio, while the mean headline figures for the old crPaO_2 was 3.1 in the same subjects under the same conditions (see Table 22).
- Figure 33 presents a new crPaO_2 that depicts both groups. The shunted group rose toward the deadspace group within the same ten simulated subjects.
- After comparing the median of the crPaO_2 for the ten simulated subjects before (Figure 35) and after (Figure 34) the correction, it was

observed that, after correction, the curve line was flatter and less varied than $crPaO_2$ before correction.

- Figure 36 presents the new calculated $crPaO_2$ median with range for the new eight test simulated subjects.

5.3.13.5. Conclusion

- The last $crPaO_2$ index was 3.3 times better than the PF ratio; however, the curve exhibited a sharp drop when FiO_2 was more that 60%. Therefore, this required a further investigation to mathematically correct this drop.

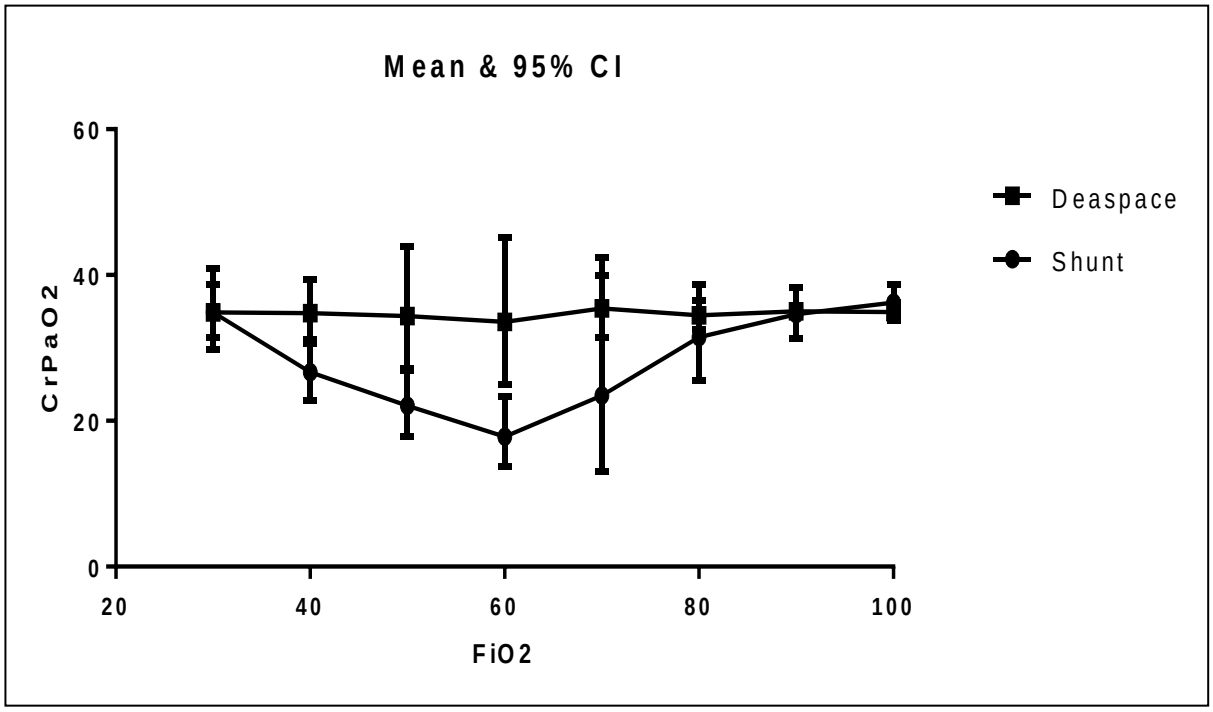


Figure 32 mean and 95% CI for $crPaO_2$ (kPa) both groups with FiO_2 % variation

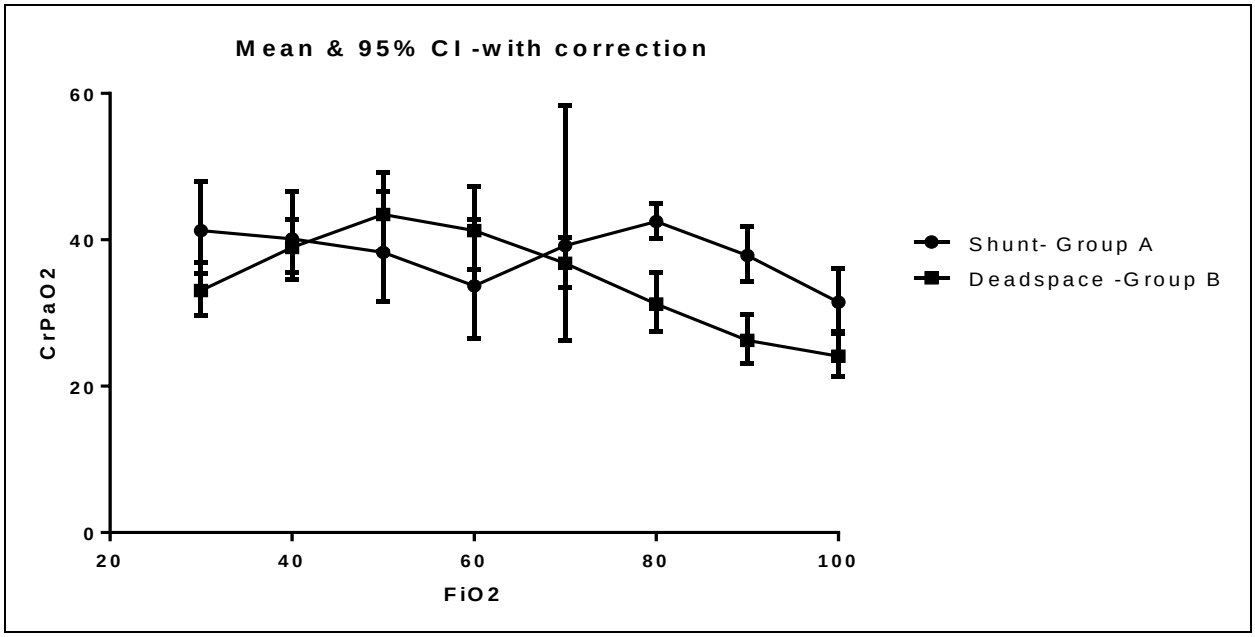


Figure 33 the mean 95% CI for $crPaO_2$ (kPa) after correction on same ten simulated subjects with FiO_2% variation.

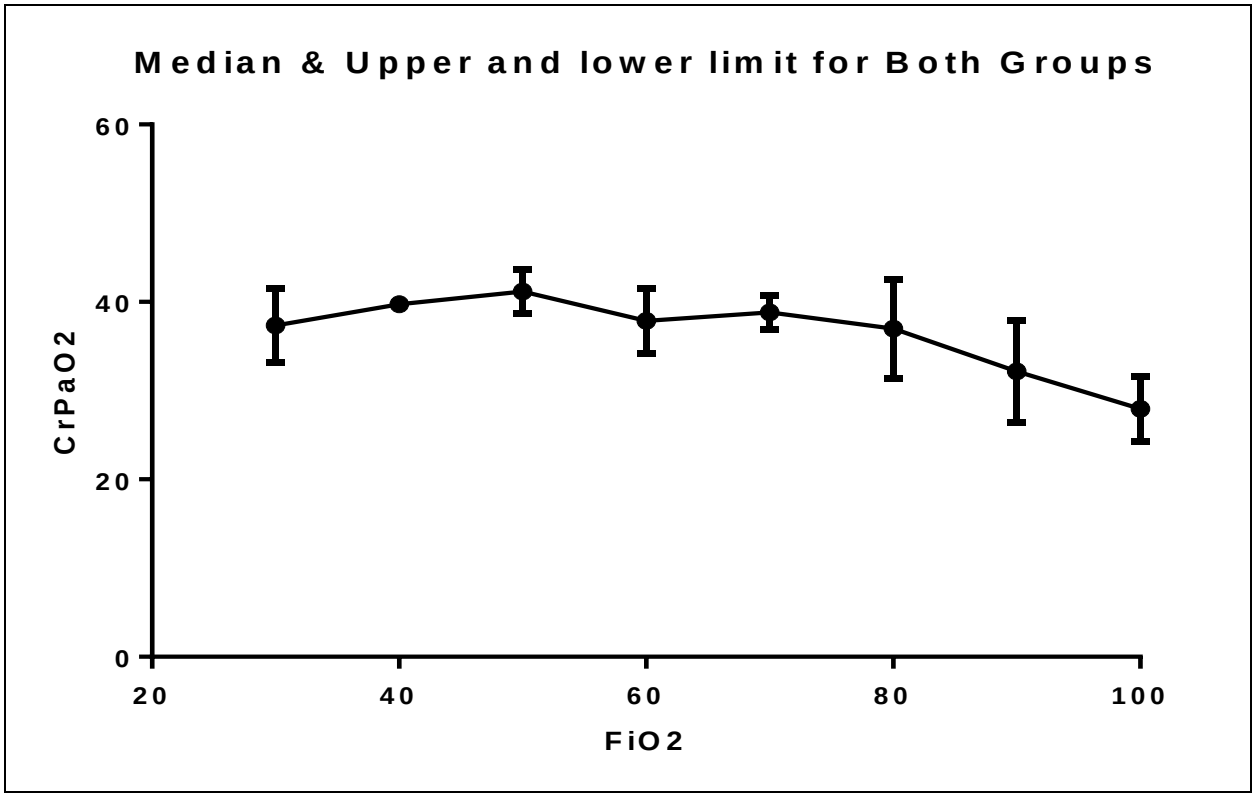


Figure 34 the $crPaO_2$ (kPa) median with range after correction on the same ten simulated subjects with FiO_2% variation.

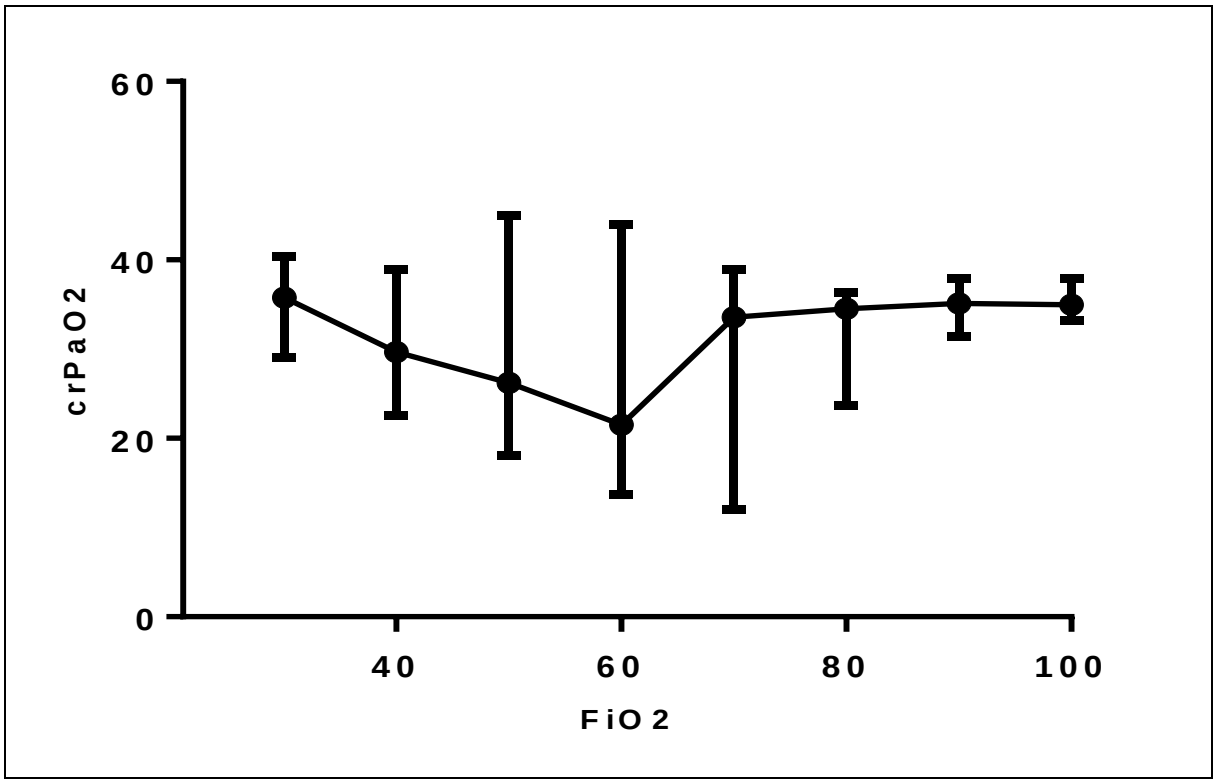


Figure 35 $crPaO_2$ (kPa) median with rang for ten simulated subjects before the new correction with FiO_2% variation.

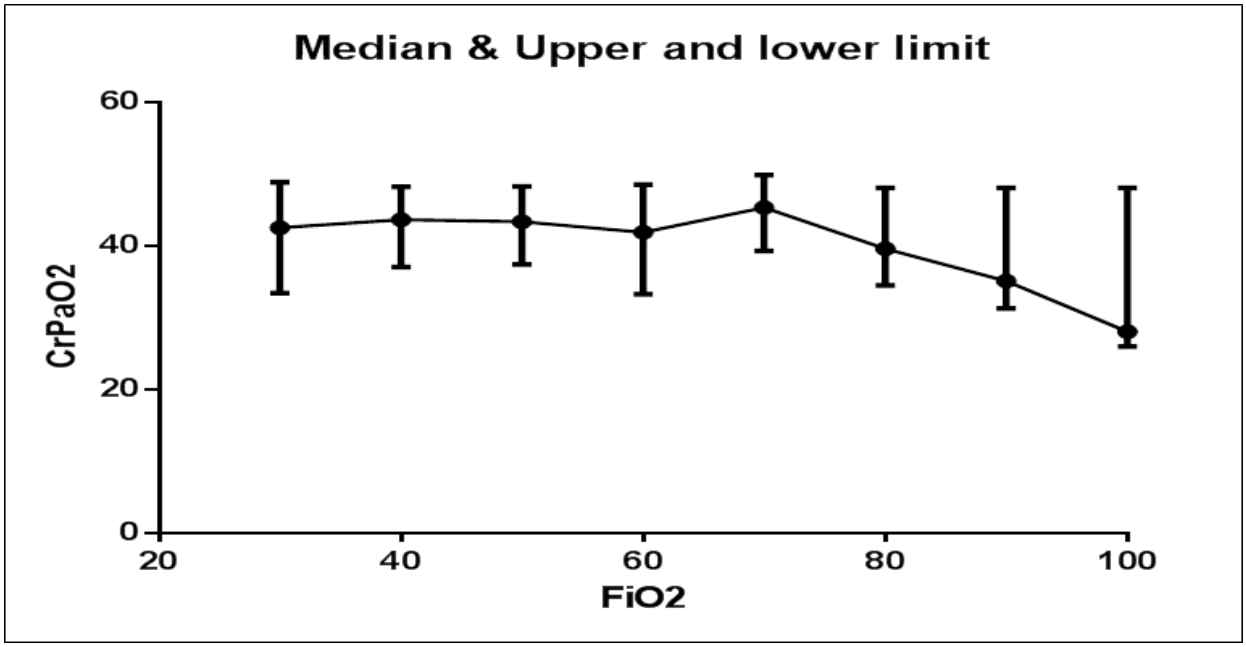


Figure 36 $crPaO_2$ (kPa) median with rang for the new 8 simulated subjects after the new correction with FiO_2% variation.

Table 22 the mean headline figures

Simulated subjects number	$crPaO_2$	$crPaO_2$ with $PAaO_2$ correction
Pt.12	5.41	1.79
Pt.13	2.54	3.74
Pt.14	3.60	3.11
Pt.15	2.56	3.88
Pt.18	2.50	3.67
Pt.19	2.65	3.06
Pt.20	2.77	3.20
Pt.21	2.78	4.18
Mean	3.10	3.33

5.3.14. Trial (14) Generating a new crPaO$_2$ with PA-aO$_2$ and PaCO$_2$ correction

5.3.14.1. Name of excel file

28.05.2015

5.3.14.2. Introduction and aims

- Improve the last crPaO$_2$
- Since the PaCO$_2$ was the major difference between our simulated subject groups, this investigation aimed to correct the PaCO$_2$ that was previously employed in Trial 9 and 13.

5.3.14.3. Methods

- The PaCO$_2$ was corrected using the alveolar gas equation :
- $\frac{PaO2}{CF} \; X \sqrt{\frac{P(A-a)O2}{10}} + ((PaCO2 \; - 5.3)/0.8))$
- After creating a new crPaO$_2$, the flatness of the curves was compared visually with the eight random simulated subjects that were used in Trial 13.
- Consequently, the headline figure was formed to compare how many times the new crPaO$_2$ and the old crPaO$_2$ performed better than the PF ratio in terms of variability.

5.3.14.4. Results

The headline figures for the three crPaO$_2$ are presented in The new crPaO$_2$ index was improved than the previous one in Trial 13; however,

the drop in the curve was not corrected. Therefore, further investigation was required to mathematically correct this drop.

Table 23 .The outputs indicate that when FiO_2 and Hb were varied, in eight modelled subjects, the mean headline figures for the new $crPaO_2$ ($crPaO_2$X PA-aO_2 corrected+$PaCO_2$ correction) was 3.7 times better than that calculated for the PF ratio, while the mean headline figures for the other two $crPaO_2$ were less that that within the same subjects under the same conditions.

5.3.14.5. Conclusion

The new $crPaO_2$ index was improved than the previous one in Trial 13; however, the drop in the curve was not corrected. Therefore, further investigation was required to mathematically correct this drop.

Table 23 the mean headline figures with three different $crPaO_2$

Simulated subjects number	$crPaO_2$	$crPaO_2$ + $PAaO_2$ correction	$crPaO_2$+ $PAaO_2$ correction+$PaCO_2$ correction
Pt.12	5.41	1.79	2.03
Pt.13	2.54	3.74	4.53
Pt.14	3.60	3.11	3.70
Pt.15	2.56	3.88	4.66
Pt.18	2.50	3.67	4.01
Pt.19	2.65	3.06	3.25
Pt.20	2.77	3.20	3.28
Pt.21	2.78	4.18	4.30
Mean	3.10	3.33	3.72

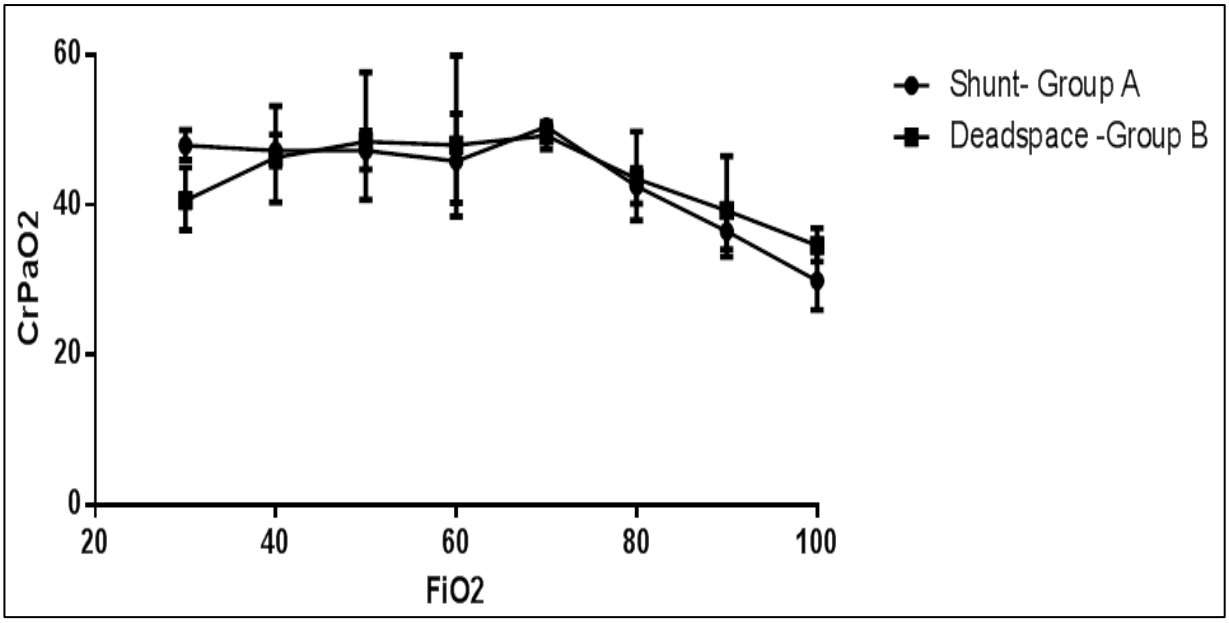


Figure 37 the mean 95% CI for the new crPaO$_2$ (kPa) after PaCO$_2$ correction (kPa) with 8 simulated subjects with FiO$_2$% variation.

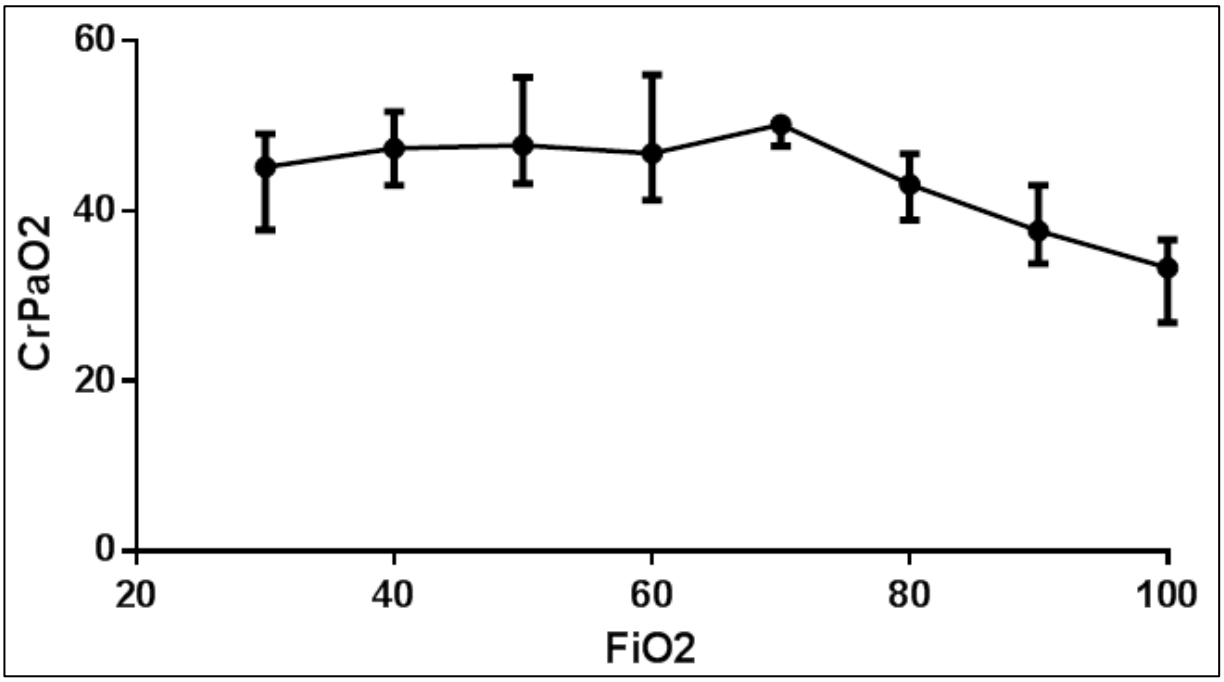


Figure 38 crPaO$_2$(kPa) median with rang for the new eight simulated subjects after the new PaCO$_2$ correction (kPa) with FiO$_2$ variation.

5.3.15. Trial (15) Generating a new $crPaO_2$ with $PAaO_2$, $PaCO_2$ and new correction factor.

5.3.15.1. Name of excel file

03.06.2015 B

5.3.15.2. Introduction and aims

- A good correction factor CF had been achieved in Trial 13 and 14 and this indicated good results with some groups. We added the groups together using the $P(A\text{-}a)O_2$ and $PaCO_2$ correction. Subsequently, these previous corrections disrupted our CF and did not improve our $crPaO_2$; therefore, our plan was to generate another correction factor for $crPaO_2$ to correct this disruption again.

5.3.15.3. Methods

- After multiple trials using Excel, we made a new correction factor (CF2) that exhibited less variation and made the $crPaO_2$ curve flat.
- The same data from the eight test simulated subjects employed in Trial 13 were used as configuration subjects.
- Eight new random subjects were generated to test our new $crPaO_2$.
- Depicts the correction process for the $crPaO_2$ curves that were employed for the FiO_2 variations.
- Subsequently, by using the polynomial trendline equation, the following equation was generated:
- $CF2 = -0.00019 \times (FiO_2^2) + 0.0206 \times (FiO_2) + 0.5$

  $new_crPaO_2 = old_crPaO_2 / CF2$

where old_crPaO_2 is the one with the P(A-a)O_2 correction and the alveolar gas correction. The new crPaO_2 is :

- $\frac{PaO2}{CF} X \sqrt{\frac{P(A-a)O2}{10}} + ((PaCo2 - 5.3)/0.8))/ - 0.00019 x (FiO_2^2) + 0.0206 x (FiO2) + 0.5$

- After creating a new crPaO_2 from the eight simulated subjects, the flatness of the curves was compared visually.
- Consequently, the headline figure was formed to compare how many times the new crPaO_2 and the previous crPaO_2s performed better in terms of variability than the PF ratio.

5.3.15.4. Results

- Table 24 presents the headline figures for the four crPaO_2s. The outputs indicate that when FiO_2 and Hb were varied in the eight modelled subjects, the mean headline figures for the new crPaO_2 was nearly five times better in terms of inconsistency than that calculated for the PF ratio, while the mean headline figures for the other three crPaO_2 were less than those for the same subjects under the same conditions.

5.3.15.5. Conclusion

- Having a third correction for our new equation crPaO_2, we created a new CF2 and tested it on eight new NPS subjects. We reached the conclusion that our new equation was five times better that the PF ratio in terms of variation.

- Since the preliminary results for the new $crPaO_2$ indicated a lower variation in simulated subjects in response to FiO_2 and Hb changes, future studies were required to examine how the $crPaO_2$ behaves in real patient data.

Table 24 the mean headline figures with four different $crPaO_2$

Simulated subjects number	$crPaO_2$	$crPaO_2$ + $PAaO_2$ correction	$crPaO_2$+ $PAaO_2$ correction+$PaCO_2$ correction	$crPaO_2$+ $PAaO_2$ correction+$PaCO_2$ correction+ CF2
$CrPaO_2$_22	2.20	3.12	3.71	3.93
$CrPaO_2$_23	2.28	3.44	4.34	4.09
$CrPaO_2$_24	2.66	4.06	4.77	5.31
$CrPaO_2$_25	2.85	2.77	3.13	4.31
$CrPaO_2$_26	3.28	2.82	2.95	4.85
$CrPaO_2$_27	3.48	2.41	2.44	3.64
$CrPaO_2$_28	2.48	3.56	3.85	5.01
$CrPaO_2$_29	2.92	3.95	4.11	6.90
mean	2.77	3.26	3.66	4.75

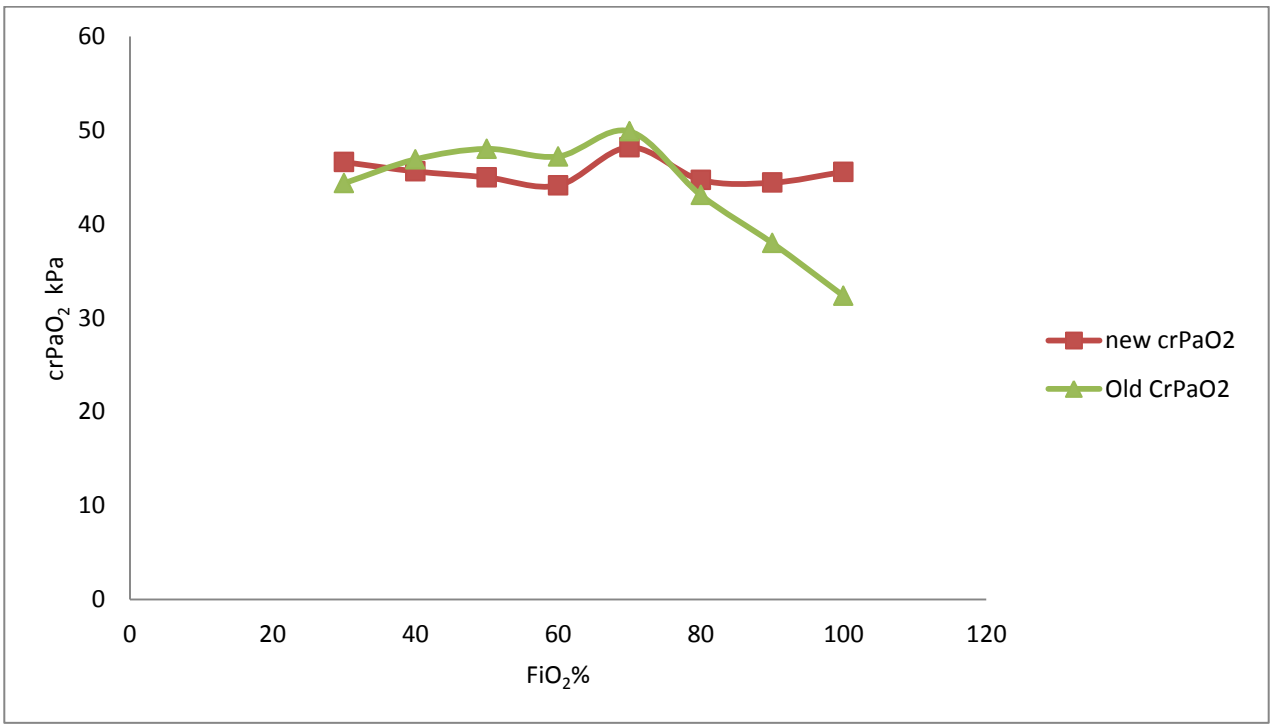


Figure 39 comparing the new and old $crPaO_2$ (kPa) index curves for with FiO_2 % variation

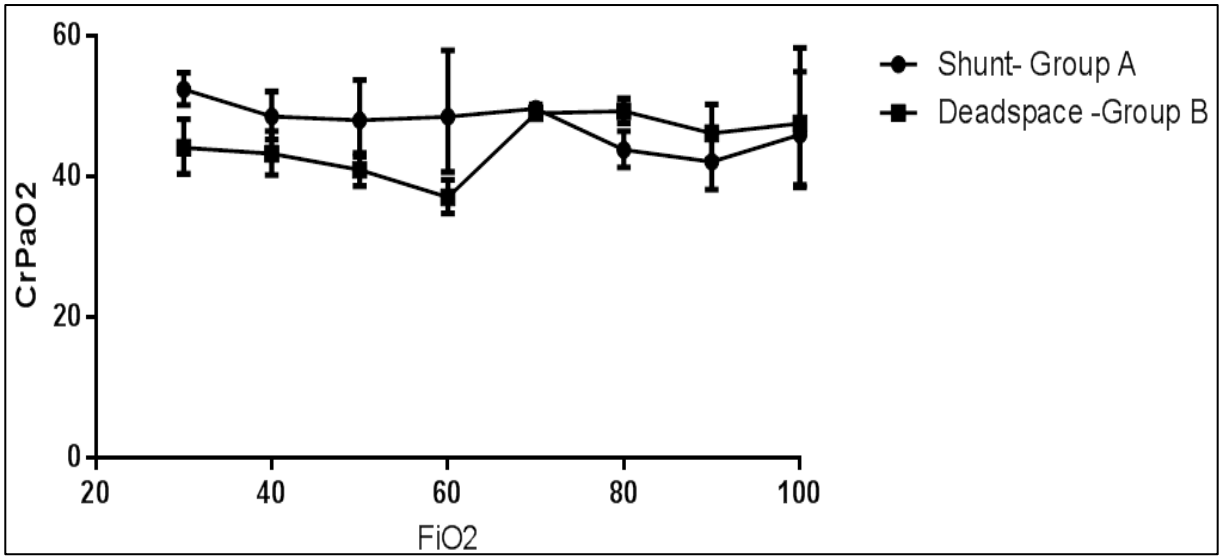


Figure 40 the mean and 95% CI for the new crPaO$_2$ (kPa) with two group subjects with FiO$_2$% variation.

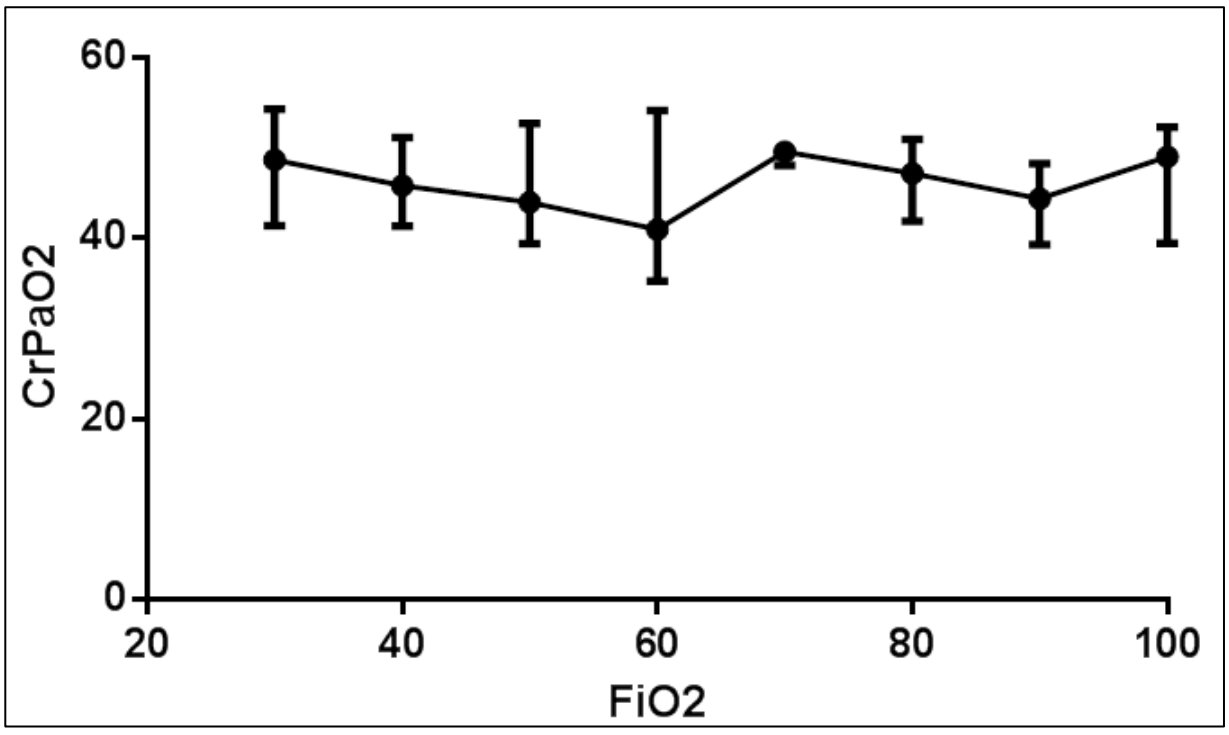


Figure 41 crPaO$_2$ (kPa) median with rang for the new eight simulated subjects after the last new PaCO$_2$ (kPa) correction with FiO$_2$% variation.

5.4. Conclusion

- This report summarises the main findings pertaining to the $crPaO_2$ that resulted from each trial. The current study involved multiple trials. These trials initially sought to correct the PF ratio before considering the PaO_2 and taking external physiological factors into consideration.

- The research concluded that we were able to create one equation that can fit different patients' disease and this topic was explored with other external factors to quantify oxygenation defects through a maze of maths, different diseases, and pathophysiology. There was a small number of ways that could lead to our aim and many dead end routes. Ultimately, the research produced an equation that was five times less varied than the PF ratio.
- Therefore, future studies are required to examine the new $crPaO_2$ index with real patient data.

CHAPTER 6

Validating $crPO_2$ with patients data

6.1. Introduction

There is a growing body of literature that recognises the importance of creating oxygen-tension-based index (24, 25, 27, 42, 104). Clinicians to determine the level of gas impairment can use the index. Currently utilised oxygen-tension-based indices such as the ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2 ratio), arterial/alveolar oxygen tension ratio (PaO_2/PAO_2), alveolar–arterial oxygen tension difference ($PA\text{-}aO_2$), and respiratory index ($RI= (PA\text{-}aO_2)/PaO_2$) have been used to indicate the severity of patients' lungs. However, external physiological factors such as (FiO_2, Hb, and $PaCO_2$) might affect the accuracy and/or the precision of these indices. Variations in these external physiological factors may affect the value of PaO_2 and may be misleading; this may arise the need for more precise index that is less affected by external physiological factors (24, 25, 42, 104).

The newly proposed index ($crPaO_2$) was developed previously in chapter five, and it has been validated on virtual simulated subjects, with a validated computer model ("The Nottingham Physiology simulator" - NPS). The NPS is a computer simulation that employ original multi-compartmental cardiovascular, pulmonary and cerebrovascular physiological models (183). The NPS has been used and validated across a spectrum of pulmonary diseases (25, 157, 163, 177-179). Furthermore, we hypothesized that $crPaO_2$ is less affected by the variation in the external pulmonary factors unlike other oxygen-tension-based indices.

However, there is a need to validate the new index with clinical patient's data. The aim of this this study is to evaluate the new $crPaO_2$ against FiO_2, Hb, and $PacO_2$ variations on a large scale of critically ill patient's data.

6.2. Methods

The institutional review board from the Ethics Committee at the King Abdullah International Medical Research Centre (KAIMRC) approved this study, National Guard hospital-affairs King Abdul-Aziz Medical City, Riyadh Saudi Arabia. 141 hemodynamically stable patients undergoing invasive mechanical ventilation in a tertiary hospital, (King Abdul-Aziz Medical City, in Riyadh, Saudi Arabia), in all adult intensive care units including general, surgical, emergency, liver, and cardiac ICUs. Patients had a variety of pathologies see Table 25 and were not excluded based on diagnosis.

All study patients were receiving mechanical ventilation (Puritan Bennett 840 or Siemens 300/A Servo). As per routine monitor and management, three different levels of FiO_2 were selected based on patient specific needs for one single day. A period of at least 10-50 minutes was allowed after FiO_2 changed and then ABG sample was obtained.

Each ABG sample was drawn from an arterial line after aspiration of 1 ml of blood. ABGs were sampled using a 1-ml AVL CibaCorning™ A-line™ plastic syringe without needle containing 30 units of calcium-balanced lithium heparin. The samples were stored immediately in

crushed ice. The blood samples were then thoroughly mixed before analysis commenced, and the first drops discarded.

Blood samples were analysed immediately at body temperature for pH, $PaCO_2$ (kPa), PaO_2 (kPa), HCO3- (mEq/L), BE (mEq/L), and Hb (g/dl).

All blood samples were obtained in the same way and analysed using the same Omni Roche® system (Roche Healthcare Diagnostics Inc., Germany). The blood gas analyser was fully automated and ran quality control (QC) with prefilled cartridges solutions. It underwent 1-point system calibration every 30 minutes and full system calibration every eight hours. QC samples were automated to run for the three QC levels analysed. pH, PaO_2, $PaCO_2$, Hb, HCO_3, BE values were recorded from ABGs at three different FiO_2 points for each patient on one single day.

Over the following inclusion and exclusion criteria, the new $crPaO_2$ and the following oxygen indices were calculated (PaO_2/FiO_2 ratio, $P(A-a)O_2$, PaO_2/PAO_2, $RI=P(A–a)O_2/PaO_2$). Each patient had three datasets the comprise ABG results at three different levels of FiO_2 that are performed within an average of 32 minutes for each FiO_2 change.

141 patient’s data were collected for analysis. Of those patients, 48 patients were excluded due to missing ABG results, PEEP changes, patients who were extubated from pulmonary ventilation. However, 93 patients met our inclusion criteria.

6.2.1. Inclusion criteria

- Intubated and receiving pulmonary ventilation with any conventional modes of ventilation.
- Hemodynamically and clinically stable (mean arterial pressure < 60 or > 110 mmHg) at offset.
- Heart rate < 50 or > 120 beats/min at offset.
- Patients with an indwelling arterial line in place.
- A minimum of three FiO_2 changes for each patient in the same day with an interval of 10-50 minutes between the FiO_2 change and the ABG result.
- A minim of three ABG results with printed ventilator parameters.

The aim of these criteria was to minimize the disruption of external confounding factors that could affect data collection.

6.2.2. Exclusion criteria

- PEEP changes.
- Less than 18 years old.
- Missing ventilator parameters or ABGs results.
- Patients on high frequency mode of ventilation.
- Patient who switched from conventional mode to High/low flow oxygen therapy devices.

6.2.3. Statistical analysis

Continuous variables were presented as mean and standard deviation (SD), categorical variables as frequencies and percentages.

Coefficient of variation percent [(CV%)= StDev/Mean] were calculated, to compare the scatter of variation for each oxygen index that was expressed in different units.

Initially, to assess the significant of differences between oxygen indices a Friedman ANOVA test was performed, as the data were not normally distributed. Further, we confirmed the statistical significance between the mean CV% for $crPaO_2$ index with mean CV% for other oxygen indices using a non-parametric test (Wilcoxon's signed rank test).

A p-value of less than 0.05 was considered statistically significant. The statistical analyses were used in this study are Microsoft Excel 2010 and SPSS (version: IBM SPSS Statistics 22).

6.3. Results

Patient's characteristics are presented in Table 25. The ventilator settings, ABG results, oxygen indices and time difference three for the readings are presented in Table 26. The majority of patients were admitted in Emergency 39(42%) and General critical care units 32(34%) (See Figure 42). Most of these patients were admitted due to motor vehicle accident and pulmonary related disease (See Figure 43). Over 60% of patients were receiving volume control ventilation (ACVC) mode of mechanical ventilator. While the rest were on the following modes of ventilation; Pressure regulated volume control (PRVC) which also known as volume control plus ventilation (VC+) in different types of mechanical ventilators, Synchronised Intermittent Mandatory Ventilation (SIMV), Pressure Control Ventilation (ACPC), and Pressure support ventilation (PSV) as shown in Figure 44.

In general, Figure 46 presents multiple histogram graphs that depict that CV% averages for different oxygen indices during three readings were not normally distributed, as well as box and whisker plot. (See Figure 45).

Therefore, a non-parametric Friedman test of differences among repeated measures was conducted and rendered a Chi-square value of 183.94 which was significant ($p<.0001$). The Friedman test shows that

there is a significant difference between all groups hence we would like to know if there is a significant difference between the mean (CV%) for $crPaO_2$ and other Indices.

Thus, a Wilcoxon signed-rank tests was conducted between mean CV% for $crPaO_2$ and each oxygen index independently, Z-score and P-value were presented in Table 27. This indicated that there were statistically significant differences between the mean CV% for $crPaO_2$ and other indices.

Consequently, a headline figure was formed to compare how many times the mean CV% $crPaO_2$ was better in terms of less variation than the other oxygen indices. The headline figure was calculated by dividing the average CV% for $crPaO_2$ over the other mean CV% index and the reciprocal was identified see Table 28. This indicated that When FiO_2, $PaCO_2$ and Hb were varied in multiple patients, the mean CV% for $crPaO_2$ was almost two times better than that calculated for the RI and $P(A\text{-}a)O_2$ and one point three times for the PaO_2/FiO_2 and PAO_2/PaO_2 indices in the same subjects under the same conditions. Moreover, there is a detailed results for the oxygen indices CV% for each patients presented in the Appendix.

Table 25 general charcteristics of patients.

Age, mean±(SD) in years	46.60±(19.9)
Gender (Male number (%)/ Female number (%)	70(75.3%)/23(24.7%)
ICU department number (%)	
Emergency	39(42)
General	32(34)
Cardiac	11(12)
Liver	6(7)
Surgical	5(5)
Mode Of ventilation number (%)	
ACVC	58(62)
VC+	20(22)
PRVC	7(8)
SIMV	3(3)
PSV	3(3)
ACPC	2(2)
Diagnosis number (%)	
Pulmonary	**36(38.7)**
ARDS	5(5.4)
Asthma	2(2.2)
Community acquired pneumonia	2(2.2)
COPD	7(7.5)
Plural Effusion	2(2.2)
Pneumothorax	9(9.7)
Pneumonia	7(7.5)
Respiratory failure due to Drug overdose	2(2.2)
Motor vehicle accident	**23**(**24.7**)
Cardiac	**17**(**18.3**)
Congestive heart failure	2(2.2)
Coronary artery bypass graft	10(10.8)
Hypertension	2(2.2)
Post cardiac arrest	3(3.2)
Other	**17**(**18.3**)
Amyotrophic lateral sclerosis	1(1.1)
Brian cancer	4(4.3)
Diabetes mellitus	2(2.2)
End Stage Renal Disease	3(3.2)
Epilepsy	1(1.1)
GI Bleeding	1(1.1)
Liver cirrhosis	1(1.1)
Liver transplant	3(3.2)
Myasthenia gravis	1(1.1)

Table 26 mean and SD for mechanical ventilator settings, ABG results ,Oxygen indices and time different for all patients in three readings.

	Over all	1st ABG reading	2nd ABG reading	3rd ABG reading
Mechanical ventilator settings mean±(SD)				
Tidal volume (ml)	430.44±(61.6)	440.23±(58.84)	428.72±(71.76)	430.57±(61.03)
Respiratory rate (bpm)	20.70±(5.32)	20.91±(6.26)	20.49±(5.41)	20.72±(5.70)
Minute ventilation (L/min)	9.52±(2.43)	9.50±(2.55)	9.55±(2.51)	9.53±(2.42)
P peak (cmH_2O)	19.22±(11.29)	24.97±(5.53)	24.54±(5.57)	19.24±(11.39)
PEEP (cmH_2O)	6.99±(2.78)	7.12±(2.78)	6.97±(2.78)	7.00±(2.77)
Mean airway pressure (cmH_2O)	12.53±(3.95)	12.65±(4.50)	12.42±(4.02)	12.55±(3.99)
Inspiratory time (sec)	0.89±(0.09)	0.88±(0.08)	0.90±(0.14)	.88±(0.10)
I:E Ratio	1:2.17±(1:0.7)	1:2.13±(0.64)	1:2.25±(1.23)	1:2.15±(0.66)
Flow (L/min)	50.81±(9.79)	50.29±(10.92)	51.40±(10.01)	50.92±(9.38)
FiO_2	0.66±(0.17)	0.79±(0.21)	0.65±(0.17)	.53±(0.16)
ABG results mean±(SD)				
pH	7.35±(0.08)	7.35±(0.09)	7.35±(0.09)	7.35±(0.07)
PaO_2 (kPa)	22.44±(10.70)	28.80±(15.78)	21.73±(10.84)	16.80±(7.72)
PAO_2 (kPa)	56.22±(16.39)	68.81±(20.24)	55.22±(16.49)	44.63±(14.97)
$PaCO_2$ (kPa)	5.64±(1.99)	5.71±(2.17)	5.61±(2.07)	5.58±(1.86)
HCO_3 (mmol/L)	22.85±(5.92)	23.23±(5.96)	22.74±(6.02)	22.86±(5.95)
Hb (g/dL)	10.58±(2.02)	10.32±(2.11)	10.61±(2.07)	10.60±(2.08)
Hct (%)	32.15±(6.99)	31.54±(6.61)	32.28±(7.81)	32.18±(11.96)
SaO_2 (%)	98.77±(3.09)	99.12±(8.34)	98.97±(1.69)	98.96±(1.81)
BE (mmol/L)	-2.60±(6.27)	-2.34±(6.35)	-2.70±(6.40)	-2.45±(6.17)
Oxygen Indices mean±(SD)				
PaO_2/FiO_2 ratio (kPa)	34.93±(14.79)	36.61±(16.20)	34.75±(15.45)	33.37±(15.24)
$P(A\text{-}a)O_2$(kPa)	33.78±(16.41)	40.01±(18.33)	33.49±(16.81)	27.82±(15.95)
PaO_2/PAO_2 (kPa)	0.42±(0.18)	0.42±(0.19)	0.41±(0.19)	.41±(0.19)
RI (kPa)	2.02±(1.50)	1.95±(1.57)	2.01±(1.53)	2.08±(1.60)
$crPaO_2$ (kPa)	14.68±(5.18)	13.94±(5.21)	14.46±(5.54)	15.65±(5.62)
Time difference mean(hh:mm:ss)	00:34:44	00:42:58	00:30:44	00:31:29

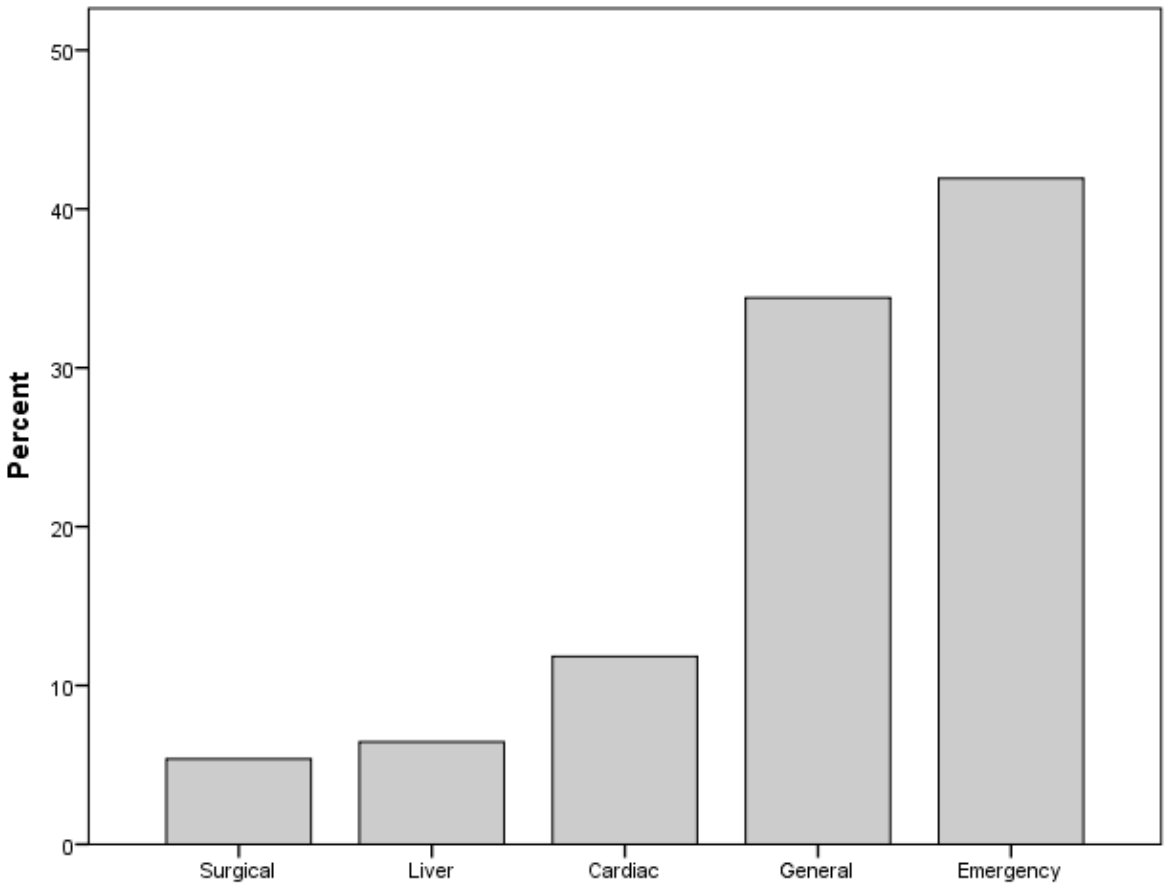


Figure 42 Patients distribution based on location

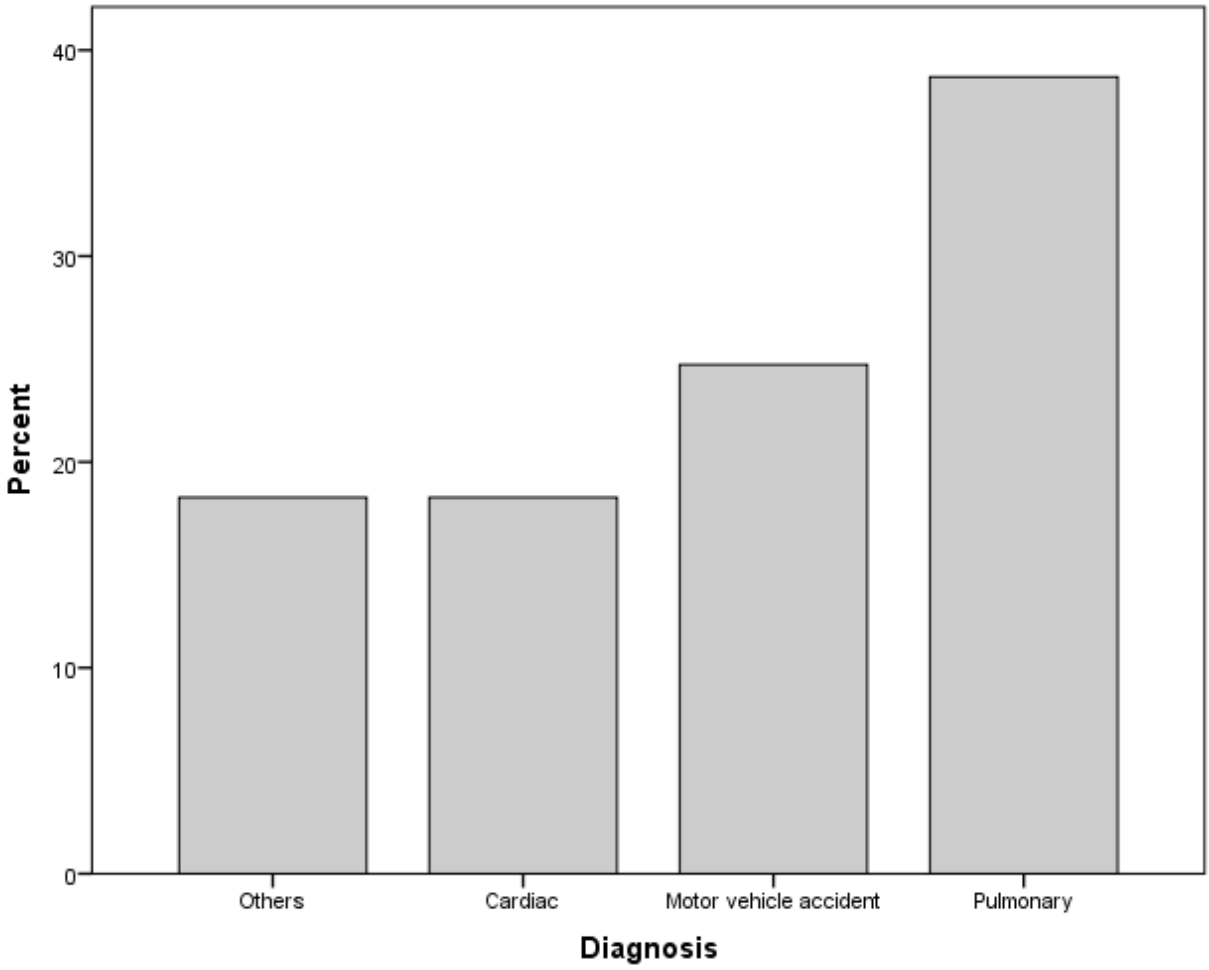


Figure 43 admission diagnosis

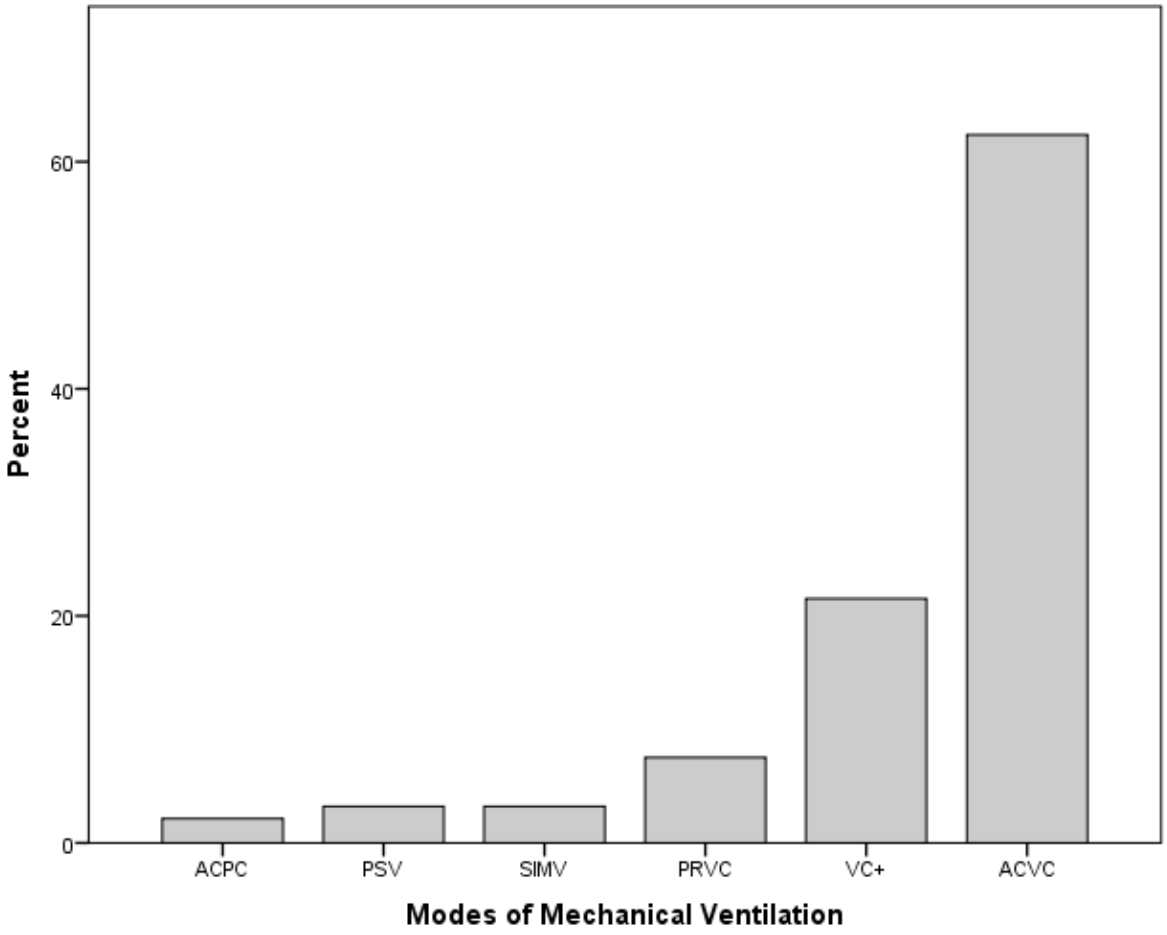


Figure 44 Modes of mechanical ventilation utilised in the study

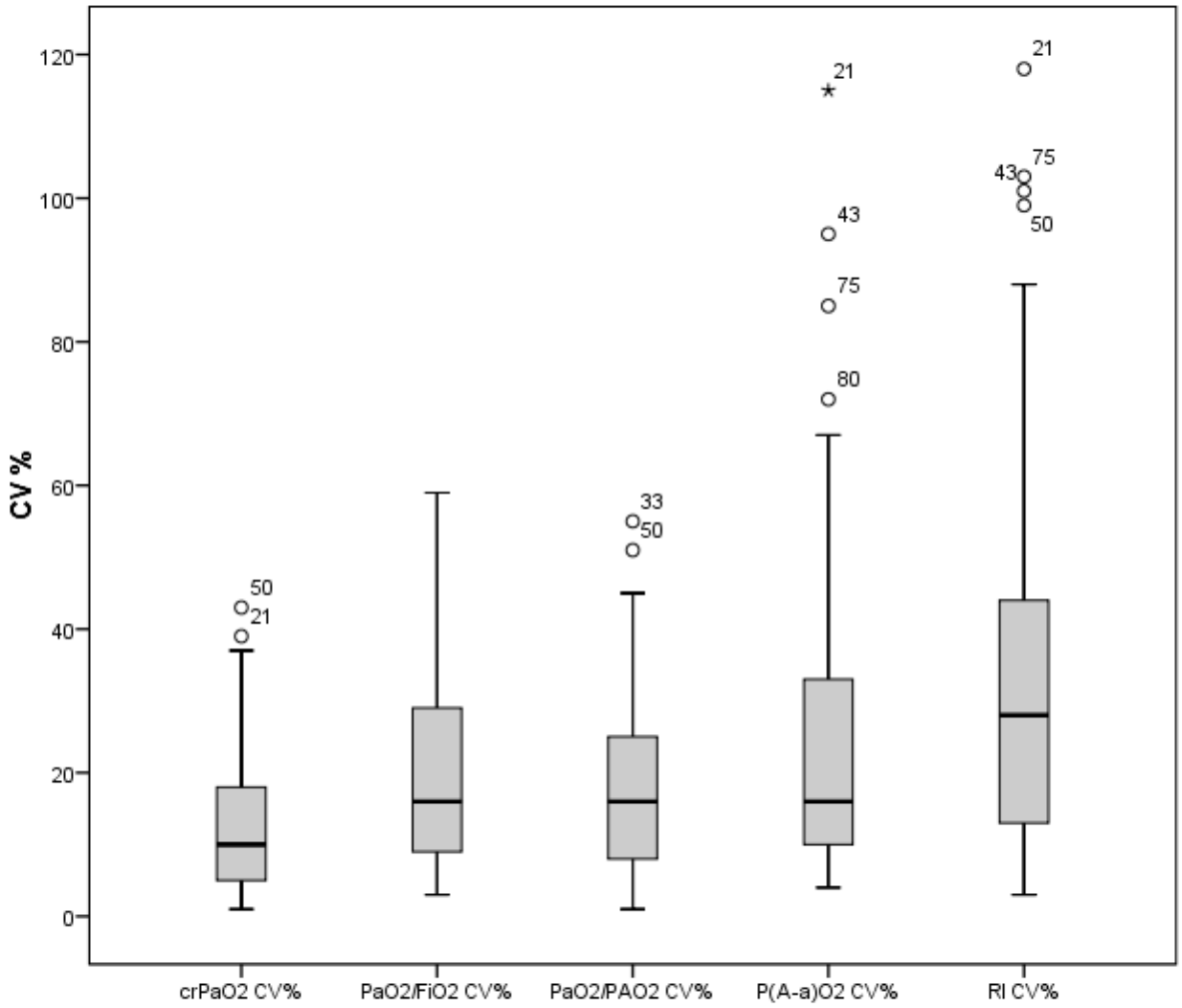


Figure 45 Box and whisker plot graph for Oxygen indices CV%.

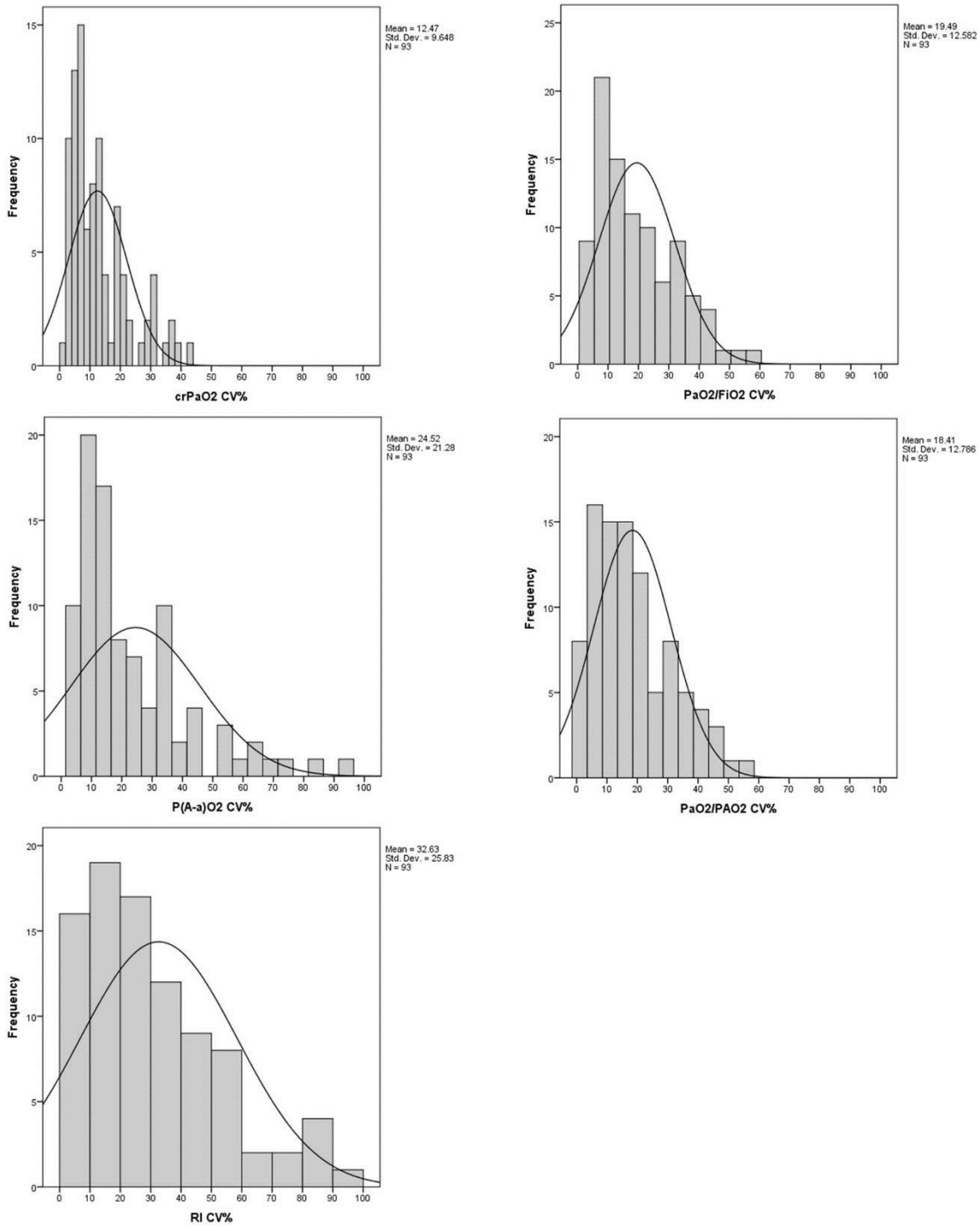


Figure 46 CV% histogram for oxygen indices.

Table 27 comparison of Oxygen indices to $crPaO_2$ index CV%.

Mean Index CV% for three readings	Min	IQR 25%	Median	IQR 75%	Max	Z-score	P-value Wilcoxon Signed Ranks Test with $crPaO_2$
$crPaO_2$	1%	5%	**10%**	18%	43%	--------	----------
PF ratio	3%	9%	**16%**	29%	59%	-7.98	**<0.001**
PaO_2/PAO_2	1%	8%	**16%**	25%	55%	-6.73	**<0.001**
$P(A\text{-}a)O_2$	4%	10%	**16%**	33%	115%	-5.58	**<0.001**
RI	3%	13%	**28%**	44%	118%	-8.21	**<0.001**

Table 28 headline figure reciprocal.

$crPaO_2$	Min	IQR 25%	Median	IQR 75%	Max
vs PaO_2/FiO_2 ratio	0.89	1.18	**1.41**	1.92	9.89
vs PaO_2/PAO_2	0.22	1.08	**1.31**	2.02	13.59
vs $P(A\text{-}a)O_2$	0.11	1.15	**2.03**	3.37	24.86
vs RI	0.60	1.51	**2.30**	3.50	20.22

6.4. Discussion and conclusion

The present study was designed to determine the effect of changes in the external physiological factors on: 1) the current pulmonary oxygen indices; and 2) the new $crPaO_2$ index. This study demonstrates that FiO_2 induced a remarkable variation than other oxygen indices (PaO_2/FiO_2 ratio, RI, $P(A\text{-}a)O_2$, and PaO_2/PAO_2). The most obvious finding is that $crPaO_2$ had less variation with changes in the external physiological factors.

The variation of oxygen indices with some external physiological factors were described theoretically with virtual subjects (25, 40, 73, 107, 191, 192). In their study, Gowda and associates used sixteen computer modelled ARDS patients in which they examined the variation of FiO_2 (21%-100%) on the following oxygen indices (PaO_2/FiO_2 ratio, PaO_2/PAO_2, $P(A\text{-}a)O_2$, RI, and Qs/Qt). They reported that oxygen indices varied with changes of FiO_2, especially for those patients with ventilation perfusion abnormalities. However, they reported that PaO_2/FiO_2 ratio was associated with less variation compared to other indices, thereby, it was suggested to be utilised as an indicator to monitor patients who received $FiO_2 \geq 50\%$ under usual clinical conditions (41).

On the contrary, using validated ARSD lung models, Nirmalan and colleagues studied the effect of within-subject variations of $C(a-\bar{v})O_2$ and FiO_2 on both oxygen-tension-based indices (PaO_2/FiO_2 ratio,

PaO_2/PAO_2, $C(a\text{-}v)O_2$, $P(A\text{-}a)O_2$) and oxygen-content-based index (Qs/Qt). They concluded that all oxygen indices showed a substantial variation with FiO_2 and $C(a-\bar{v})O_2$ except for Qs/Qt where the change was <2% (42). In the same vein, Kathirgamanathan and associates (104) evaluated the variation of four oxygen indices (Qs/Qt, RI, PaO_2/FiO_2 ratio, A-a gradient) while changing three factors (FiO_2, PCO_2, Hb) using a validated Nottingham Physiology Simulator (NPS). Their study included nine ARDS simulated patients that were divided into two groups; true-shunt-rich and true-shunt-poor lung configurations. They concluded that all four indices varied with all the three factors (the intensity of change of each factor is beyond the scope of this paper) except the Qs/Qt, which had a small variation by 30% during FiO_2 changes. Likewise, using the same NPS computational model, McCahon and colleagues (25) examined the susceptibility of four oxygen indices (Qs/Qt, RI, PaO_2/FiO_2 ratio, A-a gradient) to the variation induced by four independent factors (Hb, FiO_2, VO_2 and $PaCO_2$) without changing the lung configuration. The study showed that the smallest index variation was Qs/Qt =5.1%. Despite the fact that previous studies (25, 42, 104) showed that amongst all oxygen indices, Qs/Qt was the most reliable index to assess pulmonary oxygenation, it required direct sampling of mixed venous blood. However, this blood test carries risk especially for critically ill patients, thereby a non-invasive method is needed (25). The results from both Kathirgamanathan and McCahon studies suggested further clinical trials to

determine the robustness of these indices with a variety population and different pulmonary diseases.

Several limitations of this study need to be addressed. We hypothesised that patient's lung characteristics would have remained stable during the time interval we used (20-30 min) irrespective to varying FiO_2. This could be justified by the notion that dramatic changes in lung condition are less likely to happen within such short period of time (average of 34 min). $crPaO_2$ is more reliable with stable patients (e.g. simulated patients used in the previous chapter) because of unchanged lungs configurations, nonetheless, this is not the case with real patients whose lung can change arbitrarily. However, the values of $crPaO_2$ that were substantially reduced in real patients compared to simulated subjects could have been caused by changes the hemodynamic status. However, due the unavailability of continuous data on hemodynamic status (other than the initial measurement) for the real patients, decisive comparison cannot be made.

Beside the insufficient data of hemodynamic status, other possible factors such as patients' positioning (e.g. turning and morning care), certain procedures (e.g. endotracheal suctioning), patients comfort (e.g. pain management) which could have significantly attributed to the inconsistent $crPaO_2$.

Another practical limitation lays in the $crPaO_2$ index implications. Due to the complexity of calculating $crPaO_2$ index, it might not be appealing to many clinicians in such demanding environment (ICU) that

requires rapid, yet, accurate indices. However, this could be overcome by integrating $crPaO_2$ in mechanical ventilators or it might be possible in future investigations to create stand-alone computer application software to be more readily applied by clinicians in intensive care settings.

One of the strengths of this study is that we have collected data from different ICUs, which included patients with variety of pathologies. Moreover, another strength aspect is the thoroughness of the $crPaO_2$ index that involves vital external physiological factors, which in turn, provides a more precise measurement of pulmonary gas exchange.

In conclusion, despite the fact that there are potential benefits of oxygen indices, our results indicated that the newly proposed index was vastly more comprehensive and showed less variation compared to other oxygen indices.

CHAPTER 7

Conclusion and implication of the work

7.1. Summary of the main findings

In this thesis, I attempted to further explore the nature of the oxygen-tension-based indices response that are currently utilised in critical care settings, with the view to their use as a tool to assess pulmonary oxygenation in critically ill patients. Furthermore, this thesis developed a new index by which pulmonary oxygenation can be assessed. This topic was explored using external pulmonary factors to quantify oxygenation defect through a maze of mathematics, different diseases, and pathophysiology. There were one or two approaches that could lead us to the answer, and many dead end routes. Ultimately, the research produced an equation that was more robust than the PaO_2/FiO_2 ratio in so much that it resulted in less variation, which may help to improve the quality of patient care provided.

The first part of third chapter described two major different types of oxygen indices and their respective uses. The second part described the medical simulator in general and the Nottingham Physiology Simulator (NPS) in particular. Chapter four examined how certain oxygen indices varied according to changes in a number of external physiological factors: FiO_2, Hb, RQ, and VO_2, without changing the pulmonary configuration status. This investigation was performed on virtual ARDS patients using the validated NPS model. The study demonstrated that the external physiological factors induced a remarkable variation to the oxygen indices, and the use of each index depends on the type of the external

physiological factors. However, the research concluded that clinicians should be aware of the need to select the most appropriate index in accordance to a patient's status. However, the use of different indices that correspond to different patient statuses is not clinically applicable. Although our new MPP index showed a small change in Qs/Qt index with FiO_2 variations, there is a distinct need to develop a new independent oxygen index and to consider mathematically isolating the external independent factors (Hb, FiO_2, VO_2 and $PaCO_2$) to represent a real lung condition.

Through a series of studies, Chapter five explored the effect of a variation in certain external pulmonary factors (PaO_2, FiO_2, $PaCO_2$, Hb, respiratory rate, oxygen consumption, cardiac output, and respiratory quotient) with PaO_2 using multiple simulated subjects. Eventually, it was possible to create one equation that fitted different patients' diseases and was five times less variable than the PaO_2/FiO_2 ratio. Therefore, at this point, it was determined that future studies were required to examine the new $crPaO_2$ index using real patient data.

It was necessary to validate the newly proposed index independently with patient data (see Chapter Six). Despite the fact that there are potential benefits of oxygen indices, our results indicated that the newly proposed index was vastly more comprehensive and resulted in less variation than the other oxygen indices.

7.2. Other relevant research groups

The use of NPS has become increasingly common as a result of the research that has been conducted in a variety of fields. The popularity of the NPS can be attributed to the fact that, in addition to being simple to use, it can consistently and accurately predict patient responses. It is hard to claim that computational modelling trials represent viable alternatives to clinical trials. Even if the simulation programmes are considered to be as highly accurate, it is impossible to simulate every external factor, either physiological or psychological, that the real human subject can experience. However, researchers should produce specific questions for use in such computational modelling. Questions that suit modelling must address issues that are unsuitable for clinical studies. In particular, questions that would be unethical and impractical to investigate on real human subjects. Besides, most of the time, ICU patients are critically ill or measurements cannot be performed regularly because doing so may jeopardise a patient's health. In addition, researchers should decide whether modelling could provide valid and reliable answers to using the model.

Different groups within the University of Nottingham (UoN) are working with the NPS in different aspects that are relevant to this investigation. For instance, one group is exploring and developing different methods of calculating dead space with virtual ARDS subjects, and other groups are finding an optimal positive end-expiratory pressure

with the same ARDS subjects that were discussed in this thesis. In addition, another group from The University of Warwick, which consists of programmers, an engineer and a mathematician, are collaborating to develop a computational NPS model for an advanced level that will include different body organs in additional to the cardiopulmonary system. It is envisaged that this research will generate good opportunities for further clinical investigation and implication.

The use of NPS with the oxygen indices has been previously addressed by different research groups. Kathirgamanathan and colleagues (104) evaluated the variation of four oxygen indices (Qs/Qt, RI, PaO_2/FiO_2 ratio, A-a gradient) while changing three factors (FiO_2, PCO_2, Hb) using the NPS. They concluded that, with the exception of Qs/Qt, all four indices varied with all three factors. Likewise, using the same NPS computational model, McCahon and colleagues, who examined the validity of NPS, assessed the susceptibility of four oxygen indices (Qs/Qt, RI, PaO_2/FiO_2 ratio, A-a gradient) in terms of the variation induced by four independent factors (Hb, FiO_2, VO_2 and $PaCO_2$) without changing the lung configuration (25). The results of their study showed that the smallest index variation was Qs/Qt. One PhD graduate (193) from UoN developed a new index of predicting PaO_2 (MPP) mathematically using the NPS. This student claimed that the MPP index exhibited consistent robustness against the FiO_2 variation. Another PhD student (167) from UoN examined the validity of MPP on a larger scale of simulated subjects and with real

patients' data. Similarly, he concluded that MPP was less affected by variations in FiO_2.

Nevertheless, in order to calculate one MPP, the clinician needs a minimum of two ABG results. In my opinion, in critical care settings, intensivists require quick and accurate answers for them to make a decision. In such settings, waiting for two ABG results to calculate MPP would be time consuming and clinically impractical.

7.3. Clinical implication and suggestions for further research

The feasibility of using and calculating $crPaO_2$ manually in the ICU is an area that needs to be explored. Hypothetically, if the $crPaO_2$ was found to be practicable, it could improve the healthcare provided; reduce the cost of unnecessary blood work, and save time and effort. However, due to the time it takes to calculate $crPaO_2$ manually, using medical technology and computer applications are desirable. Medical technology is advancing and it is entirely viable that we may reach a new phase in which clinicians may employ a new technology to assess patients' conditions, predict the progression of a disease, and avoid a poor prognosis. Such diagnosis could be performed at an early stage of the disease and without the requirement for the use of costly invasive techniques. Furthermore, the

new advanced technology could be utilised in hospitals that are suffering from medical staff shortages, or increasing treatment costs.

Our new proposed index, $crPaO_2$, may eventually be integrated directly into mechanical ventilators, or ABG machines. Furthermore, there is a possibility that it could be integrated with other monitoring equipment, such as ICU monitors, smartphones, and tablets, allowing clinicians to readily track a patient's progress, even on a remote basis. Such integration needs significant computer processing power and an ability to follow the patient's progress and predict their response. However, it would provide useful data that could inform the clinician and suggest the next appropriate step to be completed in accordance with the previous series events. It may even have the functionality to warn clinicians that a risk may be emerging that can potentially be avoided. Such computer systems could automatically save patients' data and allow researchers and clinicians to perform more effective clinical investigations in the future.

Further studies could experiment with the new proposed index, $crPaO_2$, as a means of potentially improving it in the future. In our investigation, we examined the variation of certain external pulmonary factors, which were PaO_2, FiO_2, $PaCO_2$, Hb, respiratory rate, oxygen consumption, cardiac output, and respiratory quotient. However, there are additional factors that need to be investigated; for example, different physiological vital signs that are commonly used in the ICU; for instance, heart rate,

blood pressure, oxygen saturation, central venous pressure, body temperature, urine output. In addition, another area that deserves investigation includes mechanical ventilator parameters; for example, minute ventilation, peak inspiratory pressure, mean airway pressure, positive end expiratory pressure, inspiratory time, and inspiratory-to-expiratory ratio.

8. References

1. Ferkol T, Schraufnagel D. The Global Burden of Respiratory Disease. Annals of the American Thoracic Society. 2014;11(3):404-6.

2. British Thoracic Society. the burden of lung disease a statistics report from the british thoracic society Embankment, London Munro & Forster Communications; 2006 [Available from: https://www.brit-thoracic.org.uk/document-library/delivery-of-respiratory-care/burden-of-lung-disease/burden-of-lung-disease-2006/.

3. Wunsch H, Angus DC, Harrison DA, Linde-Zwirble WT, Rowan KM. Comparison of medical admissions to intensive care units in the United States and United Kingdom. American journal of respiratory and critical care medicine. 2011;183(12):1666-73.

4. Wildman MJ, Harrison DA, Brady AR, Rowan K. Case mix and outcomes for admissions to UK adult, general critical care units with chronic obstructive pulmonary disease: a secondary analysis of the ICNARC Case Mix Programme Database. Critical Care. 2005;9(Suppl 3):S38.

5. Patel C, Laboy V, Venus B, Mathru M, Wier D. Acute complications of pulmonary artery catheter insertion in critically ill patients. Critical care medicine. 1986;14(3):195-7.

6. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Intensive care medicine. 2004;30(1):51-61.

7. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. CHEST Journal. 2007;131(2):554-62.

8. Cohen A. Respiratory Management in Critical Care. British Journal of Anaesthesia. 2004;93(1):158-9.

9. Leach R, Treacher D. The pulmonary physician in critical care: Oxygen delivery and consumption in the critically ill. Thorax. 2002;57(2):170-7.

10. Davies A, Moores C. The respiratory system. Edinburgh: Churchill Livingstone; 2010.

11. Taylor AE. Clinical respiratory physiology. Philadelphia: Saunders; 1989.

12. Hess D. Respiratory care : principles and practice. Sudbury, Mass.: Jones & Bartlett Learning; 2012.

13. Albert RK, Spiro SG, Jett JR. Clinical respiratory medicine. 2008.

14. Heyland DK, Cook DJ, King DB, Kernerman P, Brun-Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Critical care medicine. 1996;24(3):517-24.

15. Tosoni A, La Rotta G, Breatnach C, Anand V, Foreman C, Davidson L, et al. Oxygen Delivery and Consumption Are Independent: Evidence from Venoarterial Extracorporeal Membrane Oxygenation in Resuscitated Children. American Journal of Respiratory and Critical Care Medicine. 2015;192(6):765-7.

16. Russell JA, Phang PT. The oxygen delivery/consumption controversy. Approaches to management of the critically ill. American Journal of Respiratory and Critical Care Medicine. 1994;149(2):533-7.

17. Granton JT, Walley KR, Phang PT, Russell JA, Lichtenstein S. Assessment of Three Methods to Reduce the Influence of Mathematical Coupling on Oxygen Consumption and Delivery Relationships. Chest. 1998;113(5):1347-55.

18. Epstein CD, Peerless JR, Martin JE, Malangoni MA. Comparison of methods of measurements of oxygen consumption in mechanically ventilated patients with multiple trauma: the Fick method versus indirect calorimetry. Critical care medicine. 2000;28(5):1363-9.

19. McClarity E, Lord K. Oxygen consumption in the intensive care unit: indirect calorimetry is the way to go, but where? Critical care medicine. 1998;26(7):1153-4.

20. Gutierrez G, Vincent JL. Tissue Oxygen Utilization. 1991.

21. Leach RM, Treacher DF. The relationship between oxygen delivery and consumption. Disease-a-month: DM. 1994;40(7):301.

22. Guyton AC, Hall JE, Reed Elsevier India Private L. Textbook of medical physiology. India: Elsevier Saunders : Reed Elsevier India Private Ltd.; 2007.

23. West JB. Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. Respiration physiology. 1969;7(1):88-110.

24. Armstrong JA, Guleria A, Girling K. Evaluation of gas exchange deficit in the critically ill. Continuing Education in Anaesthesia, Critical Care & Pain. 2007;7(4):131-4.

25. McCahon RA, Columb MO, Mahajan RP, Hardman JG. Validation and application of a high-fidelity, computational model of acute respiratory distress syndrome to the examination of the indices of oxygenation at constant lung-state. Br J Anaesth. 2008;101(3):358-65.

26. Rasanen J, Downs JB, Malec DJ, Oates K. Oxygen tensions and oxyhemoglobin saturations in the assessment of pulmonary gas exchange. Crit Care Med. 1987;15(11):1058-61.

27. Hahn CE. KISS and indices of pulmonary oxygen transfer. Br J Anaesth. 2001;86(4):465-7.

28. Gould MK, Ruoss SJ, Rizk NW, Doyle RL, Raffin TA. Indices of hypoxemia in patients with acute respiratory distress syndrome: reliability, validity, and clinical usefulness. Crit Care Med. 1997;25(1):6-8.

29. Wagner P. Assessment of gas exchange in lung disease: balancing accuracy against feasibility. Critical Care. 2007;11(6):182.

30. Horovitz JH, Carrico CJ, Shires GT. Pulmonary response to major injury. Archives of Surgery. 1974;108(3):349.

31. Modell JH, Graves SA, Ketover A. Clinical course of 91 consecutive near-drowning victims. CHEST Journal. 1976;70(2):231-8.

32. Goldfarb MA, Ciurej TF, McAslan T, Sacco WJ, Weinstein MA, Cowley R. Tracking respiratory therapy in the trauma patient. The American Journal of Surgery. 1975;129(3):255-8.

33. Hegyi T, Hiatt IM. Respiratory index: a simple evaluation of severity of idiopathic respiratory distress syndrome. Critical care medicine. 1979;7(11):500-1.

34. Gilbert R, Keighley J. The arterial-alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. The American review of respiratory disease. 1974;109(1):142.

35. Gilbert R, Jh Auchincloss J, Kuppinger M, Thomas MV. Stability of the arterial/alveolar oxygen partial pressure ratio: Effects of low ventilation/perfusion regions. Critical care medicine. 1979;7(6):267-72.

36. Peris LV, Boix JH, Salom JV, Valentin V, Garcia D, Arnau A. Clinical use of the arterial/alveolar oxygen tension ratio. Critical care medicine. 1983;11(11):888-91.

37. Farhi L, Rahn H. A theoretical analysis of the alveolar-arterial O2 difference with special reference to the distribution effect. Journal of applied physiology. 1955;7(6):699-703.

38. Kanber G, King F, Eshchar Y, Sharp J. The alveolar-arterial oxygen gradient in young and elderly men during air and oxygen breathing. The American review of respiratory disease. 1968;97(3):376.

39. Sganga G, Siegel JH, Coleman B, Giovannini I, Boldrini G, Pittiruti M. The physiologic meaning of the respiratory index in various types of critical illness. Circulatory shock. 1985;17(3):179-93.

40. Cane RD, Shapiro BA, Templin R, Walther K. Unreliability of oxygen tension-based indices in reflecting intrapulmonary shunting in critically ill patients. Crit Care Med. 1988;16(12):1243-5.

41. Gowda MS, Klocke RA. Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med. 1997;25(1):41-5.

42. Nirmalan M, Willard T, Columb MO, Nightingale P. Effect of changes in arterial-mixed venous oxygen content difference (C(a-v)O2) on indices of pulmonary oxygen transfer in a model ARDS lung. Br J Anaesth. 2001;86(4):477-85.

43. Zetterstrom H. Assessment of the efficiency of pulmonary oxygenation. The choice of oxygenation index. Acta Anaesthesiol Scand. 1988;32(7):579-84.

44. Wandrup J. Quantifying pulmonary oxygen transfer deficits in critically ill patients. Acta anaesthesiologica scandinavica. 1995;39(s107):37-44.

45. Lumb AB, Nunn JF. Nunn's Applied respiratory physiology. 6th ed. Oxford: Elsevier Butterworth-Heinemann; 2005.

46. Kac G, Durain E, Amrein C, Hérisson E, Fiemeyer A, Buu-Hoï A. Colonization and infection of pulmonary artery catheter in cardiac surgery patients: epidemiology and multivariate analysis of risk factors. Critical care medicine. 2001;29(5):971-5.

47. Liu C, Webb CC. Pulmonary artery rupture: serious complication associated with pulmonary artery catheters. Int J Trauma Nurs. 2000;6(1):19-26.

48. Elliott C, Zimmerman G, Clemmer T. Complications of pulmonary artery catheterization in the care of critically ill patients. A prospective study. CHEST Journal. 1979;76(6):647-52.

49. Katz JD, Cronau LH, Barash PG, Mandel SD. Pulmonary artery flow-guided catheters in the perioperative period. JAMA: the journal of the American Medical Association. 1977;237(26):2832-4.

50. Kelso LA. Complications associated with pulmonary artery catheterization. New horizons (Baltimore, Md). 1997;5(3):259.

51. Oliven A, Abinader E, Bursztein S. Influence of varying inspired oxygen tensions on the pulmonary venous admixture (shunt) of mechanically ventilated patients. Critical care medicine. 1980;8(2):99-101.

52. Quan SF, Kronberg GM, Schlobohm RM, Feeley TW, Don HF, Lister G. Changes in venous admixture with alterations of inspired oxygen concentration. Anesthesiology. 1980;52(6):477-82.

53. Douglas ME, Downs JB, Dannemiller FJ, Hodges MR, Munson ES. Change in pulmonary venous admixture with varying inspired oxygen. Anesthesia & Analgesia. 1976;55(5):688-93.

54. Shapiro B, Cane R, Harrison R, Steiner M. Changes in intrapulmonary shunting with administration of 100 percent oxygen. CHEST Journal. 1980;77(2):138-41.

55. Shapiro A, Virgilio R, Peters R. Interpretation of alveolar-arterial oxygen tension difference. Surgery, gynecology & obstetrics. 1977;144(4):547.

56. Suter PM, Fairley HB, Schlobohm RM. Shunt, lung volume and perfusion during short periods of ventilation with oxygen. Anesthesiology. 1975;43(6):617-27.

57. Mcaslan TC, Chiu JM, Turney SZ, Cowley RA. Influence of inhalation of 100% oxygen on intrapulmonary shunt in severely traumatized patients. The Journal of Trauma and Acute Care Surgery. 1973;13(9):811-21.

58. King T, Weber B, Okinaka A, Friedman S, Smith J, Briscoe W. Oxygen transfer in catastrophic respiratory failure. CHEST Journal. 1974;65(4_Supplement):40S-4S.

59. Santos C, Ferrer M, Roca J, Torres A, Hernandez C, Rodriguez-Roisin R. Pulmonary gas exchange response to oxygen breathing in acute lung injury. American journal of respiratory and critical care medicine. 2000;161(1):26-31.

60. Lamy M, Fallat R, Koeniger E, Dietrich H, Ratliff J, Eberhart R, et al. Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. The American review of respiratory disease. 1976;114(2):267-84.

61. Andersen PK, Brinklov MM, Stokke DB, Hole P, Rosendal T. Inaccuracy of oxygen electrodes at high blood oxygen tensions. Anesthesiology. 1978;49(1):61.

62. Dueck R, Wagner PD, West JB. Effects of positive end-expiratory pressure on gas exchange in dogs with normal and edematous lungs. Anesthesiology. 1977;47(4):359-66.

63. Shannon DC, Todres ID, Moylan FM. Regional lung function in infants. Critical care medicine. 1973;1(6):302-7.

64. Chang DW. Respiratory care calculations. Clifton Park, N.Y.; Andover: Delmar ; Cengage Learning [distributor]; 2012.

65. Lilienthal J, Riley R, Proemmel D, Franke R. An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. American Journal of Physiology--Legacy Content. 1946;147(1):199-216.

66. Shapiro BA, Peruzzi WT, Kozelowski-Tamplin R. Clinical application of blood gases. Chicago, IL: Mosby-Year Book; 1993.

67. Clark JM, Lambertsen CJ. Alveolar-arterial O2 differences in man at 0.2, 1.0, 2.0, and 3.5 Ata inspired PO2. Journal of Applied Physiology. 1971;30(5):753-63.

68. Rahn H, Farhi L. Ventilation, perfusion, and gas exchange-the VA/Q concept. Handbook of physiology. 1964;1:735.

69. Douglas ME, Downs JB, Shook D. Response of pulmonary venous admixture. a means of comparing therapies? CHEST Journal. 1980;77(6):764-70.

70. Van De Water JM, Kagey KS, Miller IT, Parker DA, O'conner NE, Sheh J-M, et al. Response of the Lung to Six to 12 Hours of 100 Per Cent Oxygen Inhalation in Normal Man. Survey of Anesthesiology. 1971;15(6):529-30.

71. Torda T. Alveolar-arterial oxygen tension difference: a critical look. Anaesthesia and intensive care. 1981;9(4):326.

72. Lecky JH, Ominsky AJ. Postoperative respiratory management. CHEST Journal. 1972;62(2_Supplement):50S-7S.

73. El-Khatib MF, Jamaleddine GW. A new oxygenation index for reflecting intrapulmonary shunting in patients undergoing open-heart surgery. CHEST Journal. 2004;125(2):592-6.

74. Cotev S, Perel A, Katzenelson R, Eimerl D. The effect of PEEP on oxygenating capacity in acute respiratory failure with sepsis. Critical care medicine. 1976;4(4):186-92.

75. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. American journal of respiratory and critical care medicine. 1994;149(3):818-24.

76. Lanspa MJ, Morris AH. The PaO2/FIO2 Ratio Categorization of Patients With Acute Respiratory Distress Syndrome Is Suboptimal*. Critical Care Medicine. 2015;43(2):488-9.

77. Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J, et al. A universal definition of ARDS: the PaO2/FiO2 ratio under a standard ventilatory setting—a

prospective, multicenter validation study. Intensive Care Medicine. 2013;39(4):583-92.

78. Choi AMK. Acute respiratory distress syndrome. New York: Informa Healthcare USA; 2010.

79. Rello J, Valles J, Kollef MH. Critical care infectious diseases textbook. Boston: Kluwer Academic Publishers; 2001.

80. Fanelli V, Ranieri VM. Mechanisms and Clinical Consequences of Acute Lung Injury. Annals of the American Thoracic Society. 2015;12(Supplement 1):S3-S8.

81. Ashbaugh D, Boyd Bigelow D, Petty T, Levine B. Acute Respiratory Distress in Adults. The Lancet. 1967;290(7511):319-23.

82. Hyers T. Adult respiratory distress syndrome: definition, risk factors, and outcome. Lung biology in health and disease. 1991;50:23-36.

83. Petty TL, Ashbaugh DG. The adult respiratory distress syndrome: clinical features, factors influencing prognosis and principles of management. CHEST Journal. 1971;60(3):233-9.

84. Murray JF, Matthay MA, Luce JM, Flick MR. An Expanded Definition of the Adult Respiratory Distress Syndrome. American Review of Respiratory Disease. 1988;138(3):720-3.

85. Rinaldo JE. THe prognosis of the adult respiratory distress syndrome. inappropriate pessimism? Chest. 1986;90(4):470-1.

86. Bone RC, Maunder R, Slotman G, Silverman H, Hyers TM, Kerstein MD, et al. An early test of survival in patients with the adult respiratory distress syndrome. The PaO2/FIo2 ratio and its differential response to conventional therapy. Prostaglandin E1 Study Group. CHEST Journal. 1989;96(4):849-51.

87. Mancebo J, Artigas A. A clinical study of the adult respiratory distress syndrome. Critical care medicine. 1987;15(3):243-6.

88. Emmanuel G, Govindaraj C, Papageorgiou C, Gharpure A, Wilen S, Khaneja S, et al. Physiologic aspects of stiff lung syndrome. CHEST Journal. 1974;65(4_Supplement):29S-32S.

89. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, et al. The American–European Consensus Conference on ARDS, Part 2 Ventilatory, Pharmacologic, Supportive Therapy, Study Design Strategies, and Issues Related to Recovery and Remodeling. American journal of respiratory and critical care medicine. 1998;157(4):1332-47.

90. Streiner DL, Norman GR, Cairney J. Health measurement scales : a practical guide to their development and use2015.

91. Phua J, Stewart TE, Ferguson ND. Acute respiratory distress syndrome 40 years later: time to revisit its definition*. Critical care medicine. 2008;36(10):2912-21.

92. Ferguson ND, Kacmarek RM, Chiche J-D, Singh JM, Hallett DC, Mehta S, et al. Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial. Intensive Care Medicine. 2004;30(6):1111-6.

93. Villar J, Pérez-Méndez L, López J, Belda J, Blanco J, Saralegui I, et al. An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 2007;176(8):795-804.

94. Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA. Interobserver variability in applying a radiographic definition for ARDS. Chest. 1999;116(5):1347-53.

95. Meade M, Cook R, Guyatt G, Groll R, Kachura J, Bedard M, et al. Interobserver Variation in Interpreting Chest Radiographs for the Diagnosis of Acute Respiratory Distress Syndrome. American Journal of Respiratory and Critical Care Medicine. 2000;161(1):85-90.

96. Ferguson ND, Meade MO, Hallett DC, Stewart TE. High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. Intensive care medicine. 2002;28(8):1073-7.

97. Wheeler A, Bernard G, Thompson B, Schoenfeld D, Wiedemann H, DeBoisblanc B, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl j Med. 2006;354(21):2213-24.

98. Komadina KH, Schenk DA, LaVeau P, Duncan CA, Chambers SL. Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. Chest. 1991;100(6):1647-54.

99. Force ADT. Acute respiratory distress syndrome. Jama. 2012;307(23):2526-33.

100. Covelli HD, Nessan VJ, Tuttle Iii WK. Oxygen derived variables in acute respiratory failure. Critical care medicine. 1983;11(8):646-9.

101. Coetzee A, Swanevelder J, Van Der Spuy G, Jansen J. Gas exchange indices-how valid are they? South African Medical Journal-Cape Town-Medical Association Of South Africa-. 1995;85:1227-12231.

102. Martyn JJ, Aikawa N, Wilson RS, Szyfelbein SK, Burke JF. Extrapulmonary factors influencing the ratio of arterial oxygen tension to inspired oxygen concentration in burn patients. Critical care medicine. 1979;7(11):492-6.

103. Granger WM, Miller DA, Ehrhart IC, Hofman WF. The effect of blood flow and diffusion impairment on pulmonary gas exchange: a computer model. Computers and biomedical research. 1987;20(5):497-506.

104. Kathirgamanathan A, McCahon RA, Hardman JG. Indices of pulmonary oxygenation in pathological lung states: an investigation using high-fidelity, computational modelling. Br J Anaesth. 2009;103(2):291-7.

105. Gross R, Israel R. A graphic approach for prediction of arterial oxygen tension at different concentrations of inspired oxygen. CHEST Journal. 1981;79(3):311-5.

106. Viale J-P, Percival CJ, Annat G, Rousselet B, Motin J. Arterial-alveolar oxygen partial pressure ratio: a theoretical reappraisal. Critical care medicine. 1986;14(2):153-4.

107. Herrick IA, Champion LK, Froese AB. A clinical comparison of indices of pulmonary gas exchange with changes in the inspired oxygen concentration. Canadian journal of anaesthesia. 1990;37(1):69-76.

108. Rosen KR. The history of medical simulation. Journal of Critical Care. 2008;23(2):157-66.

109. Chopra V. Simulators in anaesthesia. Current Anaesthesia & Critical Care. 1998;9(4):187-92.

110. Byrne A. What is simulation for? Anaesthesia. 2012;67(3):219-25.

111. Dickinso.Cj. Digital-Computer Model to Teach and Study Gas Transport and Exchange between Lungs, Blood and Tissues(Macpuf). J Physiol-London. 1972;224(1):P7-&.

112. Bencowitz H, Wagner P, West J. Effect of change in P50 on exercise tolerance at high altitude: a theoretical study. Journal of Applied Physiology. 1982;53(6):1487-95.

113. Petrini M, Robertson H, Hlastala M. Interaction of series and parallel dead space in the lung. Respiration physiology. 1983;54(1):121-36.

114. Denson DD, Thompson GA, Coyle DE. Use of a limited physiologic model to explain target organ toxicity of bupivacaine as a function of route of administration. Biopharmaceutics & Drug Disposition. 1986;7(2):121-35.

115. Schwid HA, O'Donnell D. Educational computer simulation of malignant hyperthermia. J Clin Monitor Comput. 1992;8(3):201-8.

116. Dewhurst D, Hardcastle J, Hardcastle P, Stuart E. Comparison of a computer simulation program and a traditional laboratory practical class for teaching the principles of intestinal absorption. American Journal of Physiology. 1994;267:S95-S.

117. Dickinson C. A digital computer model to teach and study gas transport and exchange between lungs, blood and tissues ('MacPuf'). The Journal of physiology. 1972;224(1):7P.

118. Oken D. Microcomputer Simulation as an Aid in Analyzing Data and Teaching the Principles of Glomerular Dynamics. Kidney and Blood Pressure Research. 1988;11(6):332-40.

119. Samsel RW, Schmidt GA, Hall JB, Wood LD, Shroff SG, Schumacker PT. Cardiovascular physiology teaching: computer simulations vs. animal demonstrations. American Journal of Physiology. 1994;266:S36-S.

120. Boyle 3rd J. Ventilatory control (Ventrol) simulation for education. The American journal of physiology. 1991;261(6 Pt 3):S25-9.

121. Seidenstein AH, Barone FC, Lytton WW. Computer modeling of ischemic stroke. Scholarpedia. 2015;10(3):32015.

122. Helikar T, Cutucache CE, Dahlquist LM, Herek TA, Larson JJ, Rogers JA. Integrating interactive computational modeling in biology curricula. PLoS Comput Biol. 2015;11(3):e1004131.

123. Schwid HA, Buffington CW, Strum DP. Computer simulation of the hemodynamic determinants of myocardial oxygen supply and demand. Journal of cardiothoracic anesthesia. 1990;4(1):5-18.

124. Thomas JD, Weyman AE. Numerical modeling of ventricular filling. Annals of biomedical engineering. 1992;20(1):19-39.

125. Dexter F, Hindman BJ. Computer simulation of brain cooling during cardiopulmonary bypass. The Annals of thoracic surgery. 1994;57(5):1171-8.

126. Dexter F. Mathematical analysis of haemodilution's direct effect on rate of brain cooling during cardiopulmonary bypass. Medical and Biological Engineering and Computing. 1995;33(1):24-6.

127. Melo MV, Loeppky J, Caprihan A, Luft U. Alveolar ventilation to perfusion heterogeneity and diffusion impairment in a mathematical model of gas exchange. Computers and biomedical research. 1993;26(2):103-20.

128. Hickling KG. The pressure–volume curve is greatly modified by recruitment: a mathematical model of ARDS lungs. American journal of respiratory and critical care medicine. 1998;158(1):194-202.

129. Suki B, Andrade Jr JS, Coughlin MF, Stamenović D, Stanley HE, Sujeer M, et al. Mathematical modeling of the first inflation of degassed lungs. Annals of biomedical engineering. 1998;26(4):608-17.

130. Burke WC, Crooke P, Marcy TW, Adams AB, Marini JJ. Comparison of mathematical and mechanical models of pressure-controlled ventilation. Journal of Applied Physiology. 1993;74(2):922-33.

131. Hotchkiss JR, Crooke PS, Adams AB, Marini JJ. Implications of a biphasic two-compartment model of constant flow ventilation for the clinical setting. Journal of critical care. 1994;9(2):114-23.

132. Habashi N, Borg U, Reynolds H. An in vitro physiologic model for cardiopulmonary simulation: a system for ECMO training. The International journal of artificial organs. 1994;17(7):399-407.

133. Good ML, Gravenstein J. Anesthesia simulators and training devices. International anesthesiology clinics. 1989;27(3):161-6.

134. Chopra V, Engbers FHM, Geerts MJ, Filet WR, Bovill JG, Spierdijk J. The Leiden anaesthesia simulator. British Journal of Anaesthesia. 1994;73(3):287-92.

135. Chopra V, Gesink BJ, DE JONG J, Bovill J, Spierdijk J, Brand R. Does training on an anaesthesia simulator lead to improvement in performance? British Journal of Anaesthesia. 1994;73(3):293-7.

136. Campos JH, Hallam EA, Ueda K. Training in placement of the left-sided double-lumen tube among non-thoracic anaesthesiologists: intubation model simulator versus computer-based digital video disc, a randomised controlled trial. Eur J Anaesth. 2011;28(3):169-74.

137. Hedlund A, Zaar B, Groth T, Arturson G. Computer simulation of fluid resuscitation in trauma. I. Description of an extensive pathophysiological model and its first validation. Computer Methods and Programs in Biomedicine. 1988;27(1):7-21.

138. Arturson G, Groth T, Hedlund A, Zaar B. Computer Simulation of Fluid Resuscitation in Trauma: First Pragmatic Validation in Thermal Injury. Journal of Burn Care & Research. 1989;10(4):292-9.

139. Hinds C, Roberts M, Ingram D, Dickinson C. Computer simulation to predict patient responses to alterations in the ventilation regime. Intensive care medicine. 1984;10(1):13-22.

140. Rutledge GW, Thomsen GE, Farr BR, Tovar MA, Polaschek JX, Beinlich IA, et al. The design and implementation of a ventilator-management advisor. Artificial Intelligence in Medicine. 1993;5(1):67-82.

141. Fleischhauer C. Decubitus research: Computer model shows, how tissue reacts under pressure. Anasthesiologie Intensivmedizin Notfallmedizin Schmerztherapie. 2007;42(9):664-.

142. Wakeland W, Agbeko R, Vinecore K, Peters M, Goldstein B. Assessing the prediction potential of an in silico computer model of intracranial pressure dynamics. Critical Care Medicine. 2009;37(3):1079-89.

143. Jones M, Blanch P, Rimes J. A mathematical method for predicting the expiratory time necessary to achieve a desired intrinsic PEEP level. Respiratory care. 1993;38(8):896-905.

144. Hope D, Jenkins B, Willis N, Maddock H, Mapleson W. Non-invasive estimation of venous admixture: validation of a new formula. British journal of anaesthesia. 1995;74(5):538-43.

145. Lawler P, Nunn J. A reassessment of the validity of the iso-shunt graph. British journal of anaesthesia. 1984;56(12):1325-36.

146. Torres A, Bentley T, Bartels J, Sarkar J, Barclay D, Namas R, et al. Mathematical modeling of posthemorrhage inflammation in mice: studies using a novel, computer-controlled, closed-loop hemorrhage apparatus. Shock. 2009;32(2):172-8.

147. Harrison M. Prediction of infusion rates: validation of a computer simulation using vecuronium. British journal of anaesthesia. 1990;64(3):287-93.

148. Hirshberg A, Frykberg ER, Mattox KL, Stein M. Triage and Trauma Workload in Mass Casualty: A Computer Model. J Trauma-Injury Infect Crit Care. 2010;69(5):1074-81.

149. Lamberti C, Sarti E, Santoro A, Spongano M, Zucchelli P, Rossi M. A digital computer model for optimal programming of hemodialytic treatment. The International journal of artificial organs. 1988;11(4):235-42.

150. Wolf MB, DeLand EC. A comprehensive, computer-model-based approach for diagnosis and treatment of complex acid-base disorders in critically-ill patients. Journal of Clinical Monitoring and Computing. 2011;25(6):353-64.

151. Brennan N, Corrigan O, Allard J, Archer J, Barnes R, Bleakley A, et al. The transition from medical student to junior doctor: today's experiences of Tomorrow's Doctors. Medical education. 2010;44(5):449-58.

152. Andrews DH. Relationships among Simulators, Training Devices, and Learning: A Behavioral View. Educational Technology. 1988;28(1):48-54.

153. Gagne RM. Training devices and simulators: Some research issues: Skill Component Research Laboratory, Air Force Personnel and Training Research Center, Air Research and Development Command; 1954.

154. Hinds CJ, Ingram D, Adams L, Cole PV, Dickinson CJ, Kay J, et al. An evaluation of the clinical potential of a comprehensive model of human respiration in artificially ventilated patients. Clinical science. 1980;58(1):83-91.

155. Joyce CJ, Hickling KG. Permissive hypercapnia and gas exchange in lungs with high Qs/Qt: A mathematical model. British Journal of Anaesthesia. 1996;77(5):678-83.

156. Rutledge GW. Ventsim - a Simulation-Model of Cardiopulmonary Physiology. J Am Med Inform Assn. 1994:878-83.

157. Hardman JG, Bedforth NM, Ahmed AB, Mahajan RP, Aitkenhead AR. A physiology simulator: validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation. Br J Anaesth. 1998;81(3):327-32.

158. Lazalde AR. Physiologic simulator to predict the arterial oxygen saturation at extreme heights. Revista Mexicana de Ingeniería Biomédica. 2011;32(1).

159. Harvey DJR, Hardman JG. Computational modelling of lung injury: is there potential for benefit? Philosophical Transactions of the Royal Society B: Biological Sciences. 2011;366(1562):300-5.

160. Masuzawa T, Fukui Y, Smith NT. Cardiovascular simulation using a multiple modeling method on a digital computer—Simulation of interaction between the cardiovascular system and angiotensin II. J Clin Monitor Comput. 1992;8(1):50-8.

161. Greenway C. Mechanisms and quantitative assessment of drug effects on cardiac output with a new model of the circulation. Pharmacological reviews. 1981;33(4):213.

162. Kelman GR. A new lung model: An investigation with the aid of a digital computer. Computers and Biomedical Research. 1970;3(3):241-8.

163. Hardman JG, Wills JS, Aitkenhead AR. Factors Determining the Onset and Course of Hypoxemia During Apnea: An Investigation Using Physiological Modelling. Anesthesia & Analgesia. 2000;90(3):619-24.

164. Rutledge G, Thomsen G, Farr B, Tovar M, Sheiner L, Fagan L, editors. VentPlan: a ventilator-management advisor. Proceedings of the Annual Symposium on Computer Application in Medical Care; 1991: American Medical Informatics Association.

165. Thomas L. Algorithms for selected blood acid-base and blood gas calculations. Journal of applied physiology. 1972;33(1):154-8.

166. Kelman GR. Computer program for the production of O_2-CO_2 diagrams. Respiration physiology. 1968;4(2):260-9.

167. Alotaibi A. New Pulmonary Indices to Assess Respiratory Status. Nottingham: the University of Nottingham 2015.

168. Slutsky AS. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. CHEST Journal. 1993;104(6):1833-59.

169. Tobin MJ. Mechanical ventilation. New England Journal of Medicine. 1994;330(15):1056-61.

170. Merlani P, Garnerin P, Diby M, Ferring M, Ricou B. Linking guideline to regular feedback to increase appropriate requests for clinical tests: blood gas analysis in intensive care. BMJ. 2001;323(7313):620-4.

171. Bedford RF, Wollman H. Complications of percutaneous radial-artery cannulation - objective prospective study in man. Anesthesiology. 1973;38(3):228-36.

172. Drucker WR, Gavett JW, Kirshner R, Messick WJ, Ingersoll G. Toward strategies for cost containment in surgical patients. Ann Surg. 1983;198(3):284-300.

173. Andrews T, Waterman H. What factors influence arterial blood gas sampling patterns? Nursing in Critical Care. 2008;13(3):132-7.

174. Bigeleisen PE. Models of venous admixture. Advances in Physiology Education. 2001;25(3):159-66.

175. Hess D. PREDICTION OF THE CHANGE IN PAO2. Critical care medicine. 1979;7(12):568-9.

176. Abizanda R, Lopez J. The possibility of predicting pao2 following changes in FIO2. Intensive care medicine. 1981;7(5):247-.

177. Bedforth NM, Hardman JG. Predicting patients' responses to changes in mechanical ventilation: a comparison between physicians and a physiological simulator. Intensive care medicine. 1999;25(8):839-42.

178. Hardman JG, Bedforth NM. Estimating venous admixture using a physiological simulator. British Journal of Anaesthesia. 1999;82(3):346-9.

179. Hardman JG, Wills JS, Aitkenhead AR. Investigating hypoxemia during apnea: validation of a set of physiological models. Anesthesia & Analgesia. 2000;90(3):614-8.

180. Das A, Cole O, Chikhani M, Wang W, Ali T, Haque M, et al. Evaluation of lung recruitment maneuvers in acute respiratory distress syndrome using computer simulation. Critical Care. 2015;19(1):8.

181. Lang TA, Secic M. How to report statistics in medicine : annotated guidelines for authors, editors, and reviewers. New York: American College of Physicians; 2006.

182. McPherson G, McPherson G. Applying and interpreting statistics : a comprehensive guide. New York: Springer; 2001.

183. Bedforth N, Hardman J. Predicting patients' responses to changes in mechanical ventilation: a comparison between physicians and a physiological simulator. Intensive care medicine. 1999;25(8):839-42.

184. Hardman JG, Aitkenhead AR. Estimating alveolar dead space from the arterial to end-tidal CO2 gradient: A modeling analysis. Anesth Analg. 2003;97(6):1846-51.

185. Brown AM. A step-by-step guide to non-linear regression analysis of experimental data using a Microsoft Excel spreadsheet. Computer Methods and Programs in Biomedicine. 2001;65(3):191-200.

186. Ivakhnenko AG. Polynomial Theory of Complex Systems. Systems, Man and Cybernetics, IEEE Transactions on. 1971;SMC-1(4):364-78.

187. Paulev PE, Siggaard-Andersen O. Clinical application of the pO2–pCO2 diagram. Acta anaesthesiologica scandinavica. 2004;48(9):1105-14.

188. Jeremias A, Brown DL. Cardiac intensive care. Philadelphia, PA: Saunders/Elsevier; 2010.

189. Barash PG. Clinical anesthesia. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009.

190. Microsoft C. LINEST function 2014 [Available from: http://office.microsoft.com/en-gb/excel-help/linest-function-HP010069838.aspx.

191. Aboab J, Louis B, Jonson B, Brochard L. Relation between PaO2/FIO2 ratio and FIO2: a mathematical description. Applied Physiology in Intensive Care Medicine: Springer; 2006. p. 41-4.

192. Whiteley JP, Gavaghan DJ, Hahn CEW. Variation of venous admixture, SF6 shunt, PaO2, and the PaO2/FiO2 ratio with FiO2. British Journal of Anaesthesia. 2002;88(6):771-8.

193. Al-Otaibi HM. Management of Mechanically Ventilated Patients: Evaluation of the Current Practice in Ventilator Adjustment, Clinicians' Performance, and Clinical Relevance of Oxygenation Indices in Critical Care Settings. UK: the University of Nottingham; 2011.

List of Figures

FIGURE 1 NPS MECHANICAL VENTILATOR CONTROL PANEL..... 40

FIGURE 2 NPS RESPIRATORY PHYSIOLOGICAL VARIABLE CONTROL PANEL..... 41

FIGURE 3 NPS PATIENT INFORMATION..... 41

FIGURE 4 NPS ILLUSTRATION..... 43

FIGURE 5 MPP AND PaO_2/FiO_2 RATIO VARIATION USING NPS SUBJECTS..... 55

FIGURE 6 MPP AND PaO_2/FiO_2 RATIO VARIATION USING CLINICAL PATIENTS DATA..... 57

FIGURE 7 THE VARIATION OF THE UTILISED INDICES WITH EFPS CHANGES. 68

FIGURE 8 THE PaO_2/FiO_2 RATIO (PF) AND THE CORRECTED PaO_2/FiO_2 RATIO (PFC) WITH FiO_2 VARIATION AND THE POLYNOMIAL TREND LINE EQUATION. 91

FIGURE 9 PaO_2/FiO_2 RATIO (KPA) FOR SIX ARDS SIMULATED PATIENTS 94

FIGURE 10 THE AVERAGE PaO_2/FiO_2 RATIO (KPA) WITH POLYNOMIAL EQUATION..... 94

FIGURE 11 THE CORRECTED PaO_2/FiO_2 RATIO KPA (PFC) FOR SIX SIMULATED PATIENTS..... 95

FIGURE 12 THE AVERAGE PaO_2/FiO_2 RATIO IN KPA (AVE.PF) AND THE CORRECTED PaO_2/FiO_2 RATIO (AVE.PFC) FOR ALL SIX NPS SUBJECTS WITH HB G/L VARIATION 97

FIGURE 13 FOUR CHARTS FOR THE AVERAGE PaO_2/FiO_2 RATIO IN KPA (AVE.PF) AND THE CORRECTED PaO_2/FiO_2 RATIO (AVE.PFC) WITH EPFS VARIATION 102

FIGURE 14 THE AVERAGE PaO_2 (KPA)AND THE CORRECTED $crPaO_2$ (KPA) WITH FiO_2% VARIATION AND THE POLYNOMIAL EQUATION 107

FIGURE 15 THE AVERAGE PaO_2 (KPA) AND THE CORRECTED $crPaO_2$ (KPA) WITH HB (G/L) VARIATION AND A LINER EQUATION.... 108

FIGURE 16 THE AVERAGE PaO_2 (KPA) AND THE CORRECTED $crPaO_2$ (KPA) WITH VO_2 (ML MIN^{-1}) VARIATION AND A LINEAR EQUATION. 109

FIGURE 17 THE AVERAGE PaO_2 (KPA) AND THE CORRECTED $crPaO_2$ (KPA) WITH WITH $PaCO_2$ VARIATION KPA AND A LINEAR EQUATION. 110

FIGURE 18 COMPARING PaO_2 (KPA) WITH $crPaO_2$ (KPA) DURING FiO_2 % VARIATION FOR 5 SIMULATED PATIENTS 115

FIGURE 19 COMPARING THE AVERAGE PaO_2 (KPA) WITH AVERAGE $crPaO_2$ (KPA) WITH FOUR EPFS VARIATION FOR 10 SIMULATED PATIENTS..... 120

FIGURE 20 AVERAGE PaO_2 (KPA) FOR GROUP A AND B WITH EPF VARIATIONS. 125

FIGURE 21 DIFFERENT $crPaO_2$ (KPA)CURVES USING EQUATION FROM GROUP B WITH FiO_2 VARIATION..... 126

FIGURE 22 DIFFERENT $crPaO_2$ (KPA) USING GROUP A EQUATION WITH FiO_2 VARIATION 127

FIGURE 23 COMPARING AVERAGE PaO_2 (KPA) AND $crPaO_2$ (KPA) FOR ALL SIMULATED SUBJECTS WITH VARIATION OF EFP(FiO_2, HB, VO_2,AND RR) 128

FIGURE 24 COMPARING THE AVERAGE PaO_2 AND AVERAGE $crPaO_2$ WITH FiO_2 VARIATION 135

FIGURE 25 COMPARING THE AVERAGE PaO_2 (KPA) AND AVERAGE $crPaO_2$ (KPA)WITH HB G/L VARIATION 135

FIGURE 26 COMPARING THE AVERAGE PaO_2/FiO_2 RATIO (KPA) FOR GROUP A AND B WITH FiO_2% VARIATION. 143

FIGURE 27 COMPARING THE AVERAGE RI FOR GROUP A AND B WITH FiO_2 % VARIATION..... 144

FIGURE 28 COMPARING THE AVERAGE PaO_2/PAO_2 FOR GROUP A AND B 144

FIGURE 29 COMPARING THE AVERAGE $P(A\text{-}a)O_2$ FOR GROUP A AND B 145

FIGURE 30 FLOWCHART 146

FIGURE 31 BOX & WHISKER PLOT FOR $P(A\text{-}a)O_2$ WITH DIFFERENT GROUPS DURING FiO_2%. 147

FIGURE 32 MEAN AND 95% CI FOR $crPaO_2$ (KPA) BOTH GROUPS WITH FiO_2 % VARIATION 151

FIGURE 33 THE MEAN 95% CI FOR $crPaO_2$ (KPA) AFTER CORRECTION ON SAME TEN SIMULATED SUBJECTS WITH FiO_2% VARIATION. 152

FIGURE 34 THE $crPaO_2$ (KPA) MEDIAN WITH RANGE AFTER CORRECTION ON THE SAME TEN SIMULATED SUBJECTS WITH FiO_2% VARIATION. 152

FIGURE 35 $crPaO_2$ (KPA) MEDIAN WITH RANG FOR TEN SIMULATED SUBJECTS BEFORE THE NEW CORRECTION WITH FiO_2% VARIATION. 153

FIGURE 36 $crPaO_2$ (KPA) MEDIAN WITH RANG FOR THE NEW 8 SIMULATED SUBJECTS AFTER THE NEW CORRECTION WITH FiO_2% VARIATION. 153

FIGURE 37 THE MEAN 95% CI FOR THE NEW $crPaO_2$ (KPA) AFTER $PaCO_2$ CORRECTION (KPA) WITH 8 SIMULATED SUBJECTS WITH FiO_2% VARIATION. 157

FIGURE 38 $crPaO_2$(KPA) MEDIAN WITH RANG FOR THE NEW EIGHT SIMULATED SUBJECTS AFTER THE NEW $PaCO_2$ CORRECTION (KPA) WITH FiO_2 VARIATION. 157

FIGURE 39 COMPARING THE NEW AND OLD $crPaO_2$ (KPA) INDEX CURVES FOR WITH FiO_2 % VARIATION 160

FIGURE 40 THE MEAN AND 95% CI FOR THE NEW $crPaO_2$ (KPA) WITH TWO GROUP SUBJECTS WITH FiO_2% VARIATION. 161

FIGURE 41 CRPAO$_2$ (KPA) MEDIAN WITH RANG FOR THE NEW EIGHT SIMULATED SUBJECTS AFTER THE LAST NEW PACO$_2$ (KPA) CORRECTION WITH FIO$_2$% VARIATION. 161

FIGURE 42 PATIENTS DISTRIBUTION BASED ON LOCATION 174

FIGURE 43 ADMISSION DIAGNOSIS 175

FIGURE 44 MODES OF MECHANICAL VENTILATION UTILISED IN THE STUDY 176

FIGURE 45 BOX AND WHISKER PLOT GRAPH FOR OXYGEN INDICES CV%. 177

FIGURE 46 CV% HISTOGRAM FOR OXYGEN INDICES. 178

FIGURE 47 FIO$_2$ % VARIATION 221

FIGURE 48 PAO$_2$/FIO$_2$ RATIO (KPA) VS FIO$_2$ %CHANGES 224

FIGURE 49 P(A-A)O$_2$ VS FIO$_2$ % CHANGES 224

FIGURE 50 PAO$_2$/PAO$_2$ VS FIO$_2$ %CHANGES 224

FIGURE 51 RI VS FIO$_2$ %CHANGES 224

FIGURE 52 QS/QT VS FIO$_2$ %CHANGES 224

FIGURE 53 MPP VS FIO$_2$ %CHANGES 224

FIGURE 54 HB G/L VARIATION ON FIO$_2$30% 226

FIGURE 55 HB G/L VARIATION ON FIO$_2$ 60% 226

FIGURE 56 PAO$_2$/FIO$_2$ VS HB ON FIO$_2$ 30% 230

FIGURE 57 PAO$_2$/FIO$_2$ VS HB ON FIO$_2$ 60% 230

FIGURE 58 P(A-A)O$_2$ VS HB ON FIO$_2$ 30% 230

FIGURE 59 P(A-A)O$_2$ VS HB ON FIO$_2$ 60% 230

FIGURE 60 PAO$_2$/PAO$_2$ VS HB ON FIO$_2$=30% 230

FIGURE 61 PAO$_2$/PAO$_2$ VS HB ON FIO$_2$=60% 230

FIGURE 62 RI VS HB ON FIO$_2$ =30% 231

FIGURE 63 RI VS HB ON FIO$_2$ 60% 231

FIGURE 64 QS/QT VS HB ON FIO$_2$=30% 231

FIGURE 65 QS/QT VS HB ON FIO$_2$ 60% 231

FIGURE 66 MPP VS HB 231

FIGURE 67 HB VARIATION FIO$_2$=30% 233

FIGURE 68 HB VARIATION ON FIO$_2$ 60% 233

FIGURE 69 PAO_2/FIO_2 VS VO_2 ON FIO_2 30% 237

FIGURE 70 PAO_2/FIO_2 VS VO_2 ON FIO_2 60% 237

FIGURE 71 $P(A-A)O_2$ VS VO_2 ON FIO_2= 30% 237

FIGURE 72 $P(A-A)O_2$ VS VO_2 ON FIO_2 60% 237

FIGURE 73 PAO_2/PAO_2 VS VO_2 ON FIO_2 30% 237

FIGURE 74 PAO_2/PAO_2 VS VO_2 ON FIO_2 60% 237

FIGURE 75 RI VS VO2 ON FIO2 30% 238

FIGURE 76 RI VS VO_2 ON FIO_2 60% 238

FIGURE 77 QS/QT VS VO_2 ON FIO_2 30% 238

FIGURE 78 QS/QT VS VO_2 ON FIO_2 60% 238

FIGURE 79 MPP VS VO_2 238

FIGURE 80 RQ VARIATION WITH FIO_2 30% 240

FIGURE 81 RQ VARIATION ON FIO_2 60% 240

FIGURE 82 PAO_2/FIO_2 VS RQ ON FIO_2 30% 244

FIGURE 83 PAO_2/FIO_2 VS RQ ON FIO_2 60% 244

FIGURE 84 P(A-A) O2 VS RQ ON FIO_2 30% 244

FIGURE 85 $P(A-A)O_2$ VS RQ ON FIO_2 60% 244

FIGURE 86 PAO_2/PAO_2 VS RQ ON FIO_2 30% 244

FIGURE 87 PAO_2/PAO_2 VS RQ ON FIO_2 60% 244

FIGURE 88 RI VS RQ ON FIO_2 30% 245

FIGURE 89 RI VS RQ ON FIO_2 60% 245

FIGURE 90 QS/QT VS RQ ON FIO_2 30% 245

FIGURE 91 QS/QT VS RQ ON FIO_2 60% 245

FIGURE 92 MPP VS RQ 245

FIGURE 93 CO VARIATION ON FIO_2 30% 247

FIGURE 94 CO VARIATION ON FIO_2 60% 247

FIGURE 95 PAO_2/FIO_2 VS CO ON FIO_2 30% 251

FIGURE 96 PAO_2/FIO_2 VS CO ON FIO_2 60% 251

FIGURE 97 $P(A-A)O_2$ VS CO ON FIO_2 30% 251

FIGURE 98 P(A-A)O_2 VS CO ON FIO_2 60%.....251

FIGURE 99 PAO_2/PAO_2 VS CO ON FIO_2 30%.....251

FIGURE 100 PAO_2/PAO_2 VS CO ON FIO_2 60%.....251

FIGURE 101 RI VS CO ON FIO_2 30%.....252

FIGURE 102 RI VS CO ON FIO_2 60%.....252

FIGURE 103 QS/QT VS CO ON FIO_2 30%.....252

FIGURE 104 QS/QT VS CO ON FIO_2 60%.....252

FIGURE 105 MPP VS CO.....252

List of Tables

TABLE 1 COMPARISON OF CV% FOR MPP AND PaO_2/FiO_2 RATIO USING NPS DATA..... 55

TABLE 2 COMPARISON OF CV% FOR MPP AND PaO_2/FiO_2 RATIO USING PATIENT'S DATA..... 56

TABLE 3 PHYSIOLOGICAL AND MECHANICAL VENTILATOR SITTINGS FOR VIRTUAL PATIENTS USED IN THIS INVESTIGATION 60

TABLE 4 CONFIGURATION FOR THE SIX ARDS VIRTUAL PATIENTS..... 62

TABLE 5 THE FOUR VARIABLES THAT ADJUSTED DURING EXAMINATION OF THE INDICES OF OXYGENATION. 64

TABLE 6 CORRECTING OF PaO_2/FiO_2 RATIO WITH FiO_2% 91

TABLE 7 PaO_2/FiO_2 RATIO (KPA)FOR 6 SIMULATED PATIENTS DURING FiO_2 % VARIATION 93

TABLE 8 CORRECTED PaO_2/FiO_2 RATIO PFC (KPA) FOR 6 SIMULATED PATIENTS DURING FiO_2 % VARIATION 93

TABLE 9 THE CV% FOR AVERAGE PF RATIO AND PFC (KPA)WITH EXTERNAL FACTORS VARIATIONS..... 101

TABLE 10 CORRECTION FOR FiO_2%..... 107

TABLE 11 CORRECTION FOR HB G/L 108

TABLE 12 CORRECTION FOR VO_2 ML MIN^{-1} 109

TABLE 13 CORRECTION FOR $PaCO_2$ (KPA) 110

TABLE 14 SUMMARY MEASURES OF ASSOCIATION BETWEEN PF RATIO AND $crPaO_2$ USING 10 SIMULATED PATIENTS 111

TABLE 15 SUMMARY RESULTS OF TRIAL SIX AVERAGE VARIATIONS FOR ALL SIMULATED PATIENTS 114

TABLE 16 CONFIGURING FOR 10 SIMULATED PATIENTS USING NPS 118

TABLE 17 THE HEADLINE FIGURE FOR NPS PATIENTS..... 119

TABLE 18 COMPARISON OF INITIAL CONFIGURATION VALUES BETWEEN GROUP A AND B 124

TABLE 19 HEADLINE FIGURE WITH DIFFERENT GROUPS USING EQUATION GENERATED FROM TRIAL NINE 131

TABLE 20 HEADLINE FIGURE WITH DIFFERENT GROUPS USING EQUATION GENERATED FROM TRIAL TEN..... 134

TABLE 21 HEADLINE FIGURE WITH DIFFERENT GROUPS USING EQUATION GENERATED FROM TRIAL ELEVEN..... 139

TABLE 22 THE MEAN HEADLINE FIGURES..... 154

TABLE 23 THE MEAN HEADLINE FIGURES WITH THREE DIFFERENT $crPaO_2$ 156

TABLE 24 THE MEAN HEADLINE FIGURES WITH FOUR DIFFERENT $crPaO_2$ 160

TABLE 25 GENERAL CHARCTERISTICS OF PATIENTS. 172

TABLE 26 MEAN AND SD FOR MECHANICAL VENTILATOR SETTINGS, ABG RESULTS ,OXYGEN INDICES AND TIME DIFFERENT FOR ALL PATIENTS IN THREE READINGS. 173

TABLE 27 COMPARISON OF OXYGEN INDICES TO CRPaO_2 INDEX CV%..... 179

TABLE 28 HEADLINE FIGURE RECIPROCAL. 179

TABLE 29 CHARACTERISTICS OF VIRTUAL PATIENTS..... 216

TABLE 30 CONFIGURATION OF THE VIRTUAL SUBJECTS 217

TABLE 31 FiO_2 VARIATION 220

TABLE 32 HAEMOGLOBIN VARIATION 225

TABLE 33 VO_2 VARIATION..... 232

TABLE 34 RQ VARIATION 239

TABLE 35 CO VARIATION 246

TABLE 36: ABG RESULTS AND THE CALCULATED OXYGEN INDICES FOR EACH PATIENT INCLUDED IN THE CLINICAL DATA. THE ABG MEASUREMENTS WERE TAKEN DURING TIME 1 253

TABLE 37 ABG RESULTS AND THE CALCULATED OXYGEN INDICES FOR EACH PATIENT INCLUDED IN THE CLINICAL DATA. THE ABG MEASUREMENTS WERE TAKEN DURING TIME 2 257

TABLE 38 ABG RESULTS AND THE CALCULATED OXYGEN INDICES FOR EACH PATIENT INCLUDED IN THE CLINICAL DATA. THE ABG MEASUREMENTS WERE TAKEN DURING TIME 3 261

TABLE 39 OXYGEN INDICES VARIATION FOR THE CLINICAL DATA 265

9. APPENDIX

9.1. Configuration and characteristic of ninety virtual NPS patients

Table 29 characteristics of virtual patients

Weight	70 kg
Height	1.70 meter
Body service area	1.83
body mass index	23.3
Inspired gas	Warmed and humidified to 37C
Inspiratory flow pattern	Constant flow
Tidal volume	6 ml kg^{-1}
Inspiratory pressure	18 cm H_2O
Respiratory rate	12 bpm
PEEP	5 cm H_2O
Inspiratory to expiratory ratio	1:2
Cardiac output	9.5 litre min^{-1}
Base excess	0 mmol $litre^{-1}$
Endotracheal tube information Length/ internal diameter	24 cm/ 8.0 mm
Air way resistance	0.732 Pa/L/min
Atmospheric pressure	101 kPa
PAH_2O	6.7 kPa
Haemoglobin	145
Oxygen consumption	250
Respiratory exchange ratio	0.80
Body temperature	37.2

Table 30 configuration of the virtual subjects

	Bronchial slider	Vascular Slider	shunt
1	302.8-1/30.3-20/1-50/1-100	1-1/1-20/1-50/25-80/302.8-100	30
2	201.6-1/15.2-20/1-50/1-80/1-100	1-1/1-20/1-50/15.2-80/201.6-100	30
3	501.8-1/36-20/1-50/1-100	1-1/1-20/1-50/36-80/501.8-100	30
4	400-1/25-20/1-50/1-80/1-100	1-1/1-20/1-50/25-80/400-100	30
5	1004.9-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/1004.9-100	30
6	1505.4-1/201.6-20/1-50/1-80/1-100	1-1/1-20/1-50/201.6-80/1505.4-100	30
7	800.9-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/50.4-80/800.9-100	30
8	2016-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/2016-100	30
9	252.8-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/30.3-80/252.8-100	24
10	400-1/20.2-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	24
11	600.2-1/171.6-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	24
12	400-1/204.6-20/1-50-/1-80/1-100	1-1/1-20/1-50/10.2-80/20.3-100	24
13	201.6-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/15.2-100	24
14	100-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/10.2-80/10.2-100	24
15	252.8-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/16-80/20.3-100	24
16	100-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/10.2-100	24
17	400-1/302.8-20/1-50/1-80/1-100	1-1/1-20/1-50/3.2-80/15.2-100	24
18	400-1/320.4-20/1-80/1-50/1-80/1-100	1-1/1-20/1-50/2-80/5.3-100	24
19	302.8-1/30.3-20/1-50/1-100	1-1/1-20/1-50/25-80/302.8-100	20
20	201.6-1/15.2-20/1-50/1-80/1-100	1-1/1-20/1-50/15.2-80/201.6-100	20
21	501.8-1/36-20/1-50/1-100	1-1/1-20/1-50/36-80/501.8-100	20
22	400-1/25-20/1-50/1-80/1-100	1-1/1-20/1-50/25-80/400-100	20
23	1004.9-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/1004.9-100	20
24	1505.4-1/201.6-20/1-50/1-80/1-100	1-1/1-20/1-50/201.6-80/1505.4-100	20
25	800.9-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/50.4-80/800.9-100	20
26	2016-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/2016-100	20
27	252.8-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/30.3-80/252.8-100	18
28	400-1/20.2-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	18
29	600.2-1/171.6-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	18
30	400-1/204.6-20/1-50-/1-80/1-100	1-1/1-20/1-50/10.2-80/20.3-100	18
31	201.6-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/15.2-100	18

32	100-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/10.2-80/10.2-100	18
33	252.8-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/16-80/20.3-100	18
34	100-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/10.2-100	18
35	400-1/302.8-20/1-50/1-80/1-100	1-1/1-20/1-50/3.2-80/15.2-100	18
36	400-1/320.4-20/1-80/1-50/1-80/1-100	1-1/1-20/1-50/2-80/5.3-100	18
37	302.8-1/30.3-20/1-50/1-100	1-1/1-20/1-50/25-80/302.8-100	15
38	201.6-1/15.2-20/1-50/1-80/1-100	1-1/1-20/1-50/15.2-80/201.6-100	15
39	501.8-1/36-20/1-50/1-100	1-1/1-20/1-50/36-80/501.8-100	15
40	400-1/25-20/1-50/1-80/1-100	1-1/1-20/1-50/25-80/400-100	15
41	1004.9-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/1004.9-100	15
42	1505.4-1/201.6-20/1-50/1-80/1-100	1-1/1-20/1-50/201.6-80/1505.4-100	15
43	800.9-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/50.4-80/800.9-100	15
44	2016-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/2016-100	15
45	252.8-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/30.3-80/252.8-100	12
46	400-1/20.2-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	12
47	600.2-1/171.6-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	12
48	400-1/204.6-20/1-50-/1-80/1-100	1-1/1-20/1-50/10.2-80/20.3-100	12
49	201.6-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/15.2-100	12
50	100-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/10.2-80/10.2-100	12
51	252.8-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/16-80/20.3-100	12
52	100-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/10.2-100	12
53	400-1/302.8-20/1-50/1-80/1-100	1-1/1-20/1-50/3.2-80/15.2-100	12
54	400-1/320.4-20/1-80/1-50/1-80/1-100	1-1/1-20/1-50/2-80/5.3-100	12
55	302.8-1/30.3-20/1-50/1-100	1-1/1-20/1-50/25-80/302.8-100	10
56	201.6-1/15.2-20/1-50/1-80/1-100	1-1/1-20/1-50/15.2-80/201.6-100	10
57	501.8-1/36-20/1-50/1-100	1-1/1-20/1-50/36-80/501.8-100	10
58	400-1/25-20/1-50/1-80/1-100	1-1/1-20/1-50/25-80/400-100	10
59	1004.9-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/1004.9-100	10
60	1505.4-1/201.6-20/1-50/1-80/1-100	1-1/1-20/1-50/201.6-80/1505.4-100	10
61	800.9-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/50.4-80/800.9-100	10
62	2016-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/2016-100	10
63	252.8-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/30.3-80/252.8-100	8
64	400-1/20.2-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	8

65	600.2-1/171.6-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	8
66	400-1/204.6-20/1-50-/1-80/1-100	1-1/1-20/1-50/10.2-80/20.3-100	8
67	201.6-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/15.2-100	8
68	100-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/10.2-80/10.2-100	8
69	252.8-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/16-80/20.3-100	8
70	100-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/10.2-100	8
71	400-1/302.8-20/1-50/1-80/1-100	1-1/1-20/1-50/3.2-80/15.2-100	8
72	400-1/320.4-20/1-80/1-50/1-80/1-100	1-1/1-20/1-50/2-80/5.3-100	8
73	302.8-1/30.3-20/1-50/1-100	1-1/1-20/1-50/25-80/302.8-100	5
74	201.6-1/15.2-20/1-50/1-80/1-100	1-1/1-20/1-50/15.2-80/201.6-100	5
75	501.8-1/36-20/1-50/1-100	1-1/1-20/1-50/36-80/501.8-100	5
76	400-1/25-20/1-50/1-80/1-100	1-1/1-20/1-50/25-80/400-100	5
77	1004.9-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/1004.9-100	5
78	1505.4-1/201.6-20/1-50/1-80/1-100	1-1/1-20/1-50/201.6-80/1505.4-100	5
79	800.9-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/50.4-80/800.9-100	5
80	2016-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/100-80/2016-100	5
81	252.8-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/30.3-80/252.8-100	3
82	400-1/20.2-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	3
83	600.2-1/171.6-20/1-50/1-80/1-100	1-1/1-20/1-50/41-80/302.8-100	3
84	400-1/204.6-20/1-50-/1-80/1-100	1-1/1-20/1-50/10.2-80/20.3-100	3
85	201.6-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/15.2-100	3
86	100-1/50.4-20/1-50/1-80/1-100	1-1/1-20/1-50/10.2-80/10.2-100	3
87	252.8-1/100-20/1-50/1-80/1-100	1-1/1-20/1-50/16-80/20.3-100	3
88	100-1/30.3-20/1-50/1-80/1-100	1-1/1-20/1-50/5.3-80/10.2-100	3
89	400-1/302.8-20/1-50/1-80/1-100	1-1/1-20/1-50/3.2-80/15.2-100	3
90	400-1/320.4-20/1-80/1-50/1-80/1-100	1-1/1-20/1-50/2-80/5.3-100	3

9.2. Detailed results for (FiO_2, Hb, VO_2, RQ, CO) variation

9.2.1. FiO_2 variation

Table 31 and Figure 7 shows the mean variation percent for each virtual pts, it shows also that the smallest variation index with FiO_2 changes is the Qs/Qt index with mean 10% and SD 5%. The MPP index behaves relatively similar to Qs/Qt index with (mean 13% and SD 11%). The largest variation is $P(A\text{-}a)O_2$ index (mean 127% SD14percentage). The rest of other indices (PaO_2/FiO_2, PaO_2/PAO_2 and RI) have a large rage of mean (70-90%).

Table 31 FiO_2 variation

Subject	PaO_2/FiO_2	$P(A\text{-}a)O_2$	PaO_2/PAO_2	RI	Qs/Qt	MPP
1	56	130	81	80	11	5
2	65	133	90	85	6	8
3	104	139	135	118	2	3
4	99	138	126	108	12	12
5	42	119	64	75	10	16
6	51	104	42	72	18	34
Mean %	70	127	90	90	10	13
SD%	26	14	36	19	5	11

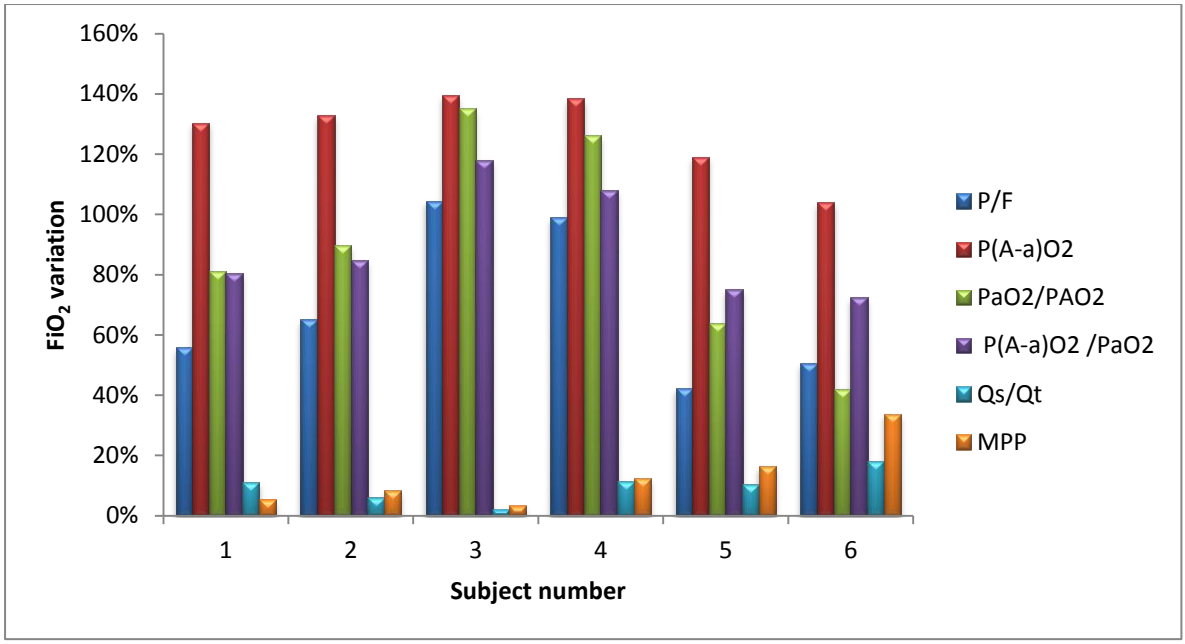


Figure 47 FiO_2 % variation

The PaO_2/FiO_2 ratio varied nonlinearly with FiO_2 with variation mean of 70% and SD 26%. Figure 8 shows that in pt6 the PaO_2/FiO_2 decrease with FiO_2 from 30-50% and between FiO_2 50-60% have no observable change, the PaO_2/FiO_2 increased substantially with FiO_2 >60%.In most of pts (pt1,pt2, pt5) the PaO_2/FiO_2 decrease with FiO_2 from 30-60% and between FiO_2 60-80% have no observable change, the PaO_2/FiO_2 increased substantially with FiO_2 >80%. In pt. 3, 4 the PaO_2/FiO_2 decreases with increase of FiO_2

the A-a gradient index varied nonlinearly with FiO_2 with variation mean of 127% and SD 14%, which is the largest variation among six indices with FiO_2 changes. Figure nine shows that in most of pts (pt1, pt2, pt3, pt4, pt5) the A-a gradient index increase with FiO_2. In pt6 the A-a gradient index increase with FiO_2, and from FiO_2 90-100% have no observable change. Among the patients group the largest patient variation is pt3

(139%) and the smallest patient variation is pt. 6 (104%). The smallest value of A-a gradient is 9.27 with Pt6 on 30% of FiO_2 and the largest value is 79.39 with Pt3 on 100% FiO_2.

The PaO_2/PAO_2 ratio index varied nonlinearly with FiO_2 with variation mean of 90% and SD 36%. Figure 10 shows that in pt1, pt2, pt5 the PaO_2/PAO_2 decrease with FiO_2 increase between 30-70% then the PaO_2/PAO_2 increased substantially with FiO_2 >70%. In pt3, pt4 the PaO_2/PAO_2 decreases within increase of FiO_2. In pt6 the PaO_2/PAO_2 decrease with FiO_2 increase between 30-60% and the PaO_2/PAO_2 increased substantially with FiO_2 >60%. Among the patients group the largest patient variation is pt3 (135%) and the smallest patient variation is pt. 6 (42%). The smallest value of PaO_2/PAO_2 is 0.09 with Pt3 on 100% of FiO_2 and the largest value is 0.53 with Pt6 on 100% FiO_2.

The Respiratory index (RI) The RI varied nonlinearly with FiO_2 with variation mean of 90% and SD 19%. Figure 11 shows that in pts (1, 2) the RI increase with FiO_2 and between FiO_2 80-90% have no observable change, the RI decrease substantially with FiO_2 >90%. In pt. (3, 4) the RI increase within increase of FiO_2. In pt. (5, 6) the RI increase with FiO_2 and between FiO_2 60-70% have no observable change, the RI decrease with FiO_2 >70%. Among the patients group the largest patient variation is pt3 (118%) and the smallest patient variation is pt. 6 (72%). The smallest value of RI is 0.84 with Pt6 on 30% of FiO_2 and the largest value is 9.13 with Pt3 on 100% FiO_2.

The Qs/Qt index varied linearly with FiO_2 with variation mean of 10% and SD 5%, which is the smallest variation among six indices with FiO_2 changes. Figure 12 shows that in all pts the Qs/Qt is relatively unaffected by FiO_2 variation .Among the patients group the largest patient variation is pt6 (18%) and the smallest patient variation is pt3 (2%). The smallest value of Qs/Qt index is 0.10 with Pt6 on 100% of FiO_2 and the largest value is 0.34 with Pt3 on 40% FiO_2.

The MPP index varied linearly with FiO_2 with variation mean of 13% and SD 11%. Figure 13 shows that in most of pts (pt1, pt2, pt3, pt4) the MPP is relatively unaffected by FiO_2 variation. In pt5, pt6 the MPP is relatively unaffected by FiO_2 variation but it increases relatively between 50-70%. Among the patients group the largest patient variation is pt6 (34%) and the smallest patient variation is pt3 (3%). The smallest value of MPP index is 7.16 with Pt3 on 90% of FiO_2 and the largest value is 22.81 with Pt6 on 90% FiO_2.

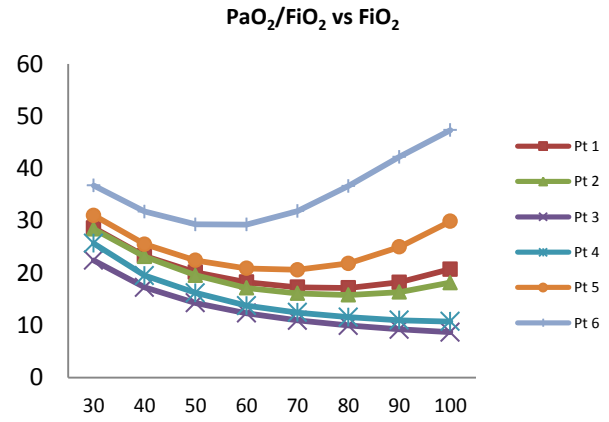


Figure 48 PaO_2/FiO_2 ratio (kPa) vs FiO_2 %changes

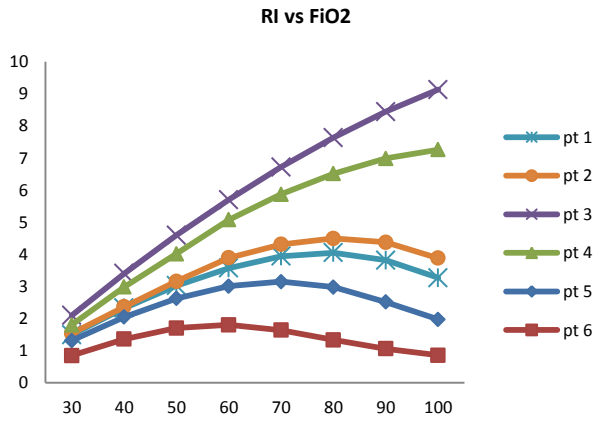


Figure 51 RI vs FiO_2 %changes

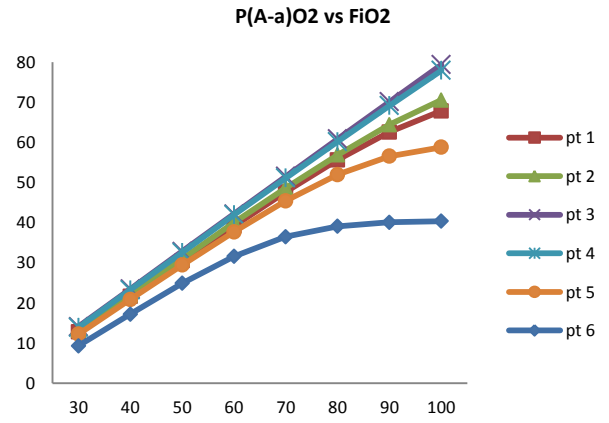


Figure 49 $P(A-a)O_2$ vs FiO_2 % changes

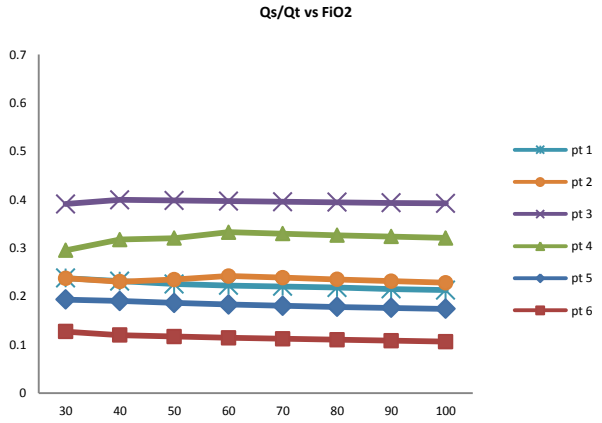


Figure 52 Qs/Qt vs FiO_2 %changes

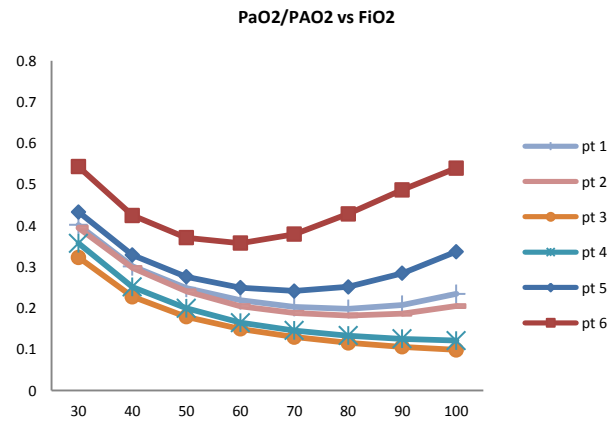


Figure 50 PaO_2/PAO_2 vs FiO_2 %changes

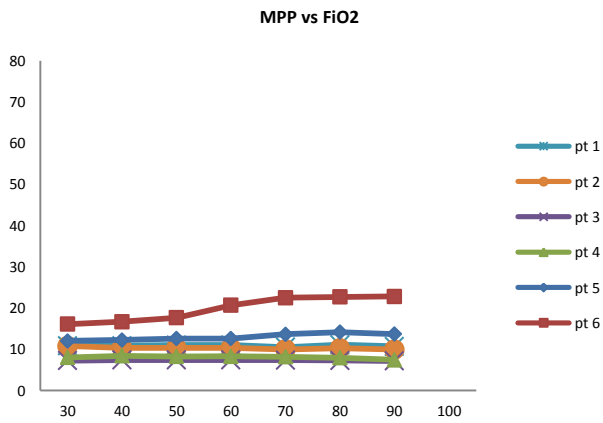


Figure 53 MPP vs FiO_2 %changes

9.2.2. Hb variation

Table 32 and Figures14, 15 shows the mean variation percent for each virtual pts with two different level of FiO_2 changes (30% and 60%) with a variation of haemoglobin (Hb). Thus, Qs/Qt index considers the lowest mean variation in both range of FiO_2 (mean 9%). Whereas, the PaO_2/PAO_2 index behaves relatively similar to Qs/Qt index, which has a mean of 12% for, both rage of FiO_2. On the other hand, the largest variation is RI index (mean 44%). The rest of other indices (PaO_2/FiO_2, $P(A\text{-}a)O_2$ and MPP) have a same mean variation percent (30%).

Table 32 Haemoglobin variation

	PaO_2/FiO_2		**PaO_2/PAO_2**		**$P(A\text{-}a)O_2$**		**RI**		**Qs/Qt**		**MPP**
FiO_2	30%	60%	30%	60%	30%	60%	30%	60%	30%	60%	30-60%
Subject											
1	32	30	31	29	17	7	51	38	7	9	30
2	32	31	31	31	17	7	51	39	7	9	31
3	37	38	36	38	13	5	52	46	2	3	38
4	30	33	30	32	13	5	46	40	3	2	33
5	29	28	29	27	18	8	49	37	8	13	28
6	24	19	23	18	22	9	47	28	15	24	19
Mean %	31	30	30	29	17	7	49	38	7	10	30
SD%	4	7	4	6	3	2	3	6	5	8	7
Mean of Both FiO_2	30		12		30		44		9		30

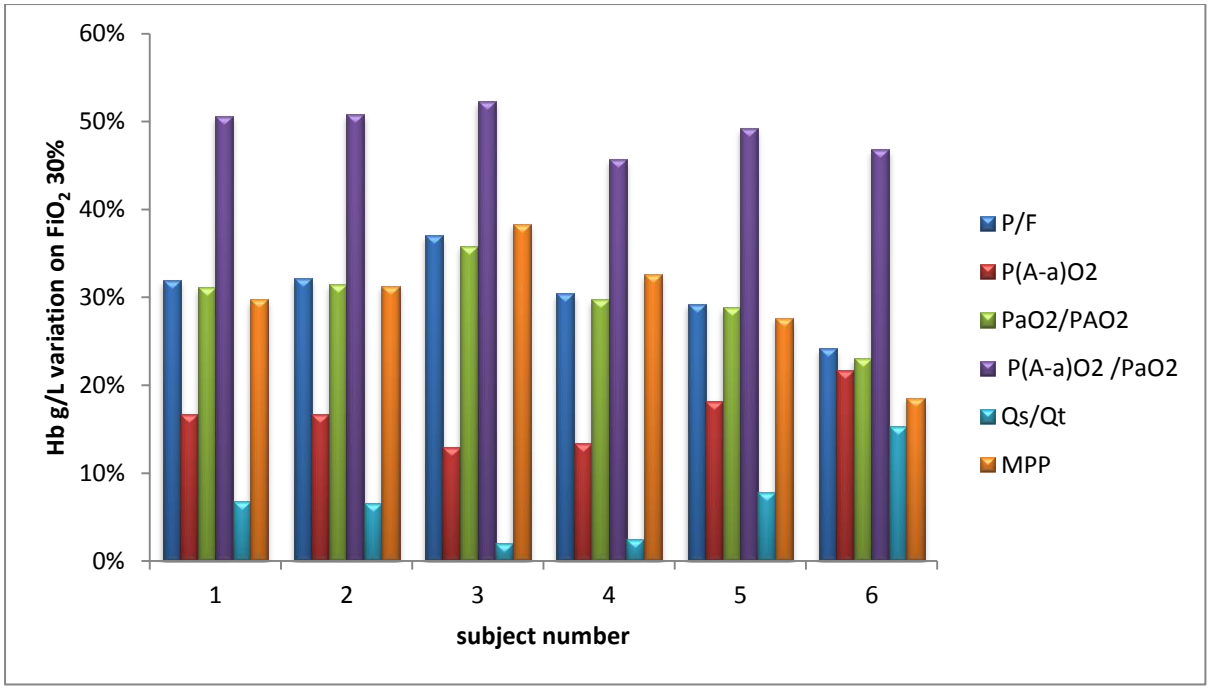


Figure 54 Hb g/l variation on $FiO_2$30%

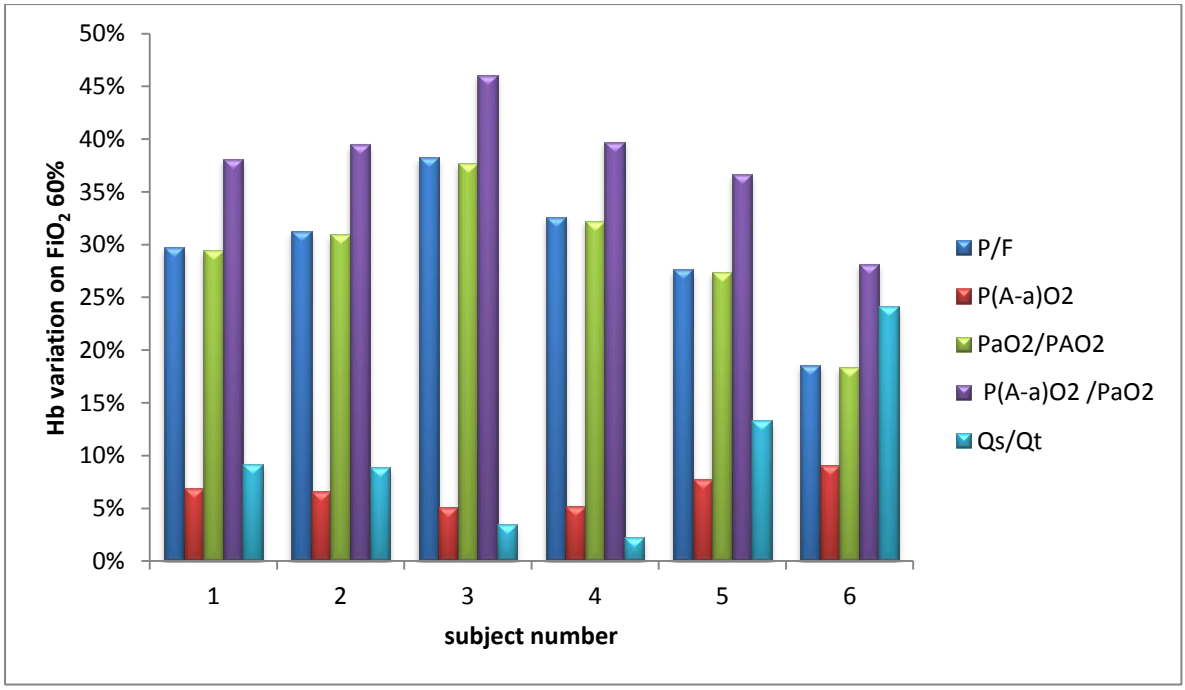


Figure 55 Hb g/l variation on FiO_2 60%

The PaO_2/FiO_2 ratio index varied linearly with an increase of Hb. Figure 16 and 17 shows that on FiO_2 30% the mean percent variation is 18% and

SD 6%, on FiO_2 60% the mean variation is 50% with SD 20%. Therefore, the mean percent for both range of Hb is 34%. Among the patients group with FiO_2 of 30% the largest patient variation is pt6 (24%) and the smallest patient variation is pt4 (9%). On the same FiO_2 level the smallest value of The PaO_2/FiO_2 ratio index is 15.84 for Pt3 on Hb=60 g/l and the largest value is 37.59 for Pt3 on Hb=160 g/l. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (76%) and the smallest patient variation is pt4 (31%). On the same FiO_2 level the smallest value of The PaO_2/FiO_2 ratio index is 8.58 for Pt3 on Hb=60 g/l and the largest value is 29.84 for Pt3 on Hb=160 g/l.

The A-a gradient varied linearly with an increase of Hb. Figures 18 and 19 shows that on FiO_2 30% the mean percent variation is 17% and SD 3%, on FiO_2 60% the mean variation is 7% with SD 2%. Therefore, the mean percent for both range of FiO_2 is 12% Among the patients group with FiO_2 of 30% the largest patient variation is pt6 (22%) and the smallest patient variation are pt3 and pt4 (13%). On the same FiO_2 level the smallest value of the A-a gradient index is 9.06 for Pt6 on Hb=160 g/l and the largest value is 15.62 for Pt4 on Hb 60g/l. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (9%) and the smallest patient variation are pt3 and pt4 (5%). On the same FiO_2 level the smallest value of the A-a gradient index is 31.29 for pt6 on Hb=160 g/l and the largest value is 43.96 for pt4 on Hb 60g/l.

The PaO_2/PAO_2 index varied linearly with an increase of Hb. Figures 20 and 21 shows that on FiO_2 30% the mean percent variation is 30% and SD 4%, on FiO_2 60% the mean variation is 29% with SD 6%. Therefore, the mean percent for both range of FiO_2 is 30%. Among the patients group with FiO_2 of 30% the largest patient variation is pt3 (36%) and the smallest patient variation is pt6 (23%). On the same FiO_2 level, the smallest value of the PaO_2/PAO_2 index is 0.23 for Pt3 on Hb=60 g/l and the largest value is 0.55 for Pt6 on Hb 160g/l. Among the patients group with FiO_2 of 60% the largest patient variation is pt3 (38%) and the smallest patient variation is pt6 (18%). On the same FiO_2 level the smallest value of the PaO_2/PAO_2 index is 0.10 for pt3 on Hb=60g/l and the largest value is 0.36 for pt6 on Hb=60g/l.

The RI index varied linearly with an increase of Hb. Figures 22 and 23 shows that on FiO_2 30% the mean percent variation is 49% and SD 3%, on FiO_2 60% the mean variation is 38% with SD 6%. Therefore, the mean percent for both range of FiO_2 is 44%. Among the patients group with FiO_2 of 30% the largest patient variation is pt3 (52%) and the smallest patient variation is pt6 (47%). On the same FiO_2 level the smallest value of the RI index is 0.80 for Pt6 on Hb=160g/l and the largest value is 3.33 for Pt3 on Hb =60g/l. Among the patients group with FiO_2 of 60% the largest patient variation is pt3 (46%) and the smallest patient variation is pt6 (28%). On the same FiO_2 level the smallest value of the RI index is 1.75 for pt6 on Hb=160g/l and the largest value is 8.57 for pt3 on Hb=60g/l.

The Qs/Qt ratio index varied linearly with an increase of Hb. Figures 24 and 25 shows that on FiO_2 30% the mean percent variation is 7% and SD 5%, on FiO_2 60% the mean variation is 10% with SD 8%. Therefore, the mean percent for both range of FiO_2 is 9%. Among the patients group with FiO_2 of 30% the largest patient variation is pt6 (15%) and the smallest patient variation is pt3 (2%). On the same FiO_2 level the smallest value of the Qs/Qt ratio index is 0.12 for Pt6 on Hb=160g/l and the largest value is 0.39 for Pt3 on Hb =80-120g/l. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (24%) and the smallest patient variation is pt4 (2%). On the same FiO_2 level the smallest value of the Qs/Qt ratio index is 0.10 for pt6 on Hb=160g/l and the largest value is .40 for pt3 on Hb=60-140g/l.

The MPP varied linearly with Hb with variation mean of 30% and SD 7%. Figure 25 shows that in most all of pts the MPP increase with Hb variation. Among the patients group the largest patient variation is pt3 (38%) and the smallest patient variation is pt6 (19%).The smallest value of MPP index is 5.15 with Pt3 on 60 g/l of Hb and the largest value is 17.98 with Pt6 on 160 g/l of Hb.

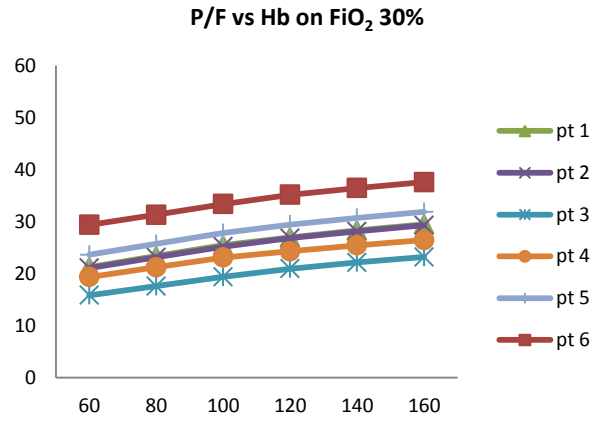


Figure 56 PaO_2/FiO_2 vs Hb on FiO_2 30%

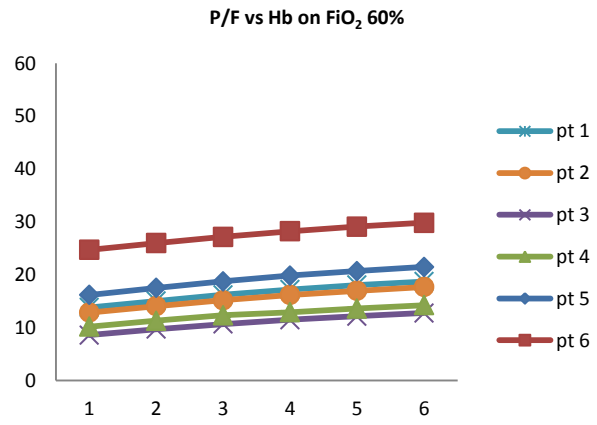


Figure 57 PaO_2/FiO_2 vs Hb on FiO_2 60%

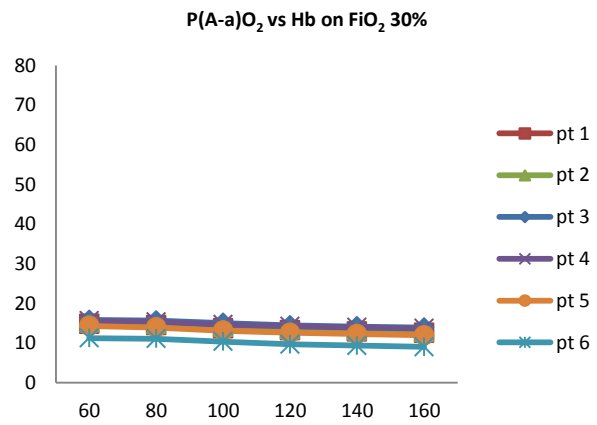


Figure 58 $P(A-a)O_2$ vs Hb on FiO_2 30%

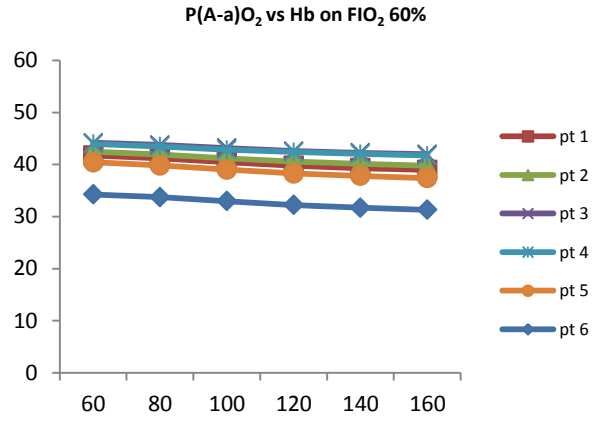


Figure 59 $P(A-a)O_2$ vs Hb on FiO_2 60%

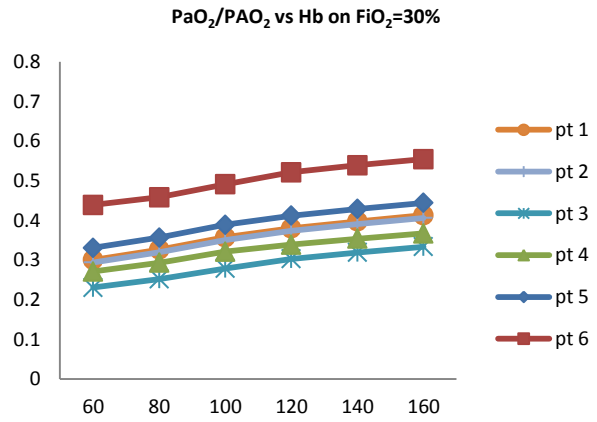


Figure 60 PaO_2/PAO_2 vs Hb on FiO_2=30%

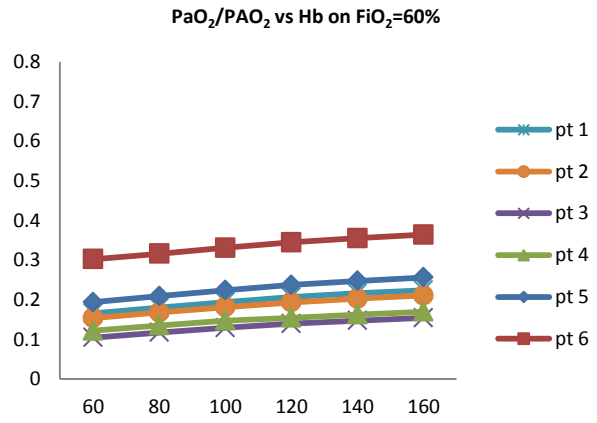


Figure 61 PaO_2/PAO_2 vs Hb on FiO_2=60%

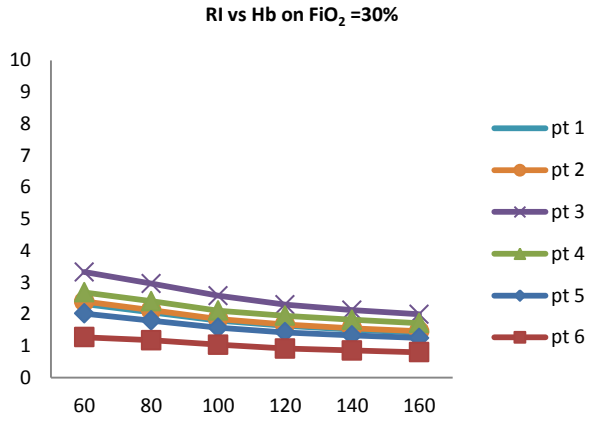


Figure 62 RI vs Hb on FiO_2 =30%

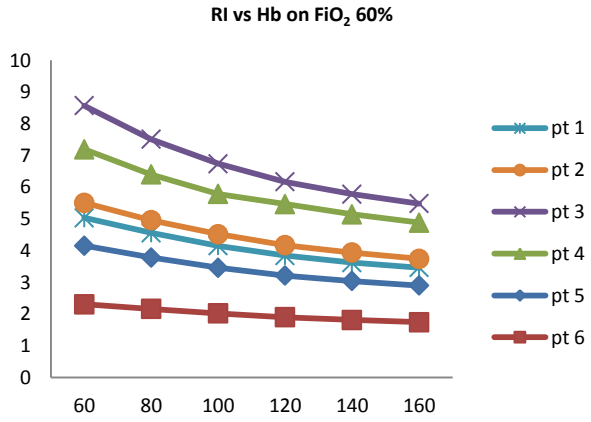


Figure 63 RI vs Hb on FiO_2 60%

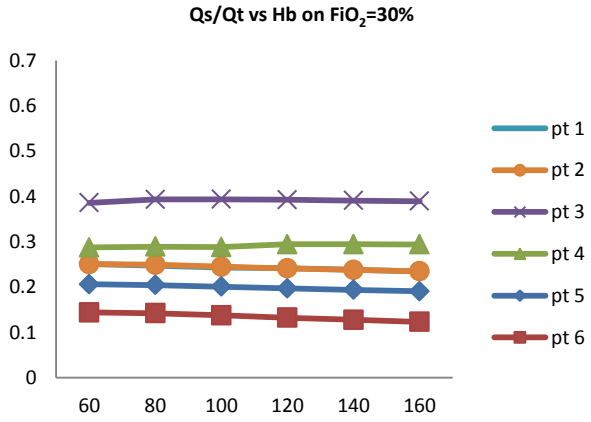


Figure 64 Qs/Qt vs Hb on FiO_2=30%

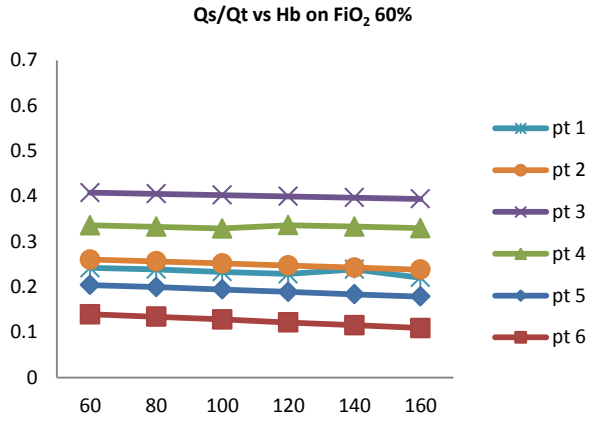


Figure 65 Qs/Qt vs Hb on FiO_2 60%

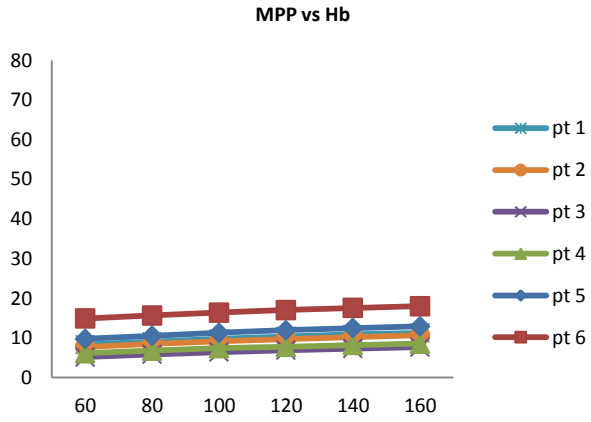


Figure 66 MPP vs Hb

9.2.3. VO_2 variation

Table 33 and Figures 27and 28 shows the mean variation percent for each virtual pts with two different levels of FiO_2 changes (30% and 60%) with a variation of Oxygen consumption (VO_2). Thus, Qs/Qt index considers the lowest mean variation in both range of FiO_2 (mean 22%). Whereas, the $P(A\text{-}a)O_2$ index behaves relatively similar to Qs/Qt index which has a mean of 23% for both rage of FiO_2. On the other hand, the largest variation is MPP index (mean 52%). The rest of other indices (PaO_2/FiO_2, PaO_2/PAO_2, and RI) their mean variation percent range between (25-34%).

Table 33 VO_2 variation

	PaO_2/FiO_2		$P(A\text{-}a)O_2$		PaO_2/PAO_2		RI		Qs/Qt		MPP
FiO_2	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30-60%**
Subject											
1	21	52	30	5	7	40	12	46	24	19	52
2	20	51	30	5	8	39	13	44	22	20	51
3	12	26	37	10	17	13	25	14	3	7	26
4	9	31	34	7	17	19	25	22	6	9	31
5	19	67	32	13	9	55	16	64	26	27	67
6	24	76	42	30	11	63	23	88	55	51	84
mean	18	50	34	12	11	38	19	46	23	22	52
SD	6	20	5	9	4	20	6	27	19	16	22
Both means	34		23		25		33		22		52

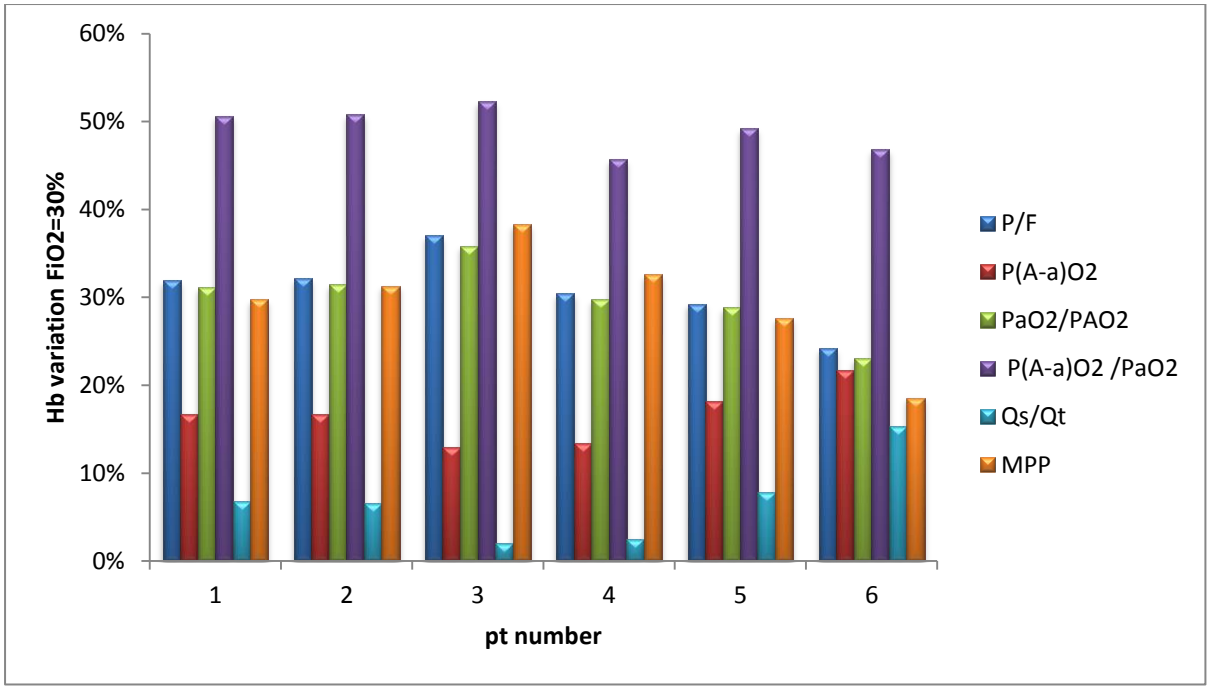


Figure 67 Hb variation FiO_2=30%

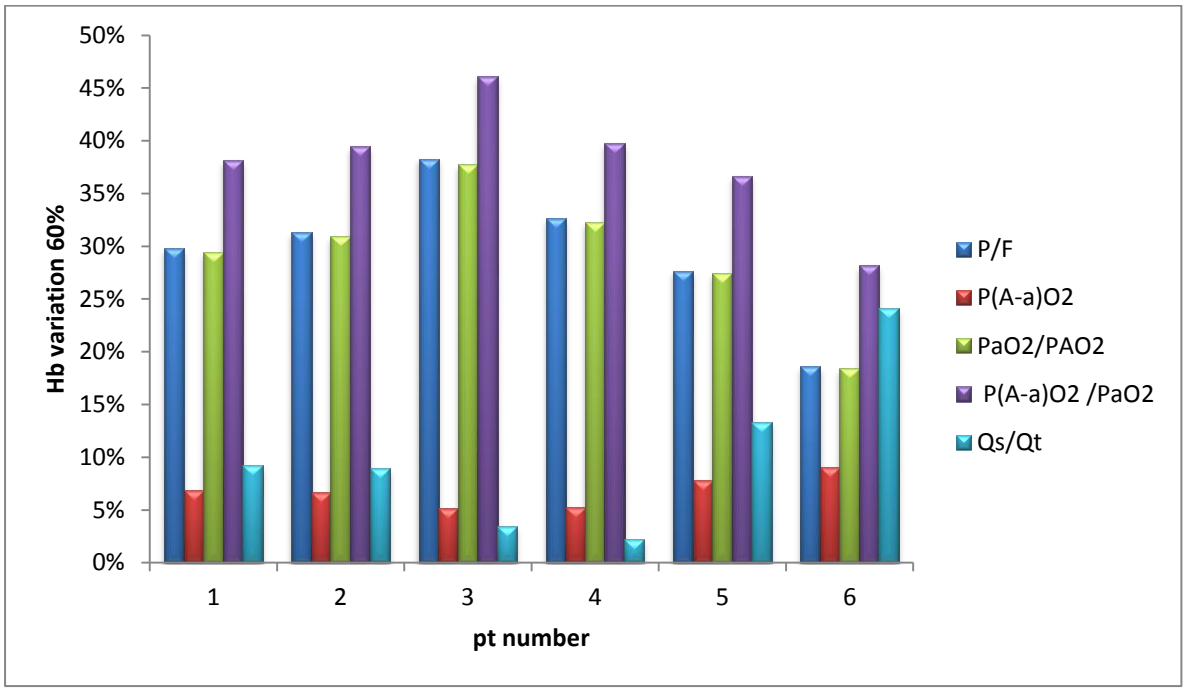


Figure 68 Hb variation on FiO_2 60%

The PaO_2/FiO_2 ratio index varied linearly with an increase of VO_2. On FiO_2 30% the mean percent variation is 18% and SD 6%, on FiO_2 60% the mean variation is 50% with SD 20%. Therefore, the mean percent for

both range of FiO_2 is 34%. Figurers 29 and 30 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (24%) and the smallest patient variation is pt4 (9%). On the same FiO_2 level the smallest value of The PaO_2/FiO_2 ratio index is 21.60 for Pt3 on VO_2=350 ml min−1 l and the largest value is 42.77 for Pt6 on Hb=150 ml min−1. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (76%) and the smallest patient variation is pt4 (31%). On the same FiO_2 level the smallest value of The PaO_2/FiO_2 ratio index is 12.64 for Pt4 on VO_2=350 ml min−1 and the largest value is 48.01 for Pt6 on VO_2=150 ml min−1.

The A-a gradient index varied linearly with an increase of VO_2. On FiO_2 30% the mean percent variation is 34% and SD 5%, on FiO_2 60% the mean variation is 12% with SD 9%. Therefore, the mean percent for both range of FiO_2 is 23%. Figures 31 and 32 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (42%) and the smallest patient variation are pt1 and pt2 (30%). On the same FiO_2 level the smallest value of the A-a gradient index is 6.92 for Pt6 on VO_2=350 ml min−1 and the largest value is 16.13 for Pt4 on VO_2=150 ml min−1. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (30%) and the smallest patient variation are pt1 and pt2 (5%). On the same FiO_2 level the smallest value of the A-a gradient index is 23.35 for Pt6 on VO_2=150 ml min−1 and the largest value is 42.67 for Pt5 on VO_2=150 ml min−1.

The PaO_2/PAO_2 ratio index varied linearly with an increase of VO_2. On FiO_2 30% the mean percent variation is 11% and SD 4%, on FiO_2 60% the mean variation is 38% with SD 20%. Therefore, the mean percent for both range of FiO_2 is 25%. Figures 33 and 34 shows that among the patients group with FiO_2 of 30% the largest patient variation are pt3 and pt4 (17%) and the smallest patient variation is pt1 (7%). On the same FiO_2 level the smallest value of The PaO_2/PAO_2 ratio index 0.30 for Pt3 on VO_2=150 ml min−1 and the largest value is 0.59 for Pt6 on VO_2=350 ml min−1. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (63%) and the smallest patient variation is pt3 (13%). On the same FiO_2 level the smallest value of the PaO_2/PAO_2 ratio index is 0.14 for Pt3 on VO_2=350 ml min−1 and the largest value is 0.55 for Pt6 on VO_2=150 ml min−1 .

The RI index varied linearly with an increase of Hb. On FiO_2 30% the mean percent variation is 19% and SD 6%, on FiO_2 60% the mean variation is 46% with SD 27%. Therefore, the mean percent for both range of FiO_2 is 33%. Figures 35 and 36 shows that among the patients group with FiO_2 of 30% the largest patient variation are pt3 and pt4 (25%) and the smallest patient variation is pt1 (12%). On the same FiO_2 level the smallest value of the RI index 0.68 for Pt6 on VO_2=350 ml min−1 and the largest value is 2.26 for Pt3 on VO_2=150 ml min−1. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (88%) and the smallest patient variation is pt3 (14%). On the same

FiO_2 level the smallest value of the RI index is 0.81 for Pt6 on VO_2=150 ml min−1 and the largest value is 5.80 for Pt3 on VO_2=350 ml min−1.

The Qs/Qt index varied linearly with an increase of VO_2. On FiO_2 30% the mean percent variation is 23% and SD 19%, on FiO_2 60% the mean variation is 22% with SD 16%. Therefore, the mean percent for both range of FiO_2 is 22%. Figures 37 and 38 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (51%) and the smallest patient variation is pt3 (7%). On the same FiO_2 level the smallest value of the Qs/Qt index is 0.08 for Pt6 on VO_2=150ml min−1 and the largest value is 0.39 for Pt3 on VO_2=250ml min−1. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (51%) and the smallest patient variation is pt3 (7%). On the same FiO_2 level the smallest value of the Qs/Qt index is 0.07 for pt6 on VO_2=15 ml min−1 and the largest value is 0.40 for Pt3 on VO_2 =350 ml min−1.

The MPP varied linearly with VO_2 and a variation mean is 52% and SD 22% that is the largest variation among five indices. Figure 39 shows that in most of all pts the MPP decrease with VO_2 variation. Among the patients group the largest patient variation is pt6 (84%) and the smallest patient variation is pt3 (26%). The smallest value of MPP index is 7.5 with Pt3 on VO_2=350 ml min−1 and the largest value is 30.82 with Pt6 on VO_2=150 ml min−1.

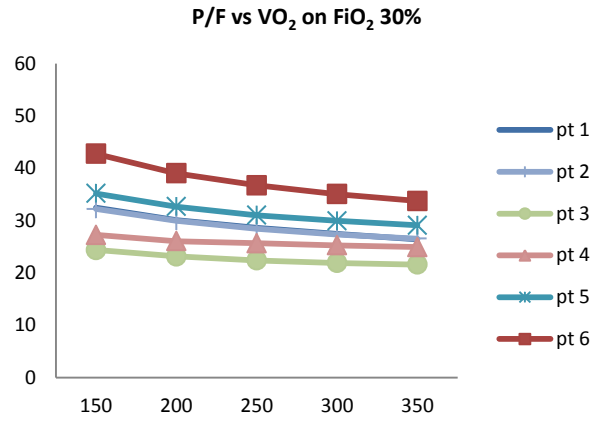


Figure 69 PaO_2/FiO_2 vs VO_2 on FiO_2 30%

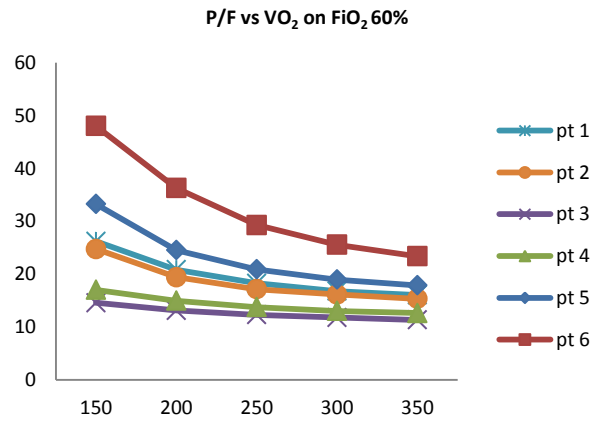


Figure 70 PaO_2/FiO_2 vs VO_2 on FiO_2 60%

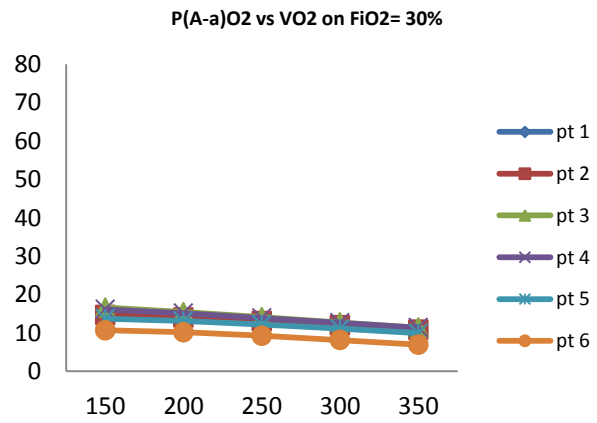


Figure 71 $P(A-a)O_2$ vs VO_2 on FiO_2= 30%

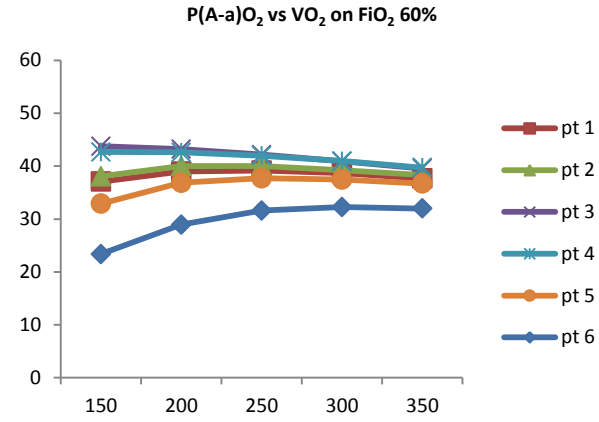


Figure 72 $P(A-a)O_2$ vs VO_2 on FiO_2 60%

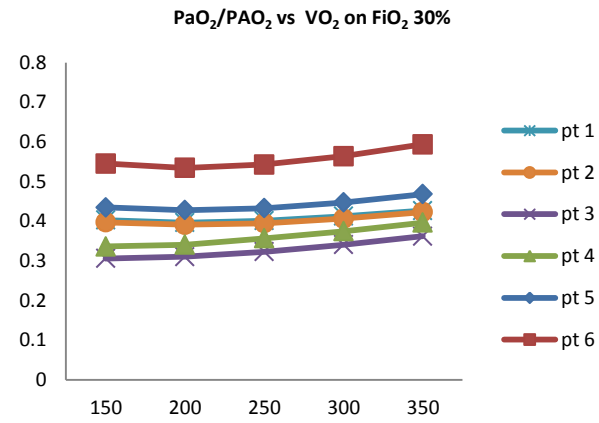


Figure 73 PaO_2/PAO_2 vs VO_2 on FiO_2 30%

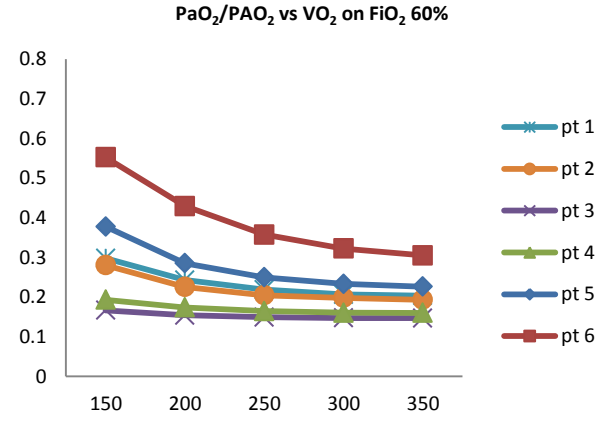


Figure 74 PaO_2/PAO_2 vs VO_2 on FiO_2 60%

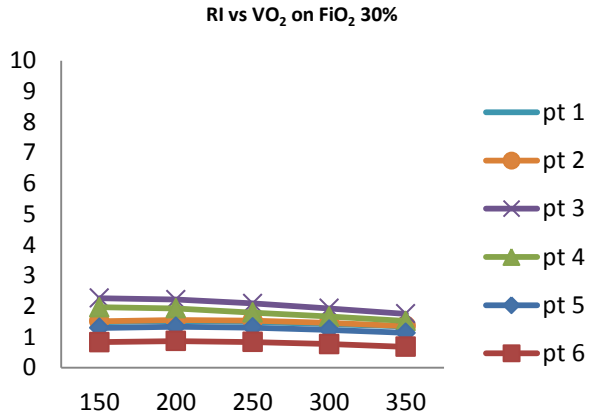


Figure 75 RI vs VO2 on FiO2 30%

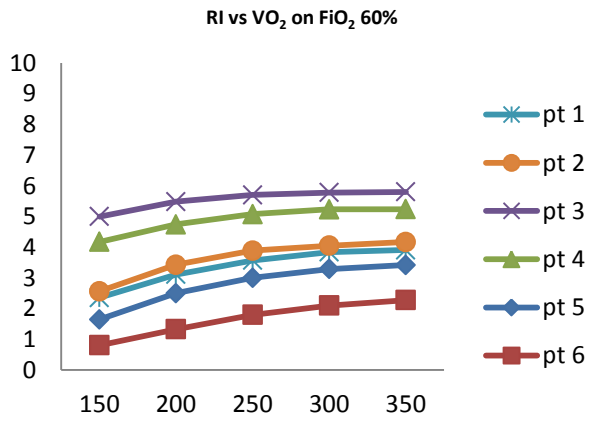


Figure 76 RI vs VO_2 on FiO_2 60%

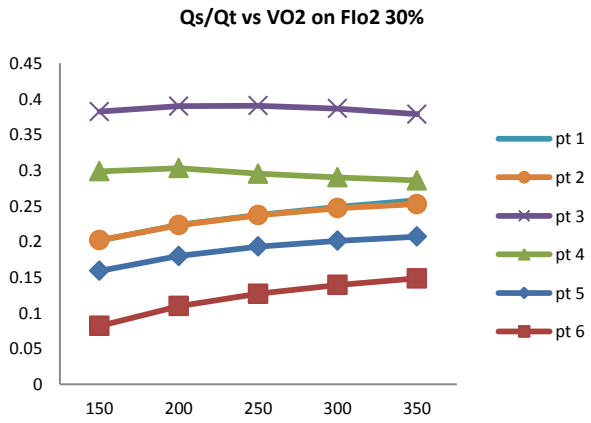


Figure 77 Qs/Qt vs VO_2 on FiO_2 30%

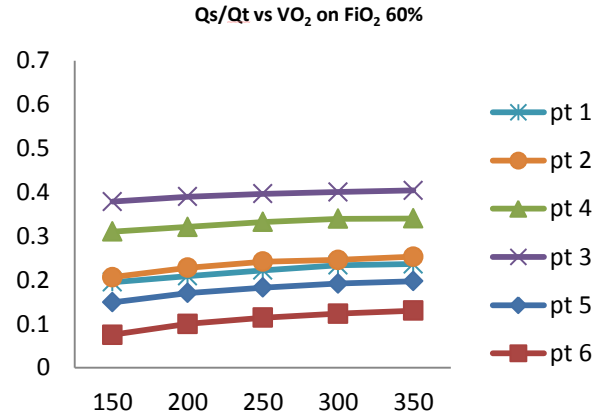


Figure 78 Qs/Qt vs VO_2 on FiO_2 60%

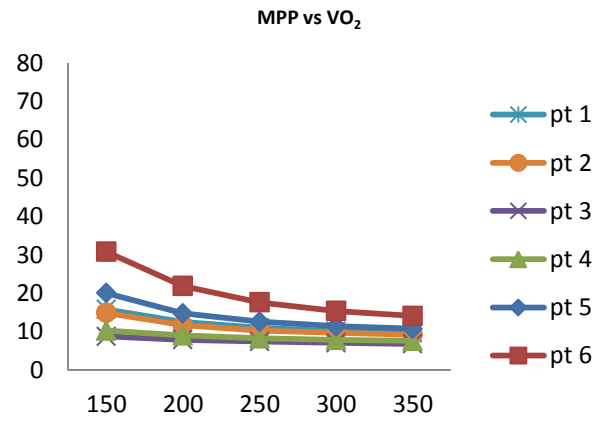


Figure 79 MPP vs VO_2

9.2.4. RQ variation

Table 34, Figures 40, and 41 shows the mean variation percent for each virtual pts with two different levels of FiO_2 changes (30% and 60%) with a variation of respiratory quotient (RQ). Thus, Qs/Qt index considers the lowest mean variation in both range of FiO_2 (mean 5%). On the other hand, the largest variation is RI index (mean 45%). The rest of other indices (PaO_2/FiO_2, $P(A\text{-}a)O_2$, PaO_2/PAO_2, and MPP) their mean variation percent range between (21-30%).

Table 34 RQ variation

	PaO_2/FiO_2		$P(A\text{-}a)O_2$		PaO_2/PAO_2		RI		Qs/Qt		MPP
FiO_2	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30-60%**
Subject											
1	23	24	26	15	30	30	50	40	6	1	24
2	23	24	26	15	30	31	50	40	7	0	24
3	27	29	25	14	35	37	52	44	2	1	29
4	23	27	24	14	30	34	48	42	7	0	27
5	22	21	28	16	29	27	51	37	10	0	21
6	18	10	36	17	25	17	55	27	20	1	10
mean	23	23	27	15	30	30	51	38	9	1	23
SD	3	7	5	1	3	7	2	6	6	0	7
Both means	23		21		30		45		5		23

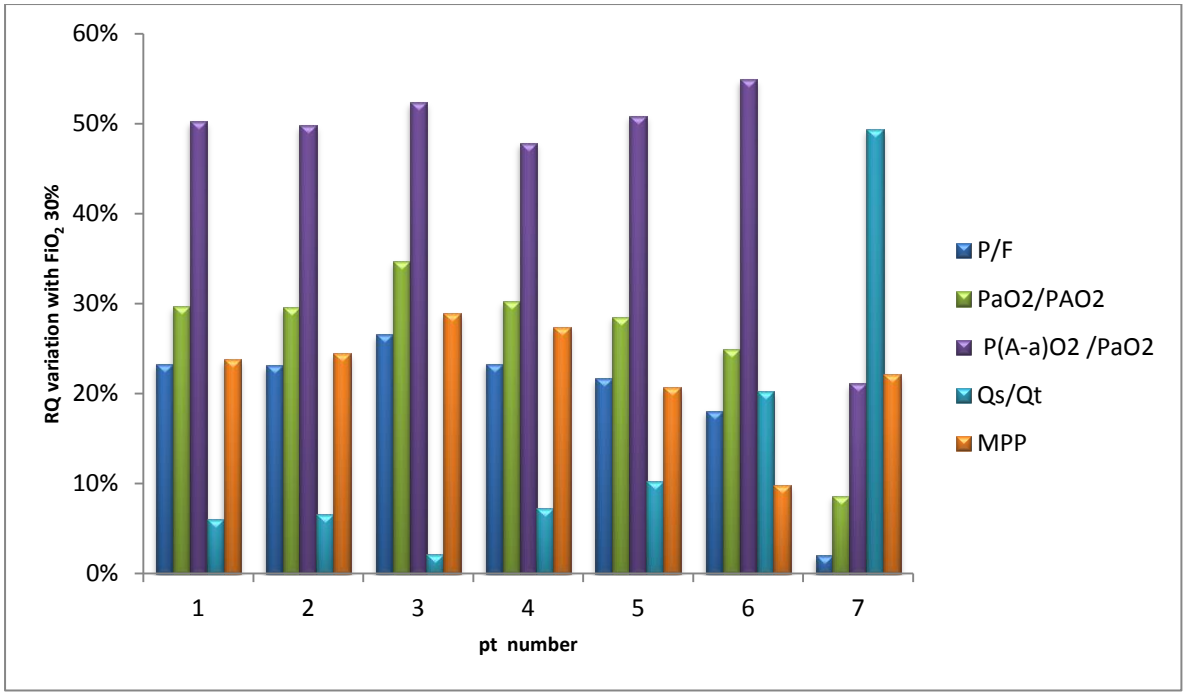


Figure 80 RQ variation with FiO_2 30%

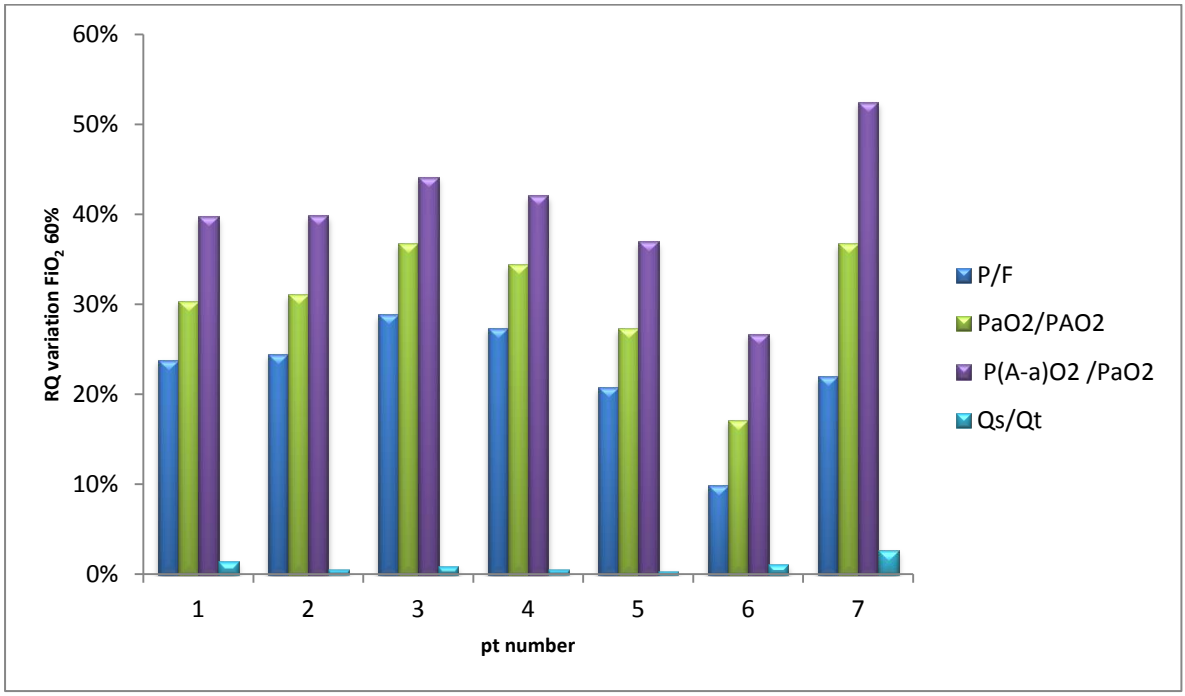


Figure 81 RQ variation on FiO_2 60%

The PaO_2/FiO_2 ratio index varied linearly with an increase of RQ. On FiO_2 30% the mean percent variation is 23% and SD 3%, on FiO_2 60% the mean variation is 23% with SD 7%. Therefore, the mean percent for both range of FiO_2 is 23%. Figures 42 and 43 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt3 (27%) and the smallest patient variation is pt4 (18%). On the same FiO_2 level the smallest value of The PaO_2/FiO_2 ratio index is 19.02 for pt3 on RQ=0.4 and the largest value is 39.19 for Pt6 on RQ=1.2. Among the patients group with FiO_2 of 60% the largest patient variation is pt3 (29%) and the smallest patient variation is pt6 (10%). On the same FiO_2 level the smallest value of the PaO_2/FiO_2 ratio index is 10.37 for pt3 on RQ=0.4 and the largest value is 30.43 for pt6 on RQ=1.2.

The A-a gradient index varied linearly with an increase of RQ. On FiO_2 30% the mean percent variation is 27% and SD 5%, on FiO_2 60% the mean variation is 15% with SD 1%. Therefore, the mean percent for both range of FiO_2 is 21%. Figures 44 and 45 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (36%) and the smallest patient variation is pt4 (24%). On the same FiO_2 level the smallest value of the A-a gradient index is 7.74 for pt6 on RQ=1.2 and the largest value is 15.65 for Pt4 on RQ=0.4. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (17%) and the smallest patient variation are pt3 and pt4 (14%). On the same FiO_2 level the smallest value of the A-a gradient index is 29.05 for pt6 on RQ=1.2 and the largest value is 44.91 for pt4 on RQ=0.4.

The PaO_2/PAO_2 ratio index varied linearly with an increase of RQ. On FiO_2 30% the mean percent variation is 30% and SD 3%, on FiO_2 60% the mean variation is 30% with SD 7%. Therefore, the mean percent for both range of FiO_2 is 30%. Figures 46 and 47 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt3 (35%) and the smallest patient variation is pt6 (25%). On the same FiO_2 level the smallest value of the PaO_2/PAO_2 ratio index is 0.26 for pt3 on RQ=0.4 and the largest value is 0.60 for pt6 on RQ=1.2. Among the patients group with FiO_2 of 60% the largest patient variation is pt3 (37%) and the smallest patient variation is pt6 (17%). On the same FiO_2 level the smallest value of $PaO2/PAO_2$ ratio index is 0.12 for pt3 on RQ=0.4 and the largest value is 0.38 for pt6 on RQ=1.2.

The RI index varied linearly with an increase of RQ. On FiO_2 30% the mean percent variation is 51% and SD 2%, on FiO_2 60% the mean variation is 38% with SD 6%. Therefore, the mean percent for both range of FiO_2 is 45%. Figures 48 and 49 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (55%) and the smallest patient variation is pt4 (48%). On the same FiO_2 level the smallest value of the RI index is 0.64 for pt6 on RQ=1.2 and the largest value is 2.79 for pt3 on RQ=0.4 .Among the patients group with FiO_2 of 60% the largest patient variation is pt3 (44%) and the smallest patient variation is pt6 (27%). On the same FiO_2 level the smallest value of RI index is 1.59 for pt6 on RQ=1.2 and the largest value is 7.26 for pt3 on RQ=0.4.

The Qs/Qt index varied linearly with an increase of RQ. On FiO_2 30% the mean percent variation is 9% and SD 6%, on FiO_2 60% the mean variation is 1% with SD 0%. Therefore, the mean percent for both range of FiO_2 is 5%. Figures 50 and 51shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (20%) and the smallest patient variation is pt3 (2%). On the same FiO_2 level the smallest value of the Qs/Qt index is 0.11 for pt6 on RQ=0.4 and the largest value is 0.39 for pt3 on RQ=1.2. Among the patients group with FiO_2 of 60% the largest patient variation are pt1, pt3, and pt6 (1%) and the smallest patient variation are pt2, pt4, and pt5 (0%). On the same FiO_2 level the smallest value of Qs/Qt index is 0.11 for pt6 on RQ=0.4-1.2 and the largest value is 0.39 for pt3 on RQ=0.4-1.2.

The MPP varied linearly with RQ and a variation mean is 23% and SD 7%. Figure 51 shows that in all pts the MPP increase relatively with RQ variation. Among the patients group the largest patient variation is pt3 (29%) and the smallest patient variation is pt6 (10%). The smallest value of MPP index is 7.01 with Pt4 on RQ=0.4 and the largest value is 18.33 with Pt6 on RQ=1.2.

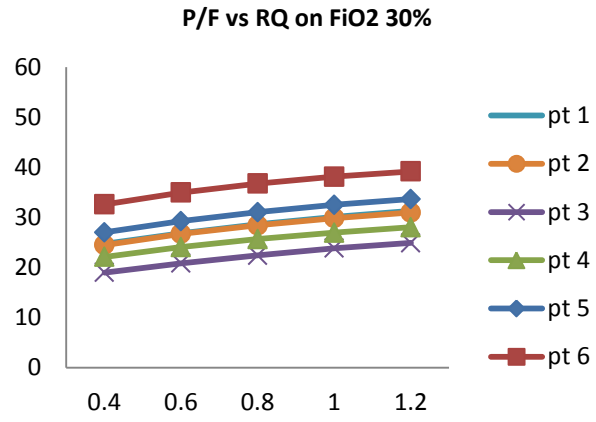


Figure 82 PaO_2/FiO_2 vs RQ on FiO_2 30%

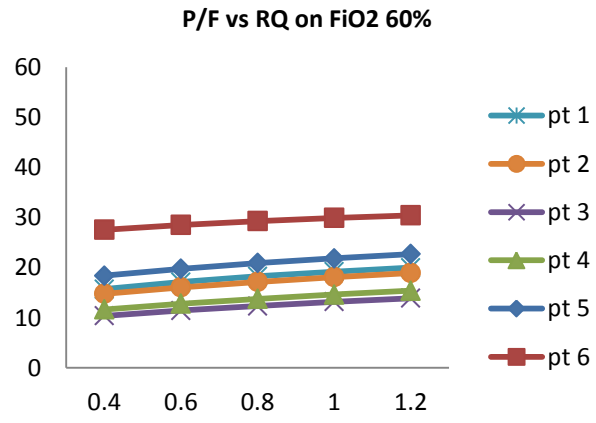


Figure 83 PaO_2/FiO_2 vs RQ on FiO_2 60%

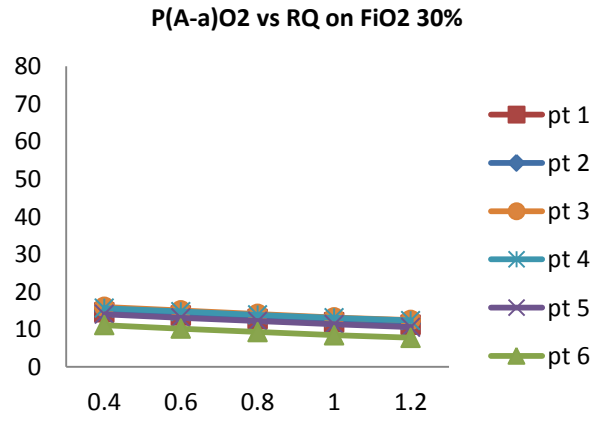


Figure 84 P(A-a) O2 vs RQ on FiO_2 30%

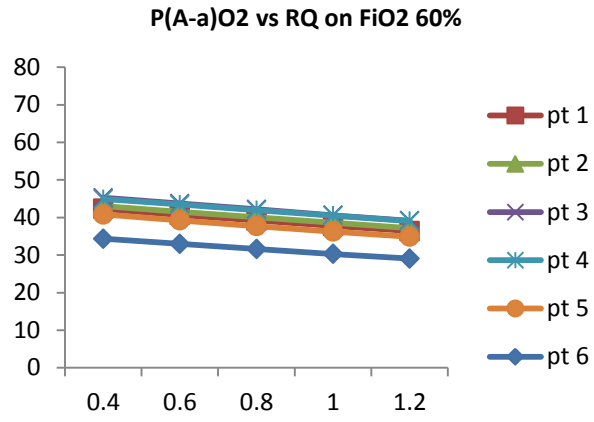


Figure 85 $P(A-a)O_2$ vs RQ on FiO_2 60%

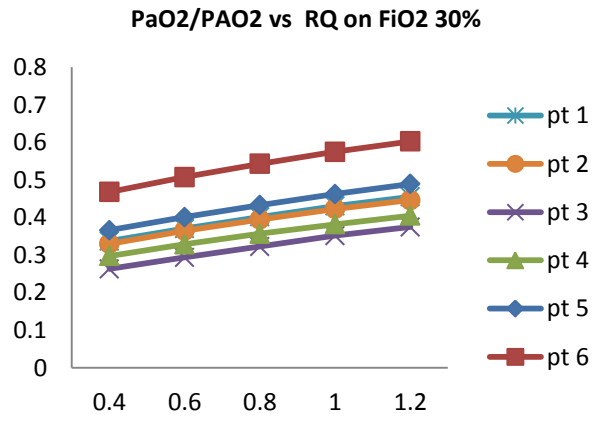


Figure 86 PaO_2/PAO_2 vs RQ on FiO_2 30%

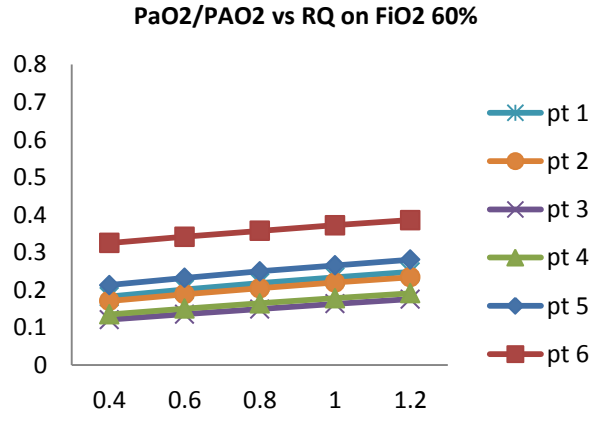


Figure 87 PaO_2/PAO_2 vs RQ on FiO_2 60%

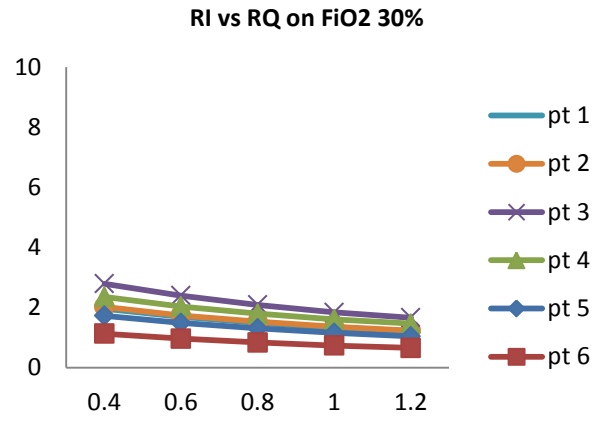


Figure 88 RI vs RQ on FiO_2 30%

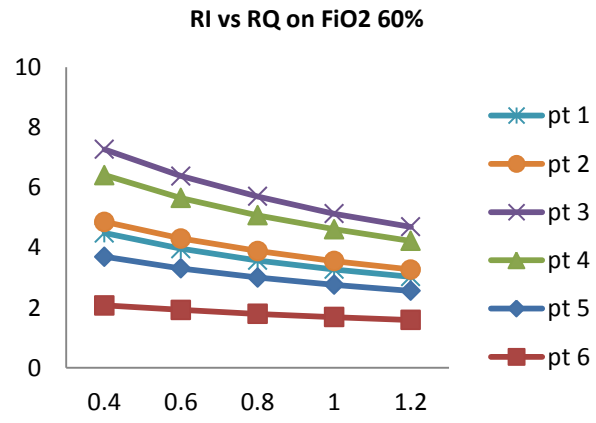


Figure 89 RI vs RQ on FiO_2 60%

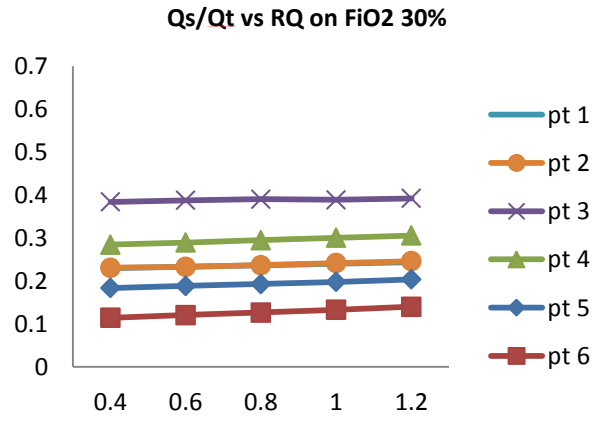


Figure 90 Qs/Qt vs RQ on FiO_2 30%

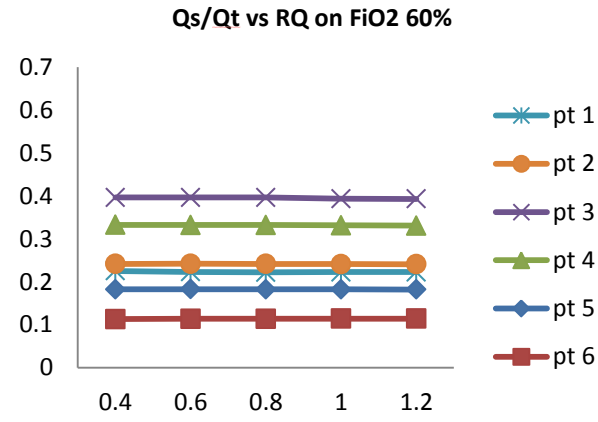


Figure 91 Qs/Qt vs RQ on FiO_2 60%

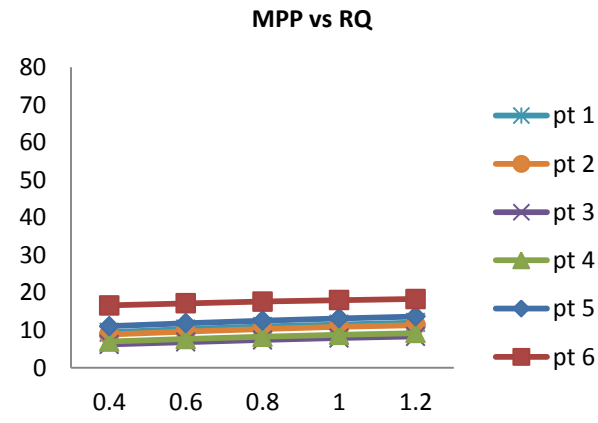


Figure 92 MPP vs RQ

9.2.5. CO variation

Table 35 and Figures 53 and 54 shows the mean variation percent for each virtual pts with two different levels of FiO_2 changes (30% and 60%) with a variation of cardiac output (CO). Thus, Qs/Qt index considers the lowest mean variation in both range of FiO_2 (mean 33%). On the other hand, the largest variation is MPP index (mean 170%). The rest of other indices (PaO_2/FiO_2, $P(A\text{-}a)O_2$, PaO_2/PAO_2, and RI) their mean variation percent range between (39-132%).

Table 35 CO variation

	PaO_2/FiO_2		$P(A\text{-}a)O_2$		PaO_2/PAO_2		RI		Qs/Qt		MPP
FiO_2	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30%**	**60%**	**30-60%**
Subject											
1	58	106	35	37	54	104	106	155	16	30	158
2	60	107	36	36	56	106	108	150	22	29	174
3	59	86	19	14	53	83	92	115	4	11	190
4	55	93	25	20	50	91	91	124	4	15	222
5	56	111	40	52	52	110	108	182	23	50	147
6	52	107	62	86	49	106	126	223	67	121	127
mean	57	102	36	41	52	100	105	158	23	43	170
SD	3	10	15	26	2	10	13	40	23	41	34
Both means	79		39		76		132		33		170

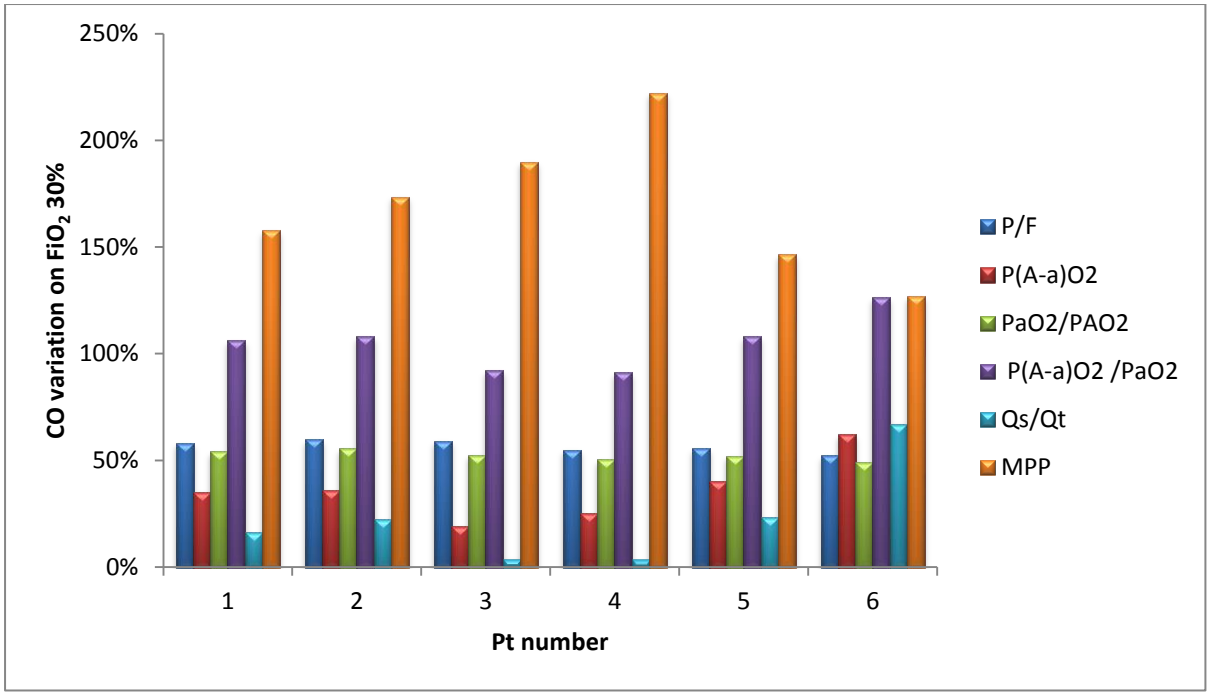


Figure 93 CO variation on FiO_2 30%

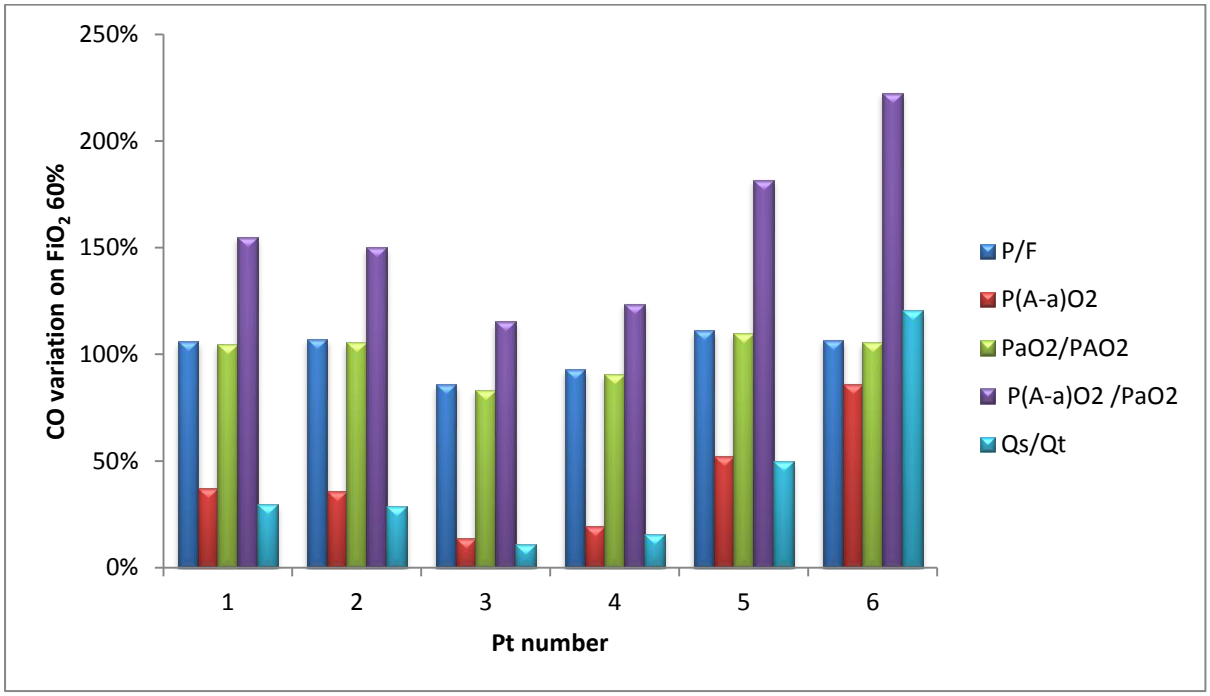


Figure 94 CO variation on FiO_2 60%

The PaO_2/FiO_2 ratio index varied linearly with an increase of CO. On FiO_2 30% the mean percent variation is 57% and SD 3%, on FiO_2 60% the mean variation is 102% with SD 10%. Therefore, the mean percent for both range of FiO_2 is 79%. Figures 55 and 56 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt2 (60%) and the smallest patient variation is pt6 (52%). On the same FiO_2 level the smallest value of The PaO_2/FiO_2 ratio index is 15.52 for pt3 on CO=2 L/min and the largest value is 47.55 for Pt6 on CO=12 L/min. Among the patients group with FiO_2 of 60% the largest patient variation is pt5 (111%) and the smallest patient variation is pt3 (86%). On the same FiO_2 level the smallest value of the PaO_2/FiO_2 ratio index is 7.84 for pt3 on CO=2 L/min and the largest value is 55.56 for pt6 on CO=12 L/min.

The A-a gradient index varied linearly with an increase of CO. On FiO_2 30% the mean percent variation is 36% and SD 15%, on FiO_2 60% the mean variation is 41% with SD 26%. Therefore, the mean percent for both range of FiO_2 is 39%. Figures 57 and 58 shows that among mong the patients group with FiO_2 of 30% the largest patient variation is pt6 (62%) and the smallest patient variation is pt3 (19%). On the same FiO_2 level the smallest value of the A-a gradient index is 6.32 for pt6 on CO=12 L/min and the largest value is 15.15 for Pt5 on CO=2 L/min. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (86%) and the smallest patient variation is pt3 (14%). On the same FiO_2 level the smallest value of the A-a gradient index is 16.11 for pt6 on CO=12 L/min and the largest value is 42.65 for pt4 on CO=2 L/min .

The PaO_2/PAO_2 ratio index varied linearly with an increase of CO. On FiO_2 30% the mean percent variation is 52% and SD 2%, on FiO_2 60% the mean variation is 100% with SD 10%. Therefore, the mean percent for both range of FiO_2 is 76%. Figures 59 and 60 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt2 (56%) and the smallest patient variation is pt3 (49%). On the same FiO_2 level the smallest value of the PaO_2/PAO_2 ratio index is 0.23 for pt3 on CO=2 L/min and the largest value is 0.69 for Pt6 on CO=12 L/min. Among the patients group with FiO_2 of 60% the largest patient variation is pt5 (110%) and the smallest patient variation is pt3 (83%). On the same FiO_2 level the smallest value of the PaO_2/PAO_2 ratio index is 0.09 for pt3 on CO=2 L/min and the largest value is 0.67 for pt6 on CO=12 L/min.

The RI index varied linearly with an increase of CO. On FiO_2 30% the mean percent variation is 105% and SD 13%, on FiO_2 60% the mean variation is 158% with SD 40%. Therefore, the mean percent for both range of FiO_2 is 132%. Figures 61 and 62 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (126%) and the smallest patient variation is pt4 (91%). On the same FiO_2 level the smallest value of the RI index is 0.44 for pt6 on CO=12 L/min and the largest value is 3.23 for Pt3 on CO=2 L/min. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (223%) and the smallest patient variation is pt3 (115%). On the same FiO_2 level the smallest value of the RI index is 0.48 for pt6 on CO=12 L/min and the largest value is 9.28 for pt3 on CO=2 L/min.

The Qs/Qt index varied linearly with an increase of CO. On FiO_2 30% the mean percent variation is 23% and SD 23%, on FiO_2 60% the mean variation is 43% with SD 41%. Therefore, the mean percent for both range of FiO_2 is 33%. Figures 63 and 64 shows that among the patients group with FiO_2 of 30% the largest patient variation is pt6 (67%) and the smallest patient variation are pt3 and p4 (4%). On the same FiO_2 level the smallest value of the Qs/Qt index is 0.07 for pt6 on CO=12 L/min and the largest value is 0.39 for Pt3 on CO=12 L/min. Among the patients group with FiO_2 of 60% the largest patient variation is pt6 (121%) and the smallest patient variation is pt3 (11%). On the same FiO_2 level the smallest value of the Qs/Qt index is 0.03 for pt6 on CO=12 L/min and the largest value is 0.40 for pt3 on CO=2 L/min .

The MPP varied linearly with CO and a variation mean is 170% and SD 34%. Figure 65 shows that in all pts the MPP increase with CO variation. Among the patients group the largest patient variation is pt4 (222%) and the smallest patient variation is pt6 (127%). The smallest value of MPP index is 4.70 with pt3 on CO=2 L/min and the largest value is 72.82 with Pt6 on CO=12 L/min.

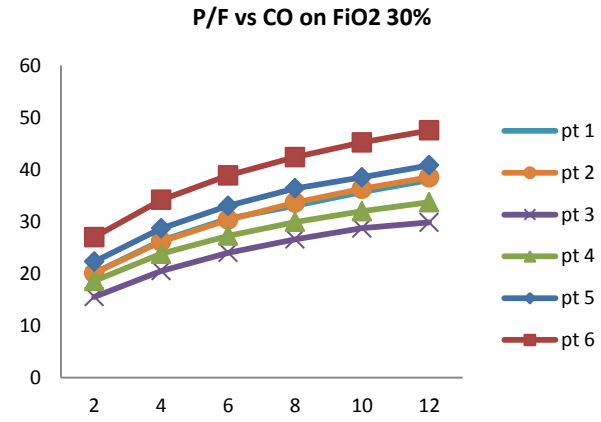


Figure 95 PaO_2/FiO_2 vs CO on FiO_2 30%

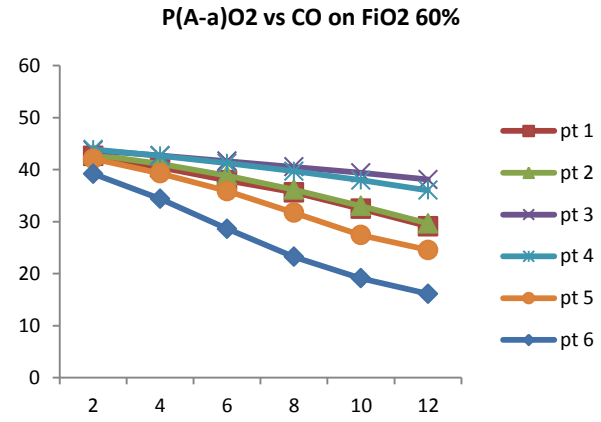


Figure 98 $P(A-a)O_2$ vs CO on FiO_2 60%

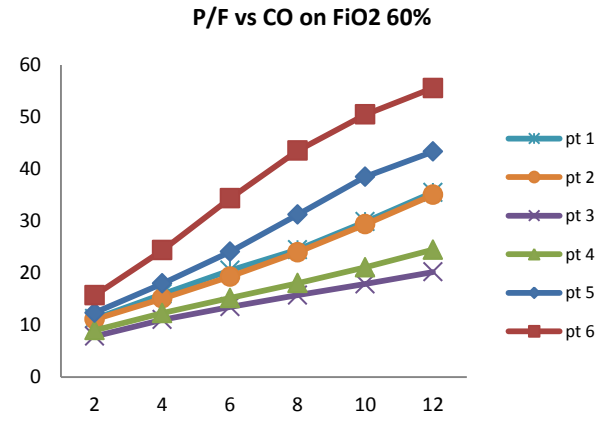


Figure 96 PaO_2/FiO_2 vs CO on FiO_2 60%

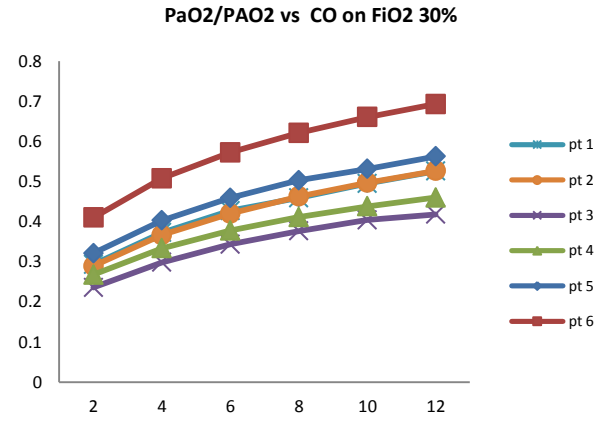


Figure 99 PaO_2/PAO_2 vs CO on FiO_2 30%

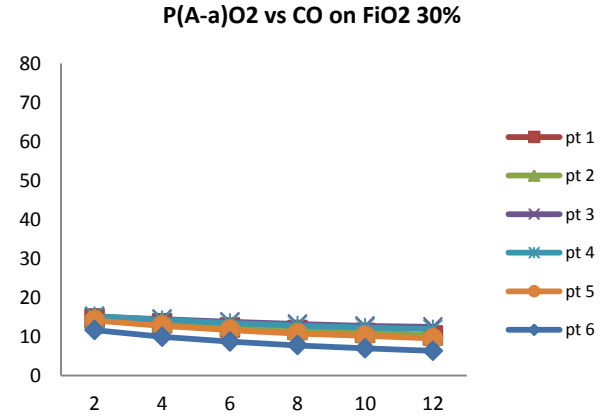


Figure 97 $P(A-a)O_2$ vs CO on FiO_2 30%

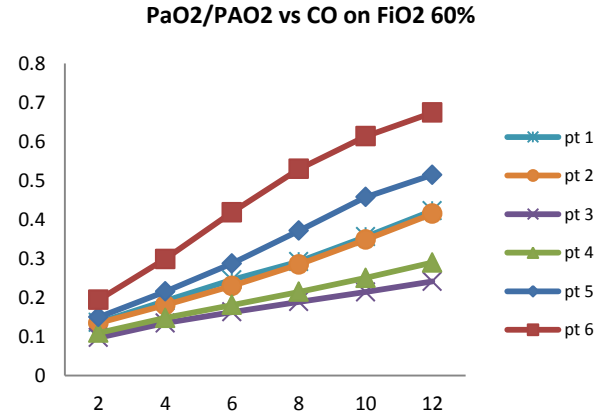


Figure 100 PaO_2/PAO_2 vs CO on FiO_2 60%

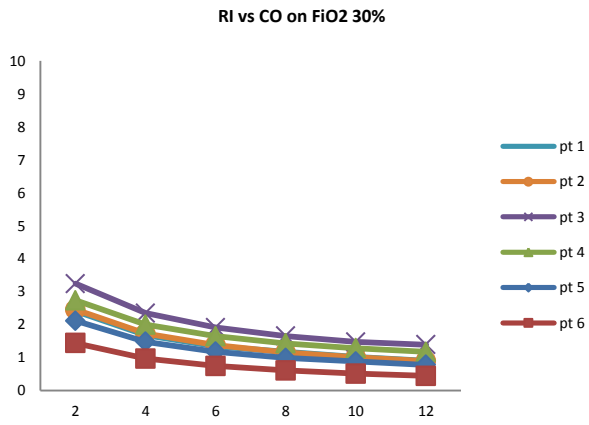


Figure 101 RI vs CO on FiO_2 30%

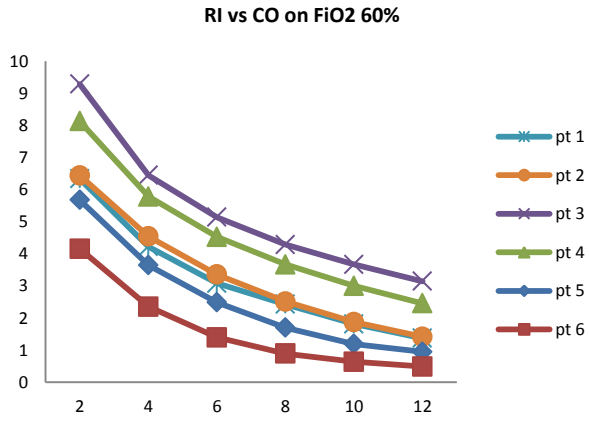


Figure 102 RI vs CO on FiO_2 60%

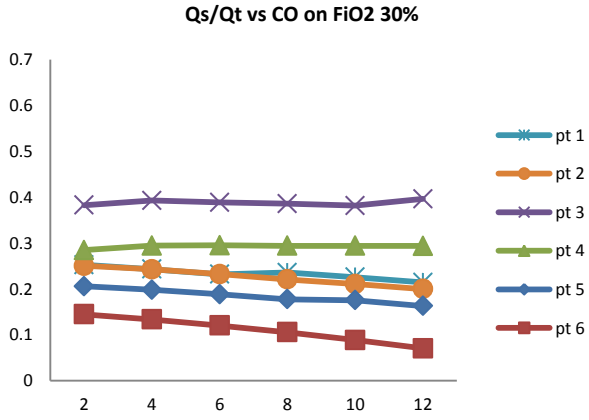


Figure 103 Qs/Qt vs CO on FiO_2 30%

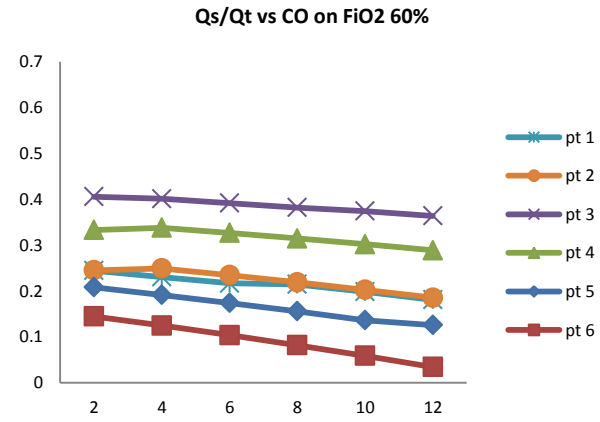


Figure 104 Qs/Qt vs CO on FiO_2 60%

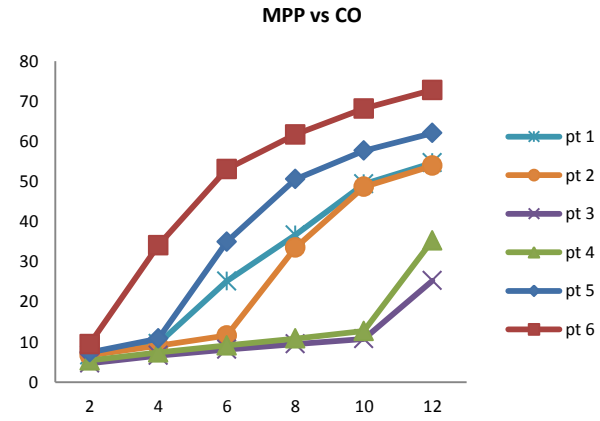


Figure 105 MPP vs CO

9.3. Detailed results for oxygen indices and variation in the clinical data

In the following section, patient's data are presented alongside with ABG results and the calculated oxygen indices during three times intervals i.e. :Table 37 measurements that taken during time 1, Table 38 measurements taken during time 2, and Table 39 measurements that taken during timme3. At the end Table 40 present the variation and ratio of the oxygen indices.

Table 36: ABG results and the calculated oxygen indices for each patient included in the clinical data. The ABG measurements were taken during time 1

#	Time1	ABGT	timDif	FiO	PCO	PaO	Hb	FiO	PF	Pa/P	RI	PCO2	PaO	PAO2	PA-a	Hb	crPaO
1	05:15:00	05:58:00	00:43	0.75	93.00	287.40	9.50	75	51	0.66	0.51	12.40	38.32	57.78	19.46	95	**13.71**
2	22:50:00	23:06:00	00:16	1.00	41.80	255.50	11.30	100	34	0.38	1.61	5.57	34.06	89.03	54.96	113	**12.26**
3	19:30:00	22:16:00	02:46	0.80	55.70	188.30	5.50	80	31	0.37	1.70	7.43	25.10	67.88	42.78	55	**12.28**
4	22:50:00	23:06:00	00:16	1.00	41.80	255.50	11.30	100	34	0.38	1.61	5.57	34.06	89.03	54.96	113	**12.26**
5	03:15:00	05:27:00	02:12	1.00	38.60	402.70	13.50	100	54	0.60	0.67	5.15	53.69	89.45	35.76	135	**15.12**
6	16:10:00	16:25:00	00:15	0.60	30.70	259.00	12.30	60	58	0.66	0.51	4.09	34.53	52.26	17.73	123	**20.42**
7	01:20:00	02:20:00	01:00	0.50	34.30	126.00	7.80	50	34	0.40	1.51	4.57	16.80	42.16	25.36	78	**20.83**
8	19:30:00	19:50:00	00:20	1.00	53.30	175.30	10.80	100	23	0.27	2.74	7.11	23.37	87.49	64.12	108	**9.16**
9	17:00:00	17:52:00	00:52	0.85	51.30	149.40	13.30	85	23	0.27	2.68	6.84	19.92	73.31	53.40	133	**8.74**
10	17:20:00	17:54:00	00:34	1.00	47.60	207.90	5.70	100	28	0.31	2.18	6.35	27.72	88.25	60.54	57	**11.35**
11	12:10:00	12:38:00	00:28	1.00	31.70	399.00	7.70	100	53	0.59	0.70	4.23	53.20	90.37	37.18	77	**16.56**
12	03:45:00	06:33:00	02:48	0.40	37.00	87.00	11.00	40	29	0.36	1.77	4.93	11.60	32.17	20.57	110	**18.19**
13	13:41:00	14:54:00	01:13	1.00	49.50	113.10	8.20	100	15	0.17	4.84	6.60	15.08	88.00	72.92	82	**6.54**
14	03:35:00	04:06:00	00:31	0.50	44.00	89.30	11.70	50	24	0.29	2.42	5.87	11.91	40.70	28.79	117	**14.92**

15	19:25:00	20:46:00	01:21	0.50	40.00	145.70	8.00	50	39	0.47	1.13	5.33	19.43	41.30	21.88	80	**22.33**
16	20:40:00	21:07:00	00:27	0.85	33.50	317.50	8.40	50	21	0.25	3.04	4.73	10.40	41.98	31.58	81	**14.33**
17	02:50:00	03:11:00	00:21	1.00	42.60	362.50	7.10	100	48	0.54	0.84	5.68	48.33	88.92	40.59	71	**15.87**
18	10:20:00	11:56:00	01:36	0.50	51.40	89.50	8.60	50	24	0.30	2.32	6.85	11.93	39.59	27.66	86	**15.33**
19	05:00:00	05:47:00	00:47	1.00	49.30	407.00	8.70	100	54	0.62	0.62	6.57	54.26	88.03	33.76	87	**15.88**
20	02:30:00	03:29:00	00:59	1.00	41.50	406.00	8.70	100	54	0.61	0.65	5.53	54.13	89.07	34.94	87	**16.11**
21	10:30:00	11:18:00	00:48	1.00	22.00	195.00	11.20	100	26	0.28	2.53	2.93	26.00	91.67	65.67	112	**10.22**
22	22:00:00	22:47:00	00:47	1.00	46.20	235.30	15.10	100	31	0.35	1.82	6.16	31.37	88.44	57.07	151	**10.93**
23	19:10:00	20:53:00	01:43	1.00	45.00	251.70	11.90	100	34	0.38	1.64	6.00	33.56	88.60	55.04	119	**11.99**
24	03:33:00	04:04:00	00:31	0.80	31.70	199.10	10.90	80	33	0.37	1.68	4.23	26.54	71.24	44.70	109	**12.25**
25	14:00:00	14:20:00	00:20	0.60	35.80	192.80	11.40	60	43	0.50	1.00	4.77	25.70	51.51	25.81	114	**18.58**
26	08:54:00	11:21:00	02:27	0.60	25.50	252.00	13.70	60	56	0.63	0.58	3.40	33.60	53.02	19.42	137	**20.39**
27	16:55:00	17:17:00	00:22	0.95	47.50	180.40	8.90	95	25	0.29	2.47	6.33	24.05	83.46	59.41	89	**10.04**
28	09:25:00	10:01:00	00:36	0.95	38.40	150.80	13.20	95	21	0.24	3.21	5.12	20.11	84.69	64.58	132	**8.24**
29	07:30:00	07:53:00	00:23	0.40	42.40	105.50	8.90	40	35	0.45	1.23	5.65	14.07	31.34	17.27	89	**20.85**
30	12:49:00	14:43:00	01:54	0.85	36.00	336.90	9.50	85	53	0.60	0.68	4.80	44.92	75.43	30.51	95	**15.68**
31	00:10:00	00:24:00	00:14	0.65	42.00	151.60	10.20	65	31	0.36	1.74	5.60	20.21	55.40	35.19	102	**13.81**
32	00:40:00	03:26:00	02:46	0.50	46.00	63.00	11.10	50	17	0.21	3.81	6.13	8.40	40.40	32.00	111	**11.20**
33	22:05:00	22:15:00	00:10	1.00	47.20	360.50	6.70	100	48	0.54	0.84	6.29	48.06	88.31	40.24	67	**15.81**
34	20:15:00	21:16:00	01:01	1.00	44.40	92.00	8.90	100	12	0.14	6.23	5.92	12.27	88.68	76.41	89	**5.39**
35	09:20:00	09:38:00	00:18	0.75	48.00	121.60	10.60	75	22	0.25	2.96	6.40	16.21	64.15	47.94	106	**8.93**
36	22:10:00	22:40:00	00:30	0.90	32.00	108.60	12.80	90	16	0.18	4.58	4.27	14.48	80.77	66.29	128	**6.51**
37	00:30:00	00:51:00	00:21	0.55	38.00	87.00	10.50	55	21	0.25	3.00	5.07	11.60	46.39	34.79	105	**12.65**
38	05:38:00	05:54:00	00:16	0.85	52.10	348.00	10.80	85	55	0.63	0.58	6.95	46.40	73.20	26.81	108	**14.92**
39	00:41:00	01:09:00	00:28	0.60	35.00	254.10	11.70	60	56	0.66	0.52	4.67	33.88	51.63	17.75	117	**20.22**
40	21:30:00	22:07:00	00:37	1.00	55.90	125.30	12.50	100	17	0.19	4.22	7.45	16.71	87.15	70.44	125	**6.71**
41	01:42:00	02:08:00	00:26	1.00	41.00	210.00	11.70	100	28	0.31	2.18	5.47	28.00	89.13	61.14	117	**10.57**
42	06:09:00	06:44:00	00:35	1.00	62.00	379.00	10.20	100	51	0.59	0.71	8.27	50.53	86.33	35.80	102	**14.92**
43	05:00:00	05:45:00	00:45	1.00	40.00	221.00	14.00	100	29	0.33	2.03	5.33	29.46	89.27	59.80	140	**10.66**

44	02:50:00	03:19:00	00:29	0.75	34.60	157.60	8.10	75	28	0.32	2.14	4.61	21.01	66.05	45.04	81	**11.60**
45	02:25:00	02:47:00	00:22	0.90	22.20	251.90	8.30	90	37	0.41	1.44	2.96	33.58	82.11	48.52	83	**13.76**
46	03:01:00	03:25:00	00:24	0.90	53.10	98.50	7.43	90	15	0.17	4.93	7.08	13.13	77.88	64.75	74	**6.32**
47	19:00:00	20:12:00	01:12	1.00	62.00	245.00	13.80	100	33	0.38	1.64	8.27	32.66	86.33	53.67	138	**11.24**
48	15:30:00	16:36:00	01:06	0.60	35.20	140.40	10.80	60	31	0.36	1.76	4.69	18.72	51.60	32.88	108	**15.39**
49	02:00:00	03:19:00	01:19	0.45	33.00	134.90	7.30	45	40	0.48	1.09	4.40	17.99	37.57	19.58	73	**24.55**
50	17:00:00	17:15:00	00:15	1.00	30.90	102.00	14.00	100	14	0.15	5.65	4.12	13.60	90.48	76.88	140	**5.57**
51	13:00:00	13:22:00	00:22	0.55	24.10	129.40	13.10	55	31	0.36	1.81	3.21	17.25	48.46	31.20	131	**17.15**
52	10:04:00	10:22:00	00:18	0.90	35.70	149.10	12.90	90	22	0.25	3.04	4.76	19.88	80.26	60.38	129	**8.53**
53	01:40:00	02:00:00	00:20	0.80	35.00	242.00	9.00	80	40	0.46	1.19	4.67	32.26	70.78	38.52	90	**14.20**
54	01:05:00	01:23:00	00:18	0.60	37.00	270.00	10.00	60	60	0.70	0.43	4.93	36.00	51.33	15.34	100	**20.45**
55	05:00:00	05:15:00	00:15	1.00	62.80	252.50	10.00	100	34	0.39	1.56	8.37	33.66	86.23	52.56	100	**12.08**
56	13:30:00	13:40:00	00:10	0.60	35.00	138.00	10.00	60	31	0.36	1.81	4.67	18.40	51.63	33.23	100	**15.38**
57	16:30:00	16:49:00	00:19	0.40	42.00	97.40	8.00	40	32	0.41	1.42	5.60	12.99	31.40	18.41	80	**20.14**
58	07:05:00	08:34:00	01:29	1.00	61.00	162.00	9.00	100	22	0.25	3.00	8.13	21.60	86.47	64.87	90	**8.74**
59	06:30:00	06:41:00	00:11	0.40	44.20	151.50	10.00	40	50	0.65	0.54	5.89	20.20	31.06	10.86	100	**23.39**
60	07:05:00	08:43:00	01:38	1.00	41.00	365.00	10.20	100	49	0.55	0.83	5.47	48.66	89.13	40.47	102	**15.26**
61	00:35:00	00:57:00	00:22	0.55	35.70	123.90	9.40	55	30	0.35	1.83	4.76	16.52	46.73	30.22	94	**17.04**
62	04:00:00	04:53:00	00:53	0.65	38.00	103.00	9.50	65	21	0.25	3.08	5.07	13.73	55.98	42.25	95	**10.37**
63	00:58:00	01:40:00	00:42	0.50	34.00	196.00	10.20	50	52	0.62	0.61	4.53	26.13	42.20	16.07	102	**24.93**
64	22:45:00	23:04:00	00:19	1.00	40.00	88.00	7.40	100	12	0.13	6.61	5.33	11.73	89.27	77.53	74	**5.30**
65	14:30:00	16:02:00	01:32	1.00	38.00	59.00	9.40	100	8	0.09	###	5.07	7.87	89.53	81.67	94	**3.54**
66	05:00:00	05:33:00	00:33	0.45	50.00	93.00	10.50	45	28	0.35	1.82	6.67	12.40	34.99	22.59	105	**17.43**
67	16:45:00	17:00:00	00:15	0.40	41.00	89.00	9.10	40	30	0.38	1.66	5.47	11.87	31.55	19.69	91	**18.72**
68	16:45:00	16:59:00	00:14	0.80	38.00	265.50	10.00	80	44	0.50	0.99	5.07	35.40	70.36	34.96	100	**14.64**
69	17:00:00	17:16:00	00:16	0.80	37.30	141.20	9.70	80	24	0.27	2.74	4.97	18.83	70.46	51.63	97	**9.50**
70	13:00:00	13:58:00	00:58	0.40	38.60	136.10	9.50	40	45	0.57	0.76	5.15	18.15	31.92	13.78	95	**23.80**
71	16:00:00	16:19:00	00:19	0.60	38.90	251.80	10.70	60	56	0.66	0.52	5.19	33.57	51.06	17.48	107	**20.17**
72	14:40:00	15:13:00	00:33	0.60	41.00	178.00	9.70	60	40	0.47	1.14	5.47	23.73	50.75	27.02	97	**17.98**

73	13:05:00	13:20:00	00:15	0.45	23.00	176.00	8.70	45	52	0.60	0.67	3.07	23.46	39.08	15.62	87	**28.00**
74	00:01:00	00:34:00	00:33	1.00	50.00	384.00	12.40	100	51	0.58	0.72	6.67	51.20	87.93	36.74	124	**14.84**
75	04:00:00	04:37:00	00:37	1.00	37.00	234.00	10.20	100	31	0.35	1.87	4.93	31.20	89.67	58.47	102	**11.75**
76	21:00:00	21:35:00	00:35	1.00	32.00	467.00	10.20	100	62	0.69	0.45	4.27	62.26	90.33	28.07	102	**16.25**
77	23:50:00	00:21:00	00:31	1.00	45.00	375.00	8.60	100	50	0.56	0.77	6.00	50.00	88.60	38.60	86	**15.66**
78	10:55:00	11:16:00	00:21	0.50	37.00	242.00	8.40	50	65	0.77	0.29	4.93	32.26	41.75	9.49	84	**24.27**
79	13:00:00	13:20:00	00:20	1.00	43.00	137.00	11.40	100	18	0.21	3.87	5.73	18.27	88.87	70.60	114	**7.44**
80	15:30:00	16:04:00	00:34	1.00	167.60	182.50	15.00	100	24	0.34	1.97	22.34	24.33	72.26	47.92	150	**7.88**
81	09:00:00	09:39:00	00:39	1.00	69.70	185.50	9.30	100	25	0.29	2.45	9.29	24.73	85.31	60.58	93	**9.63**
82	08:45:00	09:14:00	00:29	0.40	39.50	136.70	9.30	40	46	0.57	0.74	5.27	18.23	31.78	13.56	93	**23.79**
83	16:30:00	17:05:00	00:35	1.00	64.40	128.00	6.80	100	17	0.20	4.04	8.59	17.07	86.01	68.95	68	**7.35**
84	15:00:00	15:27:00	00:27	1.00	41.20	199.00	11.40	100	27	0.30	2.36	5.49	26.53	89.11	62.58	114	**10.17**
85	09:30:00	10:05:00	00:35	1.00	43.10	68.60	13.20	100	9	0.10	8.72	5.75	9.15	88.85	79.71	132	**3.86**
86	14:55:00	15:12:00	00:17	1.00	33.30	338.60	13.50	100	45	0.50	1.00	4.44	45.14	90.16	45.02	135	**14.26**
87	14:00:00	14:27:00	00:27	1.00	49.80	287.40	6.80	100	38	0.44	1.30	6.64	38.32	87.96	49.64	68	**13.98**
88	20:45:00	21:11:00	00:26	0.50	34.50	106.00	14.00	50	28	0.34	1.98	4.60	14.13	42.13	27.99	140	**16.89**
89	04:50:00	05:19:00	00:29	1.00	30.00	406.00	11.90	100	54	0.60	0.67	4.00	54.13	90.60	36.47	119	**15.72**
90	03:00:00	03:30:00	00:30	1.00	32.70	212.40	10.90	100	28	0.31	2.19	4.36	28.32	90.24	61.92	109	**10.87**
91	05:00:00	05:27:00	00:27	1.00	38.60	402.70	13.50	100	54	0.60	0.67	5.15	53.69	89.45	35.76	135	**15.12**
92	04:45:00	05:58:00	01:13	1.00	93.00	287.00	9.50	100	38	0.47	1.15	12.40	38.26	82.20	43.94	95	**12.67**
93	16:30:00	16:53:00	00:23	0.50	34.00	223.00	12.70	50	59	0.70	0.42	4.53	29.73	42.20	12.47	127	**24.14**

Table 37 ABG results and the calculated oxygen indices for each patient included in the clinical data. The ABG measurements were taken during time 2

#	Time	ABG T	Time D	FiO	PCO	PaO	Hb	FiO	PF	Pa/PA	RI	PCO2	PaO	PAO2	PA-a	Hb	crPaO2
1	06:40:00	07:01:00	00:21	0.60	100.90	180.70	9.10	60	40	0.57	0.74	13.45	24.09	41.96	17.87	91	**15.11**
2	23:30:00	23:46:00	00:16	0.75	37.90	129.30	12.10	75	23	0.26	2.80	5.05	17.24	65.58	48.34	121	**9.32**
3	22:20:00	23:09:00	00:49	0.75	34.70	210.10	5.30	75	37	0.42	1.36	4.63	28.01	66.03	38.02	53	**14.81**
4	23:30:00	23:46:00	00:16	0.75	37.90	129.30	12.10	75	23	0.26	2.80	5.05	17.24	65.58	48.34	121	**9.32**
5	06:00:00	06:47:00	00:47	0.70	36.60	129.90	13.10	70	25	0.28	2.52	4.88	17.32	60.97	43.66	131	**10.37**
6	17:30:00	18:36:00	01:06	0.35	34.00	135.00	12.70	35	51	0.65	0.55	4.53	18.00	27.84	9.84	127	**21.97**
7	02:21:00	02:45:00	00:24	0.45	33.60	109.80	7.80	45	33	0.39	1.56	4.48	14.64	37.47	22.84	78	**21.43**
8	19:55:00	20:19:00	00:24	0.90	52.00	130.00	10.70	90	19	0.22	3.50	6.93	17.33	78.03	60.70	107	**7.70**
9	18:00:00	18:27:00	00:27	0.70	55.20	119.80	12.90	70	23	0.27	2.65	7.36	15.97	58.31	42.34	129	**9.47**
10	17:55:00	18:26:00	00:31	0.80	53.80	128.10	6.10	80	21	0.25	2.99	7.17	17.08	68.15	51.07	61	**9.05**
11	12:40:00	13:02:00	00:22	0.80	32.00	196.50	7.70	80	33	0.37	1.72	4.27	26.20	71.20	45.00	77	**12.69**
12	14:30:00	15:57:00	01:27	0.50	39.70	98.70	9.90	50	26	0.32	2.14	5.29	13.16	41.35	28.19	99	**16.71**
13	14:55:00	15:36:00	00:41	0.90	48.90	101.20	8.30	90	15	0.17	4.82	6.52	13.49	78.46	64.97	83	**6.41**
14	06:25:00	06:42:00	00:17	0.55	43.20	86.80	11.80	55	21	0.25	2.94	5.76	11.57	45.62	34.05	118	**12.27**
15	20:50:00	21:20:00	00:30	0.45	43.30	138.60	7.70	45	41	0.51	0.95	5.77	18.48	36.00	17.52	77	**23.77**
16	21:10:00	21:30:00	00:20	0.70	35.10	257.00	8.50	85	50	0.56	0.79	4.47	42.33	75.78	33.45	84	**15.71**
17	03:18:00	03:52:00	00:34	0.80	43.30	242.90	6.80	80	40	0.47	1.15	5.77	32.38	69.62	37.23	68	**14.48**
18	12:10:00	13:20:00	01:10	0.45	59.70	74.40	8.50	45	22	0.30	2.38	7.96	9.92	33.52	23.60	85	**14.71**
19	05:55:00	06:14:00	00:19	0.80	33.20	276.60	8.80	80	46	0.52	0.93	4.43	36.88	71.03	34.16	88	**15.32**
20	03:30:00	03:49:00	00:19	0.80	42.70	252.90	8.70	80	42	0.48	1.07	5.69	33.72	69.70	35.99	87	**14.41**
21	11:20:00	11:54:00	00:34	0.55	25.00	275.70	11.30	55	67	0.76	0.31	3.33	36.76	48.32	11.56	113	**22.82**
22	23:00:00	23:36:00	00:36	0.80	41.30	128.40	14.10	80	21	0.24	3.08	5.51	17.12	69.90	52.78	141	**8.23**
23	20:30:00	21:46:00	01:16	0.80	47.80	125.80	12.70	80	21	0.24	3.11	6.37	16.77	68.99	52.22	127	**8.18**
24	04:07:00	04:31:00	00:24	0.60	36.70	126.10	11.30	60	28	0.33	2.06	4.89	16.81	51.38	34.57	113	**14.08**
25	15:00:00	15:28:00	00:28	0.50	36.30	147.00	11.50	50	39	0.47	1.14	4.84	19.60	41.86	22.26	115	**21.62**
26	11:25:00	12:00:00	00:35	0.40	33.60	185.00	14.10	40	62	0.75	0.33	4.48	24.66	32.69	8.02	141	**23.15**

27	17:19:00	17:42:00	00:23	0.85	44.70	161.60	9.90	85	25	0.29	2.45	5.96	21.54	74.23	52.68	99	**9.83**
28	10:04:00	10:22:00	00:18	0.90	35.70	149.10	13.20	90	22	0.25	3.04	4.76	19.88	80.26	60.38	132	**8.49**
29	07:55:00	08:25:00	00:30	0.35	41.90	82.80	9.70	35	32	0.41	1.41	5.59	11.04	26.62	15.58	97	**17.72**
30	14:45:00	15:12:00	00:27	0.70	35.60	202.90	8.60	70	39	0.44	1.26	4.75	27.05	61.12	34.07	86	**15.23**
31	00:35:00	01:04:00	00:29	0.60	40.30	125.00	10.20	60	28	0.33	2.05	5.37	16.67	50.85	34.18	102	**14.10**
32	21:40:00	22:00:00	00:20	0.60	43.00	99.00	11.10	60	22	0.26	2.82	5.73	13.20	50.45	37.25	111	**11.52**
33	23:36:00	00:01:00	00:25	0.75	52.00	155.00	10.10	75	28	0.33	2.08	6.93	20.66	63.58	42.92	101	**10.85**
34	21:20:00	21:44:00	00:24	0.90	43.70	74.20	8.90	90	11	0.12	7.00	5.83	9.89	79.17	69.28	89	**4.81**
35	11:20:00	11:39:00	00:19	0.70	52.00	61.00	10.50	70	12	0.14	6.23	6.93	8.13	58.77	50.63	105	**5.46**
36	22:40:00	23:10:00	00:30	0.85	33.10	92.40	12.80	85	14	0.16	5.16	4.41	12.32	75.83	63.51	128	**5.92**
37	00:55:00	01:22:00	00:27	0.50	39.00	81.00	10.40	50	22	0.26	2.84	5.20	10.80	41.45	30.65	104	**14.20**
38	05:59:00	06:22:00	00:23	0.40	53.10	105.00	10.80	40	35	0.47	1.12	7.08	14.00	29.70	15.70	108	**19.32**
39	01:10:00	01:45:00	00:35	0.40	34.00	108.50	10.50	40	36	0.44	1.26	4.53	14.47	32.63	18.16	105	**21.46**
40	22:08:00	22:30:00	00:22	0.90	56.20	110.50	12.00	90	16	0.19	4.26	7.49	14.73	77.46	62.73	120	**6.54**
41	02:09:00	02:36:00	00:27	0.60	38.00	85.40	11.70	60	19	0.22	3.50	5.07	11.39	51.19	39.80	117	**10.18**
42	08:15:00	08:36:00	00:21	0.55	42.20	130.60	10.40	55	32	0.38	1.63	5.63	17.41	45.77	28.36	104	**17.18**
43	05:50:00	06:22:00	00:32	0.60	41.00	254.50	14.10	60	57	0.67	0.50	5.47	33.93	50.75	16.82	141	**19.10**
44	03:20:00	03:48:00	00:28	0.65	37.40	127.60	7.80	65	26	0.30	2.30	4.99	17.01	56.07	39.06	78	**12.66**
45	02:50:00	03:11:00	00:21	0.75	30.40	187.20	8.40	75	33	0.37	1.67	4.05	24.96	66.64	41.69	84	**13.19**
46	03:27:00	04:06:00	00:39	0.85	50.80	84.60	8.10	85	13	0.15	5.51	6.77	11.28	73.38	62.10	81	**5.74**
47	20:15:00	20:47:00	00:32	0.80	53.00	121.00	13.80	80	20	0.24	3.23	7.07	16.13	68.26	52.13	138	**7.75**
48	16:50:00	17:22:00	00:32	0.50	34.60	96.30	10.70	50	26	0.30	2.28	4.61	12.84	42.11	29.27	107	**16.41**
49	03:30:00	03:59:00	00:29	0.30	32.20	110.50	7.60	30	49	0.63	0.58	4.29	14.73	23.34	8.60	76	**23.05**
50	21:28:00	21:55:00	00:27	0.85	30.80	269.80	14.00	85	42	0.47	1.12	4.11	35.97	76.15	40.18	140	**13.53**
51	13:25:00	13:59:00	00:34	0.40	29.40	104.70	13.10	40	35	0.42	1.39	3.92	13.96	33.33	19.37	131	**20.61**
52	10:23:00	10:44:00	00:21	0.85	37.60	133.40	13.00	85	21	0.24	3.23	5.01	17.79	75.21	57.42	130	**8.11**
53	02:00:00	02:22:00	00:22	0.60	35.00	149.60	8.90	60	33	0.39	1.59	4.67	19.95	51.63	31.68	89	**16.54**
54	01:25:00	02:09:00	00:44	0.40	29.00	190.00	10.50	40	63	0.76	0.32	3.87	25.33	33.39	8.06	105	**25.01**
55	05:17:00	05:42:00	00:25	0.80	47.50	157.30	10.00	80	26	0.30	2.29	6.33	20.97	69.03	48.06	100	**10.18**

56	13:40:00	14:00:00	00:20	0.50	34.00	184.00	9.30	50	49	0.58	0.72	4.53	24.53	42.20	17.67	93	**24.86**
57	16:50:00	17:16:00	00:26	0.35	42.30	87.90	8.60	35	33	0.44	1.27	5.64	11.72	26.55	14.84	86	**18.65**
58	08:45:00	09:16:00	00:31	0.70	61.00	95.00	9.00	70	18	0.22	3.54	8.13	12.67	57.48	44.81	90	**8.17**
59	06:50:00	07:48:00	00:58	0.35	42.00	137.00	10.20	35	52	0.69	0.46	5.60	18.27	26.60	8.34	102	**21.29**
60	08:45:00	09:16:00	00:31	0.70	36.00	221.50	10.50	70	42	0.48	1.07	4.80	29.53	61.06	31.53	105	**15.57**
61	01:00:00	01:28:00	00:28	0.50	31.80	107.30	8.50	50	29	0.34	1.97	4.24	14.31	42.53	28.22	85	**18.52**
62	04:55:00	05:24:00	00:29	0.60	36.30	87.20	10.40	60	19	0.23	3.42	4.84	11.63	51.44	39.81	104	**10.58**
63	01:41:00	01:48:00	00:07	0.40	36.00	130.00	10.80	40	43	0.54	0.86	4.80	17.33	32.32	14.99	108	**23.27**
64	23:05:00	23:29:00	00:24	0.95	38.00	87.00	7.20	95	12	0.14	6.31	5.07	11.60	84.74	73.14	72	**5.50**
65	17:30:00	18:06:00	00:36	0.80	36.00	90.00	9.40	80	15	0.17	4.89	4.80	12.00	70.64	58.64	94	**6.48**
66	11:30:00	13:42:00	02:12	0.30	45.00	78.00	10.50	30	35	0.49	1.05	6.00	10.40	21.33	10.93	105	**17.70**
67	17:05:00	17:25:00	00:20	0.30	40.00	76.60	9.10	30	34	0.46	1.17	5.33	10.21	22.11	11.90	91	**18.45**
68	17:10:00	17:40:00	00:30	0.70	38.00	221.00	9.10	70	42	0.48	1.06	5.07	29.46	60.77	31.31	91	**15.79**
69	17:35:00	17:55:00	00:20	0.75	44.70	111.90	9.50	75	20	0.23	3.33	5.96	14.92	64.62	49.70	95	**8.49**
70	14:05:00	14:29:00	00:24	0.37	37.40	128.00	9.30	37	46	0.58	0.71	4.99	17.07	29.23	12.17	93	**22.91**
71	16:25:00	16:50:00	00:25	0.50	38.10	200.00	11.10	50	53	0.64	0.56	5.08	26.66	41.59	14.92	111	**24.22**
72	15:15:00	15:52:00	00:37	0.50	47.00	126.00	9.80	50	34	0.42	1.40	6.27	16.80	40.25	23.45	98	**19.51**
73	13:28:00	13:50:00	00:22	0.40	27.00	147.00	8.70	40	49	0.58	0.72	3.60	19.60	33.70	14.10	87	**26.25**
74	00:35:00	01:10:00	00:35	0.80	42.00	248.00	12.30	80	41	0.47	1.11	5.60	33.06	69.80	36.74	123	**13.58**
75	04:37:00	04:58:00	00:21	0.80	34.90	421.00	11.10	80	70	0.79	0.26	4.65	56.13	70.79	14.67	111	**14.80**
76	21:35:00	22:02:00	00:27	0.70	25.00	187.00	10.20	70	36	0.40	1.51	3.33	24.93	62.64	37.71	102	**14.42**
77	00:21:00	00:42:00	00:21	0.70	42.00	204.00	8.50	70	39	0.45	1.21	5.60	27.20	60.20	33.00	85	**15.10**
78	11:16:00	11:39:00	00:23	0.40	36.50	172.20	8.00	40	57	0.71	0.40	4.87	22.96	32.24	9.29	80	**25.25**
79	13:20:00	13:43:00	00:23	0.90	39.80	117.70	11.30	90	17	0.20	4.08	5.31	15.69	79.70	64.01	113	**7.09**
80	16:04:00	16:33:00	00:29	0.80	153.90	280.00	15.10	80	47	0.69	0.45	20.52	37.33	54.14	16.81	151	**10.13**
81	09:38:00	10:04:00	00:26	0.90	71.70	131.00	9.60	90	19	0.23	3.31	9.56	17.47	75.34	57.88	96	**7.71**
82	09:14:00	09:50:00	00:36	0.35	34.30	136.10	10.90	35	52	0.65	0.53	4.57	18.15	27.79	9.65	109	**22.48**
83	17:05:00	17:30:00	00:25	0.90	62.60	112.40	6.60	90	17	0.20	4.11	8.35	14.99	76.59	61.60	66	**7.12**
84	15:27:00	15:56:00	00:29	0.80	36.90	105.50	10.70	80	18	0.20	4.01	4.92	14.07	70.51	56.45	107	**7.32**

85	10:05:00	10:45:00	00:40	0.90	40.00	67.90	13.00	90	10	0.11	7.80	5.33	9.05	79.67	70.62	130	**4.20**
86	15:12:00	15:31:00	00:19	0.80	30.20	239.70	13.50	80	40	0.45	1.24	4.03	31.96	71.45	39.49	135	**13.37**
87	14:27:00	14:46:00	00:19	0.80	46.40	149.30	6.70	80	25	0.29	2.48	6.19	19.91	69.18	49.28	67	**10.26**
88	21:11:00	21:36:00	00:25	0.45	34.00	88.00	14.00	45	26	0.31	2.19	4.53	11.73	37.41	25.68	140	**16.70**
89	05:19:00	05:41:00	00:22	0.70	32.50	234.10	11.50	70	45	0.51	0.97	4.33	31.21	61.56	30.35	115	**15.92**
90	03:33:00	04:01:00	00:28	0.80	31.20	199.00	11.30	80	33	0.37	1.69	4.16	26.53	71.31	44.78	113	**12.18**
91	06:00:00	06:47:00	00:47	0.70	36.60	129.00	13.10	70	25	0.28	2.55	4.88	17.20	60.97	43.78	131	**10.31**
92	06:40:00	07:01:00	00:21	0.60	100.00	180.00	9.10	60	40	0.57	0.75	13.33	24.00	42.09	18.10	91	**15.14**
93	17:00:00	17:31:00	00:31	0.45	39.10	186.90	12.40	45	55	0.68	0.47	5.21	24.92	36.64	11.72	124	**24.52**

Table 38 ABG results and the calculated oxygen indices for each patient included in the clinical data. The ABG measurements were taken during time 3

#	Time	ABGT	TimeD	FiO	PCO	PaO	Hb	FiO	PF	Pa/PA	RI	PCO2	PaO	PAO2	PA-a	Hb	crPaO2
1	07:02:00	07:30:00	00:28	0.40	102.30	70.60	9.30	40	24	0.42	1.35	13.64	9.41	22.16	12.74	93	**12.22**
2	23:50:00	00:37:00	00:47	0.65	38.60	82.00	12.90	65	17	0.20	4.11	5.15	10.93	55.89	44.96	129	**8.13**
3	23:10:00	23:48:00	00:38	0.60	43.70	59.30	6.10	60	13	0.16	5.37	5.83	7.91	50.35	42.45	61	**7.92**
4	23:50:00	00:37:00	00:47	0.65	38.60	82.00	12.90	65	17	0.20	4.11	5.15	10.93	55.89	44.96	129	**8.13**
5	06:54:00	07:14:00	00:20	0.60	28.00	134.00	13.10	60	30	0.34	1.95	3.73	17.87	52.65	34.79	131	**14.63**
6	18:30:00	19:08:00	00:38	0.30	40.20	108.00	12.40	30	48	0.65	0.53	5.36	14.40	22.08	7.68	124	**19.96**
7	02:46:00	03:16:00	00:30	0.40	33.50	91.90	7.90	40	31	0.37	1.67	4.47	12.25	32.70	20.45	79	**20.01**
8	20:20:00	21:01:00	00:41	0.80	53.00	133.00	10.90	80	22	0.26	2.85	7.07	17.73	68.26	50.53	109	**8.72**
9	18:30:00	19:09:00	00:39	0.60	57.20	82.60	12.90	60	18	0.23	3.39	7.63	11.01	48.37	37.36	129	**9.43**
10	18:30:00	18:58:00	00:28	0.70	47.30	91.70	10.30	70	17	0.21	3.86	6.31	12.23	59.44	47.22	103	**7.93**
11	13:05:00	13:26:00	00:21	0.60	32.40	134.90	7.70	60	30	0.35	1.89	4.32	17.99	52.01	34.02	77	**15.72**
12	16:00:00	16:56:00	00:56	0.40	38.80	94.40	10.80	40	31	0.39	1.53	5.17	12.59	31.89	19.31	108	**19.19**
13	15:40:00	16:31:00	00:51	0.80	46.20	103.30	8.40	80	17	0.20	4.03	6.16	13.77	69.21	55.44	84	**7.35**
14	06:55:00	07:10:00	00:15	0.50	44.80	73.60	11.60	50	20	0.24	3.14	5.97	9.81	40.58	30.77	116	**12.73**
15	21:25:00	21:47:00	00:22	0.40	41.00	126.60	7.60	40	42	0.53	0.87	5.47	16.88	31.55	14.68	76	**23.49**
16	21:31:00	22:04:00	00:33	0.50	35.50	78.00	8.10	70	49	0.56	0.79	4.68	34.26	61.19	26.93	85	**17.18**
17	04:00:00	04:23:00	00:23	0.60	38.20	157.80	6.90	60	35	0.41	1.43	5.09	21.04	51.16	30.12	69	**17.52**
18	19:31:00	21:33:00	02:02	0.50	52.90	85.80	8.30	50	23	0.29	2.44	7.05	11.44	39.37	27.93	83	**14.84**
19	06:18:00	06:39:00	00:21	0.40	32.00	101.00	8.80	40	34	0.41	1.45	4.27	13.47	32.93	19.47	88	**21.17**
20	03:50:00	04:14:00	00:24	0.60	42.70	135.40	8.70	60	30	0.36	1.80	5.69	18.05	50.50	32.45	87	**15.21**
21	11:55:00	12:36:00	00:41	0.35	31.50	154.60	11.90	35	59	0.73	0.37	4.20	20.61	28.23	7.62	119	**22.36**
22	23:40:00	00:15:00	00:35	0.60	40.10	108.00	13.60	60	24	0.28	2.53	5.35	14.40	50.88	36.48	136	**12.01**
23	21:40:00	22:18:00	00:38	0.70	41.00	133.00	12.80	70	25	0.29	2.40	5.47	17.73	60.34	42.61	128	**10.54**
24	15:37:00	16:20:00	00:43	0.35	37.00	144.90	11.58	35	55	0.71	0.42	4.93	19.32	27.38	8.06	116	**21.68**
25	16:00:00	16:44:00	00:44	0.30	41.50	113.00	11.80	30	50	0.69	0.45	5.53	15.07	21.88	6.81	118	**19.84**
26	12:00:00	12:56:00	00:56	0.30	46.00	100.00	14.00	30	44	0.63	0.59	6.13	13.33	21.17	7.84	140	**18.33**

27	17:50:00	18:10:00	00:20	0.75	46.60	116.00	10.20	75	21	0.24	3.16	6.21	15.47	64.35	48.88	102	**8.65**
28	10:23:00	10:44:00	00:21	0.85	37.60	133.40	13.20	85	21	0.24	3.23	5.01	17.79	75.21	57.42	132	**8.09**
29	10:56:00	11:13:00	00:17	0.30	40.30	95.40	9.70	30	42	0.58	0.73	5.37	12.72	22.07	9.35	97	**20.19**
30	15:12:00	15:34:00	00:22	0.55	34.30	114.30	8.50	55	28	0.32	2.08	4.57	15.24	46.94	31.70	85	**16.31**
31	01:05:00	01:47:00	00:42	0.55	40.90	113.00	10.00	55	27	0.33	2.05	5.45	15.07	45.96	30.90	100	**15.60**
32	22:41:00	23:16:00	00:35	0.55	44.00	87.00	11.20	55	21	0.25	2.92	5.87	11.60	45.50	33.90	112	**12.38**
33	00:05:00	00:33:00	00:28	0.60	58.80	60.20	8.00	60	13	0.17	5.00	7.84	8.03	48.14	40.11	80	**7.63**
34	22:00:00	22:32:00	00:32	0.85	42.60	79.10	8.60	85	12	0.14	6.07	5.68	10.55	74.52	63.97	86	**5.40**
35	12:50:00	13:08:00	00:18	0.60	49.50	89.10	10.90	60	20	0.24	3.17	6.60	11.88	49.50	37.62	109	**10.46**
36	23:10:00	23:40:00	00:30	0.80	34.20	82.70	13.00	80	14	0.16	5.43	4.56	11.03	70.89	59.87	130	**5.72**
37	01:50:00	02:17:00	00:27	0.30	38.00	62.00	10.30	30	28	0.37	1.71	5.07	8.27	22.43	14.16	103	**16.00**
38	06:25:00	06:46:00	00:21	0.35	51.10	93.90	10.20	35	36	0.50	1.01	6.81	12.52	25.19	12.67	102	**18.05**
39	01:45:00	02:05:00	00:20	0.30	34.00	103.00	12.40	30	46	0.60	0.68	4.53	13.73	23.05	9.32	124	**20.91**
40	22:30:00	23:22:00	00:52	0.85	57.90	99.80	12.10	85	16	0.18	4.44	7.72	13.31	72.40	59.10	121	**6.25**
41	02:40:00	03:08:00	00:28	0.50	36.00	77.00	12.30	50	21	0.25	3.08	4.80	10.27	41.90	31.63	123	**13.35**
42	08:31:00	09:05:00	00:34	0.50	44.00	120.60	10.20	50	32	0.40	1.53	5.87	16.08	40.70	24.62	102	**19.02**
43	06:50:00	07:40:00	00:50	0.50	40.70	238.00	14.00	50	63	0.77	0.30	5.43	31.73	41.20	9.46	140	**22.08**
44	03:55:00	04:19:00	00:24	0.60	36.60	104.00	7.80	60	23	0.27	2.71	4.88	13.87	51.39	37.53	78	**12.72**
45	03:12:00	03:35:00	00:23	0.65	33.40	132.00	8.50	65	27	0.31	2.22	4.45	17.60	56.65	39.05	85	**12.96**
46	04:20:00	04:41:00	00:21	0.75	54.70	70.70	8.70	75	13	0.15	5.71	7.29	9.43	63.20	53.78	87	**5.66**
47	21:44:00	22:16:00	00:32	0.70	46.00	126.00	13.70	70	24	0.28	2.55	6.13	16.80	59.63	42.83	137	**9.90**
48	18:15:00	18:41:00	00:26	0.40	39.20	81.60	10.70	40	27	0.34	1.93	5.23	10.88	31.83	20.95	107	**17.30**
49	04:10:00	04:27:00	00:17	0.30	32.90	94.00	7.70	30	42	0.54	0.85	4.39	12.53	23.23	10.69	77	**21.83**
50	21:55:00	22:33:00	00:38	0.75	29.00	236.00	14.00	75	42	0.47	1.12	3.87	31.46	66.84	35.38	140	**14.17**
51	14:00:00	14:28:00	00:28	0.50	31.00	82.30	13.10	50	22	0.26	2.89	4.13	10.97	42.65	31.68	131	**14.11**
52	10:45:00	11:02:00	00:17	0.80	39.00	119.00	13.10	80	20	0.23	3.43	5.20	15.87	70.22	54.36	131	**7.84**
53	02:26:00	02:49:00	00:23	0.35	31.00	78.00	8.80	35	30	0.37	1.72	4.13	10.40	28.31	17.91	88	**18.05**
54	02:05:00	02:31:00	00:26	0.30	29.00	97.00	10.70	30	43	0.54	0.84	3.87	12.93	23.84	10.90	107	**21.77**
55	05:45:00	06:10:00	00:25	0.60	44.70	103.60	10.00	60	23	0.28	2.63	5.96	13.81	50.20	36.39	100	**12.10**

56	14:01:00	14:20:00	00:19	0.40	36.00	175.00	7.40	40	58	0.72	0.39	4.80	23.33	32.32	8.99	74	**25.47**
57	17:18:00	17:55:00	00:37	0.30	43.20	91.00	8.90	30	40	0.56	0.78	5.76	12.13	21.61	9.48	89	**19.64**
58	09:40:00	10:03:00	00:23	0.60	58.00	83.00	9.00	60	18	0.23	3.36	7.73	11.07	48.25	37.19	90	**9.98**
59	07:49:00	08:01:00	00:12	0.30	39.00	99.00	10.00	30	44	0.59	0.69	5.20	13.20	22.27	9.07	100	**20.54**
60	09:17:00	09:42:00	00:25	0.35	35.60	94.00	10.50	35	36	0.45	1.20	4.75	12.53	27.59	15.06	105	**19.51**
61	01:30:00	01:53:00	00:23	0.40	37.00	109.00	8.90	40	36	0.45	1.21	4.93	14.53	32.17	17.63	89	**21.74**
62	05:30:00	05:49:00	00:19	0.55	34.00	64.00	10.70	55	16	0.18	4.51	4.53	8.53	46.99	38.45	107	**9.74**
63	01:49:00	02:13:00	00:24	0.30	36.00	86.00	11.20	30	38	0.50	0.98	4.80	11.47	22.74	11.27	112	**19.54**
64	00:00:00	00:52:00	00:52	0.90	41.00	87.40	7.40	90	13	0.15	5.83	5.47	11.65	79.54	67.88	74	**5.73**
65	18:13:00	18:36:00	00:23	0.70	35.00	88.00	9.40	70	17	0.19	4.22	4.67	11.73	61.20	49.47	94	**7.87**
66	15:30:00	16:32:00	01:02	0.40	47.00	83.00	10.00	40	28	0.36	1.77	6.27	11.07	30.63	19.57	100	**17.22**
67	17:46:00	18:02:00	00:16	0.35	41.10	76.80	9.00	35	29	0.38	1.61	5.48	10.24	26.74	16.50	90	**17.08**
68	17:45:00	18:10:00	00:25	0.60	42.30	146.00	8.60	60	32	0.39	1.60	5.64	19.47	50.56	31.09	86	**16.08**
69	18:05:00	18:27:00	00:22	0.70	45.80	109.20	8.80	70	21	0.24	3.10	6.11	14.56	59.66	45.10	88	**9.42**
70	15:05:00	15:30:00	00:25	0.30	30.00	128.70	9.40	30	57	0.72	0.38	4.00	17.16	23.68	6.52	94	**22.76**
71	17:20:00	17:44:00	00:24	0.30	39.10	105.00	10.80	30	47	0.63	0.59	5.21	14.00	22.25	8.26	108	**20.56**
72	16:00:00	16:22:00	00:22	0.40	47.80	101.50	9.90	40	34	0.44	1.25	6.37	13.53	30.51	16.98	99	**19.64**
73	14:00:00	14:28:00	00:28	0.30	27.00	147.00	9.00	30	65	0.81	0.23	3.60	19.60	24.15	4.55	90	**21.81**
74	01:11:00	01:35:00	00:24	0.60	38.20	163.50	12.40	60	36	0.43	1.35	5.09	21.80	51.16	29.36	124	**16.58**
75	04:58:00	05:18:00	00:20	0.60	35.00	270.00	11.20	60	60	0.70	0.43	4.67	36.00	51.63	15.63	112	**20.30**
76	22:02:00	22:37:00	00:35	0.50	36.00	242.00	10.20	50	65	0.77	0.30	4.80	32.26	41.90	9.64	102	**23.84**
77	00:42:00	01:01:00	00:19	0.40	40.00	93.00	8.70	40	31	0.39	1.56	5.33	12.40	31.71	19.31	87	**19.48**
78	11:39:00	12:08:00	00:29	0.30	36.80	116.80	8.30	30	52	0.69	0.45	4.91	15.57	22.62	7.04	83	**21.86**
79	13:43:00	14:08:00	00:25	0.80	35.60	104.70	11.00	80	17	0.20	4.06	4.75	13.96	70.70	56.74	110	**7.25**
80	16:33:00	17:06:00	00:33	0.60	129.90	178.90	15.10	60	40	0.63	0.58	17.32	23.85	37.71	13.86	151	**12.23**
81	10:04:00	10:32:00	00:28	0.80	69.10	73.70	10.00	80	12	0.15	5.72	9.21	9.83	66.01	56.18	100	**5.19**
82	09:50:00	10:14:00	00:24	0.30	32.40	112.20	10.40	30	50	0.64	0.56	4.32	14.96	23.30	8.35	104	**22.15**
83	17:30:00	18:20:00	00:50	0.80	61.60	83.00	5.60	80	14	0.17	5.06	8.21	11.07	67.06	55.99	56	**6.20**
84	15:56:00	16:20:00	00:24	0.70	32.00	91.50	10.90	70	17	0.20	4.05	4.27	12.20	61.63	49.43	109	**8.00**

85	10:45:00	11:14:00	00:29	0.80	40.70	63.70	13.30	80	11	0.12	7.24	5.43	8.49	69.98	61.49	133	**4.45**
86	15:31:00	16:00:00	00:29	0.60	28.80	97.90	13.50	60	22	0.25	3.03	3.84	13.05	52.54	39.48	135	**11.32**
87	14:46:00	15:04:00	00:18	0.70	45.00	105.20	6.60	70	20	0.23	3.26	6.00	14.03	59.77	45.75	66	**9.43**
88	21:36:00	22:02:00	00:26	0.40	36.10	86.00	14.00	40	29	0.35	1.82	4.81	11.47	32.31	20.84	140	**17.37**
89	05:41:00	06:12:00	00:31	0.40	36.00	106.00	11.60	40	35	0.44	1.29	4.80	14.13	32.32	18.19	116	**20.67**
90	04:01:00	04:38:00	00:37	0.80	31.70	171.10	11.50	80	29	0.32	2.12	4.23	22.81	71.24	48.43	115	**10.86**
91	06:54:00	07:41:00	00:47	0.60	28.90	134.00	14.30	60	30	0.34	1.94	3.85	17.87	52.52	34.66	143	**14.37**
92	07:02:00	07:30:00	00:28	0.40	102.30	70.00	9.30	40	23	0.42	1.37	13.64	9.33	22.16	12.82	93	**12.16**
93	17:31:00	18:36:00	01:05	0.35	37.00	135.00	12.50	35	51	0.66	0.52	4.93	18.00	27.38	9.38	125	**21.52**

Table 39 oxygen indices variation for the clinical data

The average CV% for each index from the three reading measurements					Headline Figure Reciprocal (crPaO2 VS oxygen index)			
crPaO2	PF ratio	Pa/PA	RI	PA-a	vs PF ratio	vs Pa/PA	vs RI	vs PA-a
11%	36%	22%	50%	21%	3.44	2.06	4.77	1.99
21%	35%	34%	44%	10%	1.65	1.57	2.05	0.48
30%	46%	45%	79%	6%	1.54	1.49	2.65	0.22
21%	35%	34%	44%	10%	1.65	1.57	2.05	0.48
20%	43%	41%	55%	13%	2.19	2.12	2.84	0.65
5%	9%	1%	3%	45%	1.83	0.22	0.63	8.88
3%	5%	3%	5%	11%	1.36	0.91	1.51	3.13
9%	10%	10%	14%	12%	1.12	1.10	1.54	1.38
4%	13%	10%	14%	19%	2.90	2.28	3.25	4.16
18%	23%	21%	28%	13%	1.26	1.15	1.51	0.70
14%	33%	31%	45%	15%	2.42	2.28	3.31	1.08
7%	9%	11%	17%	21%	1.29	1.55	2.44	3.06
7%	8%	9%	10%	14%	1.07	1.17	1.35	1.81
11%	10%	10%	13%	9%	0.93	0.95	1.23	0.80
3%	4%	6%	13%	20%	1.27	1.97	4.07	6.12
9%	41%	39%	84%	11%	4.58	4.36	9.33	1.21
10%	16%	14%	26%	15%	1.69	1.47	2.72	1.56
2%	4%	2%	3%	9%	1.81	0.83	1.18	4.18
18%	23%	20%	42%	29%	1.26	1.09	2.26	1.55
6%	29%	26%	50%	5%	5.14	4.66	8.97	0.95
39%	43%	45%	118%	115%	1.11	1.17	3.05	2.96
19%	20%	19%	26%	22%	1.08	1.01	1.36	1.19
19%	24%	22%	31%	13%	1.28	1.19	1.64	0.69
31%	37%	44%	62%	65%	1.19	1.41	1.98	2.08
8%	13%	22%	42%	55%	1.67	2.83	5.50	7.23

12%	16%	11%	30%	56%	1.38	0.90	2.55	4.80
8%	11%	10%	15%	10%	1.45	1.31	1.91	1.25
2%	3%	3%	3%	6%	1.17	1.05	1.36	2.41
8%	15%	18%	31%	30%	1.80	2.10	3.68	3.51
3%	32%	30%	53%	6%	9.21	8.68	15.26	1.64
7%	7%	6%	9%	7%	1.07	0.95	1.39	1.01
5%	14%	12%	17%	8%	2.66	2.32	3.27	1.48
36%	59%	55%	81%	4%	1.63	1.52	2.25	0.11
6%	7%	7%	8%	9%	1.01	1.01	1.20	1.38
31%	30%	30%	44%	15%	0.97	0.96	1.44	0.49
7%	8%	7%	9%	5%	1.17	1.08	1.26	0.75
12%	15%	22%	28%	41%	1.31	1.91	2.37	3.50
13%	27%	16%	32%	40%	2.04	1.26	2.45	3.11
3%	22%	19%	47%	33%	7.41	6.53	15.84	11.14
4%	3%	2%	3%	9%	0.94	0.63	0.79	2.57
15%	21%	18%	23%	34%	1.41	1.21	1.51	2.27
12%	28%	25%	39%	19%	2.34	2.09	3.25	1.60
34%	36%	39%	101%	95%	1.05	1.14	2.94	2.76
5%	10%	8%	12%	10%	1.88	1.63	2.39	1.91
3%	16%	14%	22%	11%	5.10	4.41	7.21	3.66
6%	8%	6%	7%	10%	1.26	1.07	1.24	1.58
18%	25%	24%	32%	12%	1.37	1.33	1.76	0.65
6%	10%	9%	13%	22%	1.74	1.49	2.30	3.78
6%	11%	14%	30%	45%	1.89	2.37	5.09	7.64
43%	51%	51%	99%	45%	1.17	1.18	2.30	1.03
19%	23%	24%	38%	25%	1.21	1.26	2.03	1.35
4%	5%	5%	6%	5%	1.27	1.08	1.41	1.24
12%	16%	12%	18%	36%	1.32	0.97	1.53	2.99
10%	20%	17%	52%	32%	1.87	1.60	5.00	3.06

10%	20%	19%	25%	18%	2.05	1.93	2.63	1.89
26%	31%	33%	77%	62%	1.19	1.29	2.96	2.38
4%	12%	17%	29%	32%	3.14	4.27	7.38	8.09
10%	10%	6%	8%	29%	0.97	0.63	0.80	2.84
7%	9%	7%	21%	14%	1.30	1.09	3.08	2.03
14%	15%	9%	18%	44%	1.08	0.67	1.28	3.14
13%	13%	16%	24%	27%	1.03	1.30	1.92	2.12
4%	15%	15%	20%	5%	3.61	3.52	4.77	1.12
12%	16%	11%	23%	18%	1.30	0.88	1.87	1.46
4%	5%	6%	6%	7%	1.27	1.41	1.62	1.70
37%	36%	37%	52%	26%	0.96	0.99	1.41	0.71
1%	14%	19%	28%	34%	9.89	13.59	20.22	24.86
5%	9%	12%	18%	24%	1.76	2.40	3.78	5.01
5%	16%	14%	27%	7%	3.23	2.82	5.56	1.36
6%	9%	7%	10%	7%	1.44	1.21	1.58	1.12
2%	13%	14%	33%	35%	5.51	5.67	13.81	14.52
10%	9%	2%	6%	35%	0.89	0.22	0.60	3.40
5%	9%	6%	10%	23%	1.95	1.17	2.11	4.67
13%	16%	19%	50%	53%	1.24	1.53	3.94	4.17
10%	18%	16%	30%	12%	1.75	1.61	2.99	1.24
28%	38%	38%	103%	85%	1.35	1.38	3.73	3.05
28%	30%	32%	88%	57%	1.08	1.15	3.19	2.06
14%	24%	19%	33%	33%	1.68	1.32	2.34	2.30
7%	11%	6%	21%	16%	1.49	0.82	2.89	2.15
2%	3%	2%	3%	11%	1.10	0.99	1.23	4.47
22%	31%	34%	84%	72%	1.44	1.59	3.90	3.34
30%	33%	32%	44%	4%	1.12	1.07	1.49	0.13
4%	7%	7%	19%	26%	1.72	1.82	4.99	6.80
9%	11%	10%	13%	10%	1.26	1.12	1.46	1.18

	18%	25%	25%	28%	12%	1.45	1.41	1.59	0.67
	7%	7%	8%	9%	13%	1.06	1.16	1.33	1.82
	12%	34%	33%	63%	8%	2.97	2.87	5.45	0.66
	22%	34%	33%	42%	4%	1.58	1.51	1.96	0.21
	2%	5%	6%	9%	15%	2.47	3.03	4.58	7.21
	16%	21%	16%	31%	33%	1.31	0.97	1.95	2.05
	7%	9%	10%	14%	17%	1.36	1.41	2.02	2.59
	20%	43%	42%	56%	13%	2.21	2.13	2.86	0.67
	12%	27%	16%	29%	67%	2.26	1.31	2.40	5.57
	7%	7%	3%	11%	14%	1.04	0.50	1.55	2.07
Min	1%	3%	1%	3%	4%	0.89	0.22	0.60	0.13
Mean	12%	19%	18%	33%	24%	1.96	1.86	3.28	2.90
Max	43%	59%	55%	118%	115%	9.89	13.59	20.22	24.86