Ventilatory Ratio: A Simple Bedside Index To Monitor Ventilatory Efficiency

By

Pratik Sinha

A thesis submitted for the degree of
Doctor of Philosophy of Imperial College London
and
Diploma of Imperial College London

Anaesthetics, Pain Medicine and Intensive Care Section
Division of Surgery and Cancer
Imperial College

Abstract

A lack of a simple index that monitors ventilatory efficiency at the bedside has meant that oxygenation has been the predominant variable that is used to monitor adequacy of ventilatory strategies and disease severity in mechanically ventilated patients. Due to complexities in its measurement, deadspace ventilation, the traditional method to track ventilatory failure, has failed to become integral in the management of mechanically ventilated patients.

Ventilatory ratio (VR) is an easy to calculate index that uses variables measured at the bedside:

$$VR = \frac{\dot{V}_{E_{measured}} \times P_{a_{CO_2 measured}}}{\dot{V}_{E_{predicted}} \times P_{a_{CO_2 predicted}}}$$

where $\dot{V}_{E_{predicted}}$ is taken to be 100 ml.kg^{-1}.min^{-1} based on predicted body weight and $Pa_{CO_2 predicted}$ is taken to be 5 kPa. Physiological analysis of VR dictates that it is influenced by deadspace fraction and CO_2 production.

Physiological analysis of VR was validated in a benchside lung model and a high fidelity computational cardiopulmonary physiology model. The impact of CO_2 production on VR was investigated in patients undergoing laparoscopic surgery who received exogenous intraperitoneal CO_2. This showed that delta values of the 2 variables were linear. The variability of CO_2 production was examined in ICU patients and results of the study showed that variability of CO_2 production was small. In an ICU population correlation of VR was stronger with deadspace in comparison to CO_2 production. Of these two variables, deadspace had the greater effect on VR.

The clinical uses of VR were examined in 4 databases of ICU patients. VR was significantly higher in non-survivors compared to survivors. Higher values of VR were associated with increased mortality and more ventilator days. A rising values of VR over time was also associated with worse outcome.

VR is a simple bedside index that provides clinicians with useful information regarding ventilatory efficiency and is associated with outcome.

Hypotheses

Null 1: An index that is a composite of arterial PCO_2 and minute ventilation will not be responsive to changes in ventilatory efficiency.

Null 2: Higher values and increasing values of such an index will not be associated with worsening disease severity in mechanically ventilated patients.

Declaration

The materials presented in Chapter 1, Chapter 2, and Chapter 3 have been published in various journals. The co-authors of these manuscripts are recognized in the acknowledgements section. The presented works in the thesis are original of the author unless stated otherwise. There are no conflicts of interest to declare.

Published Journal Manuscripts:

Ventilatory ratio: A simple bedside measure of ventilation. Sinha P, Fauvel NJ, Singh S, Soni N. *Br J Anaesth* 2009;102:692-697.

Deadspace ventilation: a waste of breath! Sinha P, O. Flower, Soni N. *Intensive Care Medicine* 2011 37(5): 735-746

Comparison of volumetric capnography and mixed expired gas methods to calculate physiological dead space in mechanically ventilated patients. Sinha, P, Soni N. *Intensive Care Medicine* 2012 Aug 15 [Epub ahead of print].

To Rachel

Acknowledgements

I would like to thank my supervisor Dr Neil Soni for taking me on as a PhD student. His boundless enthusiasm and exhaustive knowledge of respiratory physiology and its application in clinical practice was extremely infectious. He has constantly encouraged me to challenge the status quo and his inquisitive scientific mind has been an constant inspiration. His guidance, wit, and generosity has been essential to the completion of the project and has made the process surprisingly enjoyable……..at times.

The thesis was completed at Chelsea and Westminster Hospital, London. I would like thank to everyone at the unit who have knowing and unknowingly contributed to the completion of the thesis.

I would like to thank Dr Nicholas Fauvel for sharing his encyclopedic knowledge of human physiology and for his perspicacious eye for preparing manuscripts. I would also like to thank Dr Suveer Singh for helping with reading through chapters, and Dr Jonathan Handy and Dr Michelle Hayes for their help, guidance, and advice through out.

I would like to thank Prof Pradeep Singh for his help with some of the more challenging statistical problems. I would also like to thank Prof Jonathan Hardman for his help with understanding the Nottingham Physiology Simulator. I would like to thank Dr Simon Finney for his efforts in providing me the data for the Royal Brompton Hospital database. Prof Andrew Bersten and Prof Ognjen Gajic kindly released the ANZICS and ARDS network databases respectively.

I would like to thank the following individuals for their assistance in constructing the ICU databases: Emma Yazbek for her Microsoft Excel expertise, Chris Hogan, Claire Waterworth, Camelia Wong, Michael Quinn, and Jason Tatlock for assisting in data entry.

In addition I have some co-investigators whose assistance I would like to acknowledge. Theresa Weldring for her assistance in the CO_2 variability study. Dr Kirthi Varo and Dr Nick Bunker for their help in studying the peri-operative patients.

Dr Oliver Flower for his assistance with the review article. Dr Marija Kostic for her help with understanding the ARDSnet database. I would like to thank Ted Tabor for his enthusiasm and expertise.

I would like to thank the Westminster Medical School for funding my research.

Finally, I would like to thank my family and friends for tolerating my absenteeism.

Contents

Abbreviations

AICU = Adult intensive care unit

ALI = Acute Lung Injury

ARDS = Acute respiratory distress syndrome

BIPAP = Biphasic Positive Airway Pressure

BRS = Bronchial resistance slider

COPD = Chronic obstructive pulmonary disease

CPAP = Continuous Positive Airway Pressure

CWH = Chelsea and Westminster Hospital

DKA = Diabetic ketoacidosis

E = Efficiency ($\dot{V}_A / \dot{V}_E$)

E_{actual} = The actual fraction of alveolar ventilation

$E_{predicted}$ = The predicted fraction of alveolar ventilation

ET_{CO_2} = End–tidal carbon dioxide

$F_{A_{CO_2}}$ = Fraction of carbon dioxide in alveolar gas

$F_{D_{CO_2}}$ = Fraction of carbon dioxide in deadspace gas

$F_{E_{CO_2}}$ = Fraction of carbon dioxide in mixed expired gas

FiO_2 = Fraction of inspired oxygen

ILD = Interstitial lung disease

LRTI = Lower respiratory tract infection

MawP = Mean airway pressure

MIGET = Multiple inert gas elimination technique

NPS = Nottingham Physiology Simulator

OI = Oxygenation Index

$P_{A_{CO_2}}$ = Alveolar partial pressure of carbon dioxide

Pa_{CO_2} = Arterial partial pressure of carbon dioxide

$Pa_{CO_{2\,measured}}$ = Measured arterial partial pressure of CO_2

$Pa_{CO_{2\,predicted}}$ = Predicted arterial partial pressure of CO_2

$Pa - e_{CO_2}$ = Arterial partial pressure of CO_2 minus End-tidal partial pressure of CO_2

PaO_2, = Arterial partial pressure of Oxygen

PBW = Predicted body weight

P_{CO_2} = Partial pressure of CO_2

PCV = Pressure controlled ventilation

$P\bar{E}_{CO_2}$ = Mixed-expired partial pressure of carbon dioxide

PEEP = Peak end-expiratory pressure

PH_2O = Water vapour pressure

PIP = Peak inspiratory pressure

P_{peak} = Peak airway pressure

$\dot{Q}_S / \dot{Q}_T$ = Shunt Fraction

RBH = Royal Brompton Hospital

RQ = Respiratory Quotient

SBT-CO_2 = Single breath CO_2 waveform

SIMV = Synchronized intermittent mandatory ventilation

SpO_2 = Oxygen saturation

TPN = Total Parenteral Nutrition

V_A = Alveolar ventilation

$\dot{V}_A$ = Alveolar ventilation per unit time

V_{AE} = Alveolar ejection volume

VCV = Volume controlled ventilation

$\dot{V}CO_2$ = Rate of CO_2 elimination / production

$\dot{V}CO_{2actual}$ = Actual rate of CO_2 elimination / production

$\dot{V}CO_2^{est}$ = Estimated CO_2 production using the Harris–Benedict equation

$\dot{V}CO_{2predicted}$ = Predicted value for rate of CO_2 elimination / production

$V_{D_{alv}}$ = Alveolar deadspace

$V_{D_{aw}}$ = Airway deadspace

$V_{D_{Bohr}}$ = Bohr's deadspace

$V_{D_{phys}}$ = Physiological deadspace

V_D / V_T = Physiological deadspace

$V_D/V_{T\ Bohr}$ = Bohr's deadspace fraction

$V_D / V_{T\ DB}$ = Deadspace fraction as calculated by the Douglas Bag Method

$V_D / V_{T\ VCAP}$ = Deadspace fraction as calculated by volumetric capnography

$\dot{V}_E$ = Minute ventilation

$\dot{V}_{E_{measured}}$ = Measured minute ventilation

$\dot{V}_{E_{predicted}}$ = Predicted minute ventilation

$\dot{V}/\dot{Q}$ = Ventilation perfusion ratio

VR = Ventilatory Ratio

VRS = Vascular resistance slider

V_T = Tidal Volume

V_{Te} = Expired tidal volume

V_V = Compressible volume of the ventilator and connection tubing

Chapter 1: Introduction

Alveolar ventilation is the amount of air per unit time that is involved in gas exchange. Ventilatory efficiency describes this volume as a proportion of the tidal volume. The remainder of the tidal volume is not involved in gas exchange and is conceptually known as the physiological deadspace. Whilst deadspace ventilation is probably of minimal consequence in normal conditions, its inherent clinical importance is that pathophysiological states of the lung result in its increase and hence a reduction in ventilatory efficiency. At the bedside this will manifest as altered carbon dioxide clearance. Such pathological processes are common in the critically ill and measurement of physiological deadspace should be a most valuable and intuitive tool to manage ventilation, yet it is seldom used.

Over the last five decades emphasis in mechanical ventilation has increasingly focused on improving oxygenation, whilst avoiding iatrogenic complications. Although carbon dioxide measurements are used to guide ventilatory adequacy, most ventilatory strategies are aimed primarily at adequate oxygenation. Measurements and indices of oxygenation, such as PaO_2, SpO_2 and PaO_2 / FiO_2 or Alveolar-arterial gradients are frequently utilized to adjust ventilatory settings and aid in clinical decision-making (1-4). Whilst attention is paid to minute ventilation, respiratory rate, tidal volumes and Pa_{CO_2}, there is no common unifying index that can be easily used to assess the efficacy of CO_2 elimination at the bedside. Especially in an era where permissive hypercapnia is widely practiced (5), the development of such an index becomes ever more crucial.

The rationale behind the development of Ventilatory Ratio (VR) was to develop an easy to calculate index that monitors ventilatory efficiency at the bedside. Prior to the description of VR a brief introduction to ventilatory efficiency and use in clinical practice is presented.

1.1 Historical Perspective

The earliest recorded historical evidence of the identification of carbon dioxide is attributed to J.B.Van Helmont, a 17th century Flemish physician and chemist. He identified carbon dioxide or *"gas sylvestre"*, a gas seen on burning charcoal (6). In doing so he became one of the first chemists to acknowledge the existence of gases

that are distinguishable from air. Interest in carbon dioxide however remained low until Joseph Black, a Scottish chemist in the mid-eighteenth century, became the first person to isolate carbon dioxide in its pure form. In his experiments he isolated carbon dioxide and called it 'fixed air', describing it as a non-breathable air produced by respiration, fermentation, and burning of charcoal (7, 8). In medical practice there has been an increased interest in CO_2 since the advent of mechanical ventilation and more recently with point of care blood gas analysers. In recent years non-invasive methods for continuous carbon dioxide measurements at the bedside are also available and are regularly used in anaesthesia and critical care medicine.

The importance of carbon dioxide clearance was first appreciated in the Danish polio epidemic when clinicians rapidly realised that existing methods such as negative pressure ventilation resulted in deaths despite adequate oxygenation. The turning point was the realization that most deaths were due to inadequate ventilation (9, 10). This led to the birth of positive pressure ventilation, respiratory physiological monitoring and with it intensive care medicine. The initial primacy of carbon dioxide clearance in monitoring during mechanical ventilation was key. Since then emphasis in practice has slowly changed and adequacy of oxygenation has replaced carbon dioxide as the principle focus for managing such patients. Yet the indirect role of ventilation in oxygenation is illustrated by the ability to oxygenate by insufflation. Carbon dioxide and its clearance has been considered of still lesser importance especially with the advent of permissive hypercapnia. This correctly identifies the relatively innocuous nature of mild hypercapnia but in doing so obscures the obvious fact that hypercarpnia with adequate ventilation implies a significant increase in physiological deadspace with or without alterations in shunt. The pathophysiology underlying permissive hypercapnia is directly related to the underlying disease processes yet it is considered of secondary importance. It is a clinical paradox that while the concept of physiological deadspace has been known since the late 19th century, in the critical care setting it remains an underused and poorly understood variable in clinical practice.

At present measuring physiological dead space is the most widely used method to monitor ventilatory efficiency at the bedside. At present this is mostly limited to the research setting. Yet despite extensive evidence of its use in mechanically ventilated

patients the variable is seldom measured. Examined in this chapter are current physiological concepts of deadspace, describe methods of measurement, and describe its common uses as a clinical tool in the critical care setting. Also examined are the current available methods to assess ventilatory efficiency at the bedside.

1.2 Deadspace Ventilation

1.2.1 Terminology

Deadspace is the portion of tidal volume that does not participate in gas exchange i.e. 'wasted'. Physiological deadspace ($V_{D_{phys}}$) is a composed of airway deadspace ($V_{D_{aw}}$) and alveolar deadspace ($V_{D_{alv}}$):

$$V_{D_{phys}} = V_{D_{aw}} + V_{D_{alv}} \qquad [1]$$

In mechanically ventilated patients airway deadspace ($V_{D_{aw}}$) is the sum of anatomical deadspace (conducting airways) and apparatus deadspace. Alveolar deadspace is a construct that accounts for the remainder of the tidal volume that does not participate in gas exchange. In normal healthy subjects the alveolar deadspace is expected to be negligible.

1.2.2 History of Physiological Deadspace.

1.2.2.1 Bohr Equation

Tidal volume (V_T) is the sum of alveolar ventilation (V_A) and physiological deadspace (V_D):

$$V_T = V_A + V_D \qquad [2]$$

In 1891 Bohr made two basic assumption when considering his approach to calculating deadspace (11). Firstly a two-lung model was assumed whereby there was either gas exchange (alveolar ventilation) or deadspace. The 'deadspace' in this instance was assumed to be a fixed entity derived from previous cadaveric measurements (airway deadspace). Bohr proposed using equation [2] to calculate the alveolar volume. He also assumed that there was no carbon dioxide in inspired air. Therefore all carbon dioxide measured in mixed expired gas came from alveolar ventilation. The latter assumption is used in most current methods used to calculate deadspace.

Inserting the appropriate fractioned CO_2 concentration (F) into each of the three volumes in equation [2] and given that the concentration of CO_2 in deadspace gas ($F_{D_{CO_2}}$) is 0, using the conservation of mass principle equation [2] can be restated as:

$$V_T \cdot F_{E_{CO_2}} = V_A \cdot F_{A_{CO_2}} \qquad [3]$$

From equation 2 we also know that $V_A = V_T - V_D$ therefore:

$$V_T \cdot F_{E_{CO_2}} = (V_T - V_D) \cdot F_{A_{CO_2}} \qquad [4]$$

Solving for V_D / V_T we get:

$$\frac{V_D}{V_T} = \frac{F_{A_{CO2}} - F_{E_{CO2}}}{F_{A_{CO2}}} \qquad [5]$$

where FA_{CO_2} is the alveolar fractional concentration of CO_2 and FE_{CO_2} is the mixed expired fractional concentration of CO_2. This equation was originally used by Bohr to obtain FA_{CO_2} and the associated alveolar volume. Equation [5] is commonly known as Bohr's equation.

Since then equation [5] is frequently restated substituting fractioned CO_2 concentration with partial pressures of CO_2 (P_{CO_2}):

$$\frac{V_D}{V_T} = \frac{PA_{CO_2} - P\bar{E}_{CO_2}}{PA_{CO_2}} \qquad [6]$$

Where PA_{CO_2} is the alveolar P_{CO_2} and $P\bar{E}_{CO_2}$ is the mixed expired P_{CO_2}. Subsequent to the work of Bohr it was recognized that deadspace was a varying entity. The introduction of gas analysis allowed the use of expired CO_2 as a surrogate for alveolar CO_2 (12). Mixed expired CO_2 was collected in a reservoir bag and thereby enabling the calculation of deadspace using equation [6] (13).

1.2.2.2 Enghoff Modification of Bohr's Equation

One of the limitations of Bohr's method of calculating deadspace has been accurately measuring alveolar P_{CO_2} (PA_{CO_2}). Given the inter-alveoli heterogeneity of ventilation-perfusion ratio and the uneven emptying of lung units due to varied time constants,

end-tidal CO_2 is an inaccurate representation of $P_{A_{CO_2}}$ (14). This is especially true in the case of diseased lungs where there is increased disparity in the homogeneity of the V / Q matching and alveolar emptying. By assuming that there was no difference in the values of alveolar P_{CO_2} and arterial P_{CO_2} (Pa_{CO_2}), in 1938 Enghoff modified the Bohr deadspace equation by substituting $P_{A_{CO_2}}$ with Pa_{CO_2} (15). Accounting for this substitution we can restate equation [5]:

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}} \qquad [7]$$

Equation [7] is known as the Bohr-Enghoff equation and to this day remains the most commonly used method to calculate deadspace using mixed-expired CO_2.

1.2.2.3 Fowler's Airway Deadspace

Fowler's novel method was to use continuous nitrogen gas analysis to calculate deadspace (16). His subjects inhaled 99.6% oxygen and the expired volume and concentration of nitrogen were continuously measured. Fowler defined 'physiological deadspace' as the volume representing the conducting airways. He described it as the point where a large change in the gas composition occurred. Effectively this is the volume represented by what we now know as the airway deadspace. Fowler proposed analyzing the graph-form of the nitrogen volume-concentration of expired gas to calculate the deadspace (Figure 1.1).

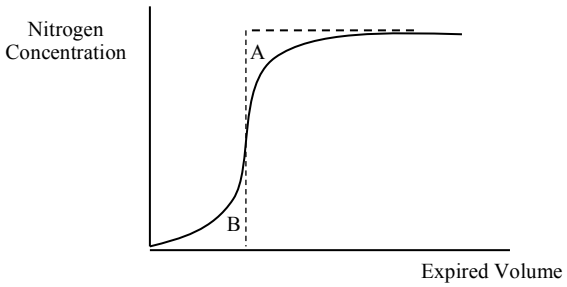


Figure 1.1. Fowler's method of calculating deadspace. The vertical dashed line is drawn such that the areas marked A and B are equal. The deadspace volume is represented by the volume where the line intercepts the x-axis. A similar waveform can be drawn for expired CO_2 concentration.

Since then Bartels and colleagues demonstrated that the deadspace for carbon dioxide was the same as that of nitrogen and Fowler's methods could be applied to calculate deadspace using single breath analysis of expired CO_2 (17).

More recently Langley and colleagues plotted the expired CO_2 volume against the expired total volume and described an alternative method of calculating airway deadspace (18). This curvilinear graph is shown in Figure 1.2. A straight best-fit line is extrapolated from the linear portion of the graph and the intercept of this line on the volume axis (x-axis) is representative of the deadspace (Figure 1.2). This method correlates with Fowler's method for calculating VD_{aw} but with the added advantage that it does not rely on the visual interpretation for determining equal areas (19, 20).

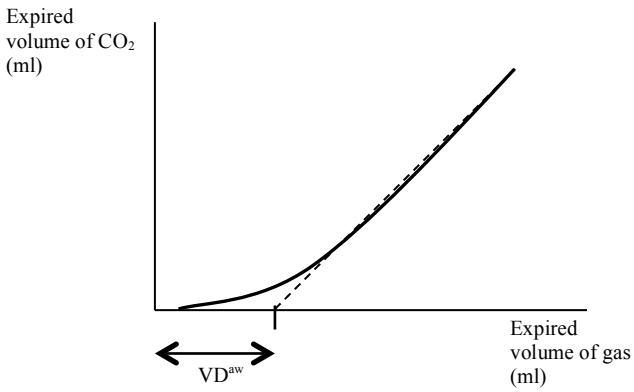


Figure 1.2. Langley's method for calculating anatomical deadspace. Plotted is the volume of expired CO_2 against the volume of expired gas. The dotted line represents the best-fit line of the linear segment of the graph. The point of interception of the dotted line on the x-axis represents the airway deadspace volume.

While several factors can influence airway deadspace, in the critical care setting this volume remains relatively unchanged. Large stepwise changes in airway deadspace in mechanically ventilated patients are usually as a result of equipment deadspace and hence easily quantifiable. Any changes in measured physiological deadspace, without added equipment deadspace, are mostly a result of changes in alveolar deadspace. It is alveolar deadspace and the inherent interaction with physiological deadspace that is clearly most important clinically.

1.3 Single Breath Test for Carbon Dioxide

The CO_2 single breath test (SBT-CO_2) of volumetric capnography can used to extract useful information about ventilatory efficiency. Breath-by-breath analysis of expired CO_2 concentrations plotted against the total expired volume allows for meaningful calculations of the area under the graph. The volumetric SBT-CO_2 expirogram can be divided into three phases (Figure 1.3). Phase I is the volume of gas that is in the airway (and the apparatus volume in ventilated patients). Phase II is composed of gas from the terminal airways and from the alveoli with the shortest transit times. Phase III is also known as the alveolar plateau and represents majority of the alveolar emptying.

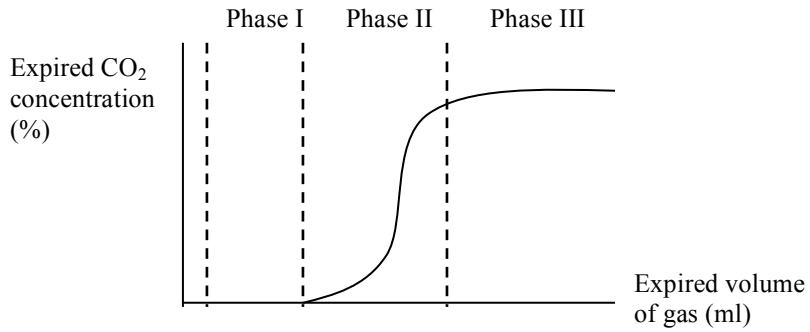


Figure 1.3. Volumetric CO_2 expirogram. Description of the 3 phases. Phase I is composed of the volume in the conducting airways and equipment. Phase II is the volume terminal broncioles and the alveoli with the shortest transit times. Phase III represents alveolar emptying.

The slopes of phase II and III can impart useful information on visual analysis. A flat alveolar plateau (phase III) would be indicative of homogenous lung emptying. Conversely an expirogram with an alveolar plateau with a steep continuous gradient represents heterogeneity in alveolar emptying. This is frequently encountered in diseased lung states. Inhomogeneity in alveolar emptying could either result from within the alveolar units where in the more distal alveoli there is likely to be lower ventilation-perfusion $\dot{V}/\dot{Q}$ ratio or due to inter-unit heterogeneity (14).

Fletcher further analyzed the SBT-CO_2 and gave a detailed proposal of measuring the various parts that contribute to physiological deadspace (21, 22). Figure 1.4 shows

that the area under the graph (x) is the volume of CO_2 eliminated in a breath. The area ABCDA describes the maximum (hypothetical) volume of gas that could be excreted in the breath. 'Efficiency' which is the portion of volume participating in gas exchange is described as:

$$\text{Efficiency} = \frac{X}{ABCDA} \qquad [8]$$

1 - efficiency represents the same fraction as deadspace. Therefore 'E' or efficiency can be restated as a product of more familiar terms:

$$\text{E} = \frac{\dot{V}_A}{\dot{V}_E} = 1 - \frac{V_D}{V_T} = \text{Efficiency}_{\text{Fletcher}} \qquad [9]$$

Where $\dot{V}_A$ represents the alveolar volume (ml) and $\dot{V}_E$ represents minute ventilation (ml).

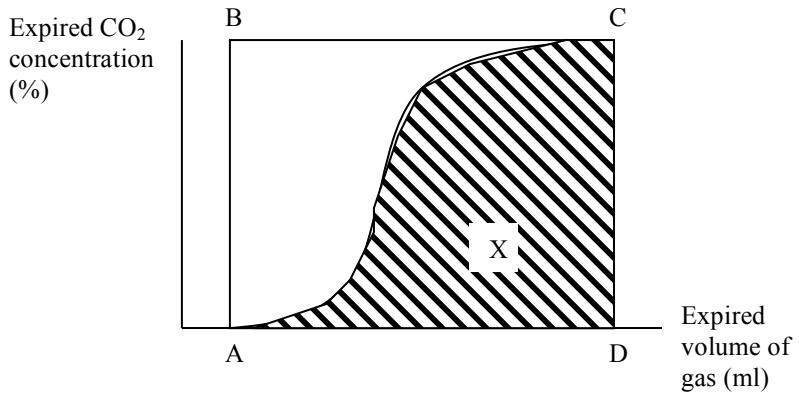


Figure 1.4. SBT-CO_2 demonstrating the fraction of 'efficiency'. The shaded area X represents the volume of CO_2 eliminated. The area ABCDA represents the potential maximum volume of elimination.

In diseased lungs where there is significant $\dot{V}/\dot{Q}$ mismatch the peak P_{CO_2} of the alveolar plateau seldom equals alveolar P_{CO_2} or arterial P_{CO_2}. Fletcher proposed using this discrepancy to calculate the alveolar deadspace. As shown in Figure 1.5A a horizontal line is drawn from the point on the y-axis that represents the arterial P_{CO_2}. As per Fowler's method a vertical line is drawn to elicit equal areas p and q. Area X

once again represents the volume of CO_2 eliminated, area Y represents the VD_{alv} and area Z represents VD_{aw}.

Therefore from the analysis we can deduce that anatomical deadspace fraction is:

$$\frac{V_D^{aw}}{V_T} = \frac{Z}{X + Y + Z} \qquad [10]$$

alveolar deadspace fraction is:

$$\frac{V_D^{alv}}{V_T} = \frac{Y}{X + Y + Z} \qquad [11]$$

and physiological deadspace can be defined as:

$$\frac{V_D^{phys}}{V_T} = \frac{Y + Z}{X + Y + Z} \qquad [12]$$

A.

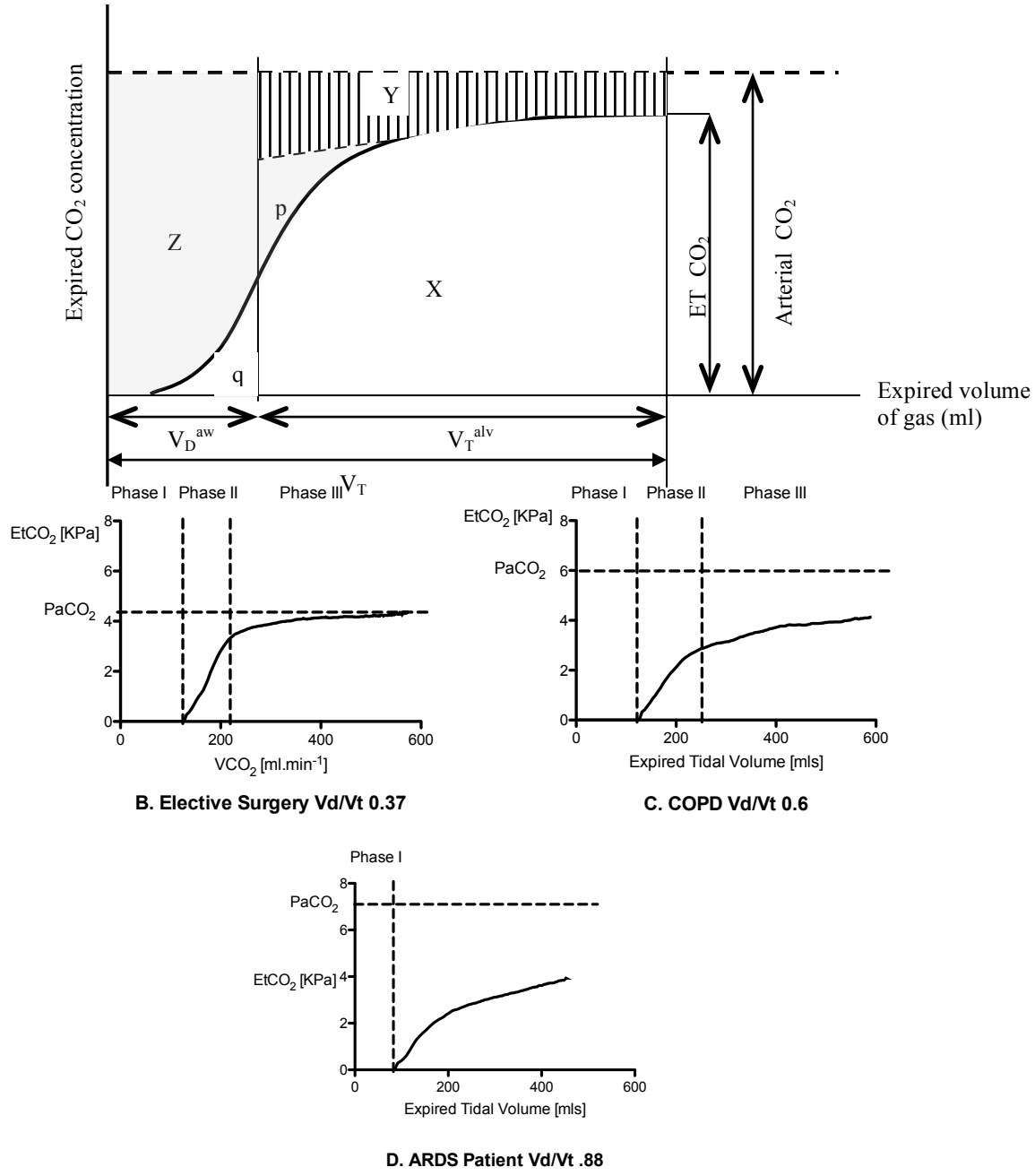


Figure 1.5(A). Components of SBT-CO_2 expirogram as described by Fletcher. Area X represents the CO_2 elimination volume, area Y is the alveolar deadspace volume, and area Z is the airway deadspace volume, where areas p and q are equal. 1.5(B) Shows the SBT-CO_2 expirogram for a mechanically ventilated patient undergoing elective surgery. 1.5(C) Shows the SBT-CO_2 expirogram for a mechanically ventilated patient with COPD admitted to intensive care, the slope of phase III is steeper. 1.5(D) shows SBT-CO_2 expirogram of a mechanically ventilated patient with ARDS, the transition between phase II and phase III is harder to define.

SBT-CO_2 deadspace calculations have been validated against the $V_{D_{Bohr}}$ in both animal models and humans (23, 24). There are several advantages to using volumetric

capnography (SBT-CO_2) over the Douglas bag method for measuring deadspace in mechanically ventilated patients. Collecting mixed expired gas in a Douglas bag is subject to inherent accuracies due to gas compression predominantly within the ventilator circuit (25, 26). On expiration this compressed gas will dilute the mixed expired CO_2 concentration in the bag, and therefore lower the measured $P\bar{E}_{CO_2}$, resulting in falsely elevated physiological deadspace. Volumetric capnography measures the expired CO_2 closer to the endotracheal tube and therefore the measurements do not require a correction factor accounting for the gas compression in the ventilator circuit. Additionally volumetric capnography provides breath-to-breath analysis of the CO_2 capnograph and enables frequent assessment of deadspace changes.

Although recent developments in both software and capnography have made this method more accessible there continue to be technical difficulties in its use. These include adequate capturing of the waveform and differentiating between phase II and phase III of the curve especially when tidal volumes are small and gradient of phase III is steep (27). Crucial to its utility is the definition of the transition point between phase II and phase III. Yet whether defined visually or calculated mathematically this point remains arbitrary and can be ambiguous (24). Currently the software programme Analysis Plus! calculates the slope of phase by least square regression analysis of all the data points between 50% - 70% of the CO_2 expirogram as plotted against volume. Paradoxically as deadspace volume increases the reliability of the method is further compromised.

To overcome these shortcomings Romero et al used the SBT-CO_2 to propose an alternative method to analyse ventilatory efficiency. This moves away from the visual description of the transition from phase II to phase III. Instead as in Figure 1.2, they plot the expired volume of CO_2 against the expired tidal volume to describe the term alveolar ejection volume (V_{AE}) as the predicted point on the $\dot{V}CO_2$ curve where alveolar emptying begins. This volume attempts quantification of the phase III of the slope. The alveolar ejection volume versus tidal volume ratio (V_{AE}/V_t) (28) is an index that monitors alveolar heterogeneity and has been shown to correlate with severity of lung diseases as well as being a useful predictor of outcome (29, 30).

Limitations of this index as a clinical tool include the requirement of relatively simple software to calculate (30) the values and that it is not a previously described physiological term.

More recently Tusman and colleagues have used the mid-point of phase III slope to describe the point most likely to represent $P_{A_{CO_2}}$. There are several potential advantages to this technique. Firstly, ability to obtain $P_{A_{CO_2}}$ allows us to estimate true Bohr deadspace. Secondly, it would also allow a non-invasive method of calculating deadspace. The method to estimate $P_{A_{CO_2}}$ and to calculate $V_D/V_{T\ Bohr}$ has been validated using Multiple inert gas elimination technique (MIGET) in porcine model with excellent correlation with volumetric capnography. There are issues with the method. The problem of estimating slope of phase III remains. In addition the concept of Bohr-Enghoff dead space and idea of "shunt deadspace" and its clinical value is lost from the method.

1.4 Concepts in Deadspace

1.4.1 Ventilation-Perfusion Mismatch

Physiological deadspace is a marriage of a tangible anatomical entity and an intangible physiological function that cannot be directly measured. Our understanding of deadspace and shunt has been largely influenced by the three-lung model as proposed by Riley and Cournand (31, 32). In this proposed model there are three compartments:

a) The first compartment is both ventilated and perfused. This is the most efficient compartment.
b) The second compartment lacks in ventilation and hence the blood supply to this compartment contributes to shunt.
c) The final compartment is ventilated but is lacking in perfusion.

This model only defines three isolated points across a broad spectrum of ventilation and perfusion matching. In reality all factors that cause inequality of $\dot{V}/\dot{Q}$ mismatch will contribute to deadspace ventilation. Not all alveoli contributing to physiological deadspace are completely devoid of perfusion. Alveolar units with excess ventilation

relative to perfusion will contribute to deadspace. Diseases such as chronic obstructive pulmonary disease or pulmonary fibrosis cause an increase in $\dot{V}/\dot{Q}$ mismatch due to defective alveolar gas mixing and inequalities in regional gas distribution (33-35). Consequently there is heterogeneous $\dot{V}/\dot{Q}$ distribution within lung units and the entire lungs. Depending on the nature and severity of the pathology the levels of $\dot{V}/\dot{Q}$ mismatch can be vastly varied.

1.4.2 Shunt and Physiological Deadspace

The Bohr-Enghoff equation calculates physiological deadspace using the difference between the arterial and mixed-expired CO_2, so any factor that influences Arterial P_{CO_2} will result in altered physiological deadspace. Therefore physiological deadspace is influenced by shunt. If the P_{CO_2} of the venous admixture is large enough and the lung compensatory mechanisms are overwhelmed, the resultant elevation of arterial P_{CO_2} would increase the calculated physiological (Bohr-Enghoff) deadspace (22, 36). Consequently physiological deadspace is not only influenced by a high $\dot{V}/\dot{Q}$ but also by a low $\dot{V}/\dot{Q}$.

The influence of shunt on deadspace is non-linear. Pa_{CO_2} and consequently physiological deadspace is only affected in disease processes that result in large shunt. At shunt fractions ($\dot{Q}_S/\dot{Q}_T$) of 0.2 the influence of shunt on Pa_{CO_2} is negligible (37). Due to the nature of the variables involved it is very difficult to directly measure the influence of shunt on physiological deadspace. Figure 1.6 shows the effects of shunt on Pa_{CO_2} and hence Enghoff's modification of deadspace in a high-fidelity computer model (38). Shunt fractions of greater than 0.5 shows a rapid increase in physiological deadspace (36, 39).

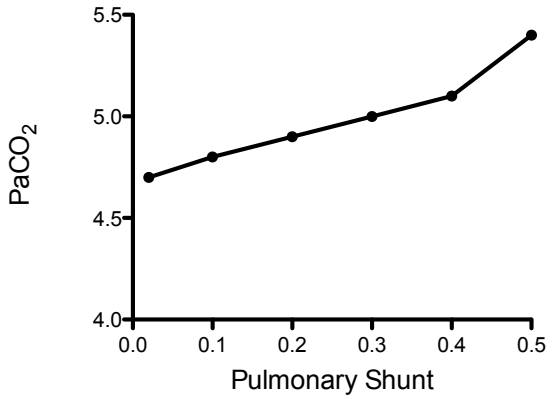


Figure 1.6. Recreation of the relationship of pulmonary shunt and Pa_{CO_2} as proposed by a computerized model by Tang and colleagues (38).

Although shunt plays a role in increasing physiological deadspace, alveolar deadspace has a much more profound impact on CO_2 elimination as illustrated by Figure 1.7 (40). Even though the contributions of shunt to alveolar deadspace are not strictly "deadspace", it none-the-less represents an abnormality in gas exchange (CO_2 elimination) and a pointer to abnormal pathology.

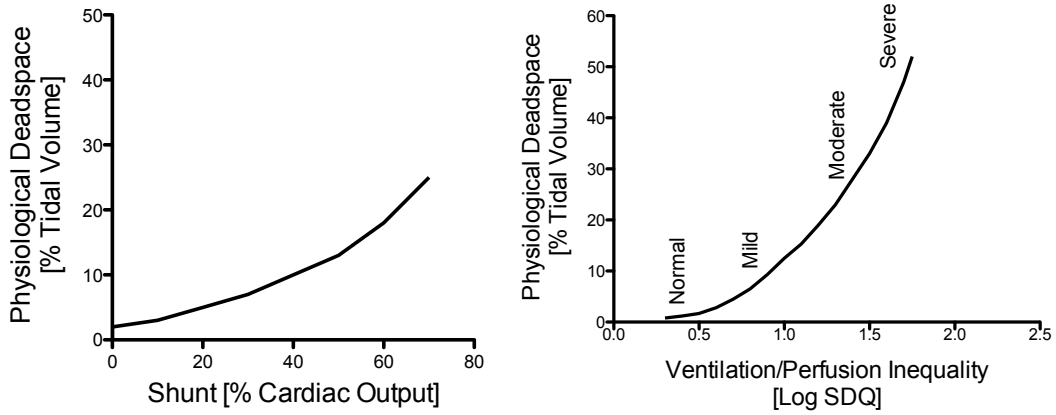


Figure 1.7A and 1.7B. Comparison of the relative effects of shunt (1.7A) and $\dot{V}/\dot{Q}$ (1.7B) mismatch on calculated physiological deadspace. Log SDQ, second moment (dispersion) of the ventilation/perfusion distribution on a log scale. Figure recreated with permission from Wagner (40). Where Log SDQ is second moment (dispersion) of the ventilation/perfusion distribution on a log scale.

Pathological processes can alter measured physiological deadspace in many ways. For example in mechanically ventilated patients with severe acute respiratory distress syndrome (ARDS), increased deadspace can result from increased alveolar deadspace

as the tidal volume is distributed to poorly or non-perfused parts of the lungs. Over-distension of segments of the lung that are functioning normally either as a manifestation of using high peak end expiratory pressure (PEEP) or due to the use of high tidal volumes / ventilatory pressures would result in areas of relatively high $\dot{V}/\dot{Q}$ which would also increase the deadspace fraction. Another frequently encountered pathological feature in ARDS is the presence of microemboli that can further result in $\dot{V}/\dot{Q}$ abnormalities. This is supported by the randomized control trial in which the use of activated protein C resulted in an associated improvement in physiological deadspace in patients with acute lung injury (41). Elsewhere the ratio of angiopoietin 2 and 1, indicators of endothelial damage, have been shown to have a prognostic association with dead space fraction which may also suggest another pathophysiological mechanism (42). Additionally, as the severity of illness increases the level of intra-pulmonary shunt increases, which would further contribute to the deadspace fraction. Theoretically a drop in cardiac output and a resultant drop in the pulmonary perfusion pressures could also contribute to raising the $\dot{V}/\dot{Q}$ ratio. In these situations positive pressure ventilation itself may actively redistribute ventilation according to local compliance and radically alter $\dot{V}/\dot{Q}$ ratio.

1.4.3 Goal Standard Measurement

As discussed previously the spectrum of gas exchange within an alveoli ranges from $\dot{V}/\dot{Q} = 0$ (shunt) to $\dot{V}/\dot{Q} = \infty$ (dead space). Heterogeneity between alveolar units is what dictates the overall $\dot{V}/\dot{Q}$ state of the lungs. Multiple inert gas elimination technique (MIGET) uses simultaneous expired measurements of 6 intravenously infused inert gases to compute the ventilation-perfusion state of the lungs. The method uses principles of mass conservation. 6 inert gases with varying spectrum of blood-gas partition coefficients are used to map the ventilation-perfusion heterogeneity within the lungs. Following slow infusion of six inert gases (acetone, cyclopropane, enflurane, ethane, ether, SF6), partial pressures measurements are made of the gases in systemic arterial, pulmonary arterial (or mixed venous), and mixed expired samples.

Measurements of these samples alongside measurements for ventilation data, cardiac output, temperature, inspired gas concentrations, blood gas measurements and calculated partition coefficients are inputted into a software programme. These are values are then used to compute the ventilation-perfusion distribution of the lungs. Data derived from this is more informative than using just P_{CO_2} and O_2 measurements. Whilst there may be several individual unit of varying inhomogeneity it is assumed that using six gases with varying partition coefficients will provide a reasonable reflection of $\dot{V}/\dot{Q}$ distribution (43).

There are several limitations to this technique such as the requirement of a steady state. The technique is difficult to execute with considerable user variation in experimentation and interpretation of results (43). Despite these shortcomings MIGET is widely considered as the most robust tool to measure $\dot{V}/\dot{Q}$ mismatch.

1.5 Deadspace Measurement in Critical Care

In the critical care setting carbon dioxide clearance or ventilatory efficiency is influenced by a limited number of factors which include ventilation, perfusion and to a lesser extent CO_2 production. This contrasts with indices of oxygenation which are determined by numerous factors that are both intrinsic (pathological) and extrinsic (physics) to the body. These factors are frequently independent of ventilation. Studies on Mount Everest with impressively low oxygen indices in exercising climbers (44, 45) clearly demonstrate that the relationship of oxygenation to clinical well-being is relatively indirect. Nevertheless oxygenation continues to be used as the primary tool for the initiation and structuring of ventilatory strategies (3). This may partly be due to the key but weak association between commonly used indices of oxygenation and survival (46). Equally important is that it is not conventional practice to be guided by deadspace either whilst describing or monitoring the severity of pulmonary failure. It may be argued that whilst describing conditions such as such as ARDS it would be more relevant to also incorporate ventilatory efficiency for categorizing disease severity. As this is in effect unexplored, there is a reasonable reluctance amongst clinicians to use this most relevant of parameters.

Recently there has been a resurgence in interest in using deadspace measurements and in particular using SBT-CO_2 in the clinical setting. Yet given the potential usefulness of ventilatory efficiency / deadspace the reasons for its absence deserve explanation:

1. The methods to calculate deadspace as described above are either the time honoured but cumbersome (Douglas bag) or expensive and ancillary (volumetric capnography) (47). There are some reliable automated commercially available methods of measuring deadspace, few are fully integrated into standard monitoring systems (see Table 1.1).

2. As it is seldom measured there is a lack of clinical familiarity with the measurement and a therefore natural tendency to continue with a standard approach based on oxygenation.

3. Similarly there is a paucity of information regarding interventions that directly manipulate deadspace and hence an assumption that it is of limited value.

4. As it is rarely measured there are very few large studies describing its behaviour in critically unwell patients and its true value as a clinical tool has yet to be evaluated.

Device	**Description**
CO_2SMO® Capnograph *Novametrix Medical Systems*	Stand-alone. Volumetric capnography. Breath-by-breath analysis of $\dot{V}CO_2$, $V_{D\,aw}$, and other respiratory parameters. $V_{D\,phys}$ on entering Pa_{CO_2}.
NICO®2 Respiratory Profile Monitor *Novametrix Medical Systems*	Stand-alone. Volumetric capnography. Breath-by-breath analysis of $\dot{V}CO_2$, $V_{D\,aw}$, and other respiratory parameters. $V_{D\,phys}$ on entering Pa_{CO_2}. Second generation.
Evita® XL Ventilator *Draeger Medical, Inc*	Integrated into the ventilator. Volumetric capnography. Calculates $\dot{V}CO_2$. Displays $P\bar{E}_{CO_2}$ and $V_D/V_{T\,phys}$. Optional extra.
Hamilton G5 Ventilator *Hamilton Medical AG*	Integrated into the ventilator. Volumetric capnography. Displays $\dot{V}CO_2$. The $P\bar{E}_{CO_2}$ can then be calculated and thus $V_D/V_{T\,phys}$. Calculates $V_{D\,aw}$. Optional extra.

Table 1.1 Some of the devices that are commercially available in Europe that measure dead space using volumetric capnography.

1.6 Indices of Ventilatory Efficiency

Recently there has been increasing interest in developing more simple 'user-friendly' indices to monitor changes in ventilatory efficiency at the bedside. These are summarized in table 2. All the indices use variables measured at the bedside and broadly fall into 2 main categories. The first uses complex calculations to predict numerical values for V_D/V_T. Unfortunately some of the assumed values inherent to either the method of derivation or the proposed calculations will inevitably lead to inaccuracies. The second do not offer explicit quantification of deadspace but rather look at tracking ventilatory efficiency using bedside variables. The latter whilst easier to reproduce and calculate would be subject to similar inaccuracies.

Most of these methods have yet to be adequately validated. The bedside method proposed by Siddiki et al uses the alveolar gas equation to estimate V_D/V_T (48). In order to obtain quantitative values of V_D/V_T they have used the Harris-Benedict equation to estimate values of $\dot{V}CO_2$ for a given patient. The Harris-Benedict equation is not only complex to calculate but also has been shown to be unreliable in the critical care setting(49, 50). This brings into question the validity of the V_D/V_T values extracted from the equation.

An alternative approach from Frankenfield et al uses regression analysis to derive a predictive equation to estimate V_D/V_T. The equation has been validated for patients in steady state with an FiO2 < 0.6. Although there is good correlation between measured and calculated values of V_D/V_T, this remains validated in a very small select group of patients. The difference between arterial and end-tidal ($Pa_{CO_2} - ET_{CO_2}$) has been proposed to be used to either predict V_{Dalv}/V_T using (51) or to track changes in V_{Dalv}/V_T (52). Once again neither methods have been validated in patients. Conceptually using ET_{CO_2} as a tool to monitor deadspace is likely to lead to inaccuracies due to its dependence on the ventilatory patterns and tidal volumes.

	Hardman JG, Aitkenhead AR (2003) (52)	**Frankfield DC, Alam S, et al (2010) (54)**	**Siddiki H, Kojicic, M et al (2010) (48)**
Index	$Pa-e_{CO_2}$ / Pa_{CO_2} Arterial-end-tidal CO_2 gradient is divided by arterial PCO_2 as a measurement to track $(V_{Dalv}/VT)_{Bohr-Enghoff}$ at the bedside.	V_D/V_T = 0.32 + 0. 0106 (Pa_{CO_2} – ET_{CO_2}) + 0. 003 (RR) + 0.0015 (age)	V_D/V_T = 1- [(0.86 x $\dot{V}CO_2^{est}$)/($\dot{V}_E$ x Pa_{CO_2}). $\dot{V}CO_2^{est}$ is the estimated CO_2 production calculated from the Harris-Benedict equation and *0.863* is a correction constant.
Derivation / Validation	Nunn and Hill first described the relationship of $P_{a-É}CO_2$ and alveolar deadspace (53). Authors calculated $(V_{Dalv}/VT)_{Bohr-Enghoff}$ and $Pa-e_{CO_2}$ / Pa_{CO_2} whilst altering variables in a computational physiological model. Linear relationship between the 2 fractions is demonstrated.	Regression analysis used to derive a predictive equation for V_D/V_T. Measurements of ventilatory and clinical variables were made in 135 patients. Respiratory rate, $Pa_{CO_2}-ET_{CO_2}$, and age were factors that significantly influenced V_D/V_T. Measured V_D/V_T was validated against estimated V_D/V_T for that population.	Uses the alveolar gas equation to solve for V_D/V_T. Uses the Harris-Benedict equation to estimate $\dot{V}CO_2$.
Advantages	- Easy to calculate at the bedside - Negates the influence of airway deadspace - Stable under various conditions	- Quantitative value for V_D/V_T - Calculated using values at the bedside.	- Quantitative value for V_D/V_T - Can be calculated at the bedside - Equation in physiologically intuitive
Disadvantages	- Untested in clinical / animal setting - No evident physiological derivation - No clinical data available - Not quantitative	- Derived from measured values. - Not intuitive. - Not tested in varying clinical conditions. - Not tested in patient with FiO2 > 0.6	- Not validated against measured V_D/V_T - Harris-Benedict equation is unreliable - Equation unreliable in unsteady state - Complicated to calculate

Table 1.2. Description of bedside indices to monitor ventilatory efficiency

1.7 Deadspace as a Clinical Tool

In the critical care setting there are diverse but isolated examples of deadspace measurements being used as a clinical tool. In pulmonary embolism deadspace-tidal volume fraction in conjunction with D-Dimer assays, has been shown to be of diagnostic value (55-57). Deadspace fraction has also been used to predict likelihood of successful extubation in paediatric patients (58). It would seem likely that from first principles monitoring ventilatory efficiency could play a vital role in weaning and prediction of extubation. The negative impact of rising deadspace on weaning has been demonstrated in the neonatal population (59). Although these population groups are distinct from adults, the pathophysiological principles that result in difficult weaning stand true in all populations. Currently the most widely used index to predict successful weaning is the frequency-tidal volume ratio and it focuses on the endurance of breathing (60). This index is simple to calculate and shows high sensitivity but has low specificity. It does not incorporate the corresponding efficiency of CO_2 elimination. A combination of the work of breathing and ventilatory efficiency would in theory provide a more refined index to predict successful weaning. Studies have demonstrated the superiority of such combined indices in small groups of patients resulting in increased specificity as compared to f / V_T (61, 62). Larger studies are needed to explore the advantages of using a combined index that intuitively appears to offer a more comprehensive evaluation of the pathophysiology of weaning failure.

Deadspace measurements have been used to assess the impact of varying PEEP on carbon dioxide elimination and to determine the optimum levels of PEEP during lung recruitment (63, 64). The SBT-CO_2 has been used to study the effects of PEEP on the 2 individual components of deadspace (VD_{aw} and VD_{alv}) in patients with acute lung injury (65). This showed that there was no uniform response to PEEP.

In animal studies it has been shown that deadspace is highly specific and sensitive in monitoring lung collapse (66). In these studies the lungs use a surfactant-depleted model and show large changes with recruitment techniques. This contrasts with the findings in adults with acute lung injury where recruitment is far less effective and excessive PEEP may exert a negative influence on V/Q matching secondary to over-

distension (67). Nevertheless lung recruitment manoeuvres have been evaluated using deadspace fraction or ventilatory efficiency.(68-70). It appears to be a more useful means of assessing the efficacy of recruitment than using indices of oxygenation (71).

1.7.1 Deadspace and ARDS

Perhaps of greatest interest and relevance in the critical care setting is the utility of deadspace measurements in the context of ARDS, and modes of ventilation. In patients with ARDS a range of pathophysiological mechanisms increase ventilatory inefficiency. Hence as one might anticipate deadspace measurements have been shown to be a useful prognostic marker for patients with ARDS. This has been clearly demonstrated in several studies where non-survivors have been shown to have a significantly higher deadspace ratio than survivors (48, 72-74). Similarly using a measurement of ventilatory efficiency, V_{AE}/V_T, has been shown to be a useful predictor of outcome in patients with lung injury (30). The timing and the magnitude of the deadspace abnormality have also been shown to predict the clinical outcome in patients with lung injury. While prognostic indicators have their place, measurements that allow both monitoring and manipulation of ventilatory management have more immediate clinical usefulness. Kallet and colleagues demonstrated that serial measurements of deadspace could be used to monitor disease progression in ARDS (75, 76). Others have demonstrated its use for monitor manoeuvres such as prone positioning that are designed to improve gas exchange (77, 78). Patients with ARDS that demonstrate a decrease in arterial P_{CO_2} i.e. increased ventilatory efficiency on prone-positioning have shown improved survival compared to those patients that show no improvement in arterial P_{CO_2} (79). Clearly measurement of ventilatory efficiency has a potential role in the management of ventilation.

There is more recently, linkage between prognosis and potential pathophysiological mechanisms underlying deadspace changes. Ong and colleagues have demonstrated a prognostic association between dead space fraction and the ratio of angiopoietin 2 and 1, which are proposed markers of endothelial damage. The interaction between deadspace and pulmonary capillary perfusion is clearly important and this may prove an exciting and fruitful new direction for clinical study (42).

1.8 Ventilatory 'Efficiency'

In the rapidly evolving field of ventilatory management where modalities such as extracorporeal membrane CO_2 removal and high frequency oscillatory ventilation are becoming increasing prevalent, a fresh look at our methods of monitoring gas exchange in ventilated patients is essential. CO_2 clearance is a crucial part of these strategies and needs to be monitored. Routine monitoring of ventilatory efficiency could lead to more appropriate diagnostic categorization of respiratory failure in terms of CO_2 clearance rather than just oxygenation. This may in turn be helpful in earlier instigation of these novel therapies. Additionally monitoring efficiency of CO_2 clearance during treatment could aide in the management of the finer aspects of extracorporeal membrane CO_2 removal such as assessing device efficacy and deciding the timeliness of return to more conventional ventilation.

The two common themes in these reports across a spectrum of clinical activity are that potential usefulness has been demonstrated but to date investigation and application of these measurements are very limited. That should in itself be enough to stimulate interest across other areas of clinical practice.

1.8.1 A Novel Index

It stands to reason that development of an index that is easy to calculate and reflect changes in ventilatory efficiency would be a marker of disease severity. In particular this should be true in patients with respiratory failure. Given the association of pathophysiological processes with deadspace one would anticipate that an increase in such an index would be suggestive of worsening lung pathology. Such a tool could also perhaps be able to re-categorise patients with ARDS according to disease severity.

In the following chapters we describe such a ratio called "Ventilatory Ratio". We then examine the physiological properties of VR in benchside and in silico lung model. The factors influencing VR are then examined in mechanically ventilated patients. Finally the clinical value of VR is examined in an ICU population.

1.9 Null Hypotheses

Null 1: An index that is a composite of arterial PCO_2 and minute ventilation will not be responsive to changes in ventilatory efficiency.

Null 2: Higher values and increasing values of such an index will not be associated with worsening disease severity in mechanically ventilated patients.

The next chapter defines Ventilatory Ratio and examines its physiological properties.

Chapter 2: Ventilatory Ratio: Definition and Analysis

In this chapter Ventilatory Ratio is defined. This is followed by physiological analysis of Ventilatory Ratio and subsequent mathematical analysis of the proposed physiological properties of VR.

We define the Ventilatory Ratio as:

$$VR = \frac{\dot{V}_{E_{measured}} \times P_{a_{CO_2 measured}}}{\dot{V}_{E_{predicted}} \times P_{a_{CO_2 predicted}}} \qquad [13]$$

Where $\dot{V}_{E_{measured}}$ is taken to be 100 ml.kg^{-1}.min^{-1} based on predicted body weight and $Pa_{CO_2 predicted}$ is taken to be 5 kPa.

2.1 Physiological Analysis

At steady state, carbon dioxide production and alveolar ventilation are the determinants of Pa_{CO_2} . Alveolar ventilation is a variable fraction of minute ventilation (about two thirds in fit unanaesthetised individuals), the remaining fraction being physiological deadspace ventilation.

VR can be analyzed in terms of carbon dioxide production and the fraction of minute ventilation that is alveolar ventilation, as follows:

Firstly,

$$\dot{V}CO_2 = \dot{V}_A \times FA_{CO_2} \qquad [14]$$

and

$$FA_{CO_2} = \frac{PA_{CO_2}}{P_B} \qquad [15]$$

where P_B is the barometric pressure. Equation [15] may be substituted into [14] and rearranged:

$$PA_{CO_2} = \frac{\dot{V}CO_2}{\dot{V}_A} \times P_B \qquad [16]$$

Assuming,

$$Pa_{CO_2} \approx PA_{CO_2} \qquad [17]$$

Equation [17] may be restated for Pa_{CO_2} :

$$Pa_{CO_2} = \frac{\dot{V}CO_2}{\dot{V}_A} \times P_B \qquad [18]$$

This is a restatement of standard concepts in respiratory physiology and the assumptions made in the derivation of the terms are conventional.

Secondly, it is helpful to have a way of speaking about alveolar ventilation as a fraction of minute ventilation. We call this the "ventilatory efficiency", E:

$$E = \frac{\dot{V}_A}{\dot{V}_E} \qquad [19]$$

From which

$$\dot{V}_E = \frac{\dot{V}_A}{E} \qquad [20]$$

Equation [21] demonstrates the relationship of ventilatory efficiency to the more usually considered deadspace ventilation:

$$E = \frac{\dot{V}_A}{\dot{V}_E} = \frac{\dot{V}_E - \dot{V}_D}{\dot{V}_E} = 1 - \frac{\dot{V}_D}{\dot{V}_E} \qquad [21]$$

(although the right hand side of equation [21] is not required for our purposes).

Thirdly, the concept of "actual" and "predicted" carbon dioxide production and ventilatory efficiency is required. Measured minute ventilation and arterial carbon dioxide will be dependent upon actual carbon dioxide production and ventilatory efficiency. Equations [19] and [21] can be applied to these concepts as follows:

$$Pa_{CO_{2\,measured}} = \frac{\dot{V}CO_{2\,actual}}{\dot{V}A_{actual}} \quad \text{and} \quad \dot{V}E_{actual} = \frac{\dot{V}A_{actual}}{E_{actual}} \qquad [22]$$

and

$$Pa_{CO_{2\,predicted}} = \frac{\dot{V}CO_{2\,predicted}}{\dot{V}A_{predicted}} \quad \text{and} \quad \dot{V}E_{predicted} = \frac{\dot{V}A_{predicted}}{E_{predicted}} \qquad [23]$$

Finally, the right hand sides of the two pairs of equations ([22] and [23]) are substituted into [13], the definition of VR, and the result simplified:

$$VR = \frac{\dot{V}CO_{2actual}}{E_{actual}} \times \frac{E_{predicted}}{\dot{V}CO_{2predicted}} \quad [24]$$

This is more conveniently rearranged to give:

$$VR = \frac{\dot{V}CO_{2actual}}{\dot{V}CO_{2predicted}} \times \frac{E_{predicted}}{E_{actual}} \quad [25]$$

Inspection of equation [25] shows that VR is governed by carbon dioxide production and ventilatory efficiency in a logically intuitive way. VR is a dimensionless numerical value. Where predicted values match actual values, as in normal individuals, the range of VR will be distributed around unity. When considering dynamic changes, a rising VR represents rising carbon dioxide production, or decreasing ventilatory efficiency or both. Conversely a falling VR represents falling carbon dioxide production, or increasing ventilatory efficiency or both. Provided the other variable remains constant, VR has linear relationship with both Pa_{CO_2} and $\dot{V}_E$. Similarly, VR would have a linear relationship to respiratory rate and tidal volume, provided the other variable remains constant. As the ratio is dependent on minute ventilation and Pa_{CO_2}, any alterations in ventilatory settings that result in a change in VR, would either be due to changes in alveolar ventilation or a significant change in the CO_2 production. Figure 2.1 shows the hyperbolic relationship of minute ventilation and Pa_{CO_2} as predicted by Equation 14. In the model when VR is higher a given change in minute ventilation would have a more profound impact on Pa_{CO_2}. This would mimic physiological response of the body. When ventilatory demands of the body are high (i.e. high VR) smaller changes in ventilation would have a more profound impact on CO_2 elimination.

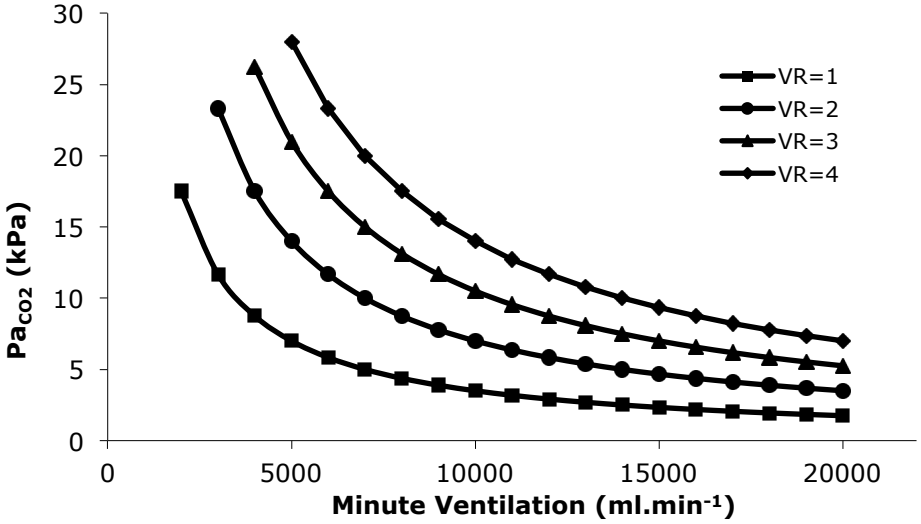


Figure 2.1. Pa_{CO_2} plotted against minute ventilation for values obtained by equation 1 in a 70 Kg patient. The isopleths represent the relationship of the 2 varibles with VR values ranging from 1-4.

2.2 Rationale for Predicted Values

In order to calculate VR we must first calculate the predicted values.

For the predicted value of minute ventilation we are using 100 ml.Kg^{-1}.min^{-1}. This value is extracted from population nomograms from anaesthesic practice (80-82). For predicted body weight (PBW) we have used the ARDSnet predicted body weight calculator. PBW (Kg) is calculated using the formula 50 + 0.91(centimeters of height – 152.4) for males, and 45.5 + 0.91(centimeters of height – 152.4) for females(83). The ideal value used for Pa_{CO_2} is 5 kPa. Because the range of Pa_{CO_2} values in healthy individuals is narrow, we have used a value that lies close to the mean to represent the predicted Pa_{CO_2}. The predicted values used to calculate VR are to an extent arbitrary and it may lead to a degree of inaccuracy. Paramount to the development of VR as a clinical tool however is the concept of keeping it calculations simple.

For clinical application at the bedside VR can be restated in a user-friendly form by the insertion of the above mentioned predicted values into Equation [13]:

$$VR = \frac{\dot{V}_{E_{measured}}(ml.\min^{-1}) \times P_{a_{CO_2}}(KPa)}{100 \times PBW \times 5} \qquad [26]$$

This can further simplified to state VR in its simplest form:

$$VR = \frac{\dot{V}_E(ml.\min^{-1}) \times Pa_{CO_2}(kPa)}{500 \times PBW} \qquad [27]$$

2.3 Mathematical Analysis of Ventilatory Ratio

Stated first is VR are described in its original form in Equation 13:

$$VR = \frac{\dot{V}_{E_{measured}} \times P_{a_{CO_2 measured}}}{\dot{V}_{E_{predicted}} \times P_{a_{CO_2 predicted}}} \qquad [13]$$

For any given individual the denominator will always remain constant. Therefore the values for VR will vary according to changes in either minute ventilation, Pa_{CO_2}, or both. Table 2.1a and 2.1b shows the relationship of VR in a 70 Kg individual with varying values of Pa_{CO_2} and $\dot{V}_E$ respectively whilst the other variable remains constant.

Table 2.1a

Pa_{CO_2} (kPa)	VR
2.0	0.4
3.0	0.6
4.0	0.8
5.0	1.0
7.5	1.5
10.0	2.0
12.5	2.5
15.0	3.0
17.5	3.5
20.0	4.0

Table 2.1b

$\dot{V}_E$ (ml.min^{-1})	VR
3000	0.429
5000	0.714
7000	1.0
10000	1.429
12500	1.786
15000	2.143
17500	2.5
20000	2.857
22500	3.214
25000	3.571

Table 2.1a and 2.1b Show values of VR in a 70 kg individual. Table 2.1a Pa_{CO_2} varies whilst minute ventilation is constant at 7000 ml.min^{-1}. Table 2.1b Varying minute volume with constant Pa_{CO_2} of 5.

Individually both Pa_{CO_2} and minute ventilation share a linear relationship with VR when the other variable remains constant (Figures 2.2A and 2.2B). This would be expected because the variables are compared against a preset standard rather than other physiological parameters. The relationship of minute ventilation and Pa_{CO_2} as illustrated in Figure 2.1 is an intimate one. Minute ventilation or more specifically alveolar ventilation exerts the greatest influence on the levels of $P_{A_{co_2}}$ and Pa_{CO_2}. However as a *mathematical* entity VR is not reliant on the influence of the variable on one another. Changes in VR are a composite of the accumulative deviation from our preset ideal Pa_{CO_2} and minute ventilation.

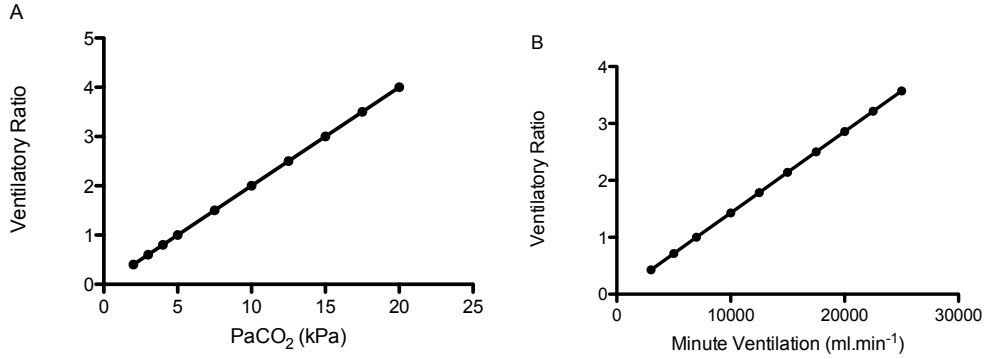


Figure 2 Relationship of Ventilatory Ratio with Pa_{CO_2} and minute ventilation in 70 Kg individual. Figure 2A represents VR versus minute ventilation when Pa_{CO_2} is constant at 5 KPa. Figure 2B relationship of VR with varying Pa_{CO_2} whilst minute ventilation is 7000 ml.min^{-1}.

Pa_{co_2}	Minute Ventilation							
	3000	5000	7000	10000	12500	14000	17500	21000
3.0	**0.257**	**0.429**	**0.6**	**0.9**	**1.071**	**1.2**	**1.5**	**1.8**
5.0	**0.429**	**0.714**	**1**	**1.5**	**1.786**	**2**	**2.5**	**3**
7.5	**0.643**	**1.071**	**1.5**	**2.25**	**2.679**	**3**	**3.75**	**4.5**
10	**0.857**	**1.429**	**2**	**3**	**3.571**	**4**	**5**	**6**
12.5	**1.071**	**1.786**	**2.5**	**3.75**	**4.464**	**5**	**6.25**	**7.5**
15	**1.286**	**2.143**	**3**	**4.5**	**5.357**	**6**	**7.5**	**9**
20.0	**1.714**	**2.857**	**4**	**6**	**7.142**	**8**	**10**	**12**

Table 2.2 VR values at varying levels of Pa_{CO_2} and varying rates of minute ventilation. The VR values are in bold.

Table 2.2 shows the mathematical effect of incremental changes in minute ventilation and Pa_{CO_2} on VR. The relationship of VR with the 2 variables remains linear when either or both of the variables change. An acknowledgment must be made regarding the fixed nature of the predicted values regardless of where the patient is on the isopleth (i.e. the predicted values are not a sliding scale). If the minute volume were to be halved PCO_2 would have to double in order to meet our predicted standards. In reality the dynamic of ventilation and CO_2 elimination is unlikely to follow such a strict mathematical relationship. As justification for the use of fixed predicted values a few arguments are proposed. There is little evidence in the literature defining the relationship of $P_{A_{co_2}}$ and alveolar ventilation in profound respiratory failure. Given the heterogeneous population group and the varying degrees of lung injury in critically unwell patients this information would be difficult obtain. Designing a model using predicted values that vary according to the relative abnormalities would be complex. Were such an index to be defined then it would be complex to calculate. As stated previously a key design feature was for the ratio to be easy to use at the bedside.

2.4 Mathematical Analysis of the Physiological Proof of Ventilatory Ratio

It is on examination of the physiological model (Equation 13) that makes the real value of VR more apparent. As stated previously VR represents the ventilatory demands on an individual. Increased ventilatory demands are as a result of either inefficient ventilation (increased dead space) or increased CO_2 production (84). Therefore changing values of VR would be as a result of changing dead space, CO_2 production, or both.

Equation 26 can be presented in a more clinically intuitive format:

$$VR = \frac{\dot{V}CO_{2\,actual}}{\dot{V}CO_{2\,predicted}} \times \frac{\left(1 - V_D/V_T\right)_{ideal}}{\left(1 - V_D/V_T\right)_{actual}} \qquad [28]$$

We can now analyse the effect of V_D/V_T and $\dot{V}CO_2$ by assigning corresponding predicted values for these variables. Carbon dioxide production ($\dot{V}CO_2$) for a 70 Kg individual is assumed to be 200 $ml.min^{-1}$ in steady state. This value can be set as the

predicted $\dot{V}CO_2$ for the above equation. If normal deadspace fraction is 0.3, then 'E' ($1-V_D/V_T$) would be 0.7, this value is set as the ideal value for 'E'.

Figure 2.3 shows the relationship of VR and 'E' (or $1-V_D/V_T$). The relationship is evidently non-linear and hyperbolic, similar to Figure 2.1. More importantly this relationship should be intuitive to clinicians as it is similar to the relationship between Pa_{CO_2} and alveolar ventilation as described by Nunn (85). Of note when large deadspace abnormalities are large, relatively small changes in 'E' lead to proportionately larger changes in VR.

Figure 2.4 show the values of VR as derived from Equation 16. The relationship of $\dot{V}CO_2$ and VR is linear. When deadspace fraction is large the gradient of $\dot{V}CO_2$ / VR line is steeper. This phenomenon is both clinically and physiologically intuitive.

In clinical settings deadspace is probably the variable of greatest interest. A rise of VR form 1 to 2 solely as a result of $\dot{V}CO_2$ would require for it to double. In mechanical ventilation this would be a rare finding. Conversely as illustrated in Figure 2.3 relatively small changes in dead space could result in the doubling of VR. Thus it is anticipated the VR may be a quick and useful reference marker for ventilatory efficiency in mechanically ventilated patients.

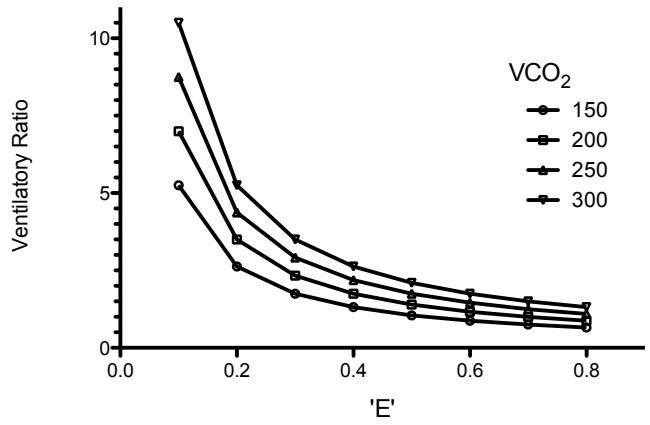


Figure 2.3 shows the Relationship of VR and efficiency 'E' ($1-V_D/V_T$) at various values of $\dot{V}CO_2$ (150, 200, 250, and 300 $ml.min^{-1}$)

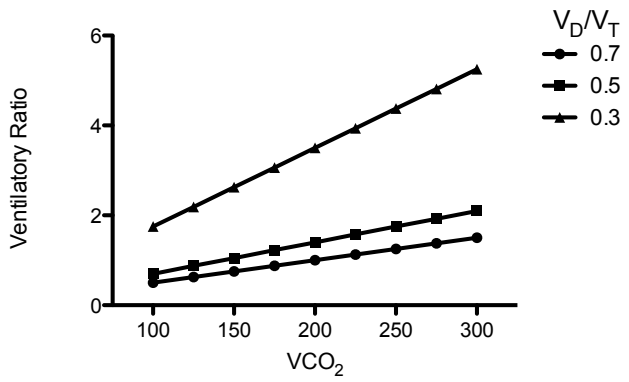


Figure 2.4 shows the Relationship of VR and $\dot{V}CO_2$ and at three different dead space fraction abnormalities (0.3, 0.5, 0.7)

2.5 Research Questions

The above description of VR alongside the physiological analysis has generated some interesting research questions. These questions listed below form the basis of the thesis:

1. Can the physiological analysis of VR as shown in this chapter be demonstrated in a benchside lung model and a high fidelity in silico lung simulation model?
2. $\dot{V}CO_2$ is one of the factors that influences VR. What is the variability $\dot{V}CO_2$ of in ICU patients?
3. What is the relative influence of changing values of $\dot{V}CO_2$ on VR?
4. Does VR demonstrate the same relationship to V_D/V_T and $\dot{V}CO_2$ in critically ill mechanically ventilated patients as described in Equation 26?
5. What are the clinical uses of VR in an ICU population?

The next chapter discusses the methods and materials used to address these questions.

Chapter 3 Methods and Instruments

Through the course of the thesis several key pieces of equipment and measurement systems have been used. The description of this equipment and techniques is presented in this chapter. A multitude of generic equipment such as patient monitoring devices that have been used in all the studies and they are too numerous to describe each in detail. Therefore detailed description of the workings of only the equipment that is integral to our understanding and reproducibility of the experiment are described in this chapter. The latter segment of the chapter also has a description of the various databases that have been constructed for analysis in the clinical studies presented in Chapters 7.

There are many disparate studies and database analyses included in this thesis. Methodologies for each of the individual studies are therefore presented in the relevant chapters. This will lead to improved flow for readers. The methods and measurement systems that are described in detail here will only be mentioned succinctly in the proceeding chapters' experiment methodology.

3.1 Artificial Lung Model

A simple mechanical model was created to replicate the lungs. An airtight Perspex bottle with 2 opening ports was created to represent the thoracic cavity. An anaesthetic latex reservoir bag was attached to one of the opening ports. This represented the lung. The opening port comprised of a modified T-piece where the top of the T-piece contained a small self-sealing opening for introducing CO_2 flow via simple gas tubing. The second port connects to the chamber within the bottle surrounding the bag (Figure 3.1). The port opening into the chamber of the Perspex bottle was connected to a pump. The pump, designed specifically for the experiment, is a spring loaded, low resistance device consisting of a corrugated self-collapsing air bag. Delivery of a breath by the ventilator results in the reservoir bag inflating. The gas in the air-tight chamber is displaced and exits via the port connected to the pump. The volume of gas is then stored in the corrugated bags of the pump. When the breath is no longer delivered, i.e. the expiratory phase of the ventilator the volume of gas in the corrugated bags is delivered back to the chamber, thereby displacing the gas that had filled the reservoir bag in the inspiratory phase. This recreates passive expiration thereby giving an expiratory CO_2 waveform similar to a normal breath. This basic mechanical lung model was used to test the physiological model of ventilatory ratio.

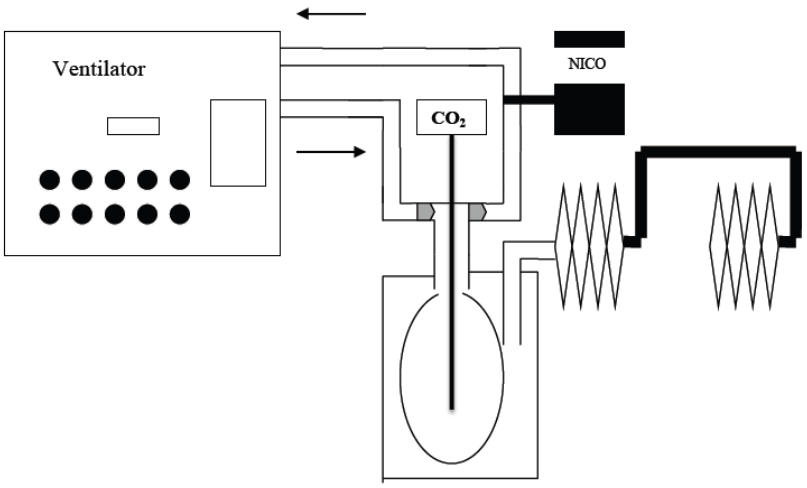


Figure 3.1 Schematic of the artificial lung model designed to examine the relationship of Ventilatory Ratio with deadspace and CO_2 production.

3.2 Nottingham Physiology Simulator

The Nottingham physiology simulator (NPS) is a computer simulation model of respiratory, cardiovascular, acid-base, cerebrovascular, and renal physiological models. For the purposes of the thesis the cardiorespiratory components of the model were of interest. The multi-compartment model has been previously described in detail (86, 87). The model uses iterative calculations over several "time-slices" to detect changes that may have occurred since the previous time-slice until equilibrium and steady state is achieved at the alveolar-capillary level. The calculations are based on the principle of mass-conservation and each time-slice represents 1 microsecond (88).

3.2.1 Components of the Respiratory Model of the Simulator

3.2.1.1 The Ventilator

Intermittent mandatory tidal ventilation was used for study and all breaths were humidified and warmed. Minute ventilation was manipulated by altering tidal volume or respiratory rate. The model is designed such that the driving pressures, alveolar inlet resistance, and inter-alveolar pressure determined distribution of flow from the ventilator to the alveoli.

3.2.1.2 The Bronchial Tree

This represents anatomical deadspace and is represented as a single tube that sub-divides into 500 bronchioles. The true volume of anatomical deadspace is fixed during the breathing and can be pre-determined by the operators; the effective volume may be affected by mixing within the deadspace. Gas flow in the bronchioles is laminar or turbulent as dictated by Reynolds's number.

3.2.1.3 The Alveoli

The 500 bronchioles open into 500 alveolar "compartments". Each compartment has an independent flow of gas in and out of the alveolus. This is determined by the alveolar compliance, bronchial resistance, and airway pressures within the compartment. Each alveolar compartment has an associated pulmonary vessel that originates from the pulmonary trunk. The effects of gravity on the interstitial pressures in the lung are included in the model and play a part in the resting volumes of the alveoli. A simple tissue elasticity model is also included in the study. This represents the viscoelasticity of the pulmonary tissue. The model is factored such that incremental increases in alveolar volume beyond its normal volume result in changes in the compliance of the compartment.

The compliance of the alveoli and the blood vessels can be configured according to the conditions required for the study. Equilibrium during gas exchange across the alveolar-capillary membrane occurs through iterative time slicing, as described above. For a particular configuration gas exchange was considered at end-point when the difference between gas tensions across the alveolar-capillary membrane was < 1%.

An additional feature of the simulator that results in more realistic modeling is that each of the 500 compartments has their own unique compliance and inlet resistance, resulting in varying time-constants. This results in inequalities in the emptying of alveoli during expiration. This is a frequently encountered phenomenon in diseased lungs.

3.2.1.4 Gases

The rate of O_2 consumption and CO_2 production could be configured to experimental demands. Bohr and Haldane effects on gas carriage are also incorporated into the model.

3.2.2 Validation of the Model

In an earlier version of the NPS responses to changes in ventilatory settings the calculated output values from the model were compared against measured output in a group of 25 adult ICU patients (86). The study found good agreement between observed and predicted values for PaO_2, Pa_{CO_2}, and pH. There was a tendency for the model to overestimate Pa_{CO_2} by 0.17 kPa.

More recently a study using a newer version of NPS validated its ability to accurately predict deadspace (88). Data from mechanically ventilated patients was used to assess the ability of the model to predict changes in dead space and dead space fraction. NPS accurately reproduced Pa_{CO_2} and $P\bar{E}_{CO_2}$ compared to values seen in healthy anaesthetized individuals.

3.3 Volumetric Capnography

Capnography allows for measurement of expired CO_2 concentrations. Integration of this technology with flow measurement sensors allows for breath-by-breath volumetric capnography. Volumetric capnography results in CO_2 curves with volume plotted against concentration. Volumetric capnography allows for useful measurement and calculation for many variables such as CO_2 elimination ($\dot{V}CO_2$), dead space, and expired tidal volumes.

3.3.1 CO_2SMO Plus!

CO_2SMO Plus! (Novametrix Medical Systems, Wallingford, Conn., USA) uses the Capnostat CO_2 sensor to measure CO_2 concentrations using infrared absorption technology. A flow sensor is the combined to the capnostat and attached proximal to the Y-tubing. Flow measurements are made by a fixed orifice differential pressure pneumotachograph. Pressure differential are transmitted to transducers in the monitor via the pneumotachograph attached to the patient. $P\bar{E}_{CO_2}$ is calculated by averaging

the volumetric gas CO_2 concentrations proximal to the sensor. Entering data for Pa_{CO_2} gives values for physiological dead space.

The additional advantages of having a flow sensor proximal to the Y-connector of the ventilator circuit is that an accurate measurement of expired tidal volume is available. Expired volumes as obtained by ventilators are subject to inaccuracies due to compressed ventilator gas. This makes volumetric capnography a more convenient method of calculating dead space compared to using a Douglas Bag, which requires a correction factor for the compressed gas volume.

CO_2SMO Plus! was used to measure $\dot{V}CO_2$ and calculate dead space in studies X1 and X2.

3.3.1.1 Manufacturer technical specifications:

- End-Tidal CO_2
    - Range: 0-150 mmHg
    - Accuracy: ± 2 mmHg for readings of 0-40 mmHg, ± 5% for readings between 40 – 71 mmHg, ± 8% of readings between 71 – 150 mmHg.
- Flow (Adult):
    - Range: 2 – 180 L/min
    - Accuracy: ± 0.5 L/min

3.3.1.2 Analysis Plus!

Analysis Plus! for windows (Novametrix Medical Systems, Wallingford, Conn., USA) version 2.0 was used for analysis of the waveforms and for calculation of dead space. Analysis plus uses the SBT-CO_2 waveform areas as described by Fletcher (22) to estimate dead space fraction and its components. Analysis Plus! was used to estimate deadspace in Studies 1, 4, and 6.

3.3.2 $NICO_2$

$NICO_2$ (Respironics, Inc, Wallingford USA) is the next generation device of the CO_2SMO plus and uses Capnostat® a capnograph that uses infrared absorption technology in combination with a pneumotacograph to measure flow. Volumetric

capnography and with it calculations of $\dot{V}CO_2$ are made by integrating expired gas flow with CO_2 concentration. The described accuracies of the above device is the same as the CO_2SMO.

3.4 Measuring Deadspace

3.4.1 Enghoff Modification of Bohr Deadspace

The Enghoff modification of the Bohr equation was used to calculate deadspace (Equation 7). Details of the methods to collect the expired gas and the correction for compressed ventilator gas are described in *study 1* later in this chapter.

3.4.2 SBT-CO_2 Method

The program Analysis Plus! for windows was used to calculate deadspace in the instances where the CO_2SMO was used. Analysis plus uses SBT-CO_2 waveforms areas to estimate deadspace. NICO_2 has inbuilt software that estimates Fowler's anatomical deadspace. Entering of the measured Pa_{CO_2} into the monitor calculates V_D / $V_{T\ phys}$ using the estimated $P\bar{E}_{CO_2}$. Alveolar dead space can be calculated by subtracting $V_{D\ anat}$.

3.5 Miscellaneous Equipment

Study 1: All patients in this study were ventilated using Drager Evita XL ventilator

Study 2: Oxford Ventilator was used as the ventilator for this study.

Study 4: All patients were ventilated using a Aestiva/5 anaesthetic machine ventilator (Datex-Ohmeda, Finland).

Study 5: All patients in this study were ventilated using Drager Evita XL ventilator

Study 6: All patients in this study were ventilated using Drager Evita XL ventilator

Study 7: All patients in this study were ventilated using Drager Evita XL ventilator

The GEM Premier 4000 (Instrumentation Laboratory) blood gas analyser was used in all the studies that required blood gas analysis. For the databases a wide variety of analyzers were used, as they were collected internationally. Specific details of these were not available.

3.6 Databases

3.6.1 Royal Brompton Hospital (RBH) Adult ICU Database

A waiver was granted from the local ethics committee to analyse previously collected data. Data were gathered for all adult patients that were ventilated for 5 days or more. The Royal Brompton Hospital is a tertiary referral centre and majority of the throughput are post-operative patients requiring prolonged ventilation. The adult intensive care unit (AICU) also acts as tertiary referral centre for patients with challenging ventilation problems.

In total 622 patients were identified that were mechanically ventilated for 5 days or more between January 2004 and January 2009. Respiratory variables for all patient admitted to the AICU were recorded hourly in a computerized clinical information system (CareVue, Phillips Medical Systems, Andover, Mass). The data from carvue was then exported and matched to the clinical notes of the patients. In total complete data was available for 497 patients. The hospital notes for the remaining patients were inaccessible. Demographic data were collected including admission diagnosis, age, sex, weight, height, and past medical history. Predicted body weight was calculated using the methods described by the ARDS network (89).

Data at the time-point of arterial blood gas analysis were recorded for the analysis. Similar to the database above respiratory variables listed in Table x were recorded and these were used to calculate VR, PaO_2 / FiO_2 ratio, OI, and dynamic compliance. Mortality outcomes and ventilator days were also recorded.

Minute Ventilation (ml/min)	$PaCO_2$ (kPa)
Tidal Volume (ml)	PaO_2 (kPa)
RR (Mandatory and spontaneous)	PaO_2 / FiO_2 Ratio
FiO_2	Ventilatory Ratio
PEEP (cmH_2O)	Oxygenation Index
Peak Inspiratory Pressure (cnH_2O)	Dynamic Compliance
Mean Airway Pressure (cmH_2O)	

Table 3.1 Summary of measured and calculated respiratory variables recorded in the CWH and RBH database.

3.6.2 Chelsea and Westminster Hospital (CWH) Adult ICU Database

The local ethics committee permission was granted to anonymously analyse data from ICU charts of mechanically ventilated patients admitted to the AICU at Chelsea and Westminster Hospital, London. The AICU is a general medical and surgical ICU. All mechanically ventilated patients admitted between October 2008 and January 2011 were considered for recruitment to the study. In total there were 322 patients were mechanically ventilated admitted to the ICU during this period. Of these patients data was captured for 229 patients. 153 patients were ventilated for 5 days or more. Complete clinical data was available for 129 patients.

Demographic data such as height, weight, gender, admission diagnosis, past medical history, and smoking history were recorded. Predicted body weight was calculated using the methods described by the ARDS network (89).

Routine respiratory data was collected daily, usually at the point of the first blood gas analysis of the day. A note was made of the mode of ventilation. Table 1 summarizes the recorded variables. These variables values were used to calculate VR, PaO_2 / FiO_2 ratio, oxygenation index (OI), and dynamic compliance were calculated. In addition mortality outcomes and ventilator days were also recorded.

In order to create a control group respiratory data and ABG measurements were also collected on patients undergoing elective surgery. Only results from patients requiring peri-operative arterial cannulation were used for the study. Most of the patients in this group were undergoing abdominal surgery. The 1st blood gas sample was recorded after a period of stability on a ventilator just prior to the start of surgery.

3.6.3 Australia-New Zealand Intensive Care Society Database

(Released by Prof Andrew Bersten)

A previously presented database of ALI/ARDS patients prospectively collected by the Australian and New Zealand Intensive Care Society Clinical Trials Group was used to evaluate the characteristics and clinical utility of VR in this population(90). In the database information was collected on all intensive care unit patients in three Australian States requiring ventilation (invasive and non-invasive) between October and November 1999. All ICU admissions requiring invasive or non-invasive

ventilation were screened daily during their entire admission for the development of ALI. In total 1,977 consecutive patients were admitted to the ICUs in the three states of whom 168 went on develop American–European Consensus Conference (AECC) definitions of ALI and ARDS. Of these 121 of these patients were invasively ventilated and these patients were considered for analysis.

Standard demographic data was collected alongside aetiology of ALI / ARDS, ventilator settings, respiratory and cardiovascular variables. Severity of illness scores (APACHE II and SOFA), chest x-ray scores, Murray lung injury score, days of mechanical ventilation, and survival outcome scores were also recorded. From the above data PaO_2 / FiO_2 ratio and ventilatory ratio were calculated. Where data was missing for the height of the patient, the mean population height specific for sex was used to calculate the ideal body weight.

3.6.4 ARDS Network databases

(Released by Prof Ognjen Gajic)

The clinical use of VR was examined in a previously collected database of ARDS Network trials (89, 91). The database was prospectively collected at University Hospitals within the network. The details of the inclusion criteria have been described elsewhere and can be accessed on the Internet (www.ardsnet.org). In summary all patients that were mechanically ventilated and met the AECC criteria for ALI / ARDS were considered eligible for recruitment into the trial. Inclusion criteria for analysis into this study were those patients mechanically ventilated for 3 days or more. The database contained information on demographics, aetiology of lung injury, the presence of shock and APACHE III score (92). Data were also available for respiratory variables such as ventilator tidal volume, respiratory rate, peak end-expiratory pressure (PEEP), peak airway pressure, plateau pressure, FiO_2, and arterial blood gas measurements.

From the above data and arterial blood gas results PaO_2 / FiO_2 ratio and ventilatory ratio were calculated. Where data was missing for the height of the patient, the mean population height specific for sex was used to calculate the ideal body weight.

3.7 Study 1: Comparison of Methods to Calculate physiological deadspace in mechanically ventilated ICU patients

As discussed in Chapter 1 there are predominantly 2 methods in clinical practice to measure deadspace. The more traditional Bohr-Enghoff method is a large container to collect the expired gas and requires correction for the compressed ventilator gas. These features make this an unattractive method in busy ICUs. The alternative method using volumetric capnography also has shortcomings particularly when transition of Phase II and Phase III of the CO_2 expirogram is difficult to assess. This method is easier in practice and potentially provides clinicians with additional information. Evidence of correlation between the two methods would allow clinicians to use the latter method with some confidence and allow for larger studies to be carried out over a shorter period of time.

The aims of this study are to compare physiological dead space using volumetric capnography and more traditional method of collecting mixed expired gas.

3.7.1 Methods

The study was approved by the local ethics committee (The National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint REC). Informed assent was obtained from family prior to recruitment to the study. Data were prospectively collected in patients aged > 18 years at the intensive care unit (ICU) at Chelsea and Westminster Hospital. All patients were emergency admissions to the ICU. Initial measurements of dead space were made following stabilization of the patient and within the first 24 hours following admission to the ICU. Measurements were then made once daily until either six consecutive recordings had been made, or the patient had been weaned from the ventilator or died, whichever was the shorter period. For each set of measurements a note was made of the mode of ventilation; mandatory (SIMV or BIPAP) or spontaneous (ASB). All modes of ventilation used non-bias flow triggering.

3.7.1.1 Deadspace Using Douglas Bag Method

Deadspace fraction was calculated using the Enghoff modification of the Bohr equation. The Enghoff modification of Bohr's equation states:

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}} \qquad [7]$$

where Pa_{CO_2} is the arterial PCO_2 and $P\bar{E}_{CO_2}$ is the mixed expired PCO_2. A modified Douglas Bag was created by attaching a fan to the bottom of a 10 litre Perspex chamber. This was used to collect and mix the expired gas from the exhaust port of the ventilator. The carbon dioxide concentration of this expired gas was measured using a BCI Capnocheck capnograph (Smiths Medical, USA).

One of the drawbacks using the Douglas Bag method (V_D / $V_{T\,DB}$) for calculating dead space fraction is that the collected expired gas contains compressed gas from the ventilator. It is difficult to separate this compressed gas from the true expired volume and leads to diluting and lowering of the measured PCO_2 of the expired gas leading to overestimation of V_D / V_T. Mixed expired CO_2 ($P\bar{E}_{CO_2}$) was calculated by correcting for gas compression in the ventilator circuit using the method described by Forbat (93). The corrected tidal volume was calculated using the following equation:

$$V_{T_C} = P_B \times \left(\frac{V_v + V_T}{P_B + P_{peak}} \right) - V_V \qquad [29]$$

where V_{T_C} is the corrected tidal volume, P_B, P_{peak} is the peak airway pressure, and V_V is the compressible volume of the ventilator and connection tubing. This was set as 1555 ml as determined by the manufacturer of the ventilator. The corrected gas volume was then calculated as follows:

$$P\bar{E}_{CO_2} = P\bar{E}_{CO_{2m}} \times \left(\frac{V_T}{V_{Tc}} \right) \qquad [30]$$

where $P\bar{E}_{CO_{2m}}$ is the measured PCO_2 in the mixing chamber. The correction method described has been shown to be comparable to physical separation of expired gas from compressed gas (93). The mean compressible volume was 2.6 (± 0.17) ml/cmH_2O of peak pressure, which is comparable to other studies where compressible gas has been previously measured (74).

Following the attachment of the mixing chamber and capnograph to the ventilator expiratory exhaust port, a period of 10 minutes was allowed to approach steady state,

before $\dot{V}_E$ was recorded, $P\bar{E}_{CO_2}$ was measured and corrected, and arterial blood drawn for measurement of Pa_{CO_2}.

3.7.1.2 Deadspace using Volumetric Capnography

V_D / $V_{T\ VCAP}$ was calculated using the CO_2SMO®Plus capnograph (Novometrix Medical Systems, Wallingford, USA). The monitor consists of a CO_2 sensor that measure CO_2 concentrations using infrared absorption technology. A flow sensor is the combined to the capnostat and attached proximal to the Y-tubing. The integration of flow with CO_2 concentrations allows the monitor to construct a single-breath CO_2 (SBT-CO_2) waveform. The SBT-CO_2 waveform can used to derive dead space and its components as described by Fletcher (22). The software programme Analysis Plus! for Windows (Novometrix Medical Systems, Wallingford, USA) was used to estimate values for physiological deadspace and its two components, anatomical deadspace and alveolar deadspace, using areas under the SBT-CO_2 waveform as described by Fletcher and colleagues (94). Analysis Plus! automatically computes the areas X, Y, and Z as seen in Figure 1.5A. Physiological deadspace is defined as (Y+Z)/(X+Y+Z).

CO_2SMO®Plus monitor estimates $P\bar{E}_{CO_2}$ by dividing the total volume of CO_2 in the breath over a minute by total expired volume over the same period. $P\bar{E}_{CO_2}$ is the volume weighted 8 breath average of this calculation and is updated every breath. The $P\bar{E}_{CO_2}$ values estimated by the monitor and the measured and corrected values from the mixing chamber were compared. The expired tidal volume (V_{Te}) as recorded by the ventilator (measure and corrected) were compared with values measured by CO_2SMO®Plus monitor. Internal self-calibration was done in both capnographs prior to all readings.

3.7.1.3 Statistical Analysis

Mean values of continuous normally distributed variables are expressed as mean ± standard deviation. Non-parametric data are presented as median (inter-quartile range). Pearson's correlation coefficient was used to examine correlation of measured values between mesurements. Bland-Altman method was used to assess agreement between paired measurements of V_D / V_T, $P\bar{E}_{CO_2}$, and V_{Te} (95).

3.7.2 Results

48 patients (33 men and 15 women) were recruited to the study. Table 3.2 summarizes the demographic data and admission values for respiratory variables for the population. In total 168 pairs of daily readings were taken. Table 3.3 summarizes the baseline physiological characteristics of the patients.

Bland-Altman analysis showed good agreement between V_D / $V_{T\ VCAP}$ and uncorrected V_D / $V_{T\ DB}$ with mean bias of 0.03 with a 95% limits of agreement between -0.04 and 0.11 (Figure 3.2A). The agreement between V_D / $V_{T\ VCAP}$ and corrected V_D / $V_{T\ DB}$ was similar with a mean bias of 0.02 with 95% agreement limit between -0.06 and 0.10 (Figure 3.2B). As would be anticipated there was excellent positive correlation between V_D / $V_{T\ VCAP}$ and both uncorrected and corrected V_D / $V_{T\ DB}$ ($r = 0.96$, $r^2 = 0.91$; $r = 0.95$, $r^2 = 0.90$ respectively; $p < 0.001$ for both).

Bland-Altman analysis of $P\bar{E}_{CO_2}$ showed good agreement between the measurements of the CO_2SMO monitor and the uncorrected (bias 0.08 kPa, 95% agreement limit -0.3 to 0.46 kPa) and corrected values (bias -0.19 kPa, 95% agreement limit -0.61 to 0.22 kPa) obtained in the mixing chamber. V_D / $V_{T\ phys}$ calculated using the Enghoff modification of the Bohr equation with $P\bar{E}_{CO_2}$ derived from the CO_2SMO showed good agreement with the Douglas bag method (mean bias 0.04, 95% agreement limit -0.09 to 0.18).

Bland-Altman analysis of uncorrected V_{Te} measured by the ventilator and the CO_2SMO monitor revealed a relatively large mean bias of 73.9 mls, with a 95% agreement limit of -0.8 ml and 148.5 ml. The agreement between corrected ventilator V_{Te} and the CO_2SMO monitor V_{Te} was better with a mean bias of 43.6 ml and 95% agreement limit between -90.1 ml and 78.4 mls. All readings were the split into 3 groups according to the V_{Te} measured by the ventilator: V_{Te} < 400 mL, V_{Te} 400-650 mL, V_{Te} > 650 mL. Bland-Altman analysis of corrected V_{Te} and V_{Te} measured showed mean bias (± SD) as follows: V_{Te} < 400 mL -25.8 mL ± 35.7 mL, V_{Te} 400-650 mL 6.0 mL ± 42.1 mL, V_{Te} > 650 mL 21.6 mL ± 41.9 mL. Linear regression analysis showed V_{Te} CO_2SMO = 0.91*$V_{T\ e}$ Ventilator – 22.1.

3.7.3 Discussion

The results of this study show that there was good agreement between deadspace as measured by the more conventional method of collecting mixed-expired gas and as measured by volumetric capnography using areas under the SBT-CO_2 waveform. There was also good agreement between $P\bar{E}_{CO_2}$ measured by the volumetric capnography and corrected and uncorrected values measured in expired collected gas. There was poor agreement between expired tidal volume measured by the ventilator and the CO_2SMO monitor. The agreement after correction for compressed gas improved between the 2 measured tidal volumes particularly in those patients ventilated with 400 – 650 mL breaths.

Calculating dead space using a Douglas bag is impractical in busy intensive care units. Yet information regarding deadspace ventilation is important because it can be used for disease progression and prognostication. The findings of this study show that there was reasonable agreement between physiological deadspace calculated using CO_2SMO plus and its software programme Analysis Plus! and the Douglas Bag method. The additional correction of for compressible gas only marginally reduced the mean bias between the 2 methods. The mean percentage bias across a wide range of physiological dead space abnormalities was 2.5% (± 7.6%). These margins are unlikely to represent a clinically significant value.

The VCAP method of calculating physiological deadspace fraction with the Douglas bag method had previously been compared in lung model and in animal model. The results of these findings found significant correlation between the 2 methods (r^2=0.84, $p < 0.001$) with a bias of 0.02. The findings of this study show a stronger correlation between the 2 methods, with a similar bias. The findings of this study were also similar to a previous study that showed similar correlation between physiological dead space calculated using volumetric capnography and metabolic cart (96). In turn the metabolic cart has been compared favourably to the Douglas Bag method of calculating deadspace (97).

The values of $P\bar{E}_{CO_2}$ derived by CO_2SMO showed similar agreement with the Douglas Bag method. Calculating V_D / $V_{T\ phys}$ using this value showed good agreement with the corrected Douglas Bag method (mean bias 6.7% ± 10.1%). The relevance of this finding is that the current generation of the volumetric capnography that are increasingly being incorporated into ventilator monitoring use these derived values to calculate deadspace. The $NICO_2$ monitor that is used in some of the following studies also uses the derived $P\bar{E}_{CO_2}$ values to calculate deadspace.

An unexpected finding of the study showed that the agreement between volumetric capnography derived $P\bar{E}_{CO_2}$ was better with the uncorrected $P\bar{E}_{CO_2}$ than corrected $P\bar{E}_{CO_2}$. This may be explained by the use of the correction factor described by Forbat and colleagues. In their study the correction factor was validated in a very small group of patients across a relatively small group of patients using volume controlled ventilation (93). The patients in this group were ventilated with both mandatory and pressure controlled ventilation. Some of patients were ventilated with pressure support ventilation and it would be assumed that the dynamics of compressed gas in this group of patients might also behave differently. The agreement between corrected V_{Te} and CO_2SMO was much better in the range of 400mL – 650mL. Either side of these tidal volumes the mean bias increased. This suggests that correction factor used in this study is subject to unreliability when the tidal volumes are either small or very large.

CO_2 rebreathing has been identified as a source of error in deadspace calculation (98). Another advantage of using volumetric capnography is that inspired PCO_2 is factored into the calculated value of $P\bar{E}_{CO_2}$. Aside from dead space measurements volumetric capnography measures flow and calculates tidal volume at the airway opening (99). Values generated by the capnograph are much more likely to represent true expired volumes in comparison to expired volumes calculated by the pneumotachograph in the ventilator, which has inherent inaccuracies of compressed gas and often over-estimates the true volumes. Volumetric capnography also allows for calculation of CO_2 elimination ($\dot{V}CO_2$). Measuring $\dot{V}CO_2$ is essential in the complete understanding the efficiency of CO_2 elimination by the lungs.

There are several limitations to this study. Firstly, the data was collected from a convenience sample, i.e. only patients with respiratory failure were included into the study. This was in order to capture a group of patients anticipated to have a wide range ventilation-perfusion mismatch. Secondly, two different measurement systems were used to measure PCO_2 in order to derive $P\bar{E}_{CO_2}$. The Douglas Bag method used the BCI capnocheck whilst the $P\bar{E}_{CO_2}$ derived by the CO_2SMO used the capnostat. Using two different methods to measure the same variable would subject the readings to inaccuracies and errors individual to the devices. Ideally both measurements would have been made using the capnostat. This was not possible as the CO_2 analyser of the capnostat requires a steady waveform to measure PCO_2 this was not feasible for the Douglas Bag.

In summary, physiological deadspace fraction derived using volumetric capnography either using the areas under the SBT-CO_2 waveform or from derived $P\bar{E}_{CO_2}$ shows good agreement with the Douglas Bag method. Future studies use these methods to measure deadspace.

Variable	Data
Age (years)	61 ± 15
Weight (Kg)	76 ± 15
Height (cm)	170 ± 9
Sex, Male / Female	33 (69) / 15 (31)
Admission Diagnosis	
LRTI / Exacerbation of COPD	15 (31)
Intra-abdominal pathology	14 (29)
Sepsis	9 (19)
Cardiac Insufficiency	7 (15)
Miscellaneous	3 (6)
Underlying COPD / ILD	7 (16)
Developed ARDS	5 (10)

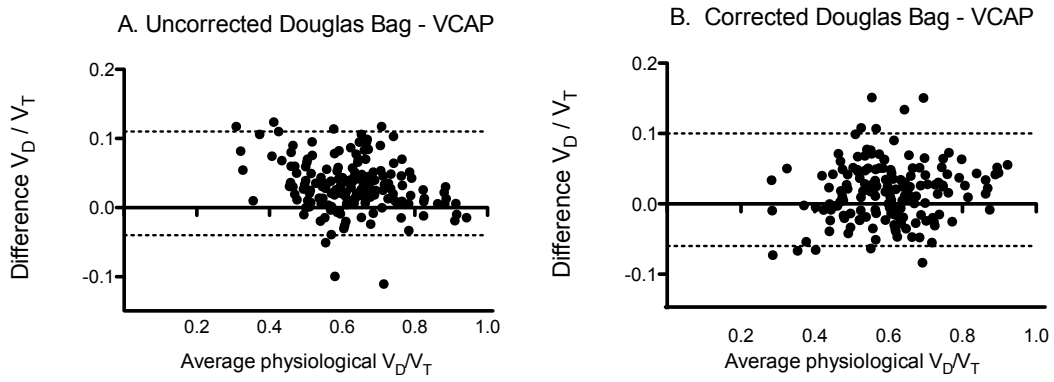
Table 3.2. Summary of baseline clinical characteristics of 48 patients. LRTI = Lower respiratory tract infection, COPD = Chronic obstructive pulmonary disease, ILD = Interstitial lung disease, ARDS = Acute respiratory distress syndrome.

Variable	Data
APACHE II Score	19 (15 – 22)
Tidal Volume (ml)	557 ± 128
Peak inspiratory pressure (cmH_2O)	24 (18.75-33)
Mean airway pressure (cmH_2O)	13 (9.75 – 16.25)
Peak end-expiratory pressure (cmH_2O)	8 (5-10)
Dynamic compliance ($ml.cmH_2O^{-1}$)	41 ± 38
$\dot{V}CO_2$ ($ml.min^{-1}$)	190 ± 59
PaO_2 / FiO_2 Ratio	26.8 ± 13
V_D / V_T	0.60 ± 0.09

Table 3.3. Summary of baseline respiratory variables of 48 patients. $\dot{V}CO_2$ = Rate of CO_2 elimination per minute, V_D / V_T = Physiological deadspace.

	Volumetric Capnography	Douglas Bag Uncorrected	Douglas Bag Corrected
$P\bar{E}_{CO_2}$ (kPa)	2.08 ± 0.69	2.00 ± 0.66	2.28 ± 0.70
V_{Te} (ml)	485.1 ± 130.1	542.1 ± 141.7	472.9 ± 145
V_D/V_T	0.61 ± 0.13	0.64 ± 0.12	0.59 ± 0.12

Table 3.4 Mean values of mixed expired CO_2 ($P\bar{E}_{CO_2}$), expired tidal volume ($V_{T\,e}$), and physiological deadspace (V_D/V_T) in all readings (n = 168).



3.2 Bland-Altman plot of differences versus average of paired measured values for physiological deadspace. The dotted lines represent the 95% agreement limit. 3.2A. Plot of agreement between the VCAP and uncorrected Douglas Bag method. 3.2B Plot of agreement between the VCAP method and corrected Douglas Bag method.

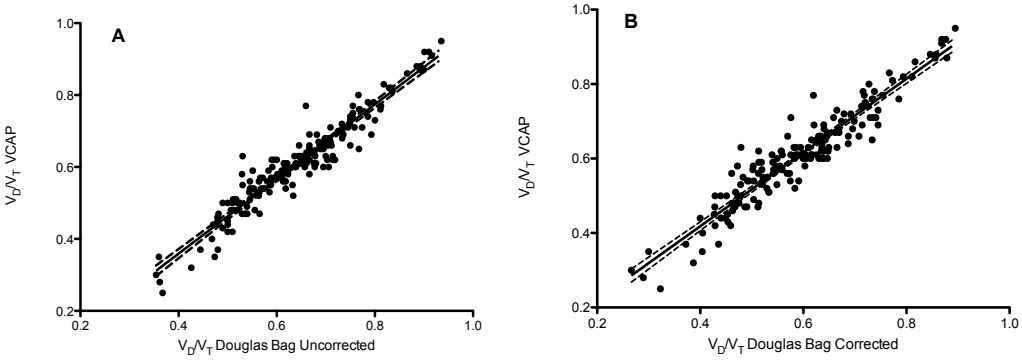


Figure 3.3 Scatter plot of V_D / V_T calculated by the 2 methods. 3.3A VCAP plotted against uncorrected Douglas bag method ($r = 0.96$, $p < 0.01$). 3.3B VCAP plotted against Douglas bag method corrected for compressed ventilator gas ($r = 0.95$, $p < 0.01$).

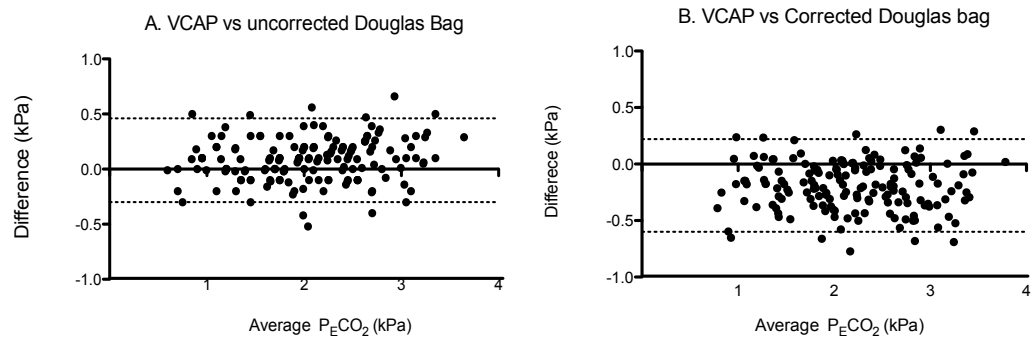


Figure 3.4 Bland-Altman plot of differences versus average of paired measured values of . The dotted lines represent the 95% agreement limit. 3.4A Plot of agreement between the values derived from VCAP and uncorrected Douglas Bag method. 3.4B Plot of agreement between the values derived from VCAP and corrected Douglas Bag method.

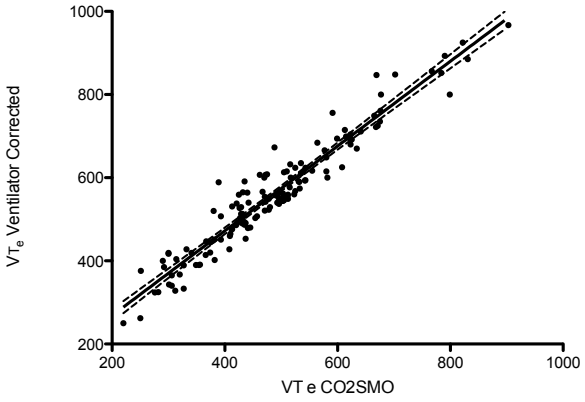


Figure 3.5 Correlation between expired tidal volume (V_{Te}) as measured by the CO_2SMO Plus! monitor and corrected V_{Te} as measured by the ventilator.

Chapter 4: Validation of the Physiological Properties of Ventilatory Ratio

4.1 Study 2: Validation of the Physiological Model of Ventilatory Ratio Using a Benchside Lung Model

The analyses in the previous chapter demonstrate the theoretical principles of VR. Before the workings of the ratio are assessed in patients, a simple lung model was designed in order calculate the ratio with measured variables. A physical bench model should enable stepwise changes to be made in either CO_2 production ($\dot{V}CO_2$) or deadspace to determine if this conforms with mathematical expectations. The aim of the study was to examine the behaviour of VR in a benchside lung model whilst controlled changes in $\dot{V}CO_2$ and deadspace were made.

4.1.1 Methods and Material

A simple ventilated lung model was designed such that the fraction of deadspace and CO_2 production ($\dot{V}CO_2$) could be controlled. The design of the benchside model is detailed in Section 3.1 and Figure 3.1.

The port leading to the reservoir bag was connected to a Y-piece connector. One limb of Y-piece was attached to an Oxford ventilator via a Wright's spirometer. This was the inspiratory limb. The second limb of the Y-piece was connected to a capnograph ($NICO_2$, Respironics-Novametrix) and then to the exhaust of the ventilator. CO_2 was added into the reservoir bag via tubing attached to a cylinder. The flow of CO_2 was controlled by a rotameter. The flow passing through was measured using a mass flow meter (Mass-View®, Bronkhorst High-Tech). The tubing delivering the CO_2 was inserted into the reservoir bag through a self-sealing valve ensuring a closed circuit. CO_2 production was controlled using the rotameter. Additional elephant tubing between the Y-connector and ventilator on the inspiratory limb was used to change deadspace volume.

The patient setting was for 70 Kg individual and the minute ventilation was set at 7000 $ml.min^{-1}$. This was achieved with a tidal volume of 500 mls and frequency of 14 breaths per minute. The apparatus deadspace was set at 150 mls.

In the first experiment $\dot{V}CO_2$ was maintained at a steady rate of 200 ml.min^{-1} and the deadspace was sequentially altered. This was achieved by adding extra volume of elephant tubing to the circuit on the inspiratory limb. End-tidal CO_2 was measured using the above mentioned capnograph and was taken as alveolar PCO_2. Prior to recording of measurements 10 breaths were allowed for the system to equilibrate after a change in conditions. ET_{CO_2} was measured for 10 consecutive breaths. For the second experiment similar recordings were made, however in these readings deadspace was left unchanged (as that of the circuit) and $\dot{V}CO_2$ was sequentially increased.

In order to calculate ventilatory ratio ET_{CO_2} was used as a substitute for Pa_{CO_2}. VR was calculated using the mean of the 10 breaths of the measured ET_{CO_2} and delivered minute ventilation.

4.1.2 Results

Tables 4.1 and 4.2 show the results of experiment 1 (steady $\dot{V}CO_2$), and experiment 2, (constant deadspace) respectively. There was little breath-to-breath variation in the recorded ET_{CO_2}. As expected there was an associated increase in the measured ET_{CO_2} as either CO_2 insufflation or deadspace increased. ET_{CO_2} and CO_2 production showed a linear relationship (Figure 4.1). The relationship of VR with deadspace was asymptotic (Figure 4.2). When deadspace volumes were large, further incremental increases in deadspace lead to a much larger increase in ET_{CO_2}. The findings of these studies were in keeping the physiological analysis in the previous chapter.

CO_2 Production ($ml.min^{-1}$)	ET_{CO_2} (kPa)	VR
150	2.9 (± 0.3)	0.58 (± 0.05)
200	4.1 (± 0.2)	0.82 (± 0.05)
250	4.9 (± 0.2)	0.98 (± 0.04)
300	6.2 (± 0.2)	1.24 (± 0.04)
350	7.0 (0.1)	1.4 (± 0.03)
400	8.35 (± 0.2)	1.65 (± 0.04)

Table 4.1. Mean values of ET_{CO_2} and Ventilatory Ratio (VR) with incremental increase in CO_2 production. Deadspace was kept constant at 150 ml. The values in the brackets represent standard deviation.

Total Deadspace (ml)	ET_{CO_2} (KPa)	VR
150	4.35 (± 0.19)	0.87 (± 0.04)
200	5.3 (± 0.20)	1.06 (± 0.17)
250	5.6 (± 0.17)	1.12 (± 0.04)
300	7.6 (± 0.26)	1.52 (± 0.05)
350	9.4 (± 0.15)	1.88 (± 0.03)
400	13.8 (± 0.22)	2.76 (± 0.43)

Table 4.2. Mean values of Pa_{CO_2} and VR with incremental increase in deadspace. CO_2 production was kept constant at 200 $ml.min^{-1}$. The values in the brackets represent standard deviation.

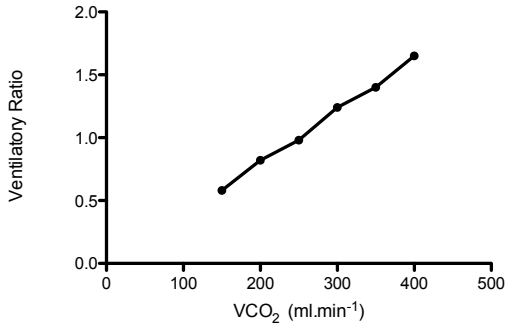


Figure 4.1. The relationship of VR and CO_2 production. Physiological dead space fraction was kept constant at 0.3.

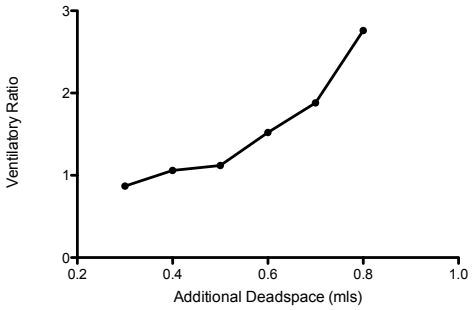


Figure 4.2. The relationship of physiological dead space and VR. $\dot{V}CO_2$ was kept constant at 200 ml.min^{-1}.

4.2 Study 3: Validation of VR using the Nottingham Physiology Simulator

Following on from previous chapters we know that Equation 25 states that:

$$VR = \frac{\dot{V}CO_{2_{actual}}}{E_{actual}} \times \frac{E_{predicted}}{\dot{V}CO_{2_{predicted}}} \quad [24]$$

and for an individual patient the predicted values would always remain constant. We can therefore restate VR for an individual patient:

$$VR = \frac{\dot{V}CO_{2_{actual}}}{E_{actual}} \times k \quad [31]$$

where k is the constant for predicted values for a given individual.

The aims of this study were to:

1. validate the physiological analysis of VR (Equation 1)
2. assess the relative values of VR in 3 simulated patients with varying ventilation-perfusion mismatch

4.2.1 Methods

Three virtual patients were configured with varying levels of $\dot{V}/\dot{Q}$ mismatch: normal, moderate, and severe. The details of the simulator configuration of each patient can be found below. In all three configurations the patient settings were for a 70 Kg, 170 cm individual, with a preset anatomical dead space of (V_{Danat}) 147 ml, Hb 14.5 g/L, Temp 37.2°C. FiO_2 was set at 0.21 for the normal and 0.3 for moderately impaired patient. For the patient with severe lung impairment FiO_2 was set at 0.5. Readings were taken with varying minute volumes at 7000 mls.min^{-1}, 6400 mls.min^{-1}, 5800 mls.min^{-1}, and 5200mls.min^{-1}. At each minute volume the respiratory rates were altered between 10, 12 and 15 breaths per minute. At each permutation of minute ventilation 3 separate readings were taken whilst altering $\dot{V}CO_2$ at 150, 200, and 250 ml.min^{-1}. This strategy ensured that VR was calculated whilst either physiological dead space fraction (V_D /$V_{T\,phys}$) or $\dot{V}CO_2$ were altered in isolation. The range of values for physiological dead space and shunt fraction for the patients were configured as follows: normal patient V_D /$V_{T\,phys}$ 0.24 – 0.44, shunt 1.2 – 2.1%; moderate mismatch V_D /$V_{T\,phys}$ 0.52 – 0.60, shunt 12 – 22.1%; Severe mismatch V_D /$V_{T\,phys}$ 0.60 – 0.71, shunt 46.1– 52.3%.

4.2.1.1 Patient Configuration

In the NPS $\dot{V}/\dot{Q}$ defects were configured by altering the bronchial resistance sliders (BRS) and vascular resistance sliders (VRS). Sliders 1–5 on each scale represents the anatomical progression from lung apex to base, with 1 being the apex. The larger the fraction the greater the dysfunction represented. The setting for the patients were as follows:

Normal Patient:

- *BRS 1* 9/2500 (1%), *BRS 2* 1/2500 (20%), *BRS 3* 1/2500 (50%), *BRS 4* 1/2500 (80%), *BRS 5* 36/2500 (100%)
- *VRS 1* 36/2500 (1%), *VRS 2* 1/2500 (20%), *VRS 3* 1/2500(50%), *VRS 4* 1/2500 (80%), *VRS 5* 9/2500 (100%)

Moderate abnormality:

- *BRS 1* 400/2500 (1%), *BRS 2* 36/2500 (20%), *BRS 3* 4/2500 (50%), *BRS 4* 4.8/2500 (80%), *BRS 5*13/2500 (1%)
- *VRS 1* 94.1/2500 (1%), *VRS 2*8.4/2500 (2.1%), *VRS 3* 1/2500 (50%), *VRS 4* 79.2/2500 (62%), *VRS 5*1560/2500 (100%)

Severe abnormality:

- *BRS 1* 2500/2500 (1%), *BRS 2* 2440.4/2500 (62%), *BRS 3* 0/2500 (64%), *BRS 4* 1/2500 (80%), *BRS 5* 1/2500 (100%)
- *VRS 1* 1/2500 (1%), *VRS 2* 1/2500 (20%), *VRS 3* 1/2500 (50%), *VRS 4* 2.6/2500 (85%), *VRS 5* 349.7/2500 (100%)

4.2.1.2 Statistics

Data is presented as mean ± standard deviation and ANOVA was used to compare mean VR values of the various ventilatory settings across the 3 simulated patients.

4.2.2 *Results*

The range of calculated values for Ventilatory Ratio from the three simulated patients was 0.63 - 2.64. As anticipated VR increases with the increasing deadspace and rate of CO_2 production. The mean values and range of VR in the 3 patients were as follows: normal 0.89 (± 0.25), moderate 1.37 (± 0.31), severe 1.76 (± 0.46) ($p < 0.01$)(figure 3). Similarly for each of the patients the values of VR were higher as $\dot{V}CO_2$ increased. Figure 2a shows the relationship of ventilatory ratio and $V_D / V_{T\ phys}$ and the interaction of $\dot{V}CO_2$ with theses variables. As would be predicted by the physiological model the results show an asymptotic relationship between $V_D / V_{T\ phys}$ and VR (Figure 4A). Figure 4B shows the relationship of VR with $1/E$ and demonstrates a linear relationship. There was also a linear relationship between $\dot{V}CO_2$ and VR when $V_D / V_{T\ ohys}$ was constant.

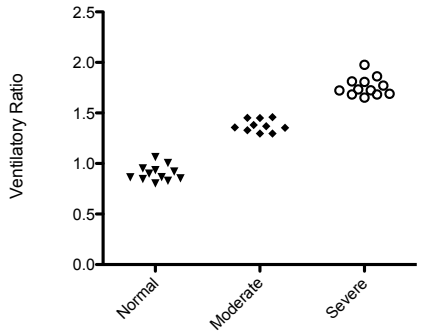


Figure 4.3 VR values in the 3 patient configurations in the NPS with $\dot{V}CO_2$ constant at 200 ml.min[1].

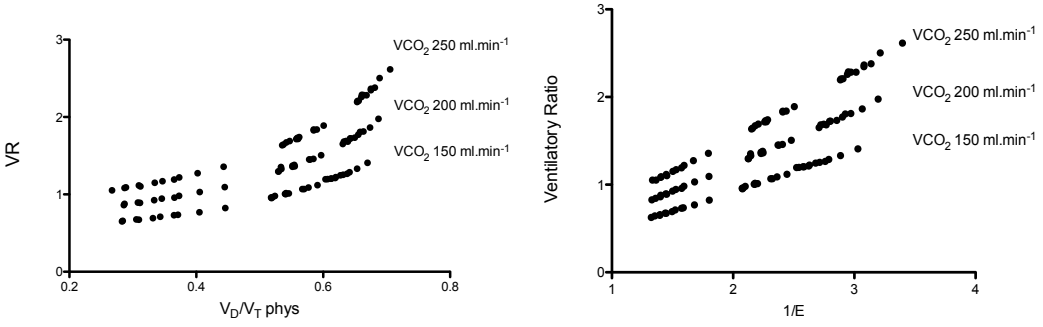


Figure 4.4A VR plotted against $V_D / V_{T\ phys}$. The isopleths represent configurations with 3 different rates of $\dot{V}CO_2$. 4.4B shows the relationship of VR with 1/E at different rates of $\dot{V}CO_2$, where E is efficiency or $1-V_D/V_T$.

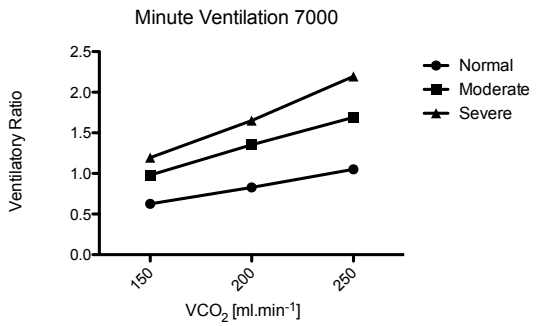


Figure 4.5. The effect of rising $\dot{V}CO_2$ on VR when dead space is kept constant for each of the configured patients. This graph is similar to the Figure 2.4.

4.3 Discussion

The aims of this chapter were to examine VR in a benchside lung model and a hi-fidelity cardiorespiratory simulator. Additionally the aim was also to validate the physiological analysis presented in Chapter II. The results from the benchside model show that the relationship of the V_D / V_T and $\dot{V}CO_2$ with VR is as described by the equations in the physiological analysis of VR. In this model VR behave as would be anticipated. The results from the Nottingham Physiology Simulator has demonstrated that both deadspace and $\dot{V}CO_2$ influence VR. In patients in steady state where $\dot{V}CO_2$ is relatively unchanged, changes observed in VR would be representative of changes in physiological deadspace and vice versa. Patients configured to have higher V_D /V_T $_{phys}$ had higher values for VR. Increasing $\dot{V}CO_2$ also led to higher values of VR. Results from the Nottingham Physiology Simulator validate the physiological model of VR described by equations 1 and 2.

The lung model used in Study 2 is a basic and crude representation of the mechanics of the lung. Hence the absolute values of the calculated dead space and VR are difficult to interpret. The results do however show that the trends of the results obtained during the experiments are similar to those obtained during the mathematical analysis of the physiological model of VR described. Figures 1 and 2 illustrate this. The experiments in the lung model serves an additional purpose by clearly demonstrating that physiological model is easily studied using measurement systems that are intended for further studies in the thesis.

The NPS allows a greater degree of sophistication when compared to the benchside model and allows testing VR under varying physiological conditions. Equation 2 states that VR is directly proportional to $\dot{V}CO_2$ and inversely proportional to 'E'. Figures 4.4a and 4.4B are representative of the graphs seen in Figures 2.3 and 2.4. The similarities between these graphs demonstrate the validity of the physiological analysis of VR.

As seen in Figure 4.4A when dead space abnormalities are high small changes in V_D / V_T lead to larger changes in VR. This may be as a result of a combination of reducing ventilatory efficiency and increased shunt fraction contributing to venous admixture. Given that arterial PCO_2 is used as a surrogate for alveolar PCO_2 the contributions of intrapulmonary shunt is incorporated in VR. Therefore changes in shunt would also influence VR. This holds true for most methods of calculating physiological dead space (100).

Another factor highlighted by figure 4.4A is that a given value of VR would represent a variety in V_D / V_T abnormalities depending on $\dot{V}CO_2$. As a pure marker for V_D / V_T, VR is a crude measure. The clinical value of VR is anticipated to be as a marker of the efficiency of the lungs to deal with the ventilatory demands of the body. A VR of 1 is unlikely to be of concern regardless of $\dot{V}CO_2$. Conversely a VR of 2 is likely to represent inefficient CO_2 elimination regardless of $\dot{V}CO_2$. It is anticipated that the clinical use of the absolute value for prognostication in respiratory failure will be as a tool to monitor efficiency of CO_2 clearance. A possible clinical use of the value VR could be to estimate and then follow the efficiency CO_2 clearance.

Examination of Figure 5 shows that the gradient of linear relationship of VR is steeper when the $\dot{V}/\dot{Q}$ abnormalities are larger. i.e. for when dead space is large an increase in CO_2 production will to a larger ventilatory road on the individual (larger VR). Whilst this may seem intuitive at first glance it is seldom factored in as a contributing factor in the rising Pa_{CO_2} observed in ventilatory failure. This physiological phenomenon may in part explain findings of a recent study where

paralysis and sedation in the early management of severe ARDS afforded survival advantage to patients (101). Deep sedation and paralysis would in theory result in lower CO_2 production. In ARDS dead space fraction is known to be high (72). Aside from improved synchrony with the ventilator, neuromuscular blockade would in theory also reduce the ventilatory load on individuals thereby minimising the deleterious effect of protective lung ventilation on body pH.

Another finding from the simulator modelling shows that 0.85 is mean VR value for the patient configured to represent 'normal' lungs. A figure close to 0.85 is probably nearer the "normal" value for VR rather than 1. Nomograms that were used as a guide to set the predicted values probably overestimate the required adequate minute ventilation (102, 103). Similarly, setting our ideal arterial PCO_2 as 5 KPa has also resulted in a small overestimation of VR. An objective during the development of the ratio was that it should be simple to calculate at the bedside. Therefore a small degree of accuracy has been knowingly relinquished for the sake of ease of calculation.

In summary the findings from the modelling work validate the theoretical analysis of the physiological properties of VR. It is anticipated that the physiologically intuitive properties of VR will stand true in patients. However the study of these variables would be more difficult as V_D/V_T and $\dot{V}CO_2$ are control in individuals. The subsequent chapters study the influence of these 2 variables on VR.

Chapter 5: CO_2 Production in Mechanical Ventilation and its Influence on Ventilatory Ratio

From the physiological analysis of VR we know CO_2 production has a direct relationship with ventilatory ratio. While this relationship has been demonstrated in a benchside and in-silico model (chapter 3), it has not been shown in clinical circumstances. The aims of this chapter are to assess the effect of $\dot{V}CO_2$ in vivo.

Of the two variables that influence VR, physiological deadspace is of greater interest to clinicians. The additional effect of $\dot{V}CO_2$ on VR may be perceived as 'noise' or as a distortion of the ventilatory inefficiency signal of VR. The variability in would to an extent dictate the contribution of the 'noise' on VR. The second part of the chapter deals with the variability of $\dot{V}CO_2$ in adult critically unwell mechanically ventilated patients.

5.1 Study 4: The effect of Exogenous CO_2 on Ventilatory Ratio

Laparoscopic surgery requires creation of a pneumoperitoneum. CO_2, due to its properties of rapid re-absorption, is the preferred gas for insufflation to create the pneumoperitoneum. Whilst direct infusion of exogenous CO_2 would not normally be possible in a clinical study, patients undergoing laparoscopic surgery provide a simple in vivo method of examining the relative contributions of excess CO_2 production on VR. Most patients selected for these procedures are ASA grade I and II where it would be anticipated that dead space volumes would remain relatively constant pre- and post-pneumoperitoneum. This would give us a unique opportunity to study the effect of $\dot{V}CO_2$ on VR in relative isolation.

5.1.1 Method

Data was collected as part of a larger observational study designed to evaluate the changes in respiratory mechanics and gas exchange in patients undergoing routine upper GI laparoscopic surgery. The anaesthetic delivered was dependent on the Consultant anaesthetist. All patients were pre-oxygenated with 100% oxygen and received fentanyl and propofol at induction. Non-depolarising muscle relaxants were used universally. Intra-operatively anaesthesia was maintained using either sevoflurane or desflurane. A combination of oxygen and air was used to ventilate the lungs.

The protocol design was, of necessity, pragmatic to minimize disruption to the theatre list. Normal weight patients undergoing upper GI laparoscopic surgery were included along with those in the obese group having bariatric surgical procedures. The study protocol was approved by the National Research Ethics Services, REC Royal Free NHS trust, London. All patients with ASA classes I and II undergoing elective upper GI laparoscopic surgery were considered eligible for the study. Written informed consent was obtained and all patients were recruited between August 2010 and December 2010.

All patients recruited underwent either laparoscopic: gastric bypass or banding, cholecystectomy, fundoplication, or removal of gastric bands / balloon. Patients were managed either using pressure controlled (PCV) or volume controlled ventilation (VCV) according to the preferences of the anaesthetist. All patients were ventilated using a Aestiva/5 anaesthetic machine ventilator (Datex-Ohmeda, Finland).

Routine physiological monitoring was used in all patients. Additionally patients were consented for in-line volumetric capnography (CO_2SMO Plus Novometrix Medical Systems USA) and radial artery catheters for blood gas sampling. Baseline measurements were taken 20 minutes after the patient had been connected to the ventilator just prior to CO_2 insufflation (T1). The second reading was taken 20-25 minutes post pneumoperitoneum (T2). Third reading was taken after 20 minutes with an increase in 5 cmH_2O of PEEP (T3). A note of the patients position (Trendelenburg or reverse Trendelenburg) was made at the time of the reading. During the first reading almost all the patients were flat whilst the second and third reading most patients were in the head-up position. In line capnography was maintained throughout the study with no disruptions to the circuit.

At each data point respiratory rate (RR), tidal volume (V_T), minute ventilation (MV), $EtCO_2$, oxygen saturation (SpO_2), volume of exhaled CO_2 ($\dot{V}CO_2$), peak inspiratory pressure (PIP) and mean inspiratory pressure (P_{mean}) were recorded. Arterial blood gas analysis was carried out at each data point and pH, PaO_2, and $PaCO_2$ were recorded. The volumetric capnography data was used to calculate values for deadspace measurements using Analysis Plus software (Novometrix Medical Systems, USA).

From Analysis Plus! anatomical deadspace, alveolar deadspace, physiological deadspace, and their respective fractions of tidal volume were calculated. Ventilatory efficiency was further assessed by calculating ventilatory ratio (Measured Minute volume*Measured $PaCO_2$ / Predicted Minute volume*Predicted $PaCO_2$). Oxygenation was assessed by calculating the alveolar-arterial gradient using the equation: $FiO_2*(P_B-PH_2O)-(PaCO_2/RQ)-PaO_2$ (where PB is the barometric pressure, PH_2O is the water vapour pressure, and RQ is the respiratory quotient). The heart rate (HR), blood pressure (BP), and abdominal pressures were also recorded at each time point.

5.1.1.1 Statistical Analysis

Average values for the variables at the various time points are expressed as mean ± standard deviation. Data were analysed using one-way ANOVA with repeated measures. Pearson's correlation coefficient was used to examine the association between delta $\dot{V}CO_2$ and delta VR. Linear regression model analysis was used to describe the relationship of $\dot{V}CO_2$ and VR.

5.1.2 Results

In total 79 patients were recruited to study. 53 of these patients underwent bariatric corrective surgery. The remainder underwent non-bariatric related surgery. Baseline characteristics and summary of physiological variables are presented in Table 5.1. The mean values for $\dot{V}CO_2$ were significantly higher at sequential time-points (pre-pneumoperitoneum T0: 193.3 ± 41.0 $ml.min^{-1}$; post-pneumoperitoneum T1: 205.6 ± 40.6 $ml.min^{-1}$; 2nd post-pneumoperitoneum T2: 227.4 ± 42.2 $ml.min^{-1}$; $p < 0.01$). Similarly mean values for VR were higher at progressive time-points (T0: 1.13 ± 0.28; T1: 1.24 ± 0.25; T2: 1.36 ± 0.27; $p < 0.01$). In contrast the mean values across the three groups were fairly similar for $V_D / V_{T\,phys}$ (T0: 0.44 ± 0.07; T1: 0.45 ± 0.06; T2: 0.43 ± 0.07; $p = 0.12$).

97 paired readings were identified where the change in $V_D / V_{T\,phys}$ was between -0.02 and 0.02. Of these 72 paired readings had a change of > 5% in $\dot{V}CO_2$ between the 1st and 2nd reading. The delta values for $\dot{V}CO_2$ and VR were calculated for these readings. Figure 5.1 shows the percentage change VR plotted against the percentage

change of $\dot{V}CO_2$. The values show good correlation between the delta values of the 2 variables (r = 0.79, p < 0.01). The range of change in $\dot{V}CO_2$ pre and post exogenous CO_2 addition (pneumoperitoneum) was – 22% to 66% (mean 13%). The range of delta VR pre and post exogenous CO_2 addition was – 14% to 44% (mean 13%). Linear regression analysis described the relation of the delta values of the 2 variables as follows: Delta (%) VR = 0.85 * Delta $\dot{V}CO_2$ (95% CI slope: 0.77 – 0.93, p < 0.01).

	Obese (53)	**Normal-Weight (26)**	**p Value**
Gender (Female:Male)	47 : 6	17 : 9	0.03[a]
Age (years)	44 (31-50.5)	48 (34.75-58.8)	0.06[b]
BMI	47.59 ± 7.025	26.81 ± 4.945	< 0.01[b]
	Mechanics		
Ventilation Mode (Volume:Pressure)	28:25	21:5	0.03[£]
Minute Volume ($l.min^{-1}$)	7.4 ± 1.6	6.6 ± 1.6	0.04
$\dot{V}CO_2$ ($ml.min^{-1}$)	173.2 ± 43.2	141.8 ± 26.64	0.01
Pmean (cm H_2O)	10.55 ± 2.18	7.231 ± 1.61	< 0.01
Static Compliance (ml/cm H_2O)	77.32 ± 41.17	82.17 ± 14.86	0.56
	Gas Exchange		
FiO_2	0.52 ± 0.02	0.54 ± 0.02	0.56
$EtCO_2$ (KPa)	4.36 ± 0.09	4.27 ± 0.13	0.61
$PaCO_2$ (KPa)	4.84 ± 0.96	4.73 ± 0.139	0.53
PaO_2 (KPa)	20.05 ± 1.21	31.23 ± 2.33	<0.01
	Intra-abdominal pressure		
T2	*14 (13-15)*	*14 (13.75-15)*	0.55[§]
T3	*14 (12-15)*	*14 (13-15)*	0.37[§]

Table 5.1 Baseline demographics of the 2 groups post induction. BMI body mass index,VCO_2 volume of expired CO_2, FiO_2 Fraction of inspired O_2, $EtCO_2$ End-tidal CO_2, $PaCO_2$ Partial pressure of arterial CO_2, and PaO_2 partial pressure of arterial O_2 (a. Fisher's exact test. b. Unpaired t test. c. Mann-Whitney test. (p values are for unpaired t test except where marked. § = Mann-Whitney test, £ = Fisher's Exact test).

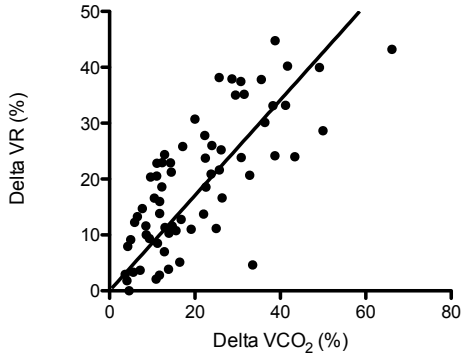


Figure 5.1. Delta $\dot{V}CO_2$ plotted against delta VR. (The delta values were calculated by subtracting Pre-pneumoperitoneum values from post-pneumoperitoneum values).

5.1.3 Discussion

The findings of this observational study are similar to those seen in the model analysis in the previous chapter. A rise in $\dot{V}CO_2$ was associated with a corresponding rise in VR if V_D / $V_{T\ phsy}$ remained unchanged. The relationship between the delta values of two variables showed reasonable linearity. There was also strong positive correlation between the 2 variables.

Linear regression equation of the delta values suggests that for a given percentage change in $\dot{V}CO_2$ the corresponding percentage change in VR is slightly smaller. The exact reasons for these findings are difficult to deduce from this study. Although they may be explained by the following:

1. The body would buffer a proportion of the exogenous CO2 absorbed during insufflation and would not all be directly eliminated. It would stand to reason that the magnitude of change in VR would be smaller than the corresponding change in VR.
2. The second readings in the pair were taken after the introduction of pneumoperitoneum. This would invariably lead to changes in ventilatory efficiency. Whilst the readings with high delta values of deadspace were excluded from the analysis invariably there would be an effect of changing deadspace that would have influenced VR.

3. Whilst adequate time was factored in for equilibration prior to readings, there was constant addition of CO_2 into the peritoneal cavity and a steady leak in the of CO_2. This would inevitably lead a slight lag in $\dot{V}CO_2$ measurements made by the capnograph.

It is unrealistic to expect the correlation to be close to 1 as seen in the physiology simulator in chapter 4. Natural variations in readings in biological systems are inherent particularly in the context of repeated readings in multiple individuals using various measurement systems. Correlation coefficient of 0.79 between the delta values is probably clinically reasonable and in line with what would be anticipated within the limitations of the study design.

In summary, findings in this study show that increased CO_2 production leads to an increase in VR. The relationship between delta values of $\dot{V}CO_2$ and VR exhibit linearity and validates the physiological analysis presented in the previous chapters.

5.2 Study 5: Variability of CO_2 Production in Critically Ill Mechanically Ventilated Adult Patients

5.2.1 Introduction

We know that physiological analysis of VR shows that it is influenced by dead space and CO_2 production ($\dot{V}CO_2$).

$$VR = \frac{\dot{V}CO_2}{1 - V_D/V_T} \times k \qquad [32]$$

where k is a constant specific to the patient and depending on their predicted values. Closer inspection of the above equation shows that VR is in effect similar to the concept of 'ventilatory demands' as described elsewhere (104-106). A rising value of VR would reflects a failure to meet the ventilatory demands of the body; be it as a result of ventilatory strategy or lung pathology or both.

Primarily the high ventilatory demands seen in acute respiratory failure are mostly thought to be due to a rise in deadspace ventilation (84, 105, 106). In contrast Kiiski and colleagues have suggested that hypermetabolism rather than dead space ventilation is the leading cause of increased ventilatory demands seen in acute respiratory failure (104). In ARDS patients however they too found that deadspace ventilation was the more relevant contributor to increased ventilatory demands. In general high CO_2 production in this group of patients is thought to be relatively uncommon (107).

Whilst there have been studies examining the role of CO_2 production in rising ventilatory demands, little is known of the variability of $\dot{V}CO_2$ in this group of patients. To gain complete understanding of CO_2 elimination it is essential to understand the dynamics of CO_2 production. CO_2 production is difficult to measure directly. As discussed in the methods section the NICO monitor combines a capnograph with a flow sensor. This allows for real time integration of CO_2 concentration with expired volume and thereby giving breath-by-breath volume of CO_2 elimination ($\dot{V}CO_2$). $\dot{V}CO_2$ measurements using this technique have shown reasonable correlation with metabolic cart which traditionally has been the standard

method of measuring $\dot{V}CO_2$ (96). In steady state the amount of CO_2 excreted by the lung equals the amount of CO_2 produced by the body. Therefore in steady state $\dot{V}CO_2$ measurements may be used as a surrogate for CO_2 production.

The primary objective of this study was to examine the variability of $\dot{V}CO_2$ in critically unwell patients in mandatory and spontaneous modes of ventilation. An understanding of the variability of $\dot{V}CO_2$ would give an indication of the resulting variability in VR.

It is anticipated that VR is likely to differ in patients breathing spontaneously compared to those in mandatory modes of ventilation. These differences in ventilatory efficiency would be as a result of either increased dead space fraction or increased CO_2 production or both during spontaneous ventilatory support. A secondary objective of the study is to assess the relative participation of each of these variables in the observed changes in VR at the transition from mandatory to spontaneous modes of ventilation.

5.2.2 Methods

5.2.2.1 Patients

This observational study involved retrospective analysis of prospectively collected data. The setting of the study was in a single-centre mixed medical-surgical adult ICU at Chelsea and Westminster Hospital, London UK. Mechanically ventilated patients anticipated to require prolonged intubation or with acute respiratory failure are routinely monitored with volumetric capnography during the first week of ventilation at the study centre. Permission was granted from the local institutional ethics board to analyse the data retrospectively. All patients were ventilated with Evita XL ventilator (Draeger, Leubeck, Germany). The modes of ventilation were either SIMV with assisted spontaneous breaths, BIPAP with assisted spontaneous breaths, or CPAP with assisted spontaneous breaths. Demographic data including age, sex, admission diagnosis, and past medical history were recorded for the purposes of the study. Only patients over the age of 18 were considered for the analysis.

For the purposes of analysis modes of ventilation were classified into three groups:

1. Mandatory ventilation: if the patient was taking less than or equal to three spontaneous breaths per minute in addition to their mandatory rate.
2. Spontaneous ventilation: when patients were in CPAP with assisted spontaneous breaths.
3. Mixed mode ventilation: if patients took more than three added spontaneous breaths per minute whilst in SIMV or BIPAP mode.

Data was only considered for analysis if patients were ventilated in a mode of ventilation for more than 10 consecutive hours. Readings for periods less than this were discarded as they were unlikely to yield meaningful information in terms of variability of CO_2 production in a particular mode. Readings for individuals who returned to mandatory modes of ventilation from spontaneous mode were not considered for analysis.

5.2.2.2 $\dot{V}CO_2$ Measurements

Patients were attached to a NICO monitor within 24 hours of their admission to the ICU. The capnograph of the NICO monitor is attached distal to the endotracheal tube and proximal to the Y-connector of the ventilator. Artifact of compressed ventilator gas is no longer a factor in the measurement of the expired volumes. This makes volumetric capnography a clinically practical tool to monitor CO_2 kinetics.

In the study $\dot{V}CO_2$ was recorded hourly at a point when the patient was undisturbed and free from nursing and medical intervention for at least 5 minutes; as is the policy for recording all hourly vital signs on the ICU chart. Values for mixed expired CO_2 ($P\bar{E}_{CO_2}$) are also calculated by NICO. These were also recorded at same time as the $\dot{V}CO_2$. In addition hourly-recorded variables that were likely to influence $\dot{V}CO_2$ variability were also used for the analysis. These included sedation, muscle paralysis, temperature, heart rate, and feeding. For the purposes of the analysis the variables were recorded to give a binary outcome. For sedation and paralysis presence of a sedative agent or muscle relaxant as an infusion were considered as a positive. Total parenteral nutrition (TPN) or naso-gastric feeding at full feeding protocol was considered as a positive for feeding. For continuous data fever was considered if the

temperature was greater than 38.0°c and tachycardia was considered as a heart rate greater than 110 beats per minute.

5.2.2.3 Measuring Dead Space

Dead space was calculated using the Enghoff's modification of the Bohr equation:

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}} \qquad [7]$$

Arterial Pa_{CO_2} values were taken from the chart and the corresponding value of $P\bar{E}_{CO_2}$ for that hour was used to calculate physiological V_D / V_T. In the case of change of mode of ventilation readings within 3 hours of the transition were not considered for analysis. This was based on a study demonstrating that a minimum of 120 minutes was necessary to interpret $\dot{V}CO_2$ measurements as a marker for metabolism following a change of ventilator settings (108).

5.2.2.4 Statistical Analysis

Data are presented as mean (± standard deviation) for continuous data and as median (inter quartile range) for ordinal data. Unpaired t-test was used to compare mean values between groups. Mann-Whitney U-test was used to compare groups where data were not normally distributed.

The first $\dot{V}CO_2$ reading after the connecting the patient to the NICO capnograph was considered as the baseline reading in that particular mode of ventilation. Variations in subsequent hourly readings were measured against this reading. The third reading after a change in mode of ventilation was considered as baseline for the new mode. Box-whisker plots of the percentage variation from baseline were constructed for individual patients in the each mode of ventilation. Box-whisker plot was also constructed for the median variability across the population in the 3 modes of ventilation. Bartlett's test for equivalence of variance was used to assess the difference in inter-group variance.

In order to assess the effect of fever, tachycardia, feeding, lack of sedation and lack of paralysis resulted in increased $\dot{V}CO_2$: two sub-groups were identified. High-change

group consisted of all readings with percentage variation was greater than the third quartile. Normal-change group consisted of readings with percentage variation within the third quartile. Chi-square test was used to assess differences in the frequency of these variables in the two groups. Stepwise multivariate logistic regression was used to examine the predictive effect of individual variables on large $\dot{V}CO_2$ percentage increase in ventilation mode groups.

To compare readings at the transition from mandatory to spontaneous ventilation Wilcoxon rank test was used to compare paired data for categorical data and paired t-test was used to compare continuous data.

5.2.3 Results

Complete data to satisfy the pre-analysis requirements were available for 45 patients. The baseline characteristics and admission diagnoses of the patients are summarized in Table 5.2. In mandatory modes of ventilation data were available for 30 patients with a total of 1587 hourly readings. In spontaneous mode of ventilation 29 patients were eligible for analysis with a total of 1514 hourly readings. Data in mixed mode of ventilation was available in 9 with a total of 314 hourly readings.

The range of $\dot{V}CO_2$ in the all the readings was 90 to 410 ml min^{-1}. Mean $\dot{V}CO_2$ for all readings was 209 (± 57) $ml.min^{-1}$. The range of $\dot{V}CO_2$ in mandatory ventilation readings was 87 – 367 $ml.min^{-1}$ with a mean value of 194 (± 50) $ml.min^{-1}$. The range for mixed ventilation readings was 90 - 340 $ml.min^{-1}$ with a mean value of 200 (± 51) $ml.min^{-1}$. The range for spontaneous ventilation readings was 90 - 426 with a mean value of 227 (± 60) $ml.min^{-1}$. Mean $\dot{V}CO_2$ was significantly higher for readings in spontaneous ventilation compared to mandatory ($p < 0.01$) and mixed ventilation ($p < 0.01$). Mean $\dot{V}CO_2$ was significantly higher in mandatory ventilation compared to mixed mode ($p = 0.02$). Table 5.3 summarizes the differences in the key variables between the mandatory and spontaneous ventilation groups.

Figure 5.2 shows the box-plot for percentage variability in mandatory and spontaneous modes of ventilation. The median percentage variation for the three modes of ventilation across the population was as follows: Mandatory 3% (IQR -4%

to 13%), mixed 0 (IQR -7% to 9%), spontaneous 3% (IQR -7% to 15%). Bartlett's test showed that variance from baseline was higher in the spontaneous group in comparison to mandatory ($p < 0.01$) and mixed ($p < 0.01$) modes of ventilation. There was no significant difference in variance between mandatory and mixed modes of ventilation ($p = 0.29$). Table 5.3 shows comparison of variance between mandatory and spontaneous modes of ventilation within individual patients in whom data was available for both modes. In 11 out of 20 patients the variance was significantly higher in spontaneous modes of ventilation (Table 5.5).

In mandatory ventilation the number of readings with absence of sedation ($p = 0.02$) and feeding ($p < 0.01$) were significantly in the high-change group compared to the normal-change group. There were no significant differences in readings with tachycardia, paralysis, and fever between the two subgroups. In spontaneous ventilation readings with absence of sedation ($p < 0.01$) was the only variable that was in significantly greater numbers in the high-change group.

After adjusting for all five variables in a stepwise logistic regression model, feeding was the only variable that significantly predicted large increases in $\dot{V}CO_2$ in the mandatory ventilation group (OR 2.70, $p < 0.01$). In the spontaneous ventilation group absence of sedation remained strongly associated with the high-change group after adjusting for other variables in multivariate logistic modelling (OR 0.58, $p < 0.01$).

Data was available for 15 patients at the transition from mandatory to spontaneous modes of ventilation. In these patients analysis of paired data showed $\dot{V}CO_2$ ($p < 0.01$) and ventilatory ratio ($p < 0.01$) were significantly higher in spontaneous modes of ventilation. There was no significant difference in V_D / V_T in paired analysis between the 2 groups ($p = 0.67$). An increase in VR of more than 10% was seen in 13 out of the 15 patients. Of these 8 were as a result of increased CO_2 production (62.5%), 4 as a result of increased physiological dead space (30.8%), and 1 patient as result of increase in both variables (7.7%).

5.2.4 Discussion

The results of the study show that variation in $\dot{V}CO_2$ in this ICU population is small. In particular variation in mandatory modes of ventilation are lower than those seen in spontaneously ventilating patients. In patients breathing in mandatory modes of ventilation feeding and absence of sedation were predictors of high $\dot{V}CO_2$ variability. During spontaneous breathing absence of sedation was the only variable that predicted higher $\dot{V}CO_2$ changes. Paired data for patients between mandatory and spontaneous modes of ventilation showed that $\dot{V}CO_2$ was significantly higher in patients breathing spontaneously. Ventilatory ratio was also significantly higher in spontaneously ventilating patients.

5.2.4.1 Carbon Dioxide Production in Critically Unwell Patients

One of the main objectives of ventilatory support in critically unwell patients should be to meet the ventilatory demands of the body. Failure to do so can result in hypercapnia and acidosis. This must however be tempered with the need to avoid barotrauma and volume-trauma both of which have been associated with poor outcomes (109). 'Permissive hypercapnia' is a widely used ventilatory strategy in critically unwell patients with survival advantage compared to more aggressive ventilatory strategies (89). Animal models suggest hypercapnic acidosis may be independently beneficial in lung injury (110, 111). This must be balanced with the known deleterious effects of severe hypercapnia seen in animal models (112) and in humans (113). A rising value of $PaCO_2$ can be viewed as failure to meet increasing ventilatory demands of the body. During permissive hypercapnia this may in part be due to ventilatory strategies and in part due to underlying lung pathology. Understanding the variability of $\dot{V}CO_2$ becomes essential in interpreting changes in ventilatory demands, and with it Ventilatory Ratio. In Study 4 we see a linear association between VR and $\dot{V}CO_2$. Yet despite the simplicity of their relationship the relative influence of $\dot{V}CO_2$ on VR in clinical practice in the ICU is difficult to map because it remains poorly studied and poorly understood. To the knowledge of the author, this is the first study that examines variability of $\dot{V}CO_2$ in the ICU population.

In the main $\dot{V}CO_2$ has been studied with respect to energy expenditure and feeding (114, 115). Metabolic processes of the body produce CO_2. In the intensive care patient several factors can influence the rate of CO_2 production. These include hyperpyrexia, shivering, exercise, and feeding. Increased $\dot{V}CO_2$ has been demonstrated during induced hyperthermia in animal models (116) and seen in malignant hyperthermia (117). Reducing temperature has been associated with lower CO_2 production (118). Likewise induced hypothermia has also been associated with reduced CO_2 production (119). Conversely shivering with or without hypothermia can lead to an increase in CO_2 production (120, 121).

The increased metabolic demand of exercise is also associated with increased CO_2 production. Weissman and colleagues have shown that routine interventions carried out in the ICU are known to transiently increase CO_2 production in non-comatose ventilated patients (122). The study showed that at rest there was minimal increase in $\dot{V}CO_2$ from its lowest values. The greatest increase was seen in activities such as chest physiotherapy where increases close to 40% from the lowest value were recorded. Even passive movements of the limbs are associated with a 10%-15% increase in $\dot{V}CO_2$ (122, 123). However these changes are thought to be transient and return to baseline shortly after the cessation of activity. In non-comatose patients rest and inactivity were associated with lower $\dot{V}CO_2$ (124).

The findings of this study are in keeping with the above-mentioned studies. $\dot{V}CO_2$ was lower in patients in mandatory modes of ventilation where the patients are likely to have lower ventilatory demands as a result of ventilatory support and increased sedation and inactivity. Patients with acute severe respiratory failure requiring mechanical ventilation are more likely to remain in a steady state of CO_2 production as a result of increased sedation (125) (126). Not only were the absolute values of $\dot{V}CO_2$ lower in the mandatory ventilation group, from Figure 5.3 we can see the median variation was also smaller. Thus the effect of $\dot{V}CO_2$ on changing values of VR in mandatory modes of ventilation is expected to be relatively small. Visual analysis of Figure 5.2 clearly demonstrates that across the population variation in $\dot{V}CO_2$ was greater whilst patients were in spontaneous ventilation. Absence of

sedation was an independent predictor of increased $\dot{V}CO_2$ variation during spontaneous ventilation. These findings are similar to with other studies that have examined the effect of sedation on $\dot{V}CO_2$ (122, 127). The finding of significantly higher respiratory rate during spontaneous ventilation would further increase metabolic demands. All these factors would explain the higher $\dot{V}CO_2$ and increased variability observed during spontaneous ventilation.

Variations of $\dot{V}CO_2$ in the region of 10% are unlikely to have a profound impact on VR. From the regression model in study 4 a change in 10% of $\dot{V}CO_2$ is likely to result in a change of 8.5% in VR. This is unlikely to represent a clinically significant change. The maximum $\dot{V}CO_2$ variation observed was during mandatory ventilation was of a magnitude of +66%. Variability of this magnitude was rarely encountered and may well have been a transient increase. Had such a change been sustained it would have resulted in an increase of VR of 56.1% as per the regression model.

Multiple studies have demonstrated the association between elevated $\dot{V}CO_2$ and high caloric enteral and parenteral feeding (128, 129). Altering the rate and type of calorie delivery has been proposed as a method to reduce the ventilatory load in patients that are difficult to wean from the ventilator (130, 131). The findings of this study showed that during mandatory ventilation feeding was a predictor of higher $\dot{V}CO_2$. This effect was not observed during spontaneous ventilation. Interesting to note is that during spontaneous ventilation the compensatory mechanisms for maintenance of CO_2 homeostasis are maintained i.e. individuals are able to respond by increasing their minute ventilation. This may be a factor why feeding was not a significant predictor of bigger changes in $\dot{V}CO_2$ during spontaneous ventilation. The rise in metabolic demands as a result of feeding would manifest itself as a rise in minute ventilation in this group of patients. The theory is in part substantiated by significantly higher minute ventilation during spontaneous ventilation. During mandatory ventilation the prescribed minute ventilation if unaltered would results in an increase in $\dot{V}CO_2$.

Although elevated $\dot{V}CO_2$ is an unquestionable adverse consequence of feeding in critical illness, its contributions to increased ventilatory demands is questionable particularly in patients with good ventilatory reserve. Raurich and colleagues showed that discontinuation of artificial nutrition only resulted in a 5% reduction $\dot{V}CO_2$ in ICU patients (132). This is likely to represent an insignificant reduction in the overall ventilatory load in weaning patients.

5.2.4.2 *Transition from Mandatory to spontaneous modes of ventilation*

Paired analysis of patients transitioning from mandatory to spontaneous modes of ventilation showed that $\dot{V}CO_2$ was significantly higher during spontaneous ventilation. The cumulative effect of higher values and greater variability of $\dot{V}CO_2$ in spontaneously ventilating patients would lead to higher values of VR in this group of patients. $\dot{V}CO_2$ will exert a greater effect on changing values of VR in comparison to mandatory modes of ventilation. Yet given that variance in $\dot{V}CO_2$ is relatively small, even in spontaneous ventilation, changing trends in VR could continued to be used as an index of ventilatory performance. Its absolute value however would be anticipated to be higher in comparison to mandatory modes of ventilation. In patients in spontaneous modes of ventilation this would limit its use as a marker to monitor disease progression and its role as a prognostication tool is at present less clear. The absolute numerical values of VR obtained during sedated and resting spontaneous ventilation requires further examination.

The increase in CO_2 production at the transition from mandatory to spontaneous mode are in keeping with the findings of Kemper and colleagues (133) They also looked at rising values of $\dot{V}CO_2$ at the point of transition as a predictor of successful weaning from mechanical ventilation. The study failed to show significant differences in $\dot{V}CO_2$ between the successful and unsuccessful groups (133). This was a small study looking specifically at post-operative patients. It may be that in bigger populations kinetics of VR at the transition point from mandatory to spontaneous modes of ventilation may be used as an index to predict successful weaning.

5.2.4.3 Limitations

There are several limitations to this study:

1. This was an observational study therefore the results must be interpreted with a degree of caution and as a platform for future studies.
2. For a patient in steady state CO_2 elimination equates to CO_2 production. The period to obtain steady state in this case was limited to 5 minutes. Whilst this may not be the ideal, in the practicalities of a busy ICU this period of time was thought sufficient. Studies have shown that 5-minute steady state measurements of $\dot{V}CO_2$ correlate well with 30-minute steady measurements (134).
3. The calculations made for physiological dead space used values for $PaCO_2$ that were taken at times that may not necessarily coincide with the exact times of the recordings of mixed-expired CO_2. Although there was little hour-by-hour variation in $P\bar{E}_{CO_2}$ and in most cases blood gases would have been obtained five minutes either side of the recording.

Summary

CO_2 production varies minimally in mandatory modes of ventilation. Large changes in ventilatory ratio in these modes of ventilation are likely to represent changes in physiological deadspace. Spontaneously ventilating patients show a significantly greater percentage variation in $\dot{V}CO_2$. VR in spontaneous mechanical ventilation is comparatively more likely to be influenced by $\dot{V}CO_2$, although this is still anticipated to be small. Transition from mandatory to spontaneous modes of ventilation led to significantly higher VR and $\dot{V}CO_2$.

In the following chapter we examine more closely the influence of dead space ventilation on ventilatory ratio and the interaction of both $\dot{V}CO_2$ and dead space on changing values of VR.

Variable	Data
Sex: Male / Female	30 / 15
Age (years)	62 (±15)
Height (cm)	172 (±8)
Weight (Kg)	76 (±12)
APACHE II score	19 (15 – 24)
Outcome: Survivors / Non-survivors	29 / 16
Admission Diagnosis:	
Respiratory Insufficiency	13
Intra-abdominal sepsis /perforation	10
Cardiac Insufficiency	7
Sepsis (Non abdominal / Respiratory)	7
Neurological Pathology	3
Others (DKA / Trauma)	2

Table 5.2 Baseline characteristics and admission diagnoses (DKA = Diabetic ketoacidosis).

Variables	Mandatory	Spontaneous	p value
Minute Ventilation ($ml.min^{-1}$)	9.7 (± 2.9)	11.1 (± 3.1)	< 0.01
Tidal Volume (ml)	582 (± 147)	586 (± 182)	0.65
Respiratory Rate	16 (12 – 20)	20 (15 – 27)	< 0.01§
Heart Rate	91 (± 20)	95 (± 19)	< 0.01
Fever (Yes / No)	37.1 (± 1.1)	37.4 (± 0.9)	0.01
Feeding (Yes / No)	1193 / 354	1093 / 338	0.66£
Sedation (Yes / No)	1371 / 178	882 / 518	< 0.01£
Paralysis (Yes / No)	228 / 1236	0 / 1432	< 0.01£

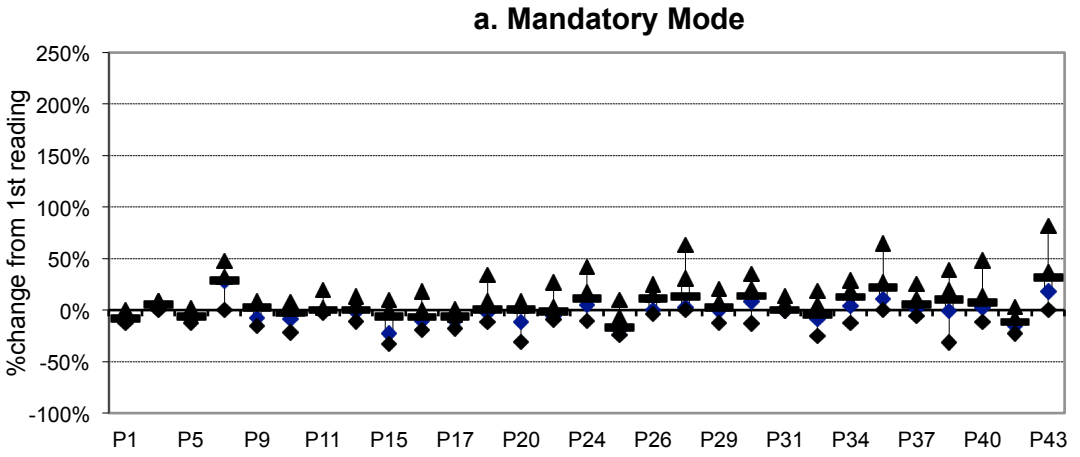
Table 5.3 Comparison of key variables in all readings between mandatory and spontaneous ventilation groups (p values are for unpaired t test except where marked. § = Mann-Whitney test, £ = Fisher's Exact test).

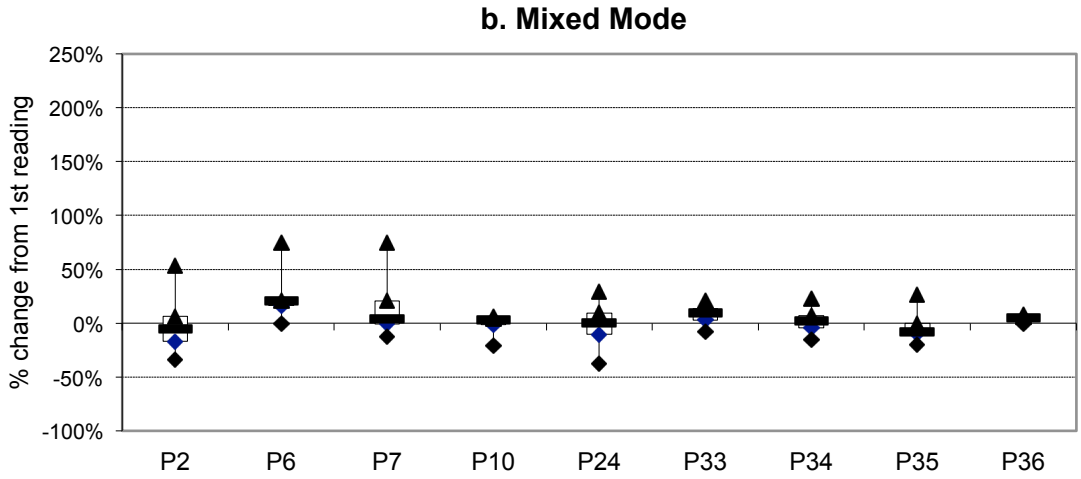
	Total	Mandatory	Mixed	Spontaneous
Minimum	-67%	- 33%	-37%	-67%
1st Quartile	-6%	-3%	-8%	-7%
Median	3%	5%	1%	3%
3rd Quartile	12%	14%	9%	16%
Maximum	225%	82%	75%	225%

Table 5.4 Summary of the percentage variation from baseline (1st reading) in all readings in and in the three ventilation groups.

Patient	Mandatory		Spontaneous		
	Count	Variance	Count	Variance	p-value
2	15	164	54	1142	<0.01*
3	28	405	11	925	0.10
9	30	169	17	198	0.72
10	26	273	43	328	0.61
11	32	1343	76	1204	0.72
12	10	827	81	1952	0.13
13	11	28	22	463	<0.01*
14	21	119	73	438	<0.01*
16	39	196	96	1265	<0.01*
17	11	30	40	524	<0.01*
20	38	1811	31	3041	0.14
22	15	661	51	1258	0.16
25	38	226	49	2450	<0.01*
27	14	986	20	5174	<0.01*
29	78	213	31	814	<0.01*
30	101	157	19	560	<0.01*
33	87	562	17	776	0.39
35	26	309	51	1327	<0.01*
43	22	661	43	3238	<0.01*
44	11	722	34	711	0.98

Table 5.5 Comparison of paired variance data within individual patients in mandatory and spontaneous modes of ventilation. Differences in variance were compared using Mann-Whitney U-test (* Denotes significant p-values).





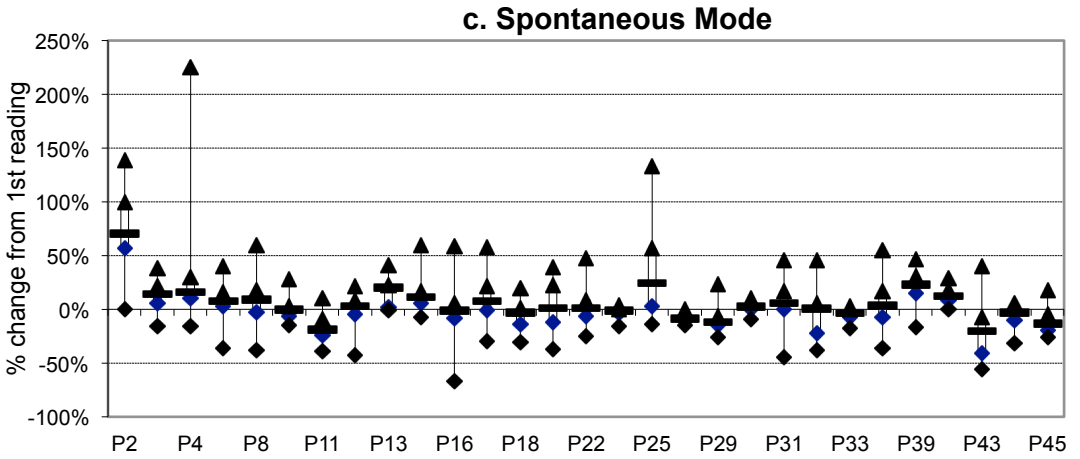


Figure 5.2 Changes in $\dot{V}CO_2$ from baseline (1st reading) in the three modes of ventilation in individual patients. Figure 5.2a shows the percentage change from baseline in mandatory mode of ventilation. Figure 5.2b shows variation in mixed mode of ventilation. Figure 5.2c shows changes from baseline in spontaneous mode of ventilation. Central line of the box represents the median percentage whilst the Box parameters represent the IQR. Whiskers represent the minimum and maximum values.

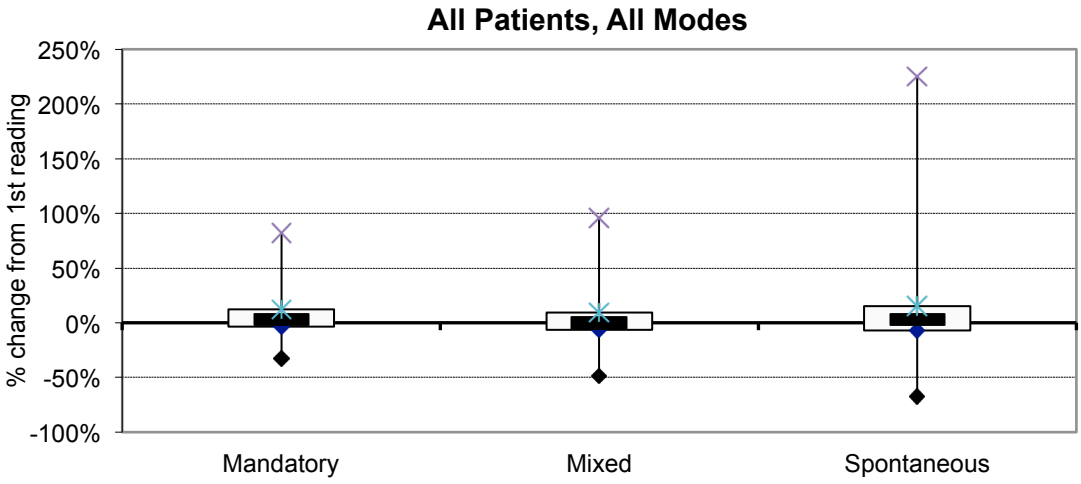


Figure 5.3 Box-whisker plots of percentage change in $\dot{V}CO_2$ across the population in the 3 modes of ventilation. Central line of the box represents the median percentage whilst the Box parameters represent the IQR. Whiskers represent the minimum and maximum values.

Chapter 6: The Influence of physiological dead space and CO_2 production on Ventilatory Ratio in Mechanically Ventilated Patients

6.1 Study 6: The Influence of Physiological Dead Space and CO_2 Production on Ventilatory Ratio- A Prospective Study

We have previously seen that VR can be defined as:

$$VR = \frac{\dot{V}CO_{2_{actual}}}{E_{actual}} \times \frac{E_{predicted}}{\dot{V}CO_{2_{predicted}}} \qquad [24]$$

For a given individual, predicted values for E and $\dot{V}CO_2$ are constants. Therefore VR can be redefined as:

$$VR = \frac{\dot{V}CO_{2_{actual}}}{E_{actual}} \times k \qquad [33]$$

where *k* is specific to the individual. From the above equation we can see that VR is directly proportional to $\dot{V}CO_2$ and inversely proportional to E. An increase in VR would be as a result of an increase in physiological deadspace fraction (V_D / V_T) or $\dot{V}CO_2$ or both. Both these variables are seldom measured in mechanically ventilated patients. The value of VR lies as a surrogate of these variables. In previous chapters we have examined the relationship in computational models. The principal aims of this observational study were to evaluate the relationships of $\dot{V}CO_2$ and V_D / V_T in vivo in a sample of mechanically ventilated critically unwell patients.

6.1.1 Methods

The study was approved by the local ethics committee (The National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint REC). The study was conducted at the intensive care unit (ICU) in Chelsea and Westminster Hospital, London. Assent was obtained from families prior to recruitment to the study. Data were prospectively collected in mechanically ventilated patients aged > 18 years and with a PaO_2 / FiO_2 ratio less than 40 kPa. All patients were emergency admissions to the ICU. Patient demographics and baseline characteristics of the study population are summarized in Table 3.2 and Table 3.3.

To evaluate the relationship of $V_D/V_{T\ phys}$, $\dot{V}CO_2$ and VR, simultaneous measurements were made of Pa_{CO_2}, $\dot{V}_E$, $V_D/ V_{T\ phys}$ and $\dot{V}CO_2$. Initial measurements were made following stabilization of the patient and within the first 24 hours

following admission to the ICU. Measurements were then made once daily until either six consecutive recordings had been made, or the patient had been weaned from the ventilator or died, whichever was the shorter period. For each set of measurements a note was made of the mode of ventilation; mandatory (SIMV or BIPAP) or spontaneous (CPAP). All modes of ventilation used non-bias flow triggering.

6.1.1.1 Measuring Deadspace

Physiological deadspace (V_D/V_T) was calculated using the CO_2SMO®Plus capnograph (Novometrix Medical Systems, Wallingford, USA). The CO_2SMO®Plus has a combined flow sensor and in-line capnograph that allows real-time simultaneous measurement of expiratory flow and expired CO_2 concentration. The expired CO_2 concentration is plotted against the expired volume to produce a simple single-breath test ($SBTCO_2$) waveform. The software programme Analysis Plus! for Windows (Novometrix Medical Systems, Wallingford, USA) was used to estimate values for physiological deadspace (V_D / V_T), using areas under the SBT-CO_2 waveform as described by Fletcher and colleagues (Figure 1.5A) (94).

As a form of internal validation for the study $V_D/V_{T\ phys}$ was estimated simultaneously using 2 methods. The second method used was the Douglas Bag method ($V_D/V_{T\ DB}$), where the mixed expired CO_2 ($P\bar{E}_{CO_2}$) was measured in the exhaust gas of the ventilator. The results of this study are detailed in Section 3.8 (Study 1).

$\dot{V}CO_2$ was measured using CO_2SMO®Plus capnography. VR was calculated from measured Pa_{CO_2} and $\dot{V}_E$ as recorded by the flow sensors of the ventilator (Evita XL, Draeger). Ideal body weight was estimated using the formula set by the ARDSnet group(89). A period of 10 minutes was allowed for patients to reach steady state before the readings were made.

6.1.1.2 Statistical Analysis

All readings were grouped together to examine the relationship between VR and $\dot{V}CO_2$ and V_D / V_T. A modified Pearson's correlation coefficient as described by Stratton and colleagues (135) was obtained to study the association between VR and V_D / V_T. This method was used to correct any bias in Pearson's correlation coefficient

as a result mathematical coupling because Pa_{CO_2} was used in computation of both VR and V_D / V_T. Multiple regression analysis was performed to evaluate the influence of V_D / V_T and $\dot{V}CO_2$ on VR.

$V_D / V_{T\,phys}$ was split into 3 categories according to clinical severity; normal: > 0.18 - < 0.51, moderate: > 0.51 - < 0.7 moderate, Severe: > 0.7 (72). Analysis of variance (ANOVA) was used to compare the mean values of VR in the V_D / V_T ordinal sub-groups. Logistic regression analysis was applied to examine predictive probabilities of VR. Unpaired t-test was used to compare means between readings in the groups.

From the previous chapter and other studies it was anticipated that $\dot{V}CO_2$ would be greater in spontaneously ventilating patients (133). Therefore for sub-group analysis readings were grouped depending on the mode of ventilation; mandatory or spontaneous. Fisher Z transformation test was used to compare correlation coefficients between subgroups. Paired t-test was used to compare variables between the 2 modes of ventilation within individuals.

In individuals where data was available for serial measurements in the same mode of ventilation a note was made of those readings where delta VR was greater than 10%. Delta values of V_D / V_T and $\dot{V}CO_2$ were also simultaneously noted. Changes in VR were apportioned to either V_D / V_T if the delta value was greater than 5% or $\dot{V}CO_2$ if the delta value was greater than 10% or both. (delta VR > 10%). A 5% change in change in V_D / V_T was considered a clinically significant change. A 10% change in $\dot{V}CO_2$ was considered a clinically significant change.

Statistical software STATA/IC 11.1 (StataCorp, USA) was used for data analysis. Graphs were constructed using Prism 5 for Mac OS X (Graphpad Software Inc, San Diego California USA, www.graphpad.com).

6.1.2 Results

48 patients (33 men and 15 women) were recruited to the study. In total 168 sets of daily readings were taken; 106 were taken whilst patients were in a mandatory mode of ventilation and 62 from patients in a weaning mode of ventilation. The median number of daily sets of readings per patient was 3 (range 2-6). The mean value of VR in all the readings was 1.97 (SD ± 0.82; range 0.79 – 5.4).

There was significant positive correlation between VR and V_D / V_T (modified correlation coefficient = 0.71, $p < 0.01$) in all readings (Figure 6.1). In comparison to mandatory modes of ventilation, readings in spontaneous modes of ventilation showed weaker correlation between VR with V_D / V_T (modified mandatory mode: modified r = 0.76, $p < 0.01$; spontaneous mode: modified r = 0.67, $p < 0.01$)(Figure 6.2A and 6.2B respectively). There was weak correlation between VR and $\dot{V}CO_2$ (r_p = 0.14, p = 0.08). Table 6.1 summarises the differences in respiratory variables during mandatory and spontaneous ventilation.

Multiple linear regression analysis was used to investigate the relative influence of V_D / V_T and $\dot{V}CO_2$ on VR. The analysis showed significant effect of V_D / V_T and $\dot{V}CO_2$ on VR (VR = - 2.37 + V_D / $V_{T\,phys}$ * 5.29 + $\dot{V}CO_2$ * 0.005; $p < 0.01$). In the model V_D / V_T had a greater effect on VR than $\dot{V}CO_2$ (standardized regression coefficients: V_D / V_T β = 0.85, $\dot{V}CO_2$ β = 0.37).

Table 6.2 shows the correlation values for VR and V_D / V_T within patients over time in all patients with five consecutive daily readings. In most cases the correlation coefficient between the two variables was greater in individuals than in the total readings pooled together.

Figure 6.3 shows VR values in different V_D / V_T ordinal sub-groups in readings taken in patients in mandatory modes of ventilation. One-way ANOVA showed that the mean values of VR in the groups were significantly different ($p < 0.01$). Concordance values obtained from logistic regression analysis was used to measure the association of predictive probabilities of VR and observed ordinal response of V_D / V_T measure. In mandatory modes of ventilation the concordance between VR and the ordinal

groups of V_D / V_T was 84.7% and in spontaneous mode of ventilation the concordance was 80.9%.

Comparison of paired values between mandatory and spontaneous modes of ventilation in 21 individuals showed that VR was significantly higher during spontaneous ventilation compared to mandatory ventilation (2.03 vs 1.73, $p < 0.01$). $\dot{V}CO_2$ was also significantly higher during spontaneous ventilation (210 $ml.min^{-1}$ vs 186 $ml.min^{-1}$, $p = 0.02$). There was no significant difference in V_D / $V_{T\ phys}$ between the 2 modes of ventilation (spontaneous 0.56 vs mandatory 0.57, $p = 0.48$).

In 57 paired readings a 10% increase in VR was observed whilst patients were in the same mode of ventilation. 37/57 (65%) of the changes were due to dead space alone. 7/57 (12%) were due to changes in $\dot{V}CO_2$ alone. 8/57 (14%) were due to changes in both variables, and in 5/57 (9%) of the readings the variables moved in the opposite direction.

6.1.3 Discussion

The principal aim of this study was to examine the relationship of VR, V_D/V_T, and $\dot{V}CO_2$ in mechanically ventilated patients in the ICU setting. Observations in these patients show that as anticipated VR is influenced by both $\dot{V}CO_2$ and V_D / $V_{T\ phys}$. There was reasonable correlation between VR and dead space. Linear regression modelling shows that in this population V_D / $V_{T\ phys}$ is more influential in predicting VR. In particular in patients in a mandatory modes of ventilation the correlation between VR and V_D / $V_{T\ phys}$ appears stronger. Correlation of VR with V_D / $V_{T\ phys}$ was also stronger in serial measurements within individual patients. VR was predictive of severity of dead space groups in 85% of the readings.

Ventilatory Ratio is a marker of the body to cope with the ventilatory demands of an individual. A rise in ventilatory demands would be as a result of either a rise in $\dot{V}CO_2$ or a rise in V_D / $V_{T\ phys}$ or both. The findings in this study show that in 79% of the patients changing values of VR was as a result of a change in dead space and in 65% of these cases this was exclusively due to changes in dead space. Ravenscraft

and colleagues have similarly shown that in mechanically ventilated patients $\dot{V}CO_2$ is less of a contributor than V_D/V_T in rising ventilatory demands encountered during respiratory failure (84). In sedated and ventilated patients in steady state it is anticipated that $\dot{V}CO_2$ will remain relatively stable and this has been observed in Study 5 in chapter 5. In such patients the changes seen in VR are much more likely to be as a result of changes in V_D / $V_{T\ phys}$. The improved correlation and predictive power of VR in patients in mandatory modes of ventilation substantiates this.

The results from this study show that $\dot{V}CO_2$ was greater when patients were spontaneously ventilating and VR was also greater in these patients. The described mathematical model of VR is similar to the physiological relationship of $\dot{V}_A$, $\dot{V}CO_2$, and Pa_{CO_2} described by Nunn (85). As $\dot{V}CO_2$ increases the isopleth describing the relationship of $\dot{V}_A$ and Pa_{CO_2} shifts upwards. Once a patient reaches steady state, i.e. they are established on an isopleth subsequent changes in VR over time could continue to be utilized as effective tool to monitor efficiency regardless of the mode of ventilation. As a result of the increased variability in $\dot{V}CO_2$ in spontaneous ventilation however its absolute value may be more difficult to interpret in this setting.

Improved correlation between VR and V_D / $V_{T\ phys}$ over repeated measures in the same patient suggest that VR is more reliable as a marker of ventilatory efficiency within individuals (Table 6.2). Figure 6.4a to 6.4e illustrates changes in VR with corresponding changes in $\dot{V}CO_2$ and V_D / $V_{T\ phys}$ in 5 selected patients. Visual analysis of these graphs show that within individuals VR behaves as would be anticipated given the respective changes in the 2 variables exerting influence on ventilatory demands.

The findings of the study also show that VR has good predictive value of categorizing patients into subgroups according to severity of their dead space abnormality (Figure 2). These findings add strength to the argument that VR could be used as a clinical tool to assess ventilatory efficiency.

It is worth restating that VR is not an absolute measure of deadspace. The premise of VR is that it should allow clinicians a relatively quick method of tracking the ability of the lungs to cope with the body's ventilatory demands. Provided there has been no change in the ventilatory strategy, in a patient in steady state a change in VR is likely to indicate a change in ventilatory efficiency. If there was no evidence of altered dead space then the changes seen would most likely be as a result of changing $\dot{V}CO_2$. As seen from the study 5 large changes in $\dot{V}CO_2$ are rare. The use of the predicted values for minute ventilation and Pa_{CO_2} allows comparison within patients over time and across populations. Whilst VR may be a relatively crude measure of ventilatory efficiency it has potential to allow clinicians to use the concept of dead space in day-to-day practice with considerable ease.

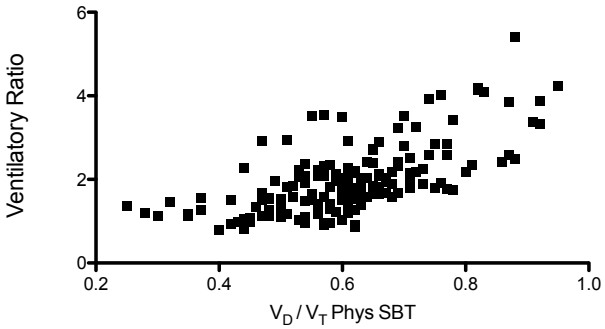


Figure 6.1 Ventilatory ratio plotted against $V_D / V_{T\,phys}$ in all readings using the single-breath test. The results demonstrate the asymptotic relationship of the 2 variables. The results are from Study 6.

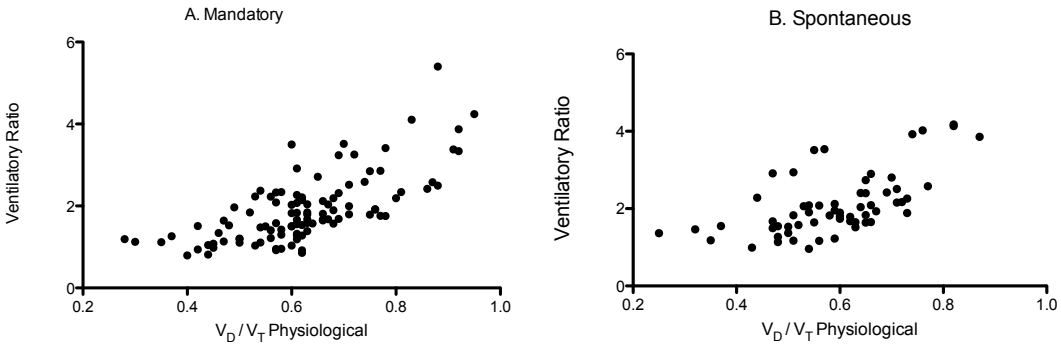


Figure 6.2 Ventilatory ratio plotted against $V_D / V_{T\,phys}$ in readings taken in mandatory (Figure 6.2A) and Spontaneous (Figure 6.2B) modes of ventilation. The results are from Study 6.

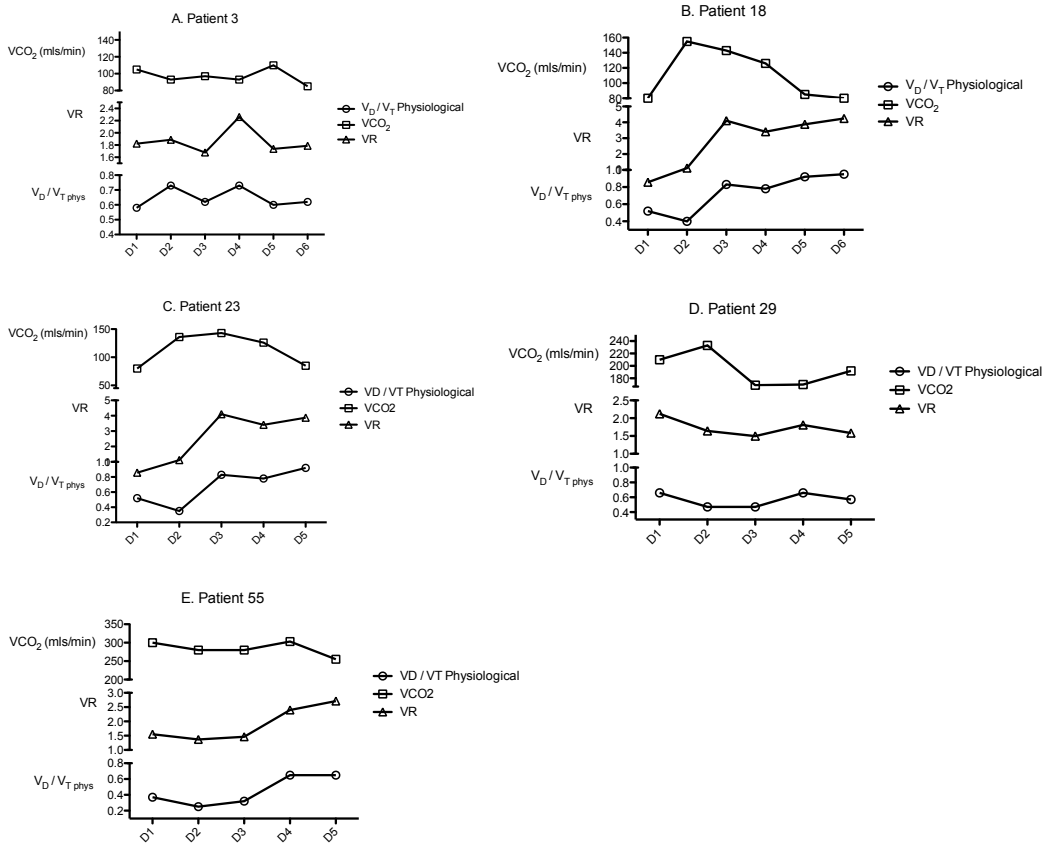


Figure 6.3. Shows VR, $\dot{V}CO_2$, and V_D / $V_{T\ phys}$ plotted over the course of time in 5 patients. The Y-axis is scaled according to the individual patients to show changing values of VR within patients and the Y-axis is not consistent between the graphs. Figure 6.3A Patient 3 with intra-abdominal sepsis and ventilator associated pneumonia. Figure 6.3B Patient 18 with sepsis and pulmonary oedema. Figure 6.3C Patient 23 with necrotizing fasciitis that develops ARDS. Figure 6.3D Patient 29 with cardiac arrest and acute pulmonary oedema. Figure 6.3E Patient 55 develops ARDS following emergency small bowel resection. The results are from Study 6.

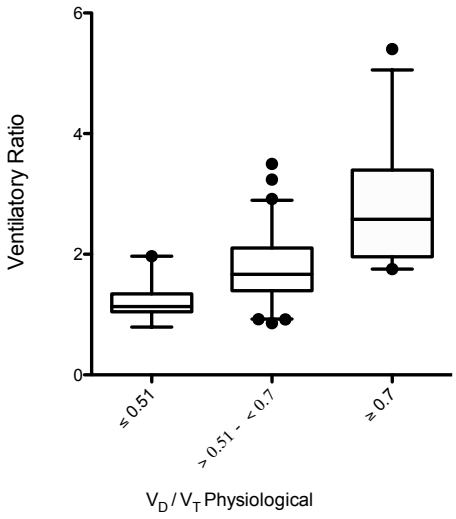


Figure 6.4 V_D / $V_{T\ phys}$ categorized into subgroups in readings taken in a mandatory mode of ventilation (n = 106). Middle bar represents the mean values and the bars above are below represents 95% confidence interval ($p < 0.01$). The results are from Study 6.

	Mandatory Mode	**Spontaneous Mode**	**p-value**
VR	1.9 (± 0.83)	2.09 (± 0.80)	0.15
V_D / V_T	0.62 (± 0.13)	0.59 (± 0.12)	0.10
$\dot{V}CO_2$ (mls.min^{-1})	186 (± 57.3)	219 (± 68.2)	< 0.01
VE (l.min^{-1})	10.3 (± 3)	13.1 (± 4)	< 0.01
$PaCO_2$	6.1 (± 1.3)	5.3 (± 1.5)	< 0.01

Table 6.1 Mean values of measured and calculated variables. Values in the brackets show standard deviations. P-values were derived using unpaired T-test.

Patient number	r
3	0.96
4	0.79
5	0.97
13	0.94
14	0.94
17	0.95
19	-0.64*
23	0.95
24	0.71
29	0.96
37	0.90
49	0.75
55	0.99

Table 6.2 Shows the correlation coefficients (corrected Pearson's r) between VR and V_D / $V_{T\,phys}$ in individual patients with readings for 5 days or more. (* represents a patient where V_D / $V_{T\,phy}$ remained relatively stable and the variation in $\dot{V}CO_2$ was greater). All coefficient value were statistically significant.

6.2 Study 7: The Influence of Physiological Dead Space and CO_2 Production on Ventilatory Ratio- A Retrospective Study

A larger database was available to analyse the relationship of physiological deadspace, $\dot{V}CO_2$ and VR. Patients in this study were the same as Study 5. Outlined briefly is a refresher of the methods used to collect data and the analysis protocol. The conditions in which data was acquired were uncontrolled. Neither the timings of the arterial blood gas sample nor the measurements of minute ventilation were regulated. These data could not be used for precise extrapolation or analysis. The purpose of the study was to examine trends in the relationship of VR, V_D / V_T, and $\dot{V}CO_2$.

6.2.1 Methods

The observational study involved retrospective analysis of prospectively collected data. The setting of the study was a single-centre mixed medical-surgical adult ICU at Chelsea and Westminster Hospital, UK. Mechanically ventilated patients anticipated to require prolonged intubation or with acute respiratory failure are routinely monitored with volumetric capnography during the first week of ventilation at the study centre. Permission was granted from the local institutional ethics board to analyse the data retrospectively. All patients were ventilated with Evita XL ventilator (Draeger, Leubeck, Germany).

Patients were attached to the NICO capnograph within 24 hours of their admission to the ICU. $\dot{V}CO_2$ was recorded hourly at a point when the patient was undisturbed and free from nursing and medical intervention for at least 5 minutes; as is the policy for recording all vital signs on the ICU chart. Values for mixed expired CO_2 ($P\bar{E}_{CO_2}$) as calculated by the NICO monitor were also recorded hourly.

Values recorded for the hour where arterial PCO_2 was measured were used for analysis in the study. Values of Pa_{CO_2} and $P\bar{E}_{CO_2}$ recorded were used to calculate dead space using the Enghoff modification of the Bohr equation. The recorded hourly value for minute ventilation was used to calculate VR.

6.2.1.1 Statistical Analysis

To recreate the graph in Figure 4.4A, three arbitrary but clinically distinct ordinal groups were created according to $\dot{V}CO_2$. The readings were grouped as follows $\dot{V}CO_2$ 125 ± 15 ml.min^{-1}, 175 ± 15 ml.min^{-1}, and 225 ± 15 ml.min^{-1}. ANOVA was used to examine the differences in mean VR values between the 3 groups.

The data were analysed for simple pattern recognition only. Graphs were constructed to examine the relationship of VR with the 2 other measured variables to elicit patterns.

6.2.2 Results

528 readings in 25 mechanically ventilated patients were available for analysis where data was available for $\dot{V}CO_2$ and for calculation of deadspace and Ventilatory Ratio. Of these 230 readings were whilst patients were in a mandatory mode of ventilation, and 298 were whilst patients were in a spontaneous mode of ventilation. Figure 6.5a and 6.5b shows VR plotted against V_D/V_T in readings in mandatory and spontaneous modes of ventilation respectively. The two variables were significantly correlated in both modes of ventilation with stronger correlation in mandatory mode (Pearson r = 0.78, $p < 0.01$) than spontaneous mode of ventilation (Pearson r = 0.54, $p < 0.01$). Figure 6.6 shows VR plotted against V_D/V_T with readings grouped according to $\dot{V}CO_2$. ANOVA showed the mean VR to be significantly different between the 3 groups ($p < 0.01$).

6.2.3 Discussion

The results from the retrospective analysis of routine ICU data show that VR has an asymptotic relationship with dead space in mandatory modes of ventilation. The correlation between the variables is stronger when patients were in mandatory modes of ventilation in comparison to spontaneous modes of ventilation. As anticipated higher $\dot{V}CO_2$ was associated with higher VR for a given value of V_D/V_T.

There are several limitations to this study and therefore few conclusions can be reached. The large number of measurements do however allow for observation of

patterns of the relationship of VR with $\dot{V}CO_2$ and V_D/V_T. One of the major shortcomings of the study was that the results were collected as part of routine monitoring and no active measures were taken to ensure that the patients were in steady state. This may account for the poor correlation between VR and deadspace during spontaneous ventilation. The timings of the ventilatory recordings were ad-hoc in relation to arterial blood gases.

Figure 6 shows the relationship of VR with physiological deadspace in the three ordinal groups of $\dot{V}CO_2$. The figure illustrates the relationship is as anticipated. Higher $\dot{V}CO_2$ resulted in higher VR for a given V_D/V_T. In the context of the limitations of this study the graph is a crude representation of the figures 4.4A observed in study 3.

It is interesting to note that there was poorer correlation between VR and V_D/V_T in readings taken in spontaneous modes of ventilation. In particular the observed relationship was vastly different in this study compared to those observed in study 6. Aside from the timing of the collection of arterial blood gas sample, expired minute ventilation recorded on ICU charts is more likely to be idiosyncratic in patients breathing in spontaneous modes of ventilation. This could therefore easily lead to inaccuracies in calculating VR. This particularly highlights the need for a period to attain steady state before using the measured minute ventilation to calculate VR as was the case in study 6. Secondly, as demonstrated in the previous chapter there is increased variability in $\dot{V}CO_2$ in spontaneously breathing patients therefore a longer period to achieve steady state may be more appropriate before recording arterial blood gas samples.

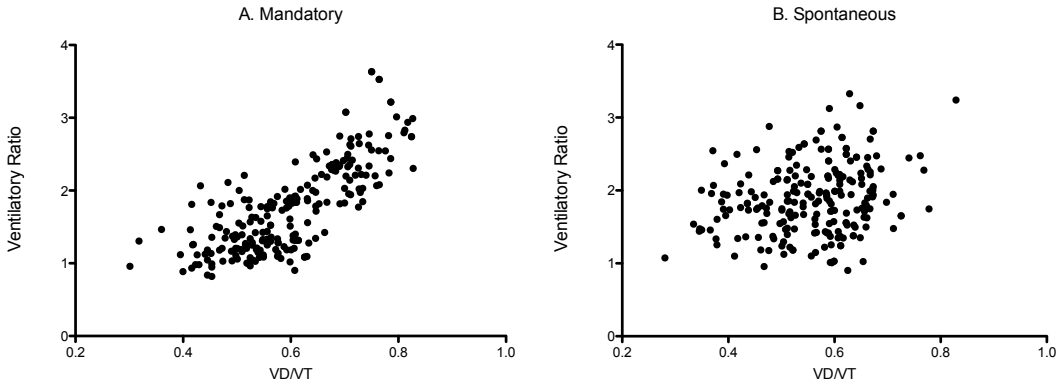


Figure 6.5 Ventilatory ratio plotted against V_D / $V_{T\ phys}$ in readings taken in mandatory (Figure 6.5A) and Spontaneous (Figure 6.5B) modes of ventilation. The results are from Study 7.

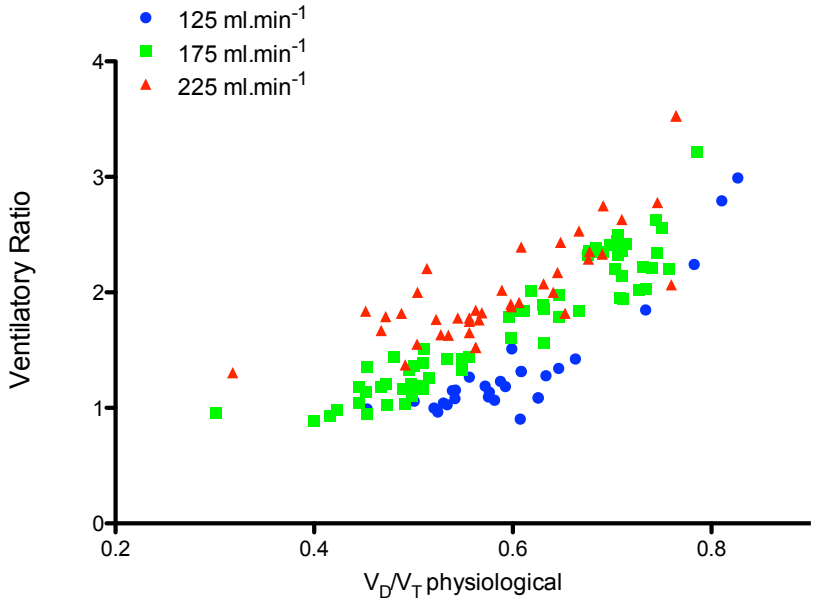


Figure 6.6 Ventilatory ratio plotted against V_D / $V_{T\ phys}$ with readings categorized into groups according to $\dot{V}CO_2$. The $\dot{V}CO_2$ were grouped as follows 125 ± 15 mls, 175 ± 15 mls, 225 ± 15 mls.

6.3 Chapter Summary

In summary, the results from this chapter validate the physiological analysis of VR presented in chapter 2. Ventilatory Ratio is an intuitive and easy to calculate index. In mandatory modes of ventilation VR strongly correlates with V_D / V_T and is able to predict the degree of abnormality. The values of VR in spontaneously ventilating did not correlate with physiological deadspace as well. Within individual patients changes in VR strongly correlates with changes in V_D / $V_{T\ phys}$. VR may be a simple and clinically useful tool for monitoring, prognostication, and researching ventilatory

efficiency in mechanically ventilated patients in steady state. Further analyses are required to assess its clinical utility in the ICU population. These are examined in the following chapter.

Chapter 7: Examination of Ventilatory Ratio as a Clinical Tool

7.1 Introduction

In previous chapters we have discussed in detail the physiology behind the derivation of VR. We have also looked at the factors influencing VR both in models and in mechanically ventilated patients. The real imperative for an index such as VR is to provide information that is clinically useful and different to what is already available at the bedside. We know that VR gives us an idea about efficiency of ventilation. This could help categorise disease severity in patients with respiratory failure and ARDS. Current methods for categorizing patients using PaO_2 / FiO_2 already exist; however VR could provide additional and different information. The objective of this chapter is to examine the use of VR as a clinical tool in 4 different databases.

To demonstrate clinical efficacy of VR we need to show:

- An association with mortality
- That it changes over time and this may reflect in changes in outcome
- That it is different from existent indices
- That it has similarities with other indices of ventilatory efficiency

In chapter 3 the methods of collecting the databases has been described. The methods section of each of the databases listed below outlines the protocol for analysis of the database.

7.2 Royal Brompton Hospital Database

7.2.1 Methods

Permission was granted from the local ethics committee to analyse the data. Data were available for demographics, admission diagnosis and co-morbidities, respiratory variables, and arterial blood gas results. All patients included in the analysis were above the age of 18. In order to capture data for individuals of interest, only data for those patients mechanically ventilated for 5 days or more were included in the analysis. Low tidal volume ventilation was in practice during the period of database collection at the institution. Most patients were considered to be in mandatory modes of ventilation if they had less than five spontaneous breaths per minute whilst they were in SIMV or BIPAP modes. Conversely spontaneous ventilation was considered if patients were managed with pressure support ventilation only.

The first blood gas sample of an admission was not used for analysis as this may have been a representation of the conditions surrounding intubation or the pre-intubation state. The second blood gas sample was used for the admission sample as this was more likely to representative of the lungs in steady state. The respiratory and ventilatory data at this time-point was considered as admission data (unless the subsequent ABG sample was > 4 hours later, in which case the first sample-point was considered as admission data). Subsequently, daily data recorded at the time of the ABG sample between 0500 – 1000 hours were used for analysis. Daily data was recorded until discharge from ICU or death. Laboratory blood results and APACHE II scores were not available for analysis.

Primary end-point was considered as death prior to ICU discharge. Ventilator days were used as a secondary outcome measure. Patients were considered free of mechanical ventilation if they were no longer receiving pressure support ventilation.

For comparison of VR with patients with lower clinical acuity, data were analysed for ventilated patients undergoing routine cardiac surgery admitted to the cardiac ICU. These patients were considered the control group. All patients in the control group were free from mechanical ventilation on either day 1 or day 2.

For subgroup analysis the study group were split into survivors and non-survivors. In addition the survivors group were further sub-divided into those with an admission VR of greater or equal to 1.4 and those with an admission VR < 1.4. The value of 1.4 was chosen as the cut off as this was population mean. These groups were used assess the association of VR with ventilator days.

To study the pattern of VR over time and its effect on outcome, VR for individual patients was plotted along time whilst they were in a mandatory mode of ventilation. Patients were excluded for analysis if there was a change in VR over time was less than 10%, the highest VR was less than 1.2, and there were less than three readings whilst the patient was in a mandatory mode of ventilation.

The behaviour of VR during the transition from mandatory to spontaneous modes of ventilation was examined in 349 survivors. Delta VR was described as the first VR value during spontaneous ventilation subtracted from the VR value immediately before during mandatory ventilation ($VR_{mandatory} - VR_{spontaneous}$). The percentage change in VR at this point was calculated. To compare the effects of changing values of VR the population was then split in to two groups: those with delta VR greater than or equal to 30% and those where delta VR was less than 30% (n = 227) at the transition point.

7.2.1.1 Statistical Analysis

Normally distributed continuous data are expressed as mean and standard deviation. Non-parametric data are expressed as median and interquartile range. Unpaired t-test was used for intergroup comparison of means and Mann-Whitney test was used to compare medians for non-parametric data. Multiple comparisons of means of groups were made using one-way analysis of variance. Univariate logistic regression analysis was used to calculate odds ratios for multiple respiratory variables to individually predict mortality. To examine the relationship of hospital mortality and VR and adjusting for confounding variables multivariate logistic regression analysis was also performed. Stepwise multiple logistic regression analysis was performed to determine the prognostic value of ventilatory ratio after adjustment for non-pulmonary outcome modifiers.

Kaplan-Meier curves were constructed to examine the association of VR sub-groups and outcome (survival and ventilator days < 30 days). Log-Rank Test was used to compare curves of the groups and hazard ratios were calculated.

7.2.2 Results

Complete data was available for 14967 individual data time-points in 497 patients. Of these, 380 were admitted to the adult ICU following post-operative problems. 117 patients were directly admitted from the wards or transferred from other centres. Table 7.1 summarises the primary admission diagnoses of the study group.

Data was analysed for a further 86 patients that underwent routine cardiac surgery and were admitted to the cardiac ICU. This group served as a control group. There were no mortalities in this group. Mean values for VR on admission were significantly higher in the study group compared to the control group (Study group 1.44, 95% CI 1.39 – 1.49 vs control group 1.02, 95% CI 0.98 – 1.06; $p < 0.01$). The differences in baseline characteristics in these groups are summarized in table 7.2.

Data on outcomes was available on 479 patients in the study group. Outcome data on 18 patients was unavailable because they were transferred to another hospital whilst still on ventilatory support. 358 (74.7%) patients in the study group survived until ICU discharge and 121 (25.3%) died whilst in ICU. Differences in demographic data and respiratory variables between survivors and non-survivors are presented in Tables 7.3 and 7.4 respectively.

Figure 7.1 shows a histogram of the admission values for VR in the study group. The range of value for VR at admission in this population was 0.6 – 5.4. Values for VR on admission were significantly higher in non-survivors compared to survivors (survivors 1.72 CI 1.58 – 1.85, non-survivors 1.33 CI 1.29 – 1.38; $p < 0.01$)(Figure 7.2). Mean value of VR was significantly higher in patients with a diagnosis of ALI / ARDS (n = 69) in comparison to the rest of the population (ARDS 2.02 CI 1.8 – 2.2, Non-ARDS 1.30 CI 1.26 – 1.34, $p < 0.01$). Mean values of VR were also higher in patients with a past medical history of COPD (n = 69) regardless of the admission diagnosis (COPD 1.71 CI 1.54 – 1.84, Non-COPD 1.34 CI 1.29 – 1.39; $p < 0.01$).

There were no significant differences in mean value of VR with patient gender (Male 1.41 vs Female 1.45, p = 0.40).

Alongside VR, $PaCO_2$, FiO_2, mean airway pressure (MawP), and peak inspiratory pressure (PIP) were significantly higher in the non-survivors group compared to the survivors group on day 1 (Table 7.4). Univariate logistic regression analysis with mortality as outcome showed VR to be an independent predictor of outcome on day 1 (OR 2.74, CI 1.81 – 4.15), day 2 (OR 2.73, CI 1.66 – 4.48), and day 3(OR 1.88 CI 1.08 – 3.14). Table 7.5 summarises the findings of univariate logistic analysis of other respiratory variables with mortality as outcome. Stepwise logistic regression analysis adjusting for PEEP, PIP, and OI showed that VR remained an independent predictor of outcome on day 1 and day 2 (Table 7.6). VR also remained an independent predictor of outcome after adjusting for COPD (OR 2.84 CI 1.84 – 4.4).

In subgroup analysis of patients with respiratory failure (defined as a PaO_2 / FiO_2 ratio of less than 40 kPa, n = 292) VR was significantly higher in non-survivors (n = 77) compared to survivors (n = 215) (1.75 vs 1.45, $p < 0.01$). Univariate logistic regression analysis showed that VR remained an independent predictor of mortality on day 1 (OR 2.75, CI 1.7– 4.5), day 2 (OR 2.59, CI 1.5 – 4.6), and day 3 (OR 1.89, CI 1.0 – 3.6).

To further analyze the ability of VR at admission to predict disease severity, ventilator days was used as a surrogate. Amongst survivors VR was greater or equal to 1.4 in 108 patients and less that 1.4 in 215. Kaplan-Meier curves were constructed to examine ventilator days in the 2 groups with the end-point being 30 days of mechanical ventilation (Figure 7.3). The median ventilation time was 16 days for the < 1.4 group and 19 days for the ≥ 1.4 group. The hazards ratio for mechanical ventilation for greater than 30 days for the ≥ 1.4 group was 1.36 (CI 1.02 – 1.75).

In total 306 patients that were included for analysis of VR over time. Values of VR were plotted against time and the gradient of the slope of each of the curves were calculated. The patients were split in to groups according to those with a positive slope and the gradient between the first and last point ≥ 0.2 (n = 112) and those with a neutral or negative slope and / or gradient of < 0.2 between the first and last point (n =

194). In the ≥ 0.2 gradient group 53 (47.3%) patients died and 59 (52.7%) patients survived. In the < 0.2 gradient group 36 (18.6%) patients died and 158 (81.4%) ($p < 0.01$).

All readings from all patients were pooled together to assess the relationship of individual respiratory variables on VR (n = 14966). The findings are summarized in Table 7.8. There was weak negative correlation between VR and indices of oxygenation. Figure 7.4 shows the relationship between VR and PaO_2 / FiO_2 ($r = -0.29$). The correlation between these two variables was stronger on day 1 ($r = -38$, $p < 0.01$).

Across all readings mean value of VR was significantly higher in patients during spontaneous modes of ventilation compared to those breathing in mandatory modes of ventilation (Mandatory 1.522 ± 0.63 vs Spontaneous 1.68 ± 0.62, $p < 0.01$). Within individuals, data for comparison in both mandatory and spontaneous modes of ventilation were available in 373 patients. In 145 of these patients VR was significantly higher during spontaneous ventilation.

At the transition point from mandatory to spontaneous ventilation there were 122 patients where delta VR was ≥ 30% and 227 patients where delta VR was < 30%. The median ventilator days in those where delta VR ≥ 30% was significantly greater than those patients where VR < 30% (≥ 30% group median ventilator days: 8, IQR 4-17, < 30% group: 4, IQR 2 – 8.5; $p < 0.01$, Figure 7.5).

Diagnosis	n (%)
Cardiovascular Insufficiency	**156 (31.4)**
Cardiogenic shock	92 (18.5)
Ventricular Failure	31 (6.2)
Cardiac Tamponade	18 (3.6)
Malignant Arrhythmia	9 (1.8)
Acute Myocardial Infarction	3 (0.6)
Pericardial Effusion	3 (0.6)
Respiratory Insufficiency	**155 (31.2)**
ALI / ARDS	43 (8.7)
Lower Respiratory Tract Infection	41 (8.3)
Acute Pulmonary Oedema	35 (7.0)
Difficult respiratory wean	13 (2.6)
Exacerbation of COPD	13 (2.6)
Massive Haemothorax	5 (1.0)
Bronchopleural Fistula	4 (0.8)
Pneumonitis	1 (0.2)
Cardiorespiratory Arrest	**58 (11.7)**
Cardiac Arrest	55 (11.1)
Respiratory Arrest	3 (0.6)
Peri / Post-operative Major Haemorrhage	**58 (11.7)**
Miscellaneous	**70 (14.1)**
Multi-organ Dysfunction	20 (4.0)
Neurological Complications	20 (4.0)
Sepsis	14 (2.8)
Acute Renal Failure	6 (1.2)
Routine Cardiovascular Monitoring	6 (1.2)
Gastrointestinal Complications	4 (0.8)

Table 7.1 ICU admission diagnosis of the study group.

	Study Group (n = 497)	Control Group (n = 83)	p values
Sex Male	316 (64%)	59 (71%)	0.19§
Age	63.4 ± 15.7	62.0 ± 15	0.44
Weight	76.2 ± 14.4	74.1 ± 17	0.28
Height	171 ± 8.5	169 ± 10	0.11
PaO_2 / FiO_2 Ratio	34.4 ± 15.6	43.4 ± 16	< 0.01
Ventilatory Ratio	1.4 ± 0.6	1.0 ± 0.2	< 0.01

Table 7.2 Comparison of key variables between study and control group. P values are for unpaired T-test for continuous variables. § P-value for Chi-square test.

	Survivors (n = 358)	Non-Survivors (n = 121)	P values
Sex Male	231 (61.1%)	73 (50.3%)	0.69§
Age (years)	64.5 ± 14.9	60.9 ± 17.4	0.03
Weight (Kg)	75.7 ± 17.4	69.0 ± 14.6	< 0.01
Height (cm)	169.7 ± 9.7	168.1 ± 9.5	0.11

Table 7.3 Comparison of demographic data between survivors and non-survivors. P values are for unpaired T-test for continuous variables; § Chi-square test.

	Survivors (n = 358)	Non-Survivors (n = 121)	p Values
Minute Ventilation ($l.min^{-1}$)	7.8 ± 0.1	7.8 ± 0.2	0.88
$PaCO_2$ (kPa)	5.6 ± 0.1	7.0 ± 0.3	< 0.01
Ventilatory Ratio	1.3 ± 0.07	1.7 ± 0.02	< 0.01
PaO_2 (kPa)	16.5 ± 0.4	17.7 ± 0.8	0.11
FiO_2	0.51 ± 0.01	0.58 ± 0.02	< 0.01
PaO_2/FiO_2 Ratio	35.1 ± 0.82	33.0 ± 1.5	0.21
PEEP (cmH_2O)	5 (5 – 7)	5 (5 – 7.75)	0.80*
Mean Airway Pressure	11 (10 – 15)	13 (10.25 – 18)	< 0.01*
Peak Inspiratory Pressure (cmH_2O)	28 (24 – 32)	30 (25 – 36)	< 0.01*
Oxygenation Index ($cmH_2O.kPa^{-1}$)	50.1 ± 2.2	67.1 ± 6.3	< 0.01

Table 7.4 Comparison of respiratory variables between survivors and non-survivors. P values are for unpaired T-test for continuous variables; * Mann-Whitney Test.

	Odds Ratio	CI	p value
Ventilatory Ratio	2.74	1.81 – 4.15	< 0.01
$PaCO_2$ (kPa)	1.26	1.20 – 1.54	< 0.01
Minute Ventilation ($ml.min^{-1}$)	1.01	0.91 – 1.13	0.80
Peak inspiratory pressure (cmH_2O)	1.06	1.02 – 1.10	0.02
Oxygenation Index ($cmH_2O.kPa^{-1}$)	1.02	1.01 – 1.05	< 0.01
Mean Airway Pressure (cmH_2O)	1.04	1.01 – 1.07	< 0.01
PaO_2 / FiO_2 Ratio	0.99	0.98 – 1.01	0.31
PEEP (cmH_2O)	0.99	0.97 – 1.01	0.67

Table 7.5 Odds ratio derived from univariate analysis of individual respiratory variables on day 1 with mortality as the outcome (n = 479).

	Day 1		Day 2	
	Odds Ratio	CI	Odds Ratio	CI
Ventilatory Ratio	2.20	1.28 – 3.61	2.04	1.17 – 3.57
PIP (cmH_2O)	1.03	0.99 -1.08	1.04	1.00 – 1.08
PEEP (cmH_2O)	0.93	0.84 – 1.04	0.92	0.83 – 1.03
Oxygenation Index ($cmH_2O.kPa^{-1}$)	1.00	1.00 – 1.01	1.01	1.00 – 1.01

Table 7.6 Stepwise multiple logistic regression analysis of respiratory variables with mortality as the outcome in all patients in the study group. Results in the table are from analysis using data from day 1 and day 2.

	Day 1		Day 2	
	Odds Ratio	CI	Odds Ratio	CI
Ventilatory Ratio	1.89	1.1 – 3.3	1.88	0.99 – 3.6
PIP (cmH_2O)	1.06	1.0 -1.1	1.05	0.99 – 1.1
PEEP (cmH_2O)	0.94	0.84 – 1.1	0.94	0.83 – 1.06
Oxygenation Index ($cmH_2O.kPa^{-1}$)	1.01	1.0 – 1.02	1.01	0.99 – 1.01

Table 7.7 Stepwise multiple logistic regression analysis of respiratory variables with mortality as the outcome in patients with respiratory failure as defined by PaO_2 / FiO_2 ratio of less than 40 kPa (n = 292). Results in the table are from analysis using data from day 1 and day 2.

	Correlation Coefficient	p Value
PaO_2 (kPa)	- 0.19	< 0.01
PaO_2 / FiO_2 Ratio (kPa)	- 0.33	< 0.01
Mean Airway Pressure (cmH_2O)	0.33*	< 0.01
Peak Inspiratory Pressure (cmH_2O)	0.29*	< 0.01
Peak End Expiratory Pressure (cmH_2O)	0.14*	< 0.01
Dynamic Compliance ($ml.cmH_2O^{-1}$)		
Oxygenation Index ($cmH_2O.kPa^{-1}$)	0.03	< 0.01

Table 7.8 Correlation coefficient for VR and other respiratory variables. * Represents Spearman's correlation coefficient. All other values are Pearson's correlation coefficient. There are a total of 14966 readings used for analysis.

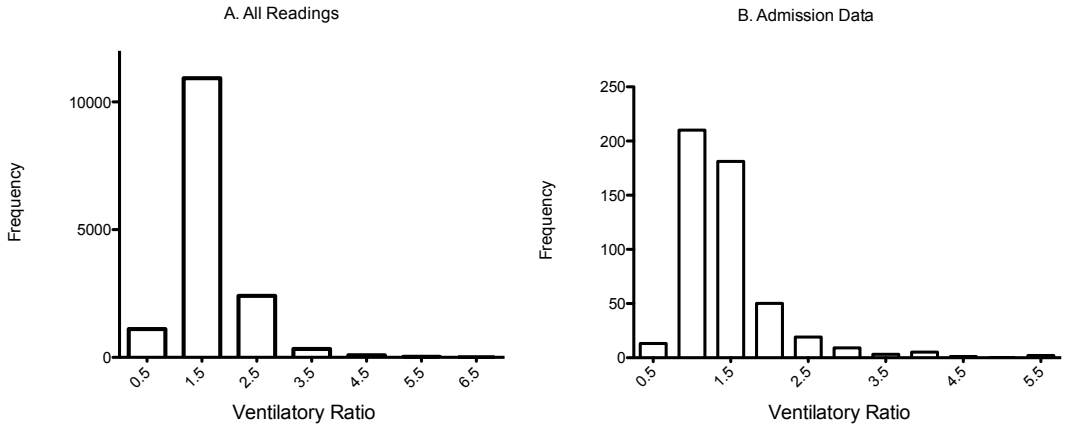


Figure 7.1 Frequency distribution of VR in the study group. 1A Frequency distribution in all readings. 1B Frequency distribution in readings taken at admission only.

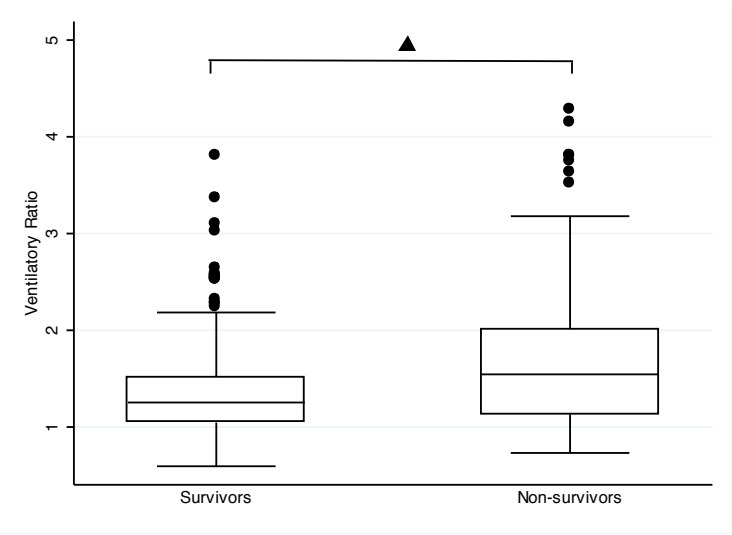


Figure 7.2 Comparison of Ventilatory Ratio between survivors and non-survivors ($p < 0.01$ unpaired t-test).

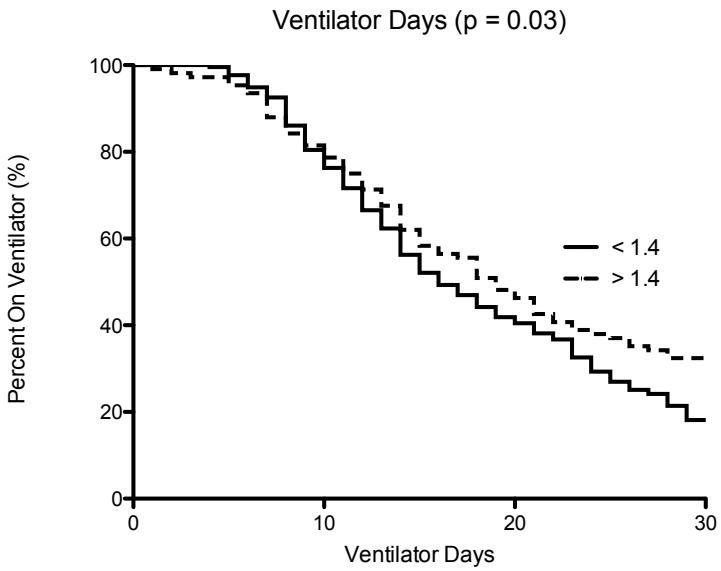


Figure 7.3 Kaplan-Meier curve for ventilator days in survivors in the study group. The groups were divided into those with VR ≥1.4 and those with VR < 1.4 at admission. Log-rank test showed the curves are significantly different ($p < 0.01$).

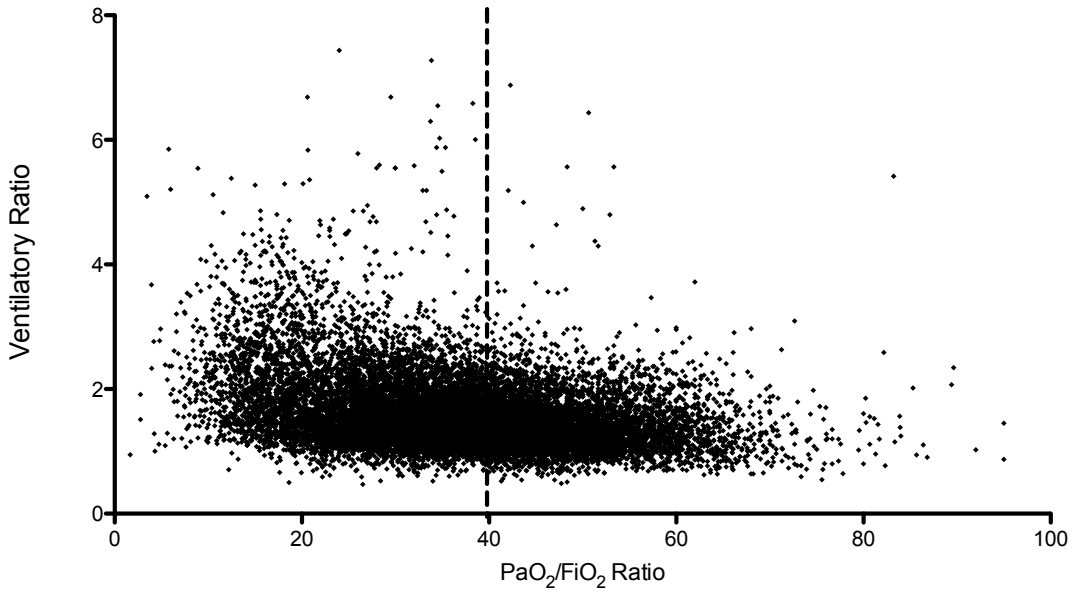


Figure 7.4 Ventilatory Ratio plotted against PaO_2 / FiO_2 Ratio. The dotted line represent the point on the axis that is the variable defining criteria for acute lung injury. There are a total of 14966 readings used for analysis.

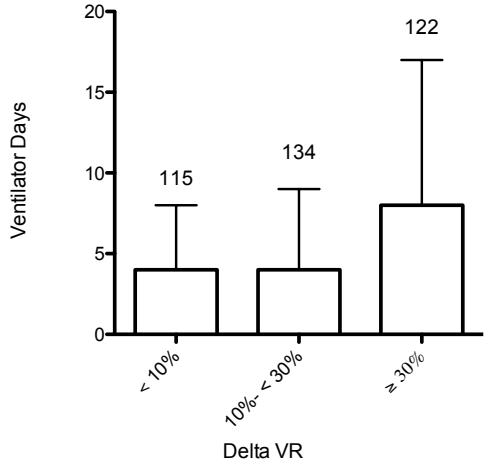


Figure 7.5 Ventilatory days in ordinal groups of delta VR at the transition point from mandatory to spontaneous ventilation. ($p < 0.01$, Kruskal-Wallis test). Values at the top of the bar represented total numbers in each group.

7.3 Chelsea and Westminster Database

7.3.1 Methods

Permission was granted from the local ethics committee to analyse the database. This database was collected in real time. Similar to the database described above arterial blood gas (ABG) samples were used to calculate VR and PaO_2 / FiO_2 ratio. The data for respiratory variables at the time of ABG were recorded and collected for analysis. As routine practice hourly data is recorded on ICU charts ensuing a short period from when the patient has been free from nursing and / or medical intervention. The second blood gas after admission was used as the admission time-point to allow the patient to reach steady state. This was considered more likely to represent the ventilation and clinical state of the lungs. The first blood gas measurement after intubation was discarded as it may be representative of conditions surrounding intubation. Subsequently daily measurements were recorded / calculated using the first ABG measurements between 0500 – 1000 hours. The specifications for mandatory and spontaneous modes of ventilation were similar to those described in the previous database. Low tidal volume ventilation was routinely practiced at this intensive care unit during the period of data collection. Daily data was recorded until the patient was discharged from ICU.

In order to compare VR values for ICU patients and patients undergoing elective surgery VR was calculated for 26 patients undergoing elective gastrointestinal surgery. Data for this study was available from part of another larger study looking at respiratory mechanics during laparoscopic surgery. The blood gas was taken 20 minutes after induction of anaesthesia prior to introduction of pneumoperitoneum. All of these patients were extubated post-operatively and none required prolonged mechanical ventilation. For subgroup analysis patients were split into survivors and non-survivors. In addition the survivors group were further sub-divided into those with an admission VR of greater or equal to 1.4 and those with an admission VR < 1.4. These groups were used to test the association of VR with ventilator days.

Data during the transition from mandatory to spontaneous modes of ventilation was available in 71 survivors. Delta VR was described as the first VR value during spontaneous ventilation subtracted from the VR value immediately before during mandatory ventilation ($VR_{mandatory} - VR_{spontaneous}$). Due to the small number of patients

available for analysis the population was divided into those with delta VR greater than to zero and those where delta VR was less than or equal to zero.

7.3.1.1 Statistical Analysis

Normally distributed continuous data are expressed as mean and standard deviation. Non-parametric data are expressed as median and interquartile range. Unpaired t-test was used for intergroup comparison of means and Mann-Whitney test was used to compare medians for non-parametric data. Multiple comparisons of means of groups were made using one-way analysis of variance. Univariate logistic regression analysis was used to calculate odds ratios for multiple respiratory variables to individually predict mortality. To examine the relationship of hospital mortality and VR and adjusting for confounding variables multivariate logistic regression analysis was also performed. Stepwise multiple logistic regression analysis was performed to determine the prognostic value of ventilatory ratio after adjustment for non-pulmonary outcome modifiers.

Kaplan-Meier curves were constructed to examine the association of VR sub-groups ventilator days (admission to 30 days). Log-Rank Test was used to compare curves of the groups and hazard ratios were calculated.

7.3.2 Results

Data were captured on 224 patients. 106 (47.5%) patients were females and 117 patients were male. Table 7.9 compares salient baseline variables between this population and patients that underwent routine elective surgery (control group). Similar to the previous database VR was significantly higher in the ICU population compared to theatre patients (ICU mean VR 1.4, CI 1.33 – 1.47; theatre mean VR 0.99, CI 0.91 – 1.08). Comparison of key variables between the 2 variables is presented in Table 2.1. Subsequent results presented are of the ICU population only.

The admission diagnoses of the ICU patients are summarized in Table 7.10. Figure 7.6 shows the frequency distribution of VR in the population. The mean value of VR on admission was 1.4 (range 0.70 – 3.49). 39 patients had underlying COPD. Values on admission were higher for these patients compared to the rest of the population (COPD VR 1.79 vs Non-COPD 1.32, $p < 0.01$). There were no significant differences

in values of VR when other premorbid conditions such as ischaemic heart disease and congestive cardiac failure were analysed.

Survival outcomes were available for 214 patients. 9 patients were transferred out of the ICU and their outcome data was not available. Table 7.11 and 7.12 show comparative summaries of the demographic data and respiratory variables between survivors and non-survivors. 154 patients survived to ICU discharged and 60 patients died. VR was higher on admission in non-survivors (Survivors 1.32, CI 1.24 – 1.39; Non-survivors 1.55, CI 1.39 – 1.70). Univariate logistic analysis showed VR was an independent predictor of mortality (OR 2.3 CI 1.3 – 4.1, $p < 0.01$). On day 2 VR remained a significant independent predictor of outcome on univariate analysis (OR 2.92, CI 1.41-6.01). Table 7.13 summarises the findings of univariate logistic analysis of respiratory variables. After adjusting for APACHE II score, PIP, and PEEP, VR remained an independent predictor of mortality (OR 2.34, CI 1.03 – 4.08, $p = 0.04$).

To further analyze the ability of VR at admission to predict disease severity, ventilator days was used as a surrogate. Amongst survivors VR was greater or equal to 1.4 in 34 patients and less that 1.4 in 120. Kaplan-Meier curves were constructed to examine ventilator days in the 2 groups with the end-point being 30 days of mechanical ventilation (Figure 7.7). VR of greater that 1.4 was more likely to results in prolonged ventilation ($p < 0.01$, HR 2.2, CI 1.4 – 3.2).

At the transition point from mandatory to spontaneous modes of ventilation delta VR greater than zero was more likely to lead to prolonged ventilation ($p < 0.01$, HR 2.24, CI 1.3 – 2.9). The Kaplan-Meier plot is presented in Figure 7.8.

	ICU (n = 223)	Theatre (n = 26)	p values
Age	57.8 ± 16.9	48.1 ± 13.5	< 0.01
Weight	74.3 ± 14.9	78.2 ± 16.4	0.24
Height	170.7 ± 7.9	170.9 ± 11.35	0.90
PaO_2 / FiO_2 Ratio	34.6 ± 18.0	57.6 ± 17.1	< 0.01
Ventilatory Ratio	1.4 ± 0.53	0.99 ± 0.51	< 0.01

Table 7.9 Comparison of key variables between patients admitted to ICU patients and patients undergoing routine surgery. p Values are for unpaired T-test.

Diagnosis	n (%)
Gastrointestinal Complications	**60 (26.9)**
Intra-abdominal Sepsis	20 (9.0)
Bowel Perforation/Obstruction	21 (9.4)
Pancreatic / Hepatic Failure	7 (3.1)
Post-operative complications	6 (2.7)
Gastrointestinal Bleeding	6 (2.7)
Respiratory Insufficiency	**47 (21.1)**
Lower Respiratory Tract Infection	21 (9.4)
Exacerbation of COPD	10 (4.5)
ALI / ARDS	10 (4.5)
Acute Pulmonary Oedema	4 (1.8)
Aspiration / Pneumonitis	3 (1.3)
Cardiorespiratory Arrest	**37 (16.6)**
Cardiac Arrest	35 (11.7)
Respiratory Arrest	2 (0.8)
Sepsis	**16 (7.2)**
Urinary	5 (2.2)
Skin	5 (2.2)
Neutropenic	2 (0.8)
Unknown	4 (1.8)
Miscellaneous	**52 (23.3)**
Neurological Complication	15 (6.7)
Poisoning / Overdose	13 (5.8)
Burns	12 (5.4)
Gynaecological Problems	8 (3.6)
Post-op Cardiovascular Monitoring	4 (1.8)
Multi-Organ failure	4 (1.8)
Metabolic / Trauma	6 (2.7)

Table 7.10 Admission diagnoses of ICU patients.

	Survivors (n = 154)	Non-Survivors (n = 60)	P values
Sex Male	82 (53.2%)	31 (51.7%)	0.84§
Age (years)	52.6 ± 19.3	62.2 ± 17.1	< 0.01
Weight (Kg)	75.7 ± 18.5	72.1 ± 13.2	0.17
Height (cm)	170.8 ± 7.9	170.7 ± 8.1	0.88
APACHE II Score	15.5 (11 – 19)	20 (19 – 23)	< 0.01*

Table 7.11 Comparison of demographic data between survivors and non-survivors. P values are for unpaired T-test for continuous variables; § Chi-square test, * Mann-Whitney test.

	Survivors (n = 154)	Non-Survivors (n = 60)	p Values
Minute Ventilation ($l.min^{-1}$)	7.7 ± 2.2	8.7 ± 3.3	< 0.01
$PaCO_2$ (kPa)	5.5 ± 1.3	5.8 ± 1.6	0.22
Ventilatory Ratio	1.32 ± 0.5	1.55 ± 0.6	< 0.01
PaO_2 (kPa)	17.0 ± 6.4	18.5 ± 11.0	0.22
FiO_2	0.54 ± 0.21	0.65 ± 0.23	< 0.01
PaO_2/FiO_2 Ratio	36.2 ± 18	31.4 ± 17.6	0.08
PEEP (cmH_2O)	5 (5 -10)	8 (5 – 10)	< 0.01*
Peak Inspiratory Pressure (cmH_2O)	21 (16 – 26)	23 (18.25 – 30.75)	< 0.01*
Dynamic Compliance	46.0 ± 29.9	38.6 ± 23.8	0.09

Table 7.12 Comparison of respiratory variables at admission between survivors and non-survivors. P values are for unpaired T-test for continuous variables; * Mann-Whitney Test.

	Odds Ratio	CI	p value
Ventilatory Ratio	2.31	1.30 – 4.11	< 0.01
$PaCO_2$ (kPa)	1.13	0.92 – 1.40	0.22
Minute Ventilation ($ml.min^{-1}$)	1.00	1.00 – 1.01	0.01
Peak inspiratory pressure (cmH_2O)	1.07	1.02 – 1.11	< 0.01
PaO_2 (kPa)	1.02	0.98 – 1.06	0.23
PaO_2 / FiO_2 Ratio	0.98	0.97 – 1.01	0.08
PEEP (cmH_2O)	1.13	1.01 – 1.27	0.03
Dynamic Compliance	0.99	0.97 – 1.00	0.1

Table 7.13 Odds ratio derived from univariate analysis of individual respiratory variables on day 1 with mortality as the outcome (n = 223).

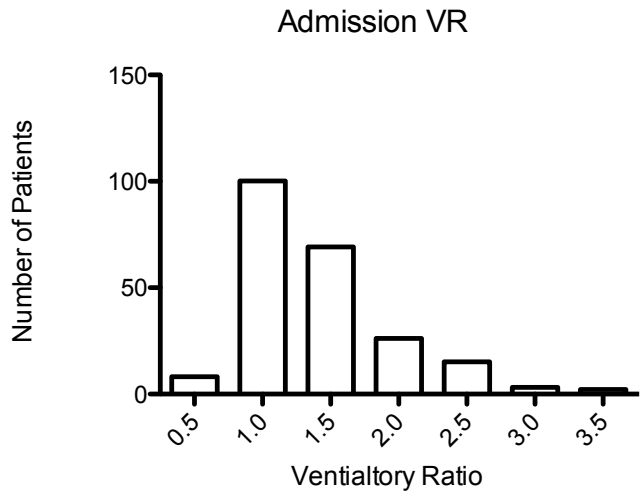


Figure 7.6 Frequency distribution of VR at admission in the ICU population.

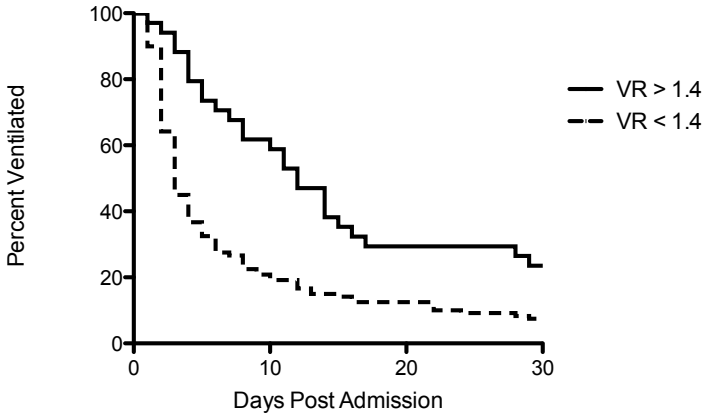


Figure 7.7 Kaplan-Meier plot of ventilator days in survivors (admission to 30 days). The population was divided into those with VR ≥1.4 (n = 34) and those with VR < 1.4 (n = 120) at admission. Log-rank test showed the curves are significantly different ($p < 0.01$).

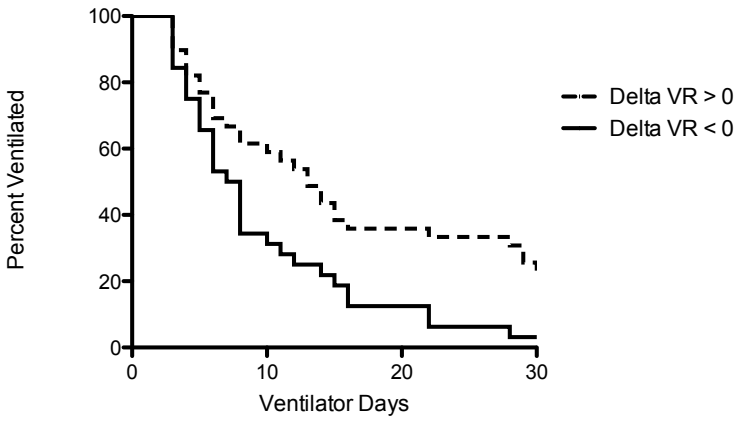


Figure 7.8 Kaplan-Meier plot of ventilator days at the transition point from mandatory to spontaneous modes of ventilation (admission to 30 days). The population was divided into those into those with delta VR > 0 and those with delta VR ≤ 0.

7.4 ALI/ARDS Australia New Zealand Intensive Care Society Database

7.4.1 Methods

This is a small database consisting of mechanically ventilated patients with ALI or ARDS. The study predates the low tidal volume paper as published by ARDS Network (89). Table 7.14 summarises the baseline respiratory variables. Although the database was collected prior to widespread use of low tidal volume ventilation, form Table 7.14 we can see the tidal volumes used were reasonable. Data was only available for analysis on the first day that patient developed ALI / ARDS. Primary outcome was ICU mortality. The population was subdivided into survivors and non survivors. Additionally, the population was divided into ALI and ARDS to compare VR values in these groups.

7.4.1.1 Statistical Analysis

Data are presented as mean ± standard deviation or median with interquartile range, where appropriate. Intergroup comparison used unpaired t-test or Mann-Whitney test (depending on the distribution of the data). Multiple comparisons of groups were made using one-way analysis of variance. Chi-squared test for trends was used to analyze the association of mortality and ordinal groups of VR.. Univariate logistic regression analysis was used to calculate odds ratios for multiple respiratory variables to individually predict mortality. To examine the relationship of hospital mortality and VR and adjusting for confounding variables multivariate logistic regression analysis was also performed. Pearson's correlation coefficient was derived to examine the relationship of VR and PaO_2 / FiO_2 ratio.

7.4.2 Results

121 of 168 of the patients from the original database were included in the data analysis. These were invasively ventilated patients only. The basic demographics of the patients are presented in Table 7.14. The range of VR in this population was 0.56 to 3.27. The mean VR in this population was 1.47 (SD ± 0.58). Mean values for VR was significantly higher in non-survivors as compared to survivors (1.7 ± 0.64 vs 1.45 ± 0.56, $p = 0.02$) (Figure 7.9). Increasing value of VR was associated with an increased risk for mortality (chi-squared test for trends $p < 0.01$) (Figure 7.10). ROC curves were constructed for VR as a predictor for mortality. Area under the curve for

this model was 0.64 (CI 0.53 – 0.73, p = 0.02). A cut-off for VR of 2.05 resulted in a specificity of 89% with a positive predictive value for mortality of 0.67. A cut-off value of 0.99 gave sensitivity of 89% for survival with a negative predictive value for mortality of 0.17.

There was no difference in VR between those with direct and indirect causes of lung injury (1.55 vs 1.37, p=0.07). As illustrated in Figure 7.11 patients with ARDS had a significantly higher mean VR in comparison to patients with ALI (1.53± 0.53 vs 1.27 ± 0.46, p=0.01). Analysis of variance by groups based on the Murray lung injury showed that VR was significantly different in each of the groups (MLI score <2 VR 1.21 ± 0.45, score >2 - <2.5 VR 1.37 ± 0.37, score > 2.5 VR 1.74 ± 0.62) (136). As seen in Figure 7.12 there was weak negative correlation between PaO_2/FiO_2 ratio and VR in the population (r - 0.4, 95% CI -0.54 to -0.23).

Univariate logistic regression analysis showed VR to be an independent predictor of mortality (OR 3.55, CI 1.61 – 7.84, p < 0.01). Stepwise multivariate logistic analysis showed that VR remained an significant independent predictor of mortality after the addition of APACHE II score to the baseline model (OR 3.05, CI 1.35 – 6.91, p < 0.01) and after addition of PEEP and PIP to the baseline model and APACHE score (VR OR 2.55, CI 1.06 – 6.14). The findings of the analysis are summarized in Table 7.15.

	Survivor (n = 85)	**Non-survivors (n = 36)**	**p-value**
Age (years)	58.6 ± 20.4	66.4 ± 13.9	0.04*
Height (cm)	1.72 ± 0.1	1.70 ± 0.08	0.65*
Weight (Kg)	77.6 ± 14.3	74.2 ± 15.1	0.24*
Tidal Volume (ml)	647 ± 112	634 ± 139	0.59*
$\dot{V}_E$ (ml.min^{-1})	7742 ± 1950	8772 ± 3104	0.22§
Peak Pressure (cmH_2O)	27 (24 – 33)	29.5 (25.25 -35)	0.19§
Plateau Pressure (cmH_2O)	22 (18 -25)	20 (19.5 – 27)	0.97§
APACHE 2 score	18.5 ± 9.1	24.7 ± 9	< 0.01*
PaO_2 / FiO_2 Ratio	24.8 ± 8.2	17.5 ± 8.6	< 0.01*
$PaCO_2$ (kPa)	5.7 ± 1.5	6.5 ± 2	0.06§

Table 7.14 Demographic data and Respiratory Variables in Survivors and Non-survivors for the ANZICS database.

Day 1	Odds Ratio	95% CI
Univariate Analysis		
Ventilatory Ratio	3.56	1.61 – 7.84
Multivariate Analysis		
Base model + APACHE II score	3.05	1.35 – 6.91
(Base model + APACHE II score) + PEEP	3.00	1.30 – 6.91
(Base model + PEEP +APACHE II score) + PIP	2.55	1.06 – 6.15

Table 7.15 The predictive value of Ventilatory Ratio with ICU mortality as primary outcome using logistic regression. Data is presented for univariate and multivariate analysis.

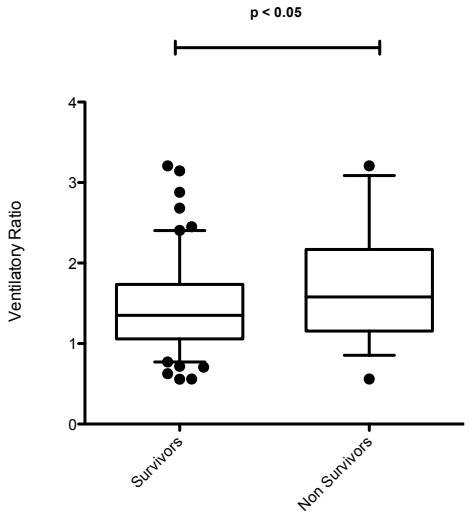


Figure 7.9 Comparison VR in survivors and non-survivors. The bars represent median values and the 5%-95% range. Mean values were compared using unpaired t-test.

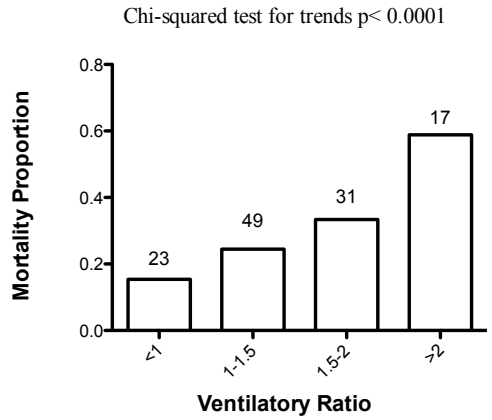


Figure 7.10 Proportion of mortality in grouped patients with rising values in VR. Numbers at the top the bar represent the total number of patients in each group.

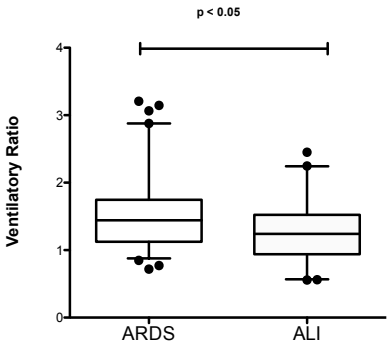


Figure 7.11 Comparison of VR in ARDS and ALI patients. The bars represent median values and the 5%-95% range. Mean values were compared using unpaired t-test.

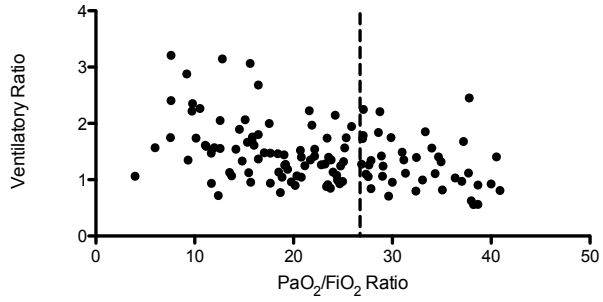


Figure 7.12 Comparison of the relationship of VR and PaO_2/FiO_2 ratio. As the PaO_2/FiO_2 ratio decreases there is a greater spread in the values of VR. The dotted line represents the transition point of ALI and ARDS.

7.5 ARDS Network Database

7.5.1 Method

The database was used to assess the use of VR in the ALI and ARDS patients. All patients ventilated for 3 days or more were included in the analysis. Limited information was released for each patient this included respiratory variables, aetiology of lung injury, and APACHE III score. The timings of each of the recordings in relation to the admission of the patient were unavailable. The main outcome for analysis was ICU mortality. Information for ventilator days was unavailable.

In addition to calculating VR and PaO_2 / FiO_2 ratio, estimated V_D / V_T and $V_{E\,40}$ were also calculated at each time-point. V_D/V_{Test} was estimated using the following equations as described by Siddiki et al:

$$V_D / V_T = 1 - \left[\frac{(0.86 \times \dot{V}CO_{2est})}{(Pa_{CO_2} \times \dot{V}_E)} \right] \qquad [34]$$

where Pa_{CO_2} is the arterial PCO_2, $\dot{V}_E$ is the minute ventilation, and V_T is the tidal volume. $\dot{V}CO_{2est}$ is the estimated CO_2 production and is calculated using the modified Harris-Benedict equation(137):

$$\dot{V}CO_{2est} = \frac{HB_{pred} \times hf \times 0.8}{6.8644} \qquad [35]$$

Where HB_{pred} is the predicted resting energy expenditure (REE) and is gender specific. For females = 655.1 + (6.56 x Wt_{Kg}) + (1.85 x Ht_{cm}) - (4.56 x age). For males = 66.45 + (13.75 x Wt_{Kg}) + (5 x Ht_{cm}) - (6.76 x age). ‘hf’ is hypermetabolic factors defined as 1.13 per °C over 37°C, 1.2 for minor surgery, 1.35 for major trauma, and 1.6 for severe infection (138). However data was not available for these correction factors and were not applied to the calculations for V_D/V_T. Finally VE40 an index described by Jabour and colleagues which is conceptually similar to VR was calculated using the following equation:

$$V_{E_{40}} = \frac{V_E}{bw} \times \frac{PaCO_2}{40} \qquad [36]$$

$V_{E\,40}$ has units of ml / kg / min and a value between 90-120 is considered in the normal range.

7.5.1.1 Statistical Analysis

Normally distributed continuous data are expressed as mean and standard deviation. Non-parametric data are expressed as median and interquartile range. Unpaired t-test was used for intergroup comparison of means and Mann-Whitney test was used to compare medians for non-parametric data. Univariate logistic regression analysis was used to calculate odds ratios for multiple respiratory variables to individually predict mortality at day 1 and day 3. To examine the relationship of hospital mortality and VR and adjusting for confounding variables multivariate logistic regression analysis was performed. Only variables that had a significant effect on mortality were included in the model.

Stepwise multiple logistic regression analysis was performed to determine the prognostic value of the ventilatory ratio after adjustment for non-pulmonary outcome modifiers. Variables such as the APACHE III score, presence of shock, PaO_2/FiO_2 ratio, and PEEP were added to the base model at day 1, day 2, and day 3 to assess the association of VR and mortality. Chi-squared test for trends was used to analyse the association of mortality and ordinal groups of VR. A modified Pearson's correlation coefficient as described by Stratton and colleagues (135) was obtained to study the association between VR and estimated V_D / V_T. This method was used to correct any bias in Pearson's correlation coefficient as a result mathematical coupling because Pa_{CO_2} was used to calculate VR and V_D / V_T. A modified Pearson's coefficient was derived to examine the relationship between VR and other variables.

7.5.2 Results

Complete physiological data and outcomes were available in 1636 mechanically ventilated patients. Overall 30.1% (n = 492) of the outcomes resulted in in-hospital mortality. A comparison of the respiratory parameters between survivors and non-

survivors is presented in Table 1. The mean value for VR was significantly higher in the mortality group (2.07 95% CI 2.00 – 2.15) when compared to the survivors (1.96 95 % CI 1.92 – 2.00; p = 0.01).

Univariate analysis it was showed that an increase in VR was associated with increased mortality at day 1 (OR 1.18 95% CI 1.04 – 1.35), day 2 (OR 1.33 95% CI 1.16 – 1.53) and day 3 (OR 1.39 95% CI 1.22 - 1.60). At day 2 and day 3 VR independently predicted mortality after adjusting for APACHE III score and shock. Addition of PaO_2/FiO_2 ratio, V_T, and PEEP separately to the base regression model showed that VR had significant effect on mortality on day 2 and day 3. This effect was not observed either at day 1 with the above variables or with oxygenation index on any of the days (Table 2). Six respiratory variables were identified on univariate analyses that were associated with increased mortality. After adjusting for these variables in a multivariate logistic regression model VR remained independently associated with increased in-hospital mortality (Table 3).

Figure 1 shows the hospital mortality rate in quintile ordinal groups of VR at day 1 and day 3. Groups with higher VR appear to be significantly associated with increased mortality (Chi-square test for trends; Day 1 $p = 0.05$; Day 3 $p < 0.01$)(Figure 1). This effect was more pronounced on day 2 and day 3. An increase in VR between day 1 to day 3 was seen in greater proportion of patients that died (survivors 27.1 % vs non-survivors 35.6%, $p < 0.01$). The positive predictive value for in-hospital mortality for those patients in whom there was an increase in VR between day 1 and day 3 was 57.6% (n = 238). ROC curves for VR, VE40, and estimated V_D / V_T showed similar results for all three variables (AUC: VR 0.58, VE40 0.53, V_D / V_T 0.61). There was weak negative correlation between VR and PaO_2 / FiO_2 ($r = - 0.32$, $p < 0.01$).

The clinical value of estimated V_D/V_T in this population has been presented elsewhere (139). There was strong correlation between V_D/V_T and VR on day 1 (modified $r = 0.80$, $p < 0.01$) (Figure 7.14) and day 3 (modified $r = 0.81$, $p < 0.01$). There was weak negative correlation between VR and PaO_2 / FiO_2 ($r = - 0.32$, $p < 0.01$).

Figure 7.15 shows VR plotted against PaO_2 / FiO_2 ratio. The vertical dotted line splits the population into ALI and ARDS. The ARDS population was then split into groups according to those with a VR of less than 2 (n = 470) and those with a VR greater or equal to 2 (n = 500). Chi-squared test showed mortality was significantly higher in the group with VR ≥ 2 (39.4% vs 28.7%; relative risk ratio 1.37, 95% CI 1.15- 1.64).

	Survivors (1144)	**Non-Survivors (492)**	**P value**
$PaCO_2$ (kPa)	5.57 ± 1.6	5.39 ± 1.6	< 0.05*
Tidal Volume (ml)	454.6 ± 161.2	484.6 ± 177.4	< 0.05*
PaO_2 / FiO_2 Ratio (kPa)	21.7 ± 9.7	19.9 ± 8.6	< 0.05*
Ventilatory Ratio	1.96 ± 0.7	2.07 ± 0.9	< 0.05*
Oxygenation Index	16.27 ± 9.5	18.58 ± 10.8	< 0.05*
Ppeak (cmH_2O)	33 (27.5 – 38.5)	35 (28.5 – 41.5)	< 0.05§
Pplat (cmH_2O)	26 (22 – 30)	28 (23 -33)	< 0.05§
PEEP (cmH_2O)	10 (7 – 13)	10 (7 – 13)	0.07§

Table 7.16 Comparison of respiratory variables between survivors and non-survivors at day 1. * Denotes unpaired t-test, § Denotes Mann-Whitney test. Ppeak = Peak pressure, Pplat = Plateau pressure, PEEP = Peak end expiratory pressure.

Day 1	Odds Ratio	95% CI	n
Per unit change			
Univariate			
Ventilatory Ratio	1.18	1.04 - 1.35	1636
Multivariate			
Base model (shock +APACHE III score)	1.10	0.96 - 1.27	1596
Base model + PaO_2/FiO_2 ratio	1.03	0.89 - 1.20	1590
Base model + PEEP	1.15	1.00 - 1.33	1636
Day 2			
Univariate			
Ventilatory Ratio	1.33	1.16 - 1.53	1417
Multivariate			
Base model (shock +APACHE III score)	1.23	1.07 - 1.42	1384
Base model + PaO_2/FiO_2 ratio	1.20	1.03 - 1.38	1411
Base model + PEEP	1.20	1.03 - 1.40	1409
Day 3			
Univariate			
Ventilatory Ratio	1.39	1.22 - 1.60	1309
Multivariate			
Base model (shock +APACHE III score)	1.30	1.13 - 1.51	1269
Base model + PaO_2/FiO_2 ratio	1.27	1.10 - 1.47	1308
Base model + PEEP	1.21	1.04 - 1.41	1306

Table 7.17 The predictive value of Ventilatory Ratio at day 1 and day 3 with hospital mortality as the dependent variable. OI = Oxygenation Index, PEEP = Peak end expiratory pressure, V_T = Tidal volume.

	Day 1		Day 3	
	Odds Ratio (95% CI)	**P Value**	**Odds Ratio (95% CI)**	**P Value**
Oxygenation Index	1.02 (1.00 – 1.03)	0.01	1.04 (1.01 – 1.07)	0.01
$PaCO_2$ (KPa)	0.81 (0.72 – 0.90)	< 0.01	0.75 (0.67 – 0.85)	< 0.01
Tidal Volume (ml)	1.00 (1.00 – 1.00)	0.05	1.00 (0.99 – 1.00)	0.95
Ventilatory Ratio	1.43 (1.14 – 1.80)	< 0.01	1.48 (1.17 – 1.88)	< 0.01
Ppeak (cmH_2O)	0.99 (0.98 – 1.01)	0.71	0.98 (0.96 – 1.01)	0.19
Pplat (cmH_2O)	1.02 (0.99 – 1.04)	0.19	1.04 (1.01 – 1.07)	< 0.01

Table 7.18 Multivariate logistic regression model of respiratory variables with in-hospital mortality as the dependent variable. OI was used in preference to PaO_2 / FiO_2 ratio because univariate analysis showed OI had a greater association with mortality. Ppeak = Peak pressure, Pplat = Plateau pressure, PEEP = Peak end expiratory pressure.

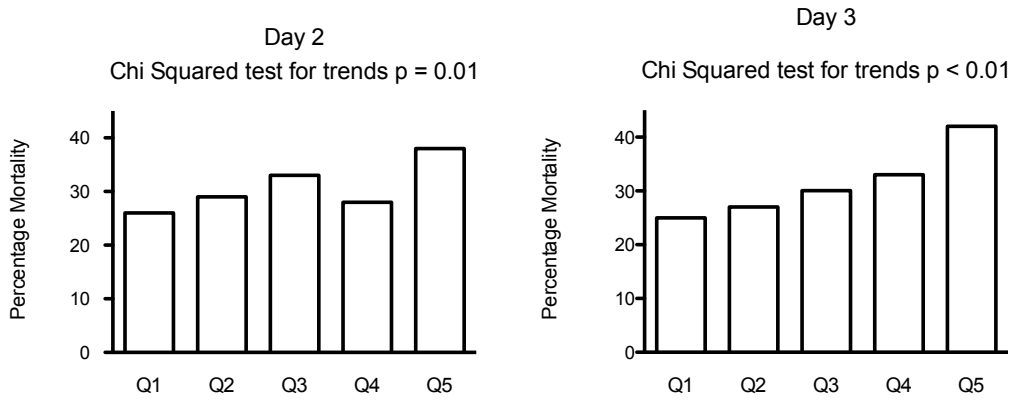


Figure 7.13 Trends in mortality in ordinal quintile groups of VR on day 2 and day 3. Day 2 Q1: < 1.46, Q2: ≥ 1.46 - < 1.76, Q3: ≥ 1.76 - < 2.06, Q4: ≥ 2.06 - < 2.56, Q5 ≥ 2.56 (Chi-Squared test for trends, p = 0.01). Day 3 Q1: < 1.46, Q2: ≥ 1.46 - < 1.77, Q3: ≥ 1.77 - < 2.06, Q4: ≥ 2.06 - < 2.57, Q5 ≥ 2.57 (Chi-Squared test for trends, p < 0.01).

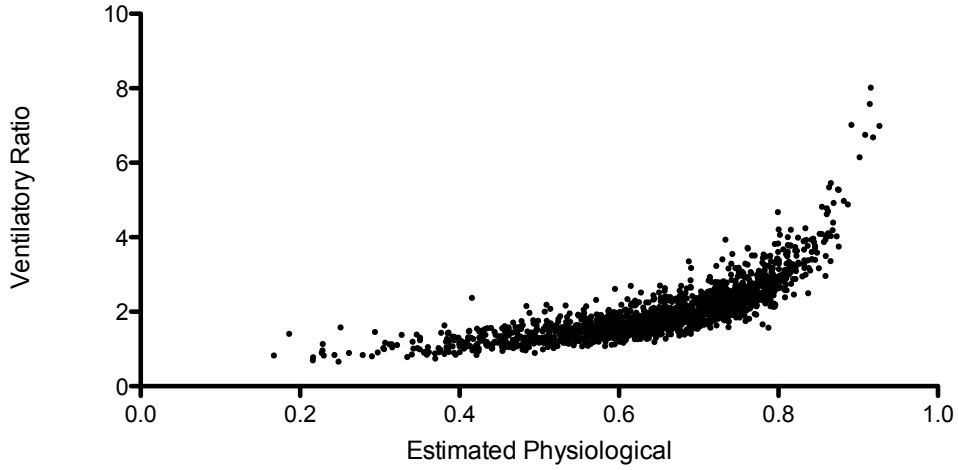


Figure 7.14 Ventilatory Ratio plotted against estimated V_D / V_T on day 1 (Modified Pearson's correlation r = 0.8).

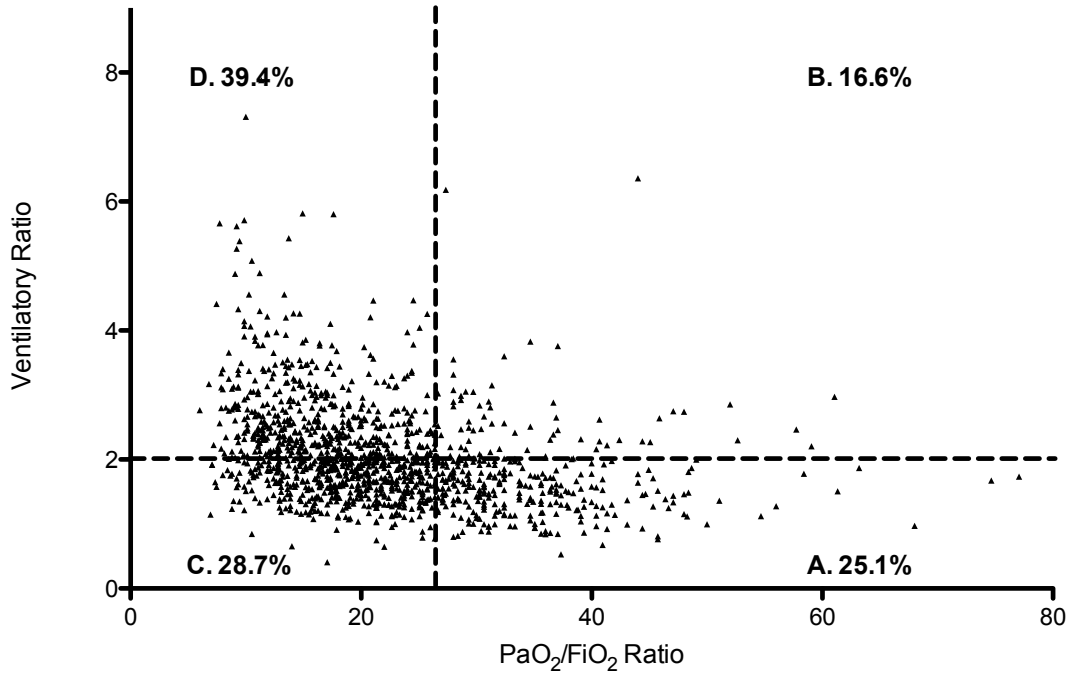


Figure 7.15 Ventilatory Ratio plotted against PaO_2 / FiO_2 Ratio at Day 3. The vertical dotted line is at the cut-off point on the x-axis that defines ARDS. The horizontal line intercepts the y-axis at VR of 2.06 (60^{th} Percentile). Area A describes patients with ALI and VR ≤ 2.2; the mortality for this group was 24.3% (n = 275). Area B describes patients with ALI and VR > 2.2; the mortality for this group was 19.6% (n = 51). Area C describes patients with ARDS and VR ≤ 2.2; the mortality for this group was 29.7% (n = 582). Area D describes patients with ARDS and VR > 2.2; the mortality for this group was 29.7% (n = 400).

7.6 Discussion

The objectives set out at the start of this chapter were to explore the clinical uses of VR. All four databases showed that higher values of VR were associated with increased risk of mortality. Non-survivors had significantly higher VR compared to survivors in all 4 databases. Values in ICU patients were also higher than in those patients undergoing elective surgery. A rising value in VR was shown to be associated with worse outcome. VR in all the databases examined showed weak negative correlation with PaO_2/FiO_2 ratio. This suggests that the information obtained from VR is unlikely to be extractable from PaO_2/FiO_2 ratio. VR also showed good correlation with estimated dead space a marker of ventilatory inefficiency derived from bedside variables.

The results from the 2 locally derived databases will be discussed first followed by the ARDS databases.

7.6.1 General ICU Population (RBH and CWH databases)

Specifically in the general ICU databases VR was significantly higher in the study groups as compared to the control groups. Both databases showed VR was significantly higher at admission for non-survivors than survivors. A VR of greater than 1.4 was associated with increased risk of prolonged ventilation in both populations. VR was an independent predictor of mortality in both populations of patients. Both adjusted and unadjusted odds ratio were higher with rising values of VR in univariate and multivariate logistic models. In the RBH database a rising value of VR over time was statistically more likely to found in patients that died and was associated with prolonged ventilation. In analysis of all readings in the RBH database VR was significantly higher during mandatory modes of ventilation compared to spontaneous modes. There was weak correlation between VR and other respiratory variables.

Figures 7.1 and 7.6 show the frequency distribution of VR at admission in the 2 general ICU populations. The figures show that VR is normally distributed. Figure 7.1A shows results of all readings in database and the data is normally distributed

although the peak of the distribution is centered more to the right with a higher population peak for VR compared to Figure 7.1B which is data from admission only. These findings can probably be explained by the fact that more readings in spontaneous modes of ventilation when all the readings are considered, this is likely to results in higher VR in the population. At admission more of the readings are likely to be whilst the patients are in mandatory modes of ventilation resulting in a more positive skew in the distribution of values.

Comparison of data between the study groups and those patients undergoing elective surgery show that VR as anticipated is higher in ICU patients admitted as emergency. This suggests that emergency admissions to ICU in itself carries a cost of efficiency of ventilation. There may be several causes that result in this inefficiency. Often patients presenting to ICU are subject to multiple organ dysfunction leading to subtle changes in ventilation-perfusion mismatch, features of sepsis may also increase carbon dioxide production in patients, and mechanical ventilation in itself can also lead to increased dead space- both anatomical and physiological. Interesting to note are the findings that mean values of VR for patients in theatre and in cardiac ICU was almost 1. From physiological analysis and the modeling work it was anticipated that normal values would be lower than 1. The value of 1 is based on a normograms for ideal minute ventilation (82, 103). The assumed ideal $PaCO_2$ of 5 may be also too high for a minute ventilation of 100 ml min^{-1}. Therefore a value of 1 may not necessarily represent the genuine mean of a normogram for $\dot{V}_E \times Pa_{CO_2}$. The figures chosen as the ideal values whilst may be arbitrary, the associated increase in anatomical dead and positive pressure ventilation leads to a VR closer to 1 rather than a lower value. Although this must be tempered with the caveat that the 'control' group in this case was small in numbers. From the findings from the analyses however, a value of 1 is likely to represent lungs that are able to meet the ventilatory demands of the body. This value seems an adequate representation of what may be considered "normal" in the critical care setting.

In both databases VR was found to be higher in patients that died. In addition logistic regression analysis showed VR was an independent predictor of mortality. This implies that as a physiological surrogate it has linkage with clinical disease severity.

There are several variables in the armamentarium of ICU physicians that are able to predict mortality. There are several features of VR that make it a potentially attractive tool for physicians in addition to markers already available. VR is simple to calculate at the bedside. To most physicians a composite function of two variables moving in opposite direction that tracks efficiency of CO_2 clearance would be intuitively valuable. Table 7.8 and Figures 7.4, 7.12 and Figure 7.15 show that there was weak correlation between VR and other commonly measured respiratory variables, particularly PaO_2 / FiO_2 ratio. Hence it may be assumed that the information concerning the pathophysiological processes represented by changes in VR are currently not easily available to physicians using bedside measurements.

The inadequacies of PaO_2 / FiO_2 ratio are well documented. Not only is its value at admission as a predictor of outcome uncertain, there are also uncertainties surrounding its ability to categorize severity of disease particularly in ALI / ARDS (140, 141). Studies also suggest that the level of PEEP and FiO_2 may manipulate PaO_2 / FiO_2 ratio (142, 143). In contrast VR appears more robust as a marker of pathological state. There are fewer variables that can be externally manipulated to alter the value of VR. Specifically tidal volume and its ratio with frequency of delivered breaths can be altered to change VR. A decrease in tidal volume is likely to increase the $V_D/V_{T\ anat}$ deadspace ratio and thereby lead to a rise in VR after a certain threshold point. The point at which this would lead to a rise in VR would depend on the underlying state of the lungs and the level of CO_2 production.

Analysis of the RBH database over time shows that in mandatory modes of ventilation an increase in VR from day 1 without a corresponding subsequent decrease, i.e. a positive gradient, was seen more frequently in patients that died. This suggests that there is an association between rising values of VR and mortality. There were similar findings in the ARDSnet database that will be discussed later in the chapter. Included in the analysis for rising VR were patient with a high VR on admission (> 2), it is highly probable that a lack of improvement in these patients would also be associated with increased mortality. The findings of this study suggest that trends in VR can be used as a tool monitor disease progression.

One of the potential problems of using VR is that it appears higher in those patients ventilating spontaneously, event though it is perceived that it is more efficient to breath spontaneously. There may be several factors that account for this. Patients breathing spontaneously are likely to be more lightly sedated. There is also the likelihood that in conventional forms of ventilation a spontaneously ventilating patient is more likely to represent an individual that is improving. Logic would dictate that efficiency of ventilation should improve. As examined in one of the previous chapters this may not be the case. Spontaneously ventilating patients may have an increase in their dead space ventilation particularly if their tidal breaths are small. Additionally in some patients there may be increased work of breathing resulting in increased CO_2 production. In those patients unable to increase their minute ventilation adequately both these factors will lead to an increase in VR. The delta values of VR at the transition point from mandatory to spontaneous modes of ventilation could potential be used to assess the ability of the lungs to cope with the body's ventilatory demands. Data from the RBH database show that there were increased ventilator days in those patients in whom there was an increase in VR of greater than 30% were ventilated longer from the point of transition. This suggests that there may be an association between big increases in VR when transitioning from mandatory to spontaneous modes of ventilation. Another potential cause for increased VR in spontaneous ventilation is the fact that VR is that the recorded tidal volume / minute ventilation is more likely to vary breath to breath. Unless the patient is in a steady restful state the recorded may be idiosyncratic. The findings from these studies suggest that unless patients are in a sedated or steady state the absolute values of VR during spontaneous ventilation should not be relied on. Further studies are required to assess the validity of VR in spontaneous ventilation under more controlled conditions where the data is collected prospectively.

7.6.2 ANZICS Database

Examination of VR in this ALI / ARDS population demonstrates that VR was significantly higher in non-survivors as compared to survivors. Higher values of VR are associated with increased mortality. Logistic regression analysis showed VR was an independent predictor of mortality after adjusting for other variables. VR was also significantly higher in patients with ARDS as compared to patients with ALI. There was weak negative correlation between VR and PaO_2/FiO_2 ratio.

The results appear to indicate that the ratio has prognostic significance with higher values associated with poorer outcome. The ratio did not differentiate between intrinsic and extrinsic aetiology of the lung injury. VR is higher in non-survivors than in survivors. VR was also significantly higher in groups with higher Murray lung injury scores. These results suggest a relationship between severity of lung injury and VR. Figure 7.10 shows that higher ordinal groups of VR were associated with an increased risk in mortality. These findings are in keeping with the findings of other studies that have looked at ventilatory efficiency as a prognostic marker (30, 72).

In the context of this study being on previously collected data, ROC curve analysis of the data allows inferences to be made regarding the clinical parameters of VR. A value of less than one is associated with much better outcomes and conversely a value of greater than 2 had a greater association with death. The results of this study suggest a direct relationship between VR and outcome.

Patients with ARDS had higher VR than those with ALI. VR appears to increase as oxygenation decreases or as lung injury worsens. Though when the relationship between PaO_2/FiO_2 ratio and VR was examined the correlation was poor (Figure 7.12). This is as expected. The value of VR as a clinical tool can be interpreted from this evaluation. A tight correlation between oxygenation and ventilatory efficiency would suggest the physiology of oxygenation and of CO_2 clearance are the same and that is clearly not the case. Therefore when looking at this database VR not only performs as might be expected it also provides clinicians with additional information about the state of the lung that cannot be extracted from indices of oxygenation.

ARDS clinically is defined by the PaO_2/FiO_2 ratio as the only measured respiratory variable (144). The adequacy of the current definition of ARDS has hence been questioned (145). Figure 7.12 shows the there is a bigger spread in VR in the ARDS group of patients in comparison to ALI group. Coupled with an increased association of death with higher values, perhaps VR could assist in better categorization of patients with ALI/ARDS.

7.6.3 ARDS Network Database

This large retrospective secondary observational study of mechanically ventilated patients with ALI / ARDS shows that higher ventilatory ratio is independently associated with mortality. Both higher values of VR and a rising value of VR were associated with increased mortality. VR was also shown to have strong positive correlation with estimated dead space fraction. VR correlated poorly with PaO_2 / FiO_2 ratio. When ALI / ARDS patients are categorised according to ordinal groups of VR there appears to be an association with better prognostic categorization of these patients.

The database has several shortcomings. Following personal communication with Prof B Taylor Thompson (ARDS Network, Mass General Hospital) these problems were highlighted. Enrollment into the database mandated a single daily arterial blood gas sample. This sample however was not necessarily taken at the same time as the respiratory and ventilatory data recorded. Whilst many of the data were collected at the same time, it is conceivable that the ABG sample may have been collected 12 hours after the respiratory variables. The study has been useful to demonstrate that even in a database where the quality of data is variable there continues to be a signal for VR and outcome.

The results of the study clearly indicate an independent association of VR and outcome. Incremental increases per unit change in the regression model results in an 18% increase in mortality on day 1. The findings were more convincing day 2 and day 3 where similar increases resulted in an increase in mortality by 33% and 39% respectively. The findings of day 3 were similar to those found by Nuckton and colleagues using V_D / V_T as a predictor of mortality (72). Figure 7.17 shows that ordinal groups of VR similarly resulted in an increase in mortality on day 2 and day 3 in groups with higher VR demonstrating an association between mortality and VR.

The suggested association of VR and ventilatory efficiency may allow early initiation of alternative methods of lung support such as high frequency oscillation or extracorporeal support. It may also offer a simple tool to monitor the sustained efficacy of recruitment manoeuvers. Although conjectural, VR may be a means of determining whether various interventions have an impact on ventilatory efficiency

and hence lung function. From the analysis it can also be observed that a rising value of VR is associated with an increase in mortality. An increase in VR between day 1 and day 3 had a positive predictive value for mortality approaching 58%. Hence monitoring VR may be a useful method of monitoring disease progression in ARDS.

Figure 7.14 shows the relationship of VR and PaO_2 / FiO_2 ratio. Similar to previous studies the correlation between these two variables was poor. The dotted lines on the graph divide the ventilated population into 4 groups. Of particular interest the ARDS group is divided into 2 groups with significantly different outcomes. Hence it is suggested that VR may potentially be a useful variable in sub-categorizing ARDS patients. The 2 groups would in all probability describe very different populations in terms of pathological processes. It has been previously suggested that dead space fraction may be used to re-define this population (146). Within the limitations of this retrospective study VR provides a more simplistic method of categorizing ARDS patients according to severity of ventilatory impairment without relying on sophisticated monitoring.

Since VR was first described, other methods to measure dead space using variables recorded at the bedside have been proposed clearly demonstrating an increased awareness for a need to monitor ventilatory efficiency. These methods describe equations to estimate V_D / $V_{T\,phys}$ using linear regression modeled from recorded dead space data (54) or the alveolar gas equation (estimating $\dot{V}CO_2$ using the Harris-Benedict equation) (139). Whilst these methods are useful, the additional complexities associated with the described methodologies for extrapolation of a quantified value for deadspace would render them less accessible as a quick reference tool. Although in comparison VR may be crude as a tracker of deadspace fraction, it is easy to calculate and appears to be useful as a clinical tool for assessing disease severity and predicting mortality. Perhaps a more intuitive way to view VR would be as a marker of an individuals ventilatory demands.

In comparisons to other methods to estimate ventilatory efficiency using bedside variables, such as 'VE40' and estimated V_D / V_T, VR performs similarly when analyzing ROC curves with mortality as the outcome. The advantages VR affords is

that it has easy to calculate in comparison to estimated V_D / V_T and in comparison to VE40 VR has been derived from sound physiological principals. VR is unit-less and both physiologically and clinically intuitive (147). In many respects recategorising ARDS using VR is akin to categorizing respiratory failure as type I and type II.

There are other several limitations to this study. The study was a retrospective analysis of prospectively collected data that was collected for various different. Any findings from the analyses of these studies can only be considered as loose associations. These factors could explain the weaker association between mortality and VR in this study. The result of logistic regression on day 1 is further testament to these observations. It is possible that the recordings on day 1 were from the very first reading at a point when the patient was not in steady state and the minute volume or $PaCO_2$ may not be indicative of the state of the patient's lung but rather of the conditions surrounding intubation or the patients pre-intubation state. This would lead to higher values of VR in comparison to those calculated in steady state. In addition there was evidence of results in the database that can only be attributed as artifact. Values of VR > 5 were frequently encountered in the database. These values were seldom encountered in any of the other database. Not only that several of these patients went on to survive. In the other databases almost of patients with a VR > 5 died. Moreover some of the patients in the ARDSnet database with VR > 5 were liberated form the ventilator within 24 hours.

7.7 Summary

Despite these major limitations of retrospective study design there appears to be compelling clinical evidence that VR may be a monitoring method that provides additional and clinically intuitive information that has previously not been available with such ease at the bedside. High values of VR and increasing values of VR associated with poorer outcomes. This has been demonstrated in four separate and discreet populations.

Chapter 8: Discussion

8.1 Summary of Chapters

In Chapter 1 we examined deadspace measurements and its uses in mechanical ventilation. We also explored some of the reasons why deadspace is seldom measured in ICU despite being a key physiological component of the efficacy of ventilation and having known associations with outcome for example in ARDS. Neither the Douglas Bag method nor volumetric capnography are widely used in ICUs although there is growing interest in the latter as well as interest in techniques such as impedance tomography to visualize efficacy of ventilation distribution.

The standard approach to looking at lung disease in ICU tends to focus on the PaO_2/FiO_2 ratio, which has been and is widely used in clinical practice. It is the basis of categorizing disease severity in ARDS. The PaO_2/FiO_2 ratio is a simple composite of two variables that are often moving in opposite directions. Ventilation and its impairment are frequently observed but rarely measured formally. One of the main reasons for this is that there are no easy indices available to monitor ventilatory failure at the bedside. Clearly a rise in arterial PCO_2 is a measure of ventilatory failure but as Nunn described so is a rise in minute ventilation. The complexity in mechanically ventilated patients is that minute ventilation often moves in the opposite direction to arterial PCO_2. A lack of an index that amalgamates the two variables has perhaps meant that this crucial portion of the breathing process is largely ignored. Keeping these principles in mind we thought that a composite of these two variables could be a marker of ventilatory efficiency and would be a clinically useful marker. Two hypotheses were generated; these were tested in the subsequent chapters.

The hypotheses were:

> *Null 1:* An index that is a composite of arterial PCO_2 and minute ventilation will not be responsive to changes in ventilatory efficiency.
>
> *Null 2:* Higher values and increasing values of such an index will not be associated with worsening disease severity in mechanically ventilated patients.

Using principles of the alveolar gas equation we have derived a simple bedside index that monitors efficiency of CO_2 clearance. In Chapter 2 Ventilatory Ratio was defined.

Proof of the derivation VR dictates that VR would be influenced by deadspace and CO_2 production. In Chapter 4 the physiological analysis of VR was validated in a benchside lung model and in a hi-fidelity in silico model. It was shown that VR increases as deadspace and CO_2 production increase. In Chapter 5 we examined the influence of rising $\dot{V}CO_2$ on VR. VR was measured in patients undergoing laparoscopic surgery, pre and post pneumoperitoneum. This model allowed us to study the effects of rising CO_2 from an exogenous source. The variability of measured $\dot{V}CO_2$ was also shown in a group of ICU patients. In general, the variability of $\dot{V}CO_2$ during the course do admission was small. The median variability across the population in hourly readings from baseline (described as 1st reading) was 3% (IQR -6 to 12%). $\dot{V}CO_2$ variability was greater during spontaneous ventilation. In Chapter 6 we saw that VR showed strong positive correlation with deadspace ventilation and the correlation was stronger during mandatory ventilation. VR showed reasonable ability to predict groups of deadspace according to levels of severity. In a high percentage of cases a changing value of VR was as a result of change in deadspace.

In Chapter 7 the clinical uses of VR were examined in 4 databases, in a total of 2468 patients. Two databases were of general ICU patients and 2 were of ARDS patients. VR was consistently higher in non-survivors compared to survivors. Higher VR was also consistently associated with mortality. In the databases where it was possible to assess VR over time an increase in VR was associated with increased mortality or increased ventilator days.

8.2 Ventilatory Ratio as a Physiological Entity

As a physiological entity VR is intuitive. Viewed simply as a product of the values from which it is derived, VR is a composite of two variables that are inversely related. At first glance this consolidates the two most crucial measured ventilatory variables. Another possible interpretation of VR is that it is a marker of how the ventilatory setting with the underlying lung pathology is coping with ventilatory demands of the body.

Alternatively VR we know is influenced by deadspace and CO_2 production. It is anticipated that deadspace fraction is much more likely to change in critically unwell patients particularly in patients that are in steady state. Equally in steady state a rising value of VR is also likely to represent changes in deadspace. It must be reiterated that VR is not an index of deadspace. In the proof of its physiological derivation VR solves for V_D/V_T but this is a conceptual construct that encompasses all forms of $\dot{V}/\dot{Q}$ abnormality termed physiological dead space and is not true dead space per se. VR may be viewed as a crude surrogate for deadspace. Clinicians encountering high VR in sedated patients must view this as an inability of the lungs to adequately clear CO_2. This in most instances would be as a result of increased deadspace either as a manifestation of the ventilatory strategies or lung pathology. Alternatively it may be a result of abnormally high carbon dioxide production, which is actually a rare occurrence in critically unwell patients and should be easily clinically discernible (e.g. agitation, tachycardia, and hyperthermia).

Caution must be exercised when interpreting deadspace. Current methods of measuring deadspace are not gold standards. In particular in severely diseased lungs deadspace measurements are difficult to interpret. This is partly to do with the current interpretation of deadspace, i.e. using the Enghoff modification of Bohr equation and partly as a result of the measurement systems. A high deadspace fraction informs us that there is a $\dot{V}/\dot{Q}$ problem, but the absolute value is relatively meaningless as it is difficult to interpret the exact contribution of high deadspace and shunt. Longitudinally over time a changing value in deadspace can be reliably interpreted as an improvement or deterioration in ventilatory efficiency. VR offers clinicians similar information. A high value of VR signifies an issue with ventilatory efficiency. Likewise longitudinally over time changes in VR are likely to represent changing ventilatory efficiency given that variation in $\dot{V}CO_2$ was generally low in the studied population. The added advantage being that VR is much simpler to calculate.

8.3 Ventilatory Ratio as a Clinical Tool

Analysis of the databases clearly demonstrates the value of VR both in the general ICU population and in patients with ARDS. Higher VR is associated with increased mortality and ventilator days. Rising values of VR were also associated with

increased mortality and prolonged ventilation. Once again this would be expected. It stands to reason that patients with failure of oxygenation and ventilation (Type II respiratory failure) respiratory would lead to a worse outcome than failure of oxygenation only (Type I respiratory failure). Compared to other respiratory variables VR was most strongly associated with mortality in all the databases. In all the databases apart from the ARDS Network database VR remained an independent predictor of mortality after adjusting for APACHE II score. As a physiological scoring system nature of the APACHE II score is comprehensive and covers most aspects. Given that VR remains an independent predictor of outcome after adjusting for APACHE II score suggests that it identifies an area of pathophysiological dysfunction that is not currently engaged by the APACHE scoring system. The addition VR appears to add prognostic value to the APACHE II. Given its poor correlation with the commonly used respiratory variables, the clinical information clinicians can derive from VR is readily extrapolated from available information. This combination of simplicity, association with mortality, and distinct clinical information makes VR an attractive clinical tool.

8.4 Ventilatory Ratio as a Tool to Classify ARDS

Currently, PaO_2/FiO_2 ratio is the only measure variable that is used to classify ARDS. This is despite the fact that PaO_2/FiO_2 ratio is widely believed to be a poor predictor of outcome (140, 148) and easily influenced by other variables(141-143). Recently, the Berlin classification of ARDS has been proposed (149). The authors of the paper should be commended on reclassifying the syndrome which was previously vague. Acute lung injury (ALI) as a condition was ambiguous and its definition arbitrary. Acute lung injury by its name suggests a pathophysiological process, however, as a clinical phenomenon it was nothing more than a milder form of ARDS.

Whilst the abandoning of ALI as a spectrum of the syndrome was welcome, the new classification goes some way short of separating the population according to underlying pathological processes. The current classification separates ARDS into mild, moderate, and severe according to their PaO_2/FiO_2 ratio with the introduction of PEEP as a very crude discriminator. The investigators of the study found that this was the only variable that could divide the studied into clinically meaningful data. There

was increased mortality associated with the increased severity of the PaO_2/FiO_2 abnormality.

In the database examined in the study, the majority of which was the ARDS Network, the authors examined the utility of the corrected minute ventilation ($\dot{V}_{E_{CORR}}$). $\dot{V}_{E_{CORR}}$ is defined as the measured minute ventilation multiplied by the measured arterial PCO_2 divided by 40 mmHg. This was used a surrogate for deadspace. The authors used a $\dot{V}_{E_{CORR}}$ of 10L as their cut-off to test for association with mortality. They failed to find a significant association with mortality. There are several reasons to explain these findings. Factors inherent to the calculation of $\dot{V}_{E_{CORR}}$ lend it to be a less powerful tool than VR. $\dot{V}_{E_{CORR}}$ does not adjust for predicted minute ventilation. Calculations of $\dot{V}_{E_{CORR}}$ are independent of the patient's weight. The analysis of association of $\dot{V}_{E_{CORR}}$ with mortality was adjusted for weight in the Berlin classification study and despite this they found no significant association. VR accounts for the patient's weight for its calculations. Accounting for individual weight when assessing ventilatory inefficiency is much more likely to have meaningful yield than retrospective adjustments. The findings of the thesis suggest that had VR been used to split the ARDS population (as seen in Figure 7.15), the results may have been clinically significant in terms of outcome.

The majority of the patients in the database used to analyse the association of the variables with mortality were from the ARDS Network database. As previously discussed the collection of data for minute ventilation and the arterial blood gases were not synchronous. $\dot{V}_{E_{CORR}}$ values calculated are therefore unlikely to be clinically relevant.

Finally, it is unsurprising that the variable for recruitment of patients into a database is the one that splits the population into clinically meaningful groups. Invariably, given its nature of the Berlin classification is only marginally better than the previous classification. Some of the inadequacies of the previous classification remain. These include the problems of using PaO_2/FiO_2 as the sole measured variable. The division

of ARDS into groups according to oxygenation may be clinically relevant but adds little new information about pathophysiology. It gives us little or no insight into the underlying abnormalities, be it at a physical or cellular level. ARDS is not a disease but a syndrome. If a syndrome containing several different aetiological entities is classified according to two distinct variables it is much more likely that we can phenotype ARDS according to cause in large epidemiological studies. Current classification does not change the heterogeneous nature of the ARDS population, thereby making it difficult to implement treatment strategies studied in these populations to individuals. The ability for VR to define ARDS according to patients with respiratory failure and ventilatory failure needs further exploration. In an age where novel strategies to support CO_2 elimination are clinically viable, these questions take on additional importance.

8.5 Limitations of Ventilatory Ratio

As documented in previous chapters there are several limitations to VR. Ventilatory ratio is a crude measure of deadspace. If solely viewed as a measure of deadspace it offers many opportunities for misinterpretation. If however it is viewed as a tool to assess the ability of the lungs to cope with the ventilatory demands of the body, VR becomes easier to interpret. Like most measurements of physiological system VR is influenced by several factors. Clinicians interpreting VR must be aware of these. VR is specific for an individual and over-time it can used to assess changes in either deadspace or CO_2 production, although as seen from previous results the latter is uncommon in the critical care setting.

The effect of CO_2 production can lead to misinterpretation of the value of VR as a surrogate of deadspace. A person with the same deadspace fraction can have a range of VR depending on the rate of CO_2 production. This is specifically true for patients that are not breathing in steady state. The additional variability of CO_2 production during spontaneous ventilation whilst the patients are being weaned means that results during spontaneous ventilation is difficult to assess.

Shunt fraction will also affect VR. Using $PaCO_2$ as a surrogate for shunt means that the contribution of venous admixture to overall arterial PCO_2 will lead to an increase in VR as a result of shunt.

Accurate calculation of VR is dependent on accurate measurement of minute ventilation. This becomes an issue in patients that have large breath-to-breath variation in their tidal volumes or in those patients in whom the respiratory rate is subject to big variations. Patients in weaning modes of ventilation and those with frequent added spontaneous breaths in mandatory modes of ventilation are more likely to be subjected to these conditions. The interpretation in this group of patients would be uncertain.

8.6 Limitations of the Thesis

There are several limitations to the thesis. The limitations to each of the individual studies have been discussed in the relevant chapters. This section discusses overall shortcomings in the thesis:

- The exact role of CO_2 production and its influence on VR in sedated patients that were spontaneously ventilating was not closely examined. Spontaneously ventilating ICU patients recruited to validation study (Study 6) were patients spontaneously ventilating with a view to liberation from the ventilator. It is anticipated that these patients would have higher $\dot{V}CO_2$ because they are generally without sedative agents. Increasingly patients are spontaneously ventilating even in the context of severe respiratory failure. This population sub-group were not specifically studied.

- Factors dictating $\dot{V}CO_2$ at ICU admission were not studied either. This would be a complex investigation and was beyond the scope of the studies. Several factors would dictate the level of CO_2 production. The patients weight would be anticipated to be a factor. Conventionally, 3 ml $Kg^{-}1\ min^{-1}$ is considered to be the average $\dot{V}CO_2$ in adults. In addition, the patients underlying pathology may also dictate the amount of CO_2 production. Severe sepsis illustrates the complexity measuring $\dot{V}CO_2$ in the ICU population. We know that in acute severe sepsis when the patient is in hyperdynamic cardiovascular state the resting energy expenditure is high. Alternatively at other times acute sepsis may results in lower energy expenditure. This may be as a result of

mitochondrial dysfunction. As patients recover from sepsis their energy expenditure and $\dot{V}CO_2$ increases. As discussed in previous chapters the level of sedation would also influence $\dot{V}CO_2$. Whilst it is difficult to predict the absolute level of $\dot{V}CO_2$ of an individual, the fact that VR uses predicted body weight as part of its calculation does mean that across the population there is a degree of standardization.

- Three of four databases analysed and collected were retrospective and therefore direct causal relationship of rising values of VR and outcome cannot be established. There are biases that exist that as a result of the study and analysis designs. Using 4 different databases, 2 of which were not constructed by the author, addresses some of the issues with selection bias. The thesis lacks a large prospective study of patients with respiratory failure. This would be important in establishing the validity of the ratio as a clinical tool. Using the ANZICS database as a framework (SD 0.58), to detect a difference of 0.3 in VR between survivors and non-survivors in ARDS patients with a power of 0.8 and two-sided 0.05 significance level, 120 patients would need to be recruited to the study.

- The study looking at the validation of the ratio in the ICU population suffers from some design weaknesses. In hindsight the recordings should have been made with greater attention being paid to the ventilatory modes and levels of sedation. The transition from mandatory to spontaneous ventilation and the changing ventilatory efficiency during this transition point needs further examination. There may be some useful clinical information to be extracted from this data in regards to the readiness or success of weaning.

8.7 Future Investigations

The thesis has allowed the exploration of VR as a physiological entity and its use in clinical practice. Whilst the studies may have answered some questions, several others have been generated and remain unanswered. The future line of investigations would look to answer these questions and address some of the shortcomings of the thesis.

- VR needs to be validated in an ICU population where the data has been collected prospectively. The advantage of collecting prospective data is that it eliminates some of the biases inherent to retrospective data analysis. Preferably the investigation would be a multicenter study.

- The differences in ventilatory efficiency in different modes of ventilation need closer examination. In particular in those patients that are in steady state. Spontaneous modes of ventilation offer many advantages. The ability to instigate protective lung strategies being one. The alterations in ventilatory efficiency between these tools in unknown. The transition from mandatory to spontaneous also requires closer examination.

- The relative contributions of dead space and carbon dioxide production towards the increased ventilatory demands in ARDS are controversial. A study looking at the relative contributions of each of these variables in ARDS would be interesting.

- In theory we could use VR to assess changes in ventilatory efficiency following interventions. It would be interesting to observe changes in VR following recruitment maneouvers, draining of effusions, and prone positioning. VR could also be potentially used for assessing progress and changes in the endogenous ventilatory efficiency of lungs whilst patients are on extra-corporeal respiratory support. A falling VR in the context of constant extra-corporeal CO_2 removal would signify improving lungs and vice versa. We have looked at the behaviour of VR in patients on extracorporeal CO_2 removal. The findings of these studies are not presented here. The results show that in patients that are improving VR usually decreases over-time whilst other variables are remains constant. Conversely, VR tends to remain constant in patients that fail to respond to therapy.

- Computerized Tomography (CT) scans are increasingly being used to gauge the severity of ARDS. It would be interesting to evaluate CT scores of patients and look at correlation of scores with abnormalities in VR. A comparison with

other respiratory variables and the relative strength correlation would be interesting. The ability to tie physiological abnormalities with specific CT abnormalities could potentially allow finger-printing and matching ARDS abnormalities according to CT and observed physiological abnormalities.

8.8 Achievements of the Thesis

- A new index to monitor ventilatory efficiency using bedside parameters has been described.
- The physiological analysis of the ratio has been validated in a benchside, hi-fidelity simulation model, and ventilated patients with respiratory failure.
- Deadspace measurements using volumetric capnography has been shown to agree well with the Douglas Bag method of measuring deadspace.
- VR has been shown to be associated with clinically useful outcomes (mortality and / or ventilator days) in 4 databases. Changing values of VR over time was shown to be associated with outcome.

8.9 Conclusions

Ventilatory Ratio is an index that offers a simple solution to monitoring ventilatory efficiency at the bedside. Increased VR is associated with adverse outcome, be it mortality or ventilator days. VR offers information that is currently not easily available from bedside measurements or indices. Incorporating VR into general ICU practice could offer clinicians with clinically meaningful information and would allow us the opportunity to study ventilatory failure in large populations. A greater emphasis on monitoring CO_2 clearance will lead to a better understanding of respiratory failure and its interaction with mechanical ventilation. VR may be at the forefront in the resurgence in our understanding of ventilatory failure.

References:

1. 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. Intensive Care Med. 1998 Apr;24(4):378-98.
2. 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. Am J Respir Crit Care Med. 1994 Mar;149(3 Pt 1):818-24.
3. Gowda MS, Klocke RA. Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med. 1997 Jan;25(1):41-5.
4. Jubran A, Tobin MJ. Reliability of pulse oximetry in titrating supplemental oxygen therapy in ventilator-dependent patients. Chest. 1990 Jun;97(6):1420-5.
5. Tuxen DV. Permissive hypercapnic ventilation. Am J Respir Crit Care Med. 1994 Sep;150(3):870-4.
6. Rosenfeld L. The last alchemist--the first biochemist: J.B. van Helmont (1577-1644). Clin Chem. 1985 Oct;31(10):1755-60.
7. Atkinson RS, Boulton TB, Royal Society of Medicine. The history of anaesthesia. London: Royal Society of Medicine Services; 1989.
8. Rosenfeld L. Joseph Black--rediscoverer of fixed air. JAMA. 1966 Apr 25;196(4):362-3.
9. Andersen EW, Ibsen B. The anaesthetic management of patients with poliomyelitis and respiratory paralysis. Br Med J. 1954 Apr 3;1(4865):786-8.
10. Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proc R Soc Med. 1954 Jan;47(1):72-4.
11. Bohr C. Ueber die Lungenathmung. Skand Arch Physiol. 1891;2::236-8.
12. Haldane JS, Priestley JG. The regulation of the lung-ventilation. J Physiol. 1905 May 9;32(3-4):225-66.
13. Douglas CG, Haldane JS. The capacity of the air passages under varying physiological conditions. J Physiol. 1912 Oct 22;45(4):235-8.
14. Drummond GB, Fletcher R. Deadspace: invasive or not? Br J Anaesth. 2006 Jan;96(1):4-7.

15. Englhoff H. Volumen inefecax. Bemerkungen zur Frage des schaedlichen Raumes. Uppsala La¨ k Fo¨ r Fo¨ rh. 1938;44::191–218.
16. Fowler WS. Lung function studies; the respiratory dead space. Am J Physiol. 1948 Sep 1;154(3):405-16.
17. Bartels J, Severinghaus JW, Forster RE, Briscoe WA, Bates DV. The respiratory dead space measured by single breath analysis of oxygen, carbon dioxide, nitrogen or helium. J Clin Invest. 1954 Jan;33(1):41-8.
18. Langley FE, P. Duroux, P. Nicolas, RL. Cumming, G. Ventilatory consequences of unilateral pulmonary artery occlusion. Les Colloques de l'Institut National de la Santeet de la Recherche Medicale. 1975;51:209-12.
19. Fletcher R. Airway deadspace, end-tidal CO2, and Christian Bohr. Acta Anaesthesiol Scand. 1984 Aug;28(4):408-11.
20. Blanch L, Romero PV, Lucangelo U. Volumetric capnography in the mechanically ventilated patient. Minerva Anestesiol. 2006 Jun;72(6):577-85.
21. Fletcher R, Jonson B. Deadspace and the single breath test for carbon dioxide during anaesthesia and artificial ventilation. Effects of tidal volume and frequency of respiration. Br J Anaesth. 1984 Feb;56(2):109-19.
22. Fletcher R, Jonson B, Cumming G, Brew J. The concept of deadspace with special reference to the single breath test for carbon dioxide. Br J Anaesth. 1981 Jan;53(1):77-88.
23. Riou Y, Leclerc F, Neve V, Dupuy L, Noizet O, Leteurtre S, et al. Reproducibility of the respiratory dead space measurements in mechanically ventilated children using the CO2SMO monitor. Intensive Care Med. 2004 Jul;30(7):1461-7.
24. Arnold JH, Thompson JE, Arnold LW. Single breath CO2 analysis: description and validation of a method. Crit Care Med. 1996 Jan;24(1):96-102.
25. Forbat AF, Her C. Correction for gas compression in mechanical ventilators. Anesth Analg. 1980 Jul;59(7):488-93.
26. Crossman PF, Bushnell LS, Hedley-Whyte J. Dead space during artificial ventilation: gas compression and mechanical dead space. J Appl Physiol. 1970 Jan;28(1):94-7.
27. Wenzel U, Wauer RR, Schmalisch G. Comparison of different methods for dead space measurements in ventilated newborns using CO2-volume plot. Intensive Care Med. 1999 Jul;25(7):705-13.

28. Romero PV, Lucangelo U, Lopez Aguilar J, Fernandez R, Blanch L. Physiologically based indices of volumetric capnography in patients receiving mechanical ventilation. Eur Respir J. 1997 Jun;10(6):1309-15.
29. Blanch L, Lucangelo U, Lopez-Aguilar J, Fernandez R, Romero PV. Volumetric capnography in patients with acute lung injury: effects of positive end-expiratory pressure. Eur Respir J. 1999 May;13(5):1048-54.
30. Lucangelo U, Bernabe F, Vatua S, Degrassi G, Villagra A, Fernandez R, et al. Prognostic value of different dead space indices in mechanically ventilated patients with acute lung injury and ARDS. Chest. 2008 Jan;133(1):62-71.
31. Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J Appl Physiol. 1949 Jun;1(12):825-47.
32. Riley RL, Cournand A, Donald KW. Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs; methods. J Appl Physiol. 1951 Aug;4(2):102-20.
33. Wagner PD, Naumann PF, Laravuso RB. Simultaneous measurement of eight foreign gases in blood by gas chromatography. J Appl Physiol. 1974 May;36(5):600-5.
34. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest. 1977 Feb;59(2):203-16.
35. Yamaguchi K, Mori M, Kawai A, Takasugi T, Oyamada Y, Koda E. Inhomogeneities of ventilation and the diffusing capacity to perfusion in various chronic lung diseases. Am J Respir Crit Care Med. 1997 Jul;156(1):86-93.
36. Niklason L, Eckerstrom J, Jonson B. The influence of venous admixture on alveolar dead space and carbon dioxide exchange in acute respiratory distress syndrome: computer modelling. Crit Care. 2008;12(2):R53.
37. Kuwabara S, Duncalf D. Effect of anatomic shunt on physiologic deadspace-to-tidal volume ratio--a new equation. Anesthesiology. 1969 Dec;31(6):575-7.
38. Tang Y, Turner MJ, Baker AB. Effects of alveolar dead-space, shunt and V/Q distribution on respiratory dead-space measurements. Br J Anaesth. 2005 Oct;95(4):538-48.
39. Mecikalski MB, Cutillo AG, Renzetti AD, Jr. Effect of right-to-left shunting on alveolar dead space. Bull Eur Physiopathol Respir. 1984 Nov-Dec;20(6):513-9.

40. Wagner PD. Causes of a high physiological dead space in critically ill patients. Crit Care. 2008;12(3):148.
41. Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am J Respir Crit Care Med. 2008 Sep 15;178(6):618-23.
42. Ong T, McClintock DE, Kallet RH, Ware LB, Matthay MA, Liu KD. Ratio of angiopoietin-2 to angiopoietin-1 as a predictor of mortality in acute lung injury patients. Crit Care Med. 2010 Sep;38(9):1845-51.
43. Wagner PD. The multiple inert gas elimination technique (MIGET). Intensive Care Med. [Review]. 2008 Jun;34(6):994-1001.
44. West JB, Hackett PH, Maret KH, Milledge JS, Peters RM, Jr., Pizzo CJ, et al. Pulmonary gas exchange on the summit of Mount Everest. J Appl Physiol. 1983 Sep;55(3):678-87.
45. Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in climbers on Mount Everest. N Engl J Med. 2009 Jan 8;360(2):140-9.
46. Ware LB. Prognostic determinants of acute respiratory distress syndrome in adults: impact on clinical trial design. Crit Care Med. 2005 Mar;33(3 Suppl):S217-22.
47. Badal JJ, Chen KJ, Loeb RG. Measurement of Dead Space in Subjects Under General Anesthesia Using Standard Anesthesia Equipment. Anesth Analg. Jan 6.
48. Siddiki H, Kojicic M, Li G, Yilmaz M, Thompson TB, Hubmayr RD, et al. Bedside quantification of dead-space fraction using routine clinical data in patients with acute lung injury: secondary analysis of two prospective trials. Crit Care. Jul 29;14(4):R141.
49. Flancbaum L, Choban PS, Sambucco S, Verducci J, Burge JC. Comparison of indirect calorimetry, the Fick method, and prediction equations in estimating the energy requirements of critically ill patients. Am J Clin Nutr. 1999 Mar;69(3):461-6.
50. Frankenfield D, Hise M, Malone A, Russell M, Gradwell E, Compher C. Prediction of resting metabolic rate in critically ill adult patients: results of a systematic review of the evidence. J Am Diet Assoc. 2007 Sep;107(9):1552-61.
51. Hardman JG, Aitkenhead AR. Estimation of alveolar deadspace fraction using arterial and end-tidal CO2: a factor analysis using a physiological simulation. Anaesth Intensive Care. 1999 Oct;27(5):452-8.

52. Hardman JG, Aitkenhead AR. Estimating alveolar dead space from the arterial to end-tidal CO(2) gradient: a modeling analysis. Anesth Analg. 2003 Dec;97(6):1846-51.
53. Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man. J Appl Physiol. 1960 May;15:383-9.
54. Frankenfield DC, Alam S, Bekteshi E, Vender RL. Predicting dead space ventilation in critically ill patients using clinically available data. Crit Care Med. Jan;38(1):288-91.
55. Kline JA, Israel EG, Michelson EA, O'Neil BJ, Plewa MC, Portelli DC. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study. JAMA. 2001 Feb 14;285(6):761-8.
56. Kline JA, Kubin AK, Patel MM, Easton EJ, Seupal RA. Alveolar dead space as a predictor of severity of pulmonary embolism. Acad Emerg Med. 2000 Jun;7(6):611-7.
57. Verschuren F, Liistro G, Coffeng R, Thys F, Roeseler J, Zech F, et al. Volumetric capnography as a screening test for pulmonary embolism in the emergency department. Chest. 2004 Mar;125(3):841-50.
58. Hubble CL, Gentile MA, Tripp DS, Craig DM, Meliones JN, Cheifetz IM. Deadspace to tidal volume ratio predicts successful extubation in infants and children. Crit Care Med. 2000 Jun;28(6):2034-40.
59. Estay A, Claure N, D'Ugard C, Organero R, Bancalari E. Effects of instrumental dead space reduction during weaning from synchronized ventilation in preterm infants. J Perinatol. Jul;30(7):479-83.
60. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med. 1991 May 23;324(21):1445-50.
61. Jabour ER, Rabil DM, Truwit JD, Rochester DF. Evaluation of a new weaning index based on ventilatory endurance and the efficiency of gas exchange. Am Rev Respir Dis. 1991 Sep;144(3 Pt 1):531-7.
62. Gluck EH. Predicting eventual success or failure to wean in patients receiving long-term mechanical ventilation. Chest. 1996 Oct;110(4):1018-24.
63. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, et al. Compliance and dead space fraction indicate an optimal level of positive end-

expiratory pressure after recruitment in anesthetized patients. Anesth Analg. 2008 Jan;106(1):175-81, table of contents.
64. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med. 1975 Feb 6;292(6):284-9.
65. Beydon L, Uttman L, Rawal R, Jonson B. Effects of positive end-expiratory pressure on dead space and its partitions in acute lung injury. Intensive Care Med. 2002 Sep;28(9):1239-45.
66. Tusman G, Suarez-Sipmann F, Bohm SH, Pech T, Reissmann H, Meschino G, et al. Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med. 2006 Nov;32(11):1863-71.
67. Lucangelo U, Blanch L. Dead space. Intensive Care Med. 2004 Apr;30(4):576-9.
68. Tusman G, Bohm SH, Sipmann FS, Maisch S. Lung recruitment improves the efficiency of ventilation and gas exchange during one-lung ventilation anesthesia. Anesth Analg. 2004 Jun;98(6):1604-9, table of contents.
69. Tusman G, Bohm SH, Suarez-Sipmann F, Turchetto E. Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. Can J Anaesth. 2004 Aug-Sep;51(7):723-7.
70. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006 Apr 27;354(17):1775-86.
71. Calzia E, Radermacher P, Bein T. Unveiling alveolar recruitment: the fascinating trail between theory and practice. Intensive Care Med. 2006 Nov;32(11):1686-8.
72. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002 Apr 25;346(17):1281-6.
73. Shimada Y, Yoshiya I, Tanaka K, Sone S, Sakurai M. Evaluation of the progress and prognosis of adult respiratory distress syndrome. Simple respiratory physiologic measurement. Chest. 1979 Aug;76(2):180-6.
74. Raurich JM, Vilar M, Colomar A, Ibanez J, Ayestaran I, Perez-Barcena J, et al. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir Care. Mar;55(3):282-7.

75. Valta P, Uusaro A, Nunes S, Ruokonen E, Takala J. Acute respiratory distress syndrome: frequency, clinical course, and costs of care. Crit Care Med. 1999 Nov;27(11):2367-74.
76. Kallet RH, Alonso JA, Pittet JF, Matthay MA. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. Respir Care. 2004 Sep;49(9):1008-14.
77. Johannigman JA, Davis K, Jr., Miller SL, Campbell RS, Luchette FA, Frame SB, et al. Prone positioning for acute respiratory distress syndrome in the surgical intensive care unit: who, when, and how long? Surgery. 2000 Oct;128(4):708-16.
78. Davis K, Jr., Johannigman JA, Campbell RS, Marraccini A, Luchette FA, Frame SB, et al. The acute effects of body position strategies and respiratory therapy in paralyzed patients with acute lung injury. Crit Care. 2001;5(2):81-7.
79. Gattinoni L, Vagginelli F, Carlesso E, Taccone P, Conte V, Chiumello D, et al. Decrease in PaCO2 with prone position is predictive of improved outcome in acute respiratory distress syndrome. Crit Care Med. 2003 Dec;31(12):2727-33.
80. Nunn JF. Ventilation nomograms during anaesthesia. Anaesthesia. 1960 Jan;15:65.
81. Kenny S. The Adelaide ventilation guide. Br J Anaesth. 1967 Jan;39(1):21-3.
82. Radford EP, Jr., Ferris BG, Jr., Kriete BC. Clinical use of a nomogram to estimate proper ventilation during artificial respiration. The New England journal of medicine. 1954 Nov 25;251(22):877-84.
83. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000 May 4;342(18):1301-8.
84. Ravenscraft SA, McArthur CD, Path MJ, Iber C. Components of excess ventilation in patients initiated on mechanical ventilation. Crit Care Med. 1991 Jul;19(7):916-25.
85. Lumb AB, Nunn JF. Nunn's applied respiratory physiology. 7th ed. / Andrew B. Lumb ; foreword by Ronald G. Pearl. ed. Edinburgh: Churchill Livingstone; 2010.
86. 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 Sep;81(3):327-32.

87. Hardman JG, Aitkenhead AR. Estimating alveolar dead space from the arterial to end-tidal CO(2) gradient: a modeling analysis. Anesth Analg. 2003 Dec;97(6):1846-51.
88. Hardman JG, Aitkenhead AR. Validation of an original mathematical model of CO(2) elimination and dead space ventilation. Anesth Analg. 2003 Dec;97(6):1840-5.
89. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. The New England journal of medicine. 2000 May 4;342(18):1301-8.
90. Bersten AD, Edibam C, Hunt T, Moran J. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med. 2002 Feb 15;165(4):443-8.
91. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. The New England journal of medicine. 2004 Jul 22;351(4):327-36.
92. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991 Dec;100(6):1619-36.
93. Forbat AF, Her C. Correction for gas compression in mechanical ventilators. Anesth Analg. 1980 Jul;59(7):488-93.
94. Fletcher R, Jonson B, Cumming G, Brew J. The concept of deadspace with special reference to the single breath test for carbon dioxide. Br J Anaesth. [Research Support, Non-U.S. Gov't]. 1981 Jan;53(1):77-88.
95. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-10.
96. Kallet RH, Daniel BM, Garcia O, Matthay MA. Accuracy of physiologic dead space measurements in patients with acute respiratory distress syndrome using volumetric capnography: comparison with the metabolic monitor method. Respir Care. 2005 Apr;50(4):462-7.
97. Lum L, Saville A, Venkataraman ST. Accuracy of physiologic deadspace measurement in intubated pediatric patients using a metabolic monitor: comparison with the Douglas bag method. Crit Care Med. 1998 Apr;26(4):760-4.

98. Fletcher R, Werner O, Nordstrom L, Jonson B. Sources of error and their correction in the measurement of carbon dioxide elimination using the Siemens-Elema CO2 Analyzer. Br J Anaesth. 1983 Feb;55(2):177-85.
99. Castle RA, Dunne CJ, Mok Q, Wade AM, Stocks J. Accuracy of displayed values of tidal volume in the pediatric intensive care unit. Crit Care Med. 2002 Nov;30(11):2566-74.
100. Niklason L, Eckerstrom J, Jonson B. The influence of venous admixture on alveolar dead space and carbon dioxide exchange in acute respiratory distress syndrome: computer modelling. Critical care. 2008;12(2):R53.
101. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010 Sep 16;363(12):1107-16.
102. Kenny S, Lewis M. The Adelaide respirator. Br J Anaesth. 1960 Sep;32:444-6.
103. Radford EP, Jr. Ventilation standards for use in artificial respiration. J Appl Physiol. 1955 Jan;7(4):451-60.
104. Kiiski R, Takala J. Hypermetabolism and efficiency of CO2 removal in acute respiratory failure. Chest. 1994 Apr;105(4):1198-203.
105. Kinney JM, Askanazi J, Gump FE, Foster RJ, Hyman AI. Use of the ventilatory equivalent to separate hypermetabolism from increased dead space ventilation in the injured or septic patient. J Trauma. 1980 Feb;20(2):111-9.
106. Coss-Bu JA, Walding DL, David YB, Jefferson LS. Dead space ventilation in critically ill children with lung injury. Chest. 2003 Jun;123(6):2050-6.
107. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care 2010;14(2):220.
108. Brandi LS, Bertolini R, Santini L, Cavani S. Effects of ventilator resetting on indirect calorimetry measurement in the critically ill surgical patient. Crit Care Med. 1999 Mar;27(3):531-9.
109. Anzueto A, Frutos-Vivar F, Esteban A, Alia I, Brochard L, Stewart T, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med. 2004 Apr;30(4):612-9.
110. Rai S, Engelberts D, Laffey JG, Frevert C, Kajikawa O, Martin TR, et al. Therapeutic hypercapnia is not protective in the in vivo surfactant-depleted rabbit lung. Pediatr Res. 2004 Jan;55(1):42-9.

111. Masood A, Yi M, Lau M, Belcastro R, Shek S, Pan J, et al. Therapeutic effects of hypercapnia on chronic lung injury and vascular remodeling in neonatal rats. Am J Physiol Lung Cell Mol Physiol. 2009 Nov;297(5):L920-30.
112. Shiota S, Okada T, Naitoh H, Ochi R, Fukuchi Y. Hypoxia and hypercapnia affect contractile and histological properties of rat diaphragm and hind limb muscles. Pathophysiology. 2004 Jul;11(1):23-30.
113. Gregory GA, Eger EI, Smith NT, Cullen BF. The cardiovascular effects of carbon dioxide in man awake and during diethyl ether anesthesia. Anesthesiology. 1974 Mar;40(3):301-4.
114. Dark DS, Pingleton SK, Kerby GR. Hypercapnia during weaning. A complication of nutritional support. Chest. 1985 Jul;88(1):141-3.
115. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs high proportion of carbohydrate calories. Chest. 1992 Aug;102(2):551-5.
116. de las Alas V, Voorhees WD, Geddes LA, Bourland JD, Schoenlein WE. End-tidal carbon dioxide concentration, carbon dioxide production, heart rate, and blood pressure as indicators of induced hyperthermia. J Clin Monit. 1990 Jul;6(3):183-5.
117. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. Orphanet J Rare Dis. 2007;2:21.
118. Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. Am J Respir Crit Care Med 1995 Jan;151(1):10-4.
119. Prakash O, Jonson B, Bos E, Meij S, Hugenholtz PG, Hekman W. Cardiorespiratory and metabolic effects of profound hypothermia. Crit Care Med. 1978 Sep-Oct;6(5):340-6.
120. Ralley FE, Wynands JE, Ramsay JG, Carli F, MacSullivan R. The effects of shivering on oxygen consumption and carbon dioxide production in patients rewarming from hypothermic cardiopulmonary bypass. Can J Anaesth. 1988 Jul;35(4):332-7.
121. Delaunay L, Bonnet F, Duvaldestin P. Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. Br J Anaesth. 1991 Oct;67(4):397-401.

122. Weissman C, Kemper M, Damask MC, Askanazi J, Hyman AI, Kinney JM. Effect of routine intensive care interactions on metabolic rate. Chest. 1984 Dec;86(6):815-8.
123. Baarends EM, Schols AM, Slebos DJ, Mostert R, Janssen PP, Wouters EF. Metabolic and ventilatory response pattern to arm elevation in patients with COPD and healthy age-matched subjects. Eur Respir J. 1995 Aug;8(8):1345-51.
124. Weissman C, Kemper M, Elwyn DH, Askanazi J, Hyman AI, Kinney JM. The energy expenditure of the mechanically ventilated critically ill patient. An analysis. Chest. 1986 Feb;89(2):254-9.
125. Gama de Abreu M, Guldner A, Pelosi P. Spontaneous breathing activity in acute lung injury and acute respiratory distress syndrome. Curr Opin Anaesthesiol. 2012 Apr;25(2):148-55.
126. Kallet RH. Patient-ventilator interaction during acute lung injury, and the role of spontaneous breathing: part 2: airway pressure release ventilation. Respir Care. 2011 Feb;56(2):190-203; discussion -6.
127. Swinamer DL, Phang PT, Jones RL, Grace M, King EG. Effect of routine administration of analgesia on energy expenditure in critically ill patients. Chest 1988 Jan;93(1):4-10.
128. Askanazi J, Rosenbaum SH, Hyman AI, Silverberg PA, Milic-Emili J, Kinney JM. Respiratory changes induced by the large glucose loads of total parenteral nutrition. Jama 1980 Apr 11;243(14):1444-7.
129. Liposky JM, Nelson LD. Ventilatory response to high caloric loads in critically ill patients. Crit Care Med. 1994 May;22(5):796-802.
130. van den Berg B, Stam H. Metabolic and respiratory effects of enteral nutrition in patients during mechanical ventilation. Intensive Care Med. 1988;14(3):206-11.
131. al-Saady NM, Blackmore CM, Bennett ED. High fat, low carbohydrate, enteral feeding lowers PaCO2 and reduces the period of ventilation in artificially ventilated patients. Intensive Care Med. 1989;15(5):290-5.
132. Raurich JM, Ibanez J, Marse P. [CO2 production and thermogenesis induced by enteral and parenteral nutrition]. Nutr Hosp. 1996 Mar-Apr;11(2):108-13.
133. Kemper M, Weissman C, Askanazi J, Hyman AI, Kinney JM. Metabolic and respiratory changes during weaning from mechanical ventilation. Chest 1987 Dec;92(6):979-83.

134. Petros S, Engelmann L. Validity of an abbreviated indirect calorimetry protocol for measurement of resting energy expenditure in mechanically ventilated and spontaneously breathing critically ill patients. Intensive Care Med. 2001 Jul;27(7):1164-8.
135. Stratton HH, Feustel PJ, Newell JC. Regression of calculated variables in the presence of shared measurement error. J Appl Physiol. 1987 May;62(5):2083-93.
136. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988 Sep;138(3):720-3.
137. Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. Am J Clin Nutr. 1984 Jul;40(1):168-82.
138. Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN J Parenter Enteral Nutr. 1979 Nov-Dec;3(6):452-6.
139. Siddiki H, Kojicic M, Li G, Yilmaz M, Thompson TB, Hubmayr RD, et al. Bedside quantification of dead-space fraction using routine clinical data in patients with acute lung injury: secondary analysis of two prospective trials. Crit Care. 2010 Jul 29;14(4):R141.
140. Ware LB. Prognostic determinants of acute respiratory distress syndrome in adults: impact on clinical trial design. Crit Care Med 2005 Mar;33(3 Suppl):S217-22.
141. Ferguson ND, Kacmarek RM, Chiche JD, 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 Med 2004 Jun;30(6):1111-6.
142. Estenssoro E, Dubin A, Laffaire E, Canales HS, Saenz G, Moseinco M, et al. Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome. Intensive Care Med. 2003 Nov;29(11):1936-42.
143. Allardet-Servent J, Forel JM, Roch A, Guervilly C, Chiche L, Castanier M, et al. FIO2 and acute respiratory distress syndrome definition during lung protective ventilation. Crit Care Med 2009 Jan;37(1):202-7, e4-6.
144. 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. Acute respiratory distress syndrome. Am J Respir Crit Care Med. 1998 Apr;157(4 Pt 1):1332-47.

145. Rumbak MJ, Solomon DA. Does the clinical consensus definition of ALI/ARDS continue to fit our needs? Chest. 2009 Feb;135(2):251-2.
146. Atabai K, Matthay MA. The pulmonary physician in critical care. 5: Acute lung injury and the acute respiratory distress syndrome: definitions and epidemiology. Thorax 2002 May;57(5):452-8.
147. Sinha P, Fauvel NJ, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of ventilation. Br J Anaesth. 2009 May;102(5):692-7.
148. Seeley E, McAuley DF, Eisner M, Miletin M, Matthay MA, Kallet RH. Predictors of mortality in acute lung injury during the era of lung protective ventilation. Thorax 2008 Nov;63(11):994-8.
149. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama 2012 Jun 20;307(23):2526-33.

Index of Equations

Index of Figures

Index of Tables