

***Estimating Dead Space
Ventilation: A Computational
Modelling Approach towards
Evaluation of Clinical Estimates
of Dead Space Fraction in
Critically Ill Patients***

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List of Abbreviation

P_{aCO_2}	Arterial partial pressure of CO_2
P_{ACO_2}	Mean alveolar partial pressure of CO_2
$P_{\bar{E}CO_2}$	Mixed expired partial pressure of CO_2
$E'CO_2$	End-tidal partial pressure of CO_2
$P_a-E'CO_2$	Arterial to end-tidal PCO_2 gradient
FiO_2	Inspired oxygen fraction
V_{O_2}	Oxygen consumption
V_{CO_2}	Carbon dioxide production
VR	Ventilatory ratio
RR	Respiratory rate
V/Q	Ventilation/Perfusion
V_E	Minute ventilation
V_T	Tidal volume
$V_{T_{exh}}$	Exhaled tidal volume
$V_{d_{anat}}$	Anatomical dead space
V_D/V_T	Dead space to tidal volume ratio
$V_{d_{phys}}/V_t$	Physiological dead space to tidal volume ratio
$V_{D_{alv}}/V_{T_{alv}}$	Alveolar dead space to alveolar tidal volume ratio
PEEP	Positive end-expiratory pressure

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ABSTRACT

Dead space is the part of tidal volume that does not participate in gas exchange and represents wasted ventilation. It is often increased in pulmonary diseases. Quantification of dead space by the original Bohr's equation requires measuring mean alveolar pressure of CO₂ ($P_{A_{CO_2}}$) and mixed expired partial pressure of CO₂ ($P_{\bar{E}_{CO_2}}$). Because of the difficulties and technical issues related with measuring $P_{A_{CO_2}}$ and $P_{\bar{E}_{CO_2}}$, alternative methods have been proposed for the estimation of dead space. This thesis attempts to explore the performance of some methods proposed for the estimation of dead space to tidal volume ratio (V_D/V_T) in different pulmonary configurations and clinical scenarios.

In the first study, we compared the performance of 5 different methods for the estimation V_D/V_T with the gold standard method in multiple ventilation/perfusion (V/Q) relationships. Six pulmonary configurations all with same alveolar dead space fraction of 0.25, but with different specific pattern of V/Q distribution were created within the Nottingham Physiology Simulator (NPS). Next, variations in the methods of estimating V_D/V_T upon varying 4 physiological factors were analysed. We

concluded that the estimation of alveolar dead space ratio by 5 methods of estimating V_D/V_T is influenced by pattern of V/Q distribution and alterations in the relevant physiological factors.

In the second study, we further analysed performance of 5 methods for estimating dead space ratio in patients with acute respiratory distress syndrome (ARDS). Nineteen ARDS subjects were created within the NPS and alveolar dead space fraction was measured by the gold standard method. Then, dead space fraction was determined by 5 different methods for estimating dead space fraction. We found that the estimates of dead space fraction measure different than the conventional equation in ARDS.

In the third study, we compared efficacy of three lung recruitment maneuvers (RMs) in patients with ARDS. Six virtual ARDS patients were created and changes in dead space fraction, $(Pa-E'CO_2)/Pa_{CO_2}$ and other parameters were observed following the RMs. The results of this study showed that changes in $(Pa-E'CO_2)/Pa_{CO_2}$ closely relate with changes in V_D/V_T . These findings suggest that in clinical settings where it is not possible to measure dead space fraction, a simple estimate of V_D/V_T may be used to monitor the efficacy of RMs and titration of positive end-expiratory pressure.

Simplified approaches for the estimation of dead space fraction may allow widespread use of this important physiological variable for diagnostic and prognostic purposes in critical care settings.

CHAPTER 1

Introduction

Definition of Dead Space

In 1891, Christian Bohr first described the concept of pulmonary dead space as the part of tidal volume that does not participate in gas exchange and represents wasted ventilation (2-4). Physiological dead space comprises of anatomical dead space and alveolar dead space (5).

Physiological dead space = Anatomical dead space + Alveolar dead space

Anatomical dead space

Anatomical dead space refers to the volume of the conducting airways (i.e. from nostrils to terminal bronchioles) (1). It is also referred as series dead space and includes any equipment dead space, such as mouthpiece and endotracheal tube (6). The normal value is about 150 ml and depends on size and posture of a subject (1).

Alveolar dead space

Alveolar dead space refers to the volume of air in respiratory bronchioles and alveoli that does not take part in gas exchange. It is the volume of alveoli that are ventilated but not perfused (7) or minimally perfused (8). Alveolar dead space is negligible in a

healthy person and the normal value of dead space to tidal volume ratio ranges from 0.2 to 0.35 during resting breathing (1).

Measuring the Dead Space

Dead space is an important physiological variable that indicates wasted ventilation. The following section describes the conventional methods for the measurement of dead space fraction.

Fowler's method

In this method, the subject inhales 100% oxygen through a valve box, and a sampling tube of a rapid nitrogen analyser continuously samples expired gas (1). Nitrogen concentration is plotted against the expired volume of gas. Initially, exhaled volume contains no nitrogen and nitrogen concentration rises as alveolar air is exhaled, followed by a plateau phase (Fig. 1). Dead space was determined from the graph by drawing a vertical line down the upstroke curve of the graph, such that area A and area B are equal. The point where vertical line intercepts x-axis is dead space volume and now termed as anatomical dead space (5). Bartels et al. used Fowler's method but they traced expired carbon dioxide instead of nitrogen. The calculated dead space volume did not change and they proposed that expired carbon dioxide analysis can be used as an alternative to nitrogen (9).

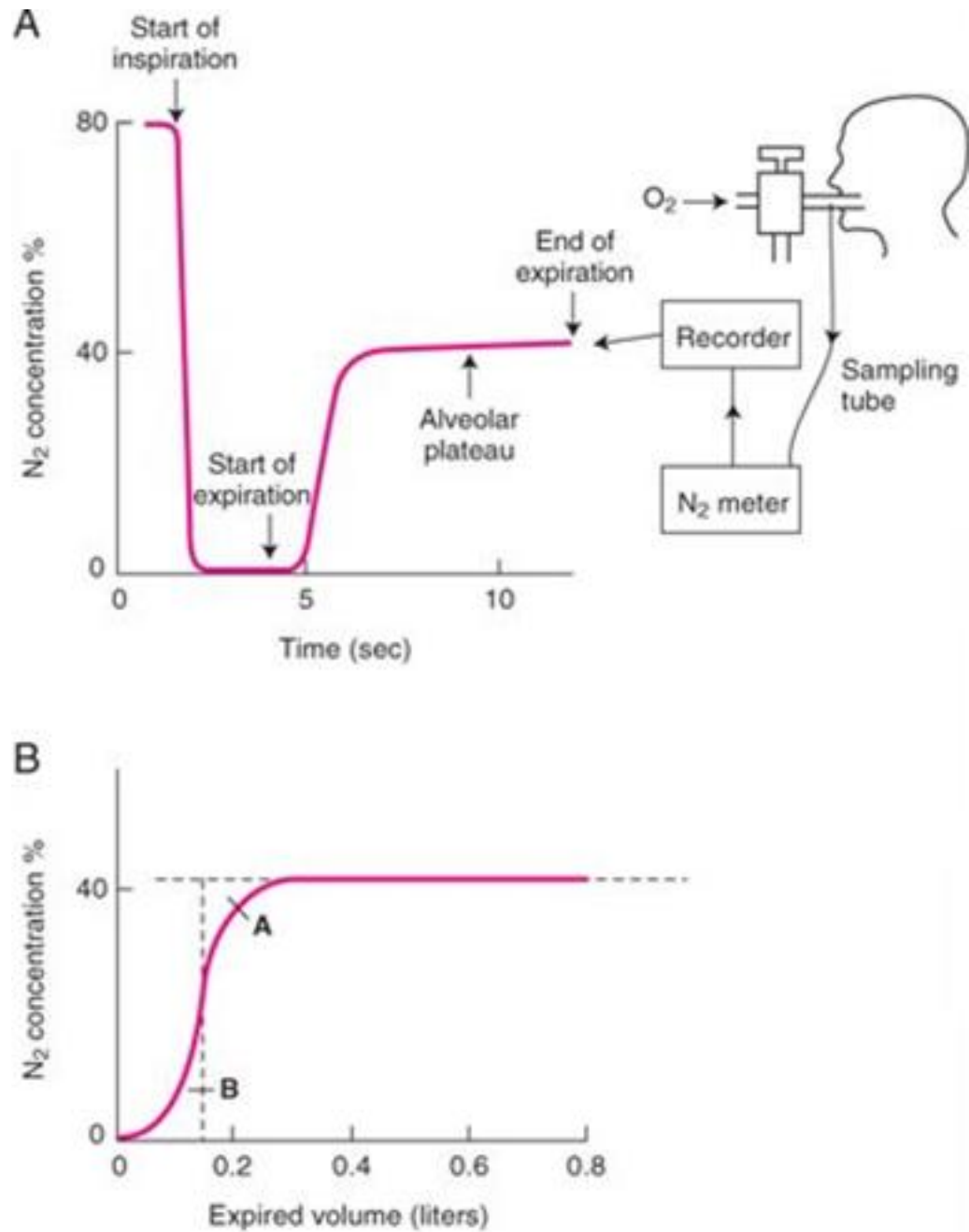


Figure 1: Fowler's method of measuring anatomical dead space.

The above figure is adapted from West, 2012 (1).

The Bohr equation of dead space

Christian Bohr named the portion of tidal volume (V_T) that does not participate in gas exchange as "schadliche Raume" (damaging space) (2). He assumed that inspired air does not contain any carbon dioxide. Thus, CO_2 in the expired air comes from alveolar ventilation and he derived the following equation for the calculation of dead space fraction.

$$\frac{V_D}{V_T} = 1 - \frac{F_{E_{CO_2}}}{F_{A_{CO_2}}} \quad (\text{Equation 1})$$

where, $F_{E_{CO_2}}$ is mixed expired fractional concentration of carbon dioxide and $F_{A_{CO_2}}$ is mean alveolar fractional concentration of CO_2 . Fractional concentrations are commonly substituted with partial pressure of CO_2 as follows:

$$\frac{V_D}{V_T} = 1 - \frac{P_{E_{CO_2}}}{P_{A_{CO_2}}} \quad (\text{Equation 2})$$

The Bohr-Enghoff dead space equation

The Bohr's equation of dead space requires measurement of mean alveolar partial pressure of CO_2 . This limits its use for practical purposes (5). In 1938, Enghoff substituted arterial partial pressure

of carbon dioxide (P_{aCO_2}) for mean alveolar partial pressure of carbon dioxide. He modified Bohr's dead space equation as follows:

$$\frac{V_D}{V_T} = 1 - \frac{P_{\bar{E}CO_2}}{P_{aCO_2}} \quad (\text{Equation 3})$$

The above equation is termed as the Bohr-Enghoff dead space equation. This is the most commonly used equation for measurement of dead space to tidal volume ratio. Partial pressure of CO_2 in expired gas can be measured by following three methods:

- 1) Douglas Bag
- 2) Indirect Calorimetry
- 3) Capnography

Douglas bag

This method involves the collection of expired gas for several minutes in a large bag and expired CO_2 is then measured by blood gas analyser (10). This is an old and traditional method of measuring mixed expired CO_2 . It is rarely used in intensive care unit nowadays (11) and it also requires a correction factor for compressed gas that varies with physiological factors, such as tidal volume (11).

Indirect calorimetry

A monitor measures oxygen consumption and CO₂ production and the measurements are displayed on a monitor. It is also known as metabolic monitor.

Capnography

Capnography refers to the measurement and graphic display of carbon dioxide concentration in exhaled air (12). Capnography devices detect CO₂ by a number of mechanisms, such as infrared spectroscopy, molecular correlation spectroscopy, mass spectroscopy, Raman spectroscopy and photoacoustic spectroscopy (12, 13). Carbon dioxide concentration can be plotted against time or exhaled tidal volume i.e. time-based or volume-based capnography, respectively (12, 14). Time-based capnography monitors end-tidal CO₂ concentration and respiratory rate (RR). Capnography allows earlier detection of hypoventilation than oxygen desaturation (15) and it has been used extensively as a monitoring tool during procedural sedation and analgesia (16). Volumetric capnography or single-breath test for CO₂ (SBT-CO₂) is more informative than simple time-based capnography, as it also allows for the measurement of CO₂ production and dead space (5, 17). Figure 2 illustrates phases of capnography.

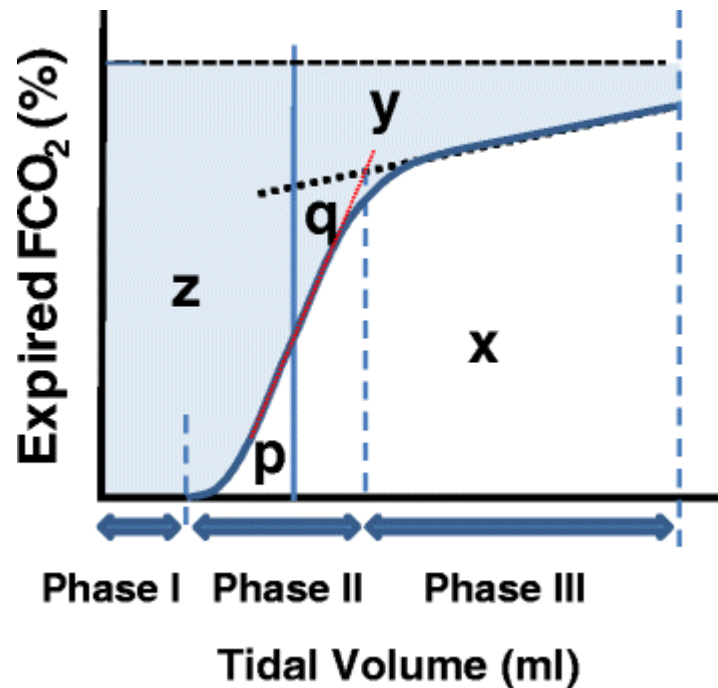


Figure 2: Phases of volumetric capnography.

In the above figure, shaded area represents total dead space. Area z (area to the left of solid line) represents anatomical dead space, area y (area above the slope of phase III) represents alveolar dead space and area x represents volume of CO₂ expired per breath (Adapted from Verscheure, 2016 (14)).

Phase I: Represents inspiration and CO₂ is at baseline.

Phase II: Represents expiration. The concentration of CO₂ rises sharply after initial series dead space.

Phase III: Represents expiration plateau and indicates alveolar emptying. End-tidal carbon dioxide is the concentration of CO₂ at the end of phase III.

Volumetric capnography provides detailed information on ventilation/perfusion relationship of lung as indicated by the slope of phase III. A plateau phase III represents homogenous emptying of alveoli as seen in healthy individuals. The deviation of phase III from plateau shape indicates inhomogeneous lung units that are common in respiratory diseases (5, 13).

The Clinical Relevance of Dead Space Fraction

Dead space ventilation is often increased in pulmonary diseases (18-20). A large number of studies have demonstrated an association between dead space ventilation and clinical outcomes in critically ill patients (18, 21-29). It has been shown as an independent predictor of mortality in patients with acute respiratory distress syndrome (ARDS) (18). A few studies have also examined prognostic importance of dead space in patients who had suffered trauma (30-32). It has also been used to monitor progression of disease and respiratory response following therapeutic interventions (33-39). For example, dead space to tidal volume ratio was used to monitor the effect of prone position

in patients with ARDS (40), for diagnosis of pulmonary embolism (20, 41, 42), separating patients with asthma from patients with emphysema with the same degree of airways obstruction (43) and to monitor the efficacy of activated protein C in patients with ARDS (35, 44). Importance of dead space ventilation has been studied in infant and children (45, 46) and a few clinical applications of dead space fraction in this group include predicting outcome of extubation (47), to determine pulmonary improvements in neonates with extracorporeal membrane oxygenation (48), prediction of survival in infants with congenital diaphragmatic hernia (49), and to compare duration of mechanical ventilation (50, 51). Estimation of dead space to tidal volume ratio is important as it may help in making decisions regarding clinical management of a critically ill patient.

Chapter 2

ARDS and Prognostic Significance of Dead Space Fraction

Acute Respiratory Distress Syndrome

ARDS was first described by Ashbaugh et al. in late 20th century (52). Before the American-European Consensus Conference (AECC), various definitions of ARDS were used for clinical and research purposes (53, 54). According to AECC recommendations, ARDS was defined as acute onset of hypoxaemia with $\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg (regardless of positive end-expiratory pressure level) with bilateral infiltrates on chest X-ray and pulmonary capillary wedge pressure ≤ 18 mmHg (no clinical signs of left atrial hypertension) and the term acute lung injury (ALI) was defined as hypoxaemia with the same characteristics but with $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 300 mmHg (55-59). There were few limitations of ARDS definition, such as ambiguities in defining the term "acute", sensitivity of $\text{PaO}_2/\text{FiO}_2$ to ventilator settings and poor reliability of chest X-ray (59-62). A panel of experts met at Berlin in 2011 to address the limitations of ARDS definition and they updated AECC definition of ARDS. The revised Berlin definition of ARDS had better predictive validity for mortality than previous AECC definition with an area under the receiver operative curve of 0.577 (95% CI, 0.561-0.593) vs. 0.536 (95% CI, 0.520-0.553; $P < .001$) (60).

The Berlin Definition of ARDS

According to the Berlin definition ARDS is defined as: the onset of respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms, appearance of bilateral opacities on chest radiograph, presence of non-cardiogenic oedema and $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 300 mmHg with positive end-expiratory pressure (PEEP) of ≥ 5 cm H₂O (55, 58). The term acute lung injury was removed from the definition and ARDS was classified as mild, moderate or severe depending upon $\text{PaO}_2/\text{FiO}_2$ ratio (58). Associated risk factors of ARDS include both direct lung injury (e.g. pneumonia, aspiration of gastric contents, drowning and inhalational injury) and indirect lung injury (trauma, burns, pancreatitis and non-cardiogenic shock) (58). A recent study that collected data from 459 intensive care units (ICUs) from 50 countries reports period prevalence of mild ARDS 30.0%, of moderate ARDS 46.6% and of severe ARDS 23.4% (3). The mortality was 34.9% for patients with mild ARDS, 40.3% for patients with moderate ARDS and 46.1% for patients with severe ARDS (3).

ARDS and dead space fraction

Previous research has establish that increase dead space ventilation is a feature of ARDS (18, 63, 64). Lung-protective mechanical ventilation strategies are used to treat hypoxaemia

in patients with ARDS (65-67). Indices of oxygenation, such as $\text{PaO}_2/\text{FiO}_2$, oxygen saturation, and oxygenation index have been used to determine prognosis in ARDS (18, 68). An increase in the dead space fraction has been shown as a more sensitive predictor of mortality in ARDS patients than conventional physiological parameters (22).

Various pathophysiological mechanisms can contribute to the increase in measured physiological dead space (5). Uneven distribution of pulmonary blood flow results in elevated dead space fraction (69). Two main pathophysiological processes result in alterations in pulmonary blood flow in ARDS patients (70). First, shock causes pulmonary hypoperfusion or hyperperfusion states. Pulmonary hyperperfusion is associated with hyperdynamic cardiovascular states (such as severe sepsis) that create lung regions with very high V/Q ratios (70-72). Second, pulmonary blood flow is altered due to inflammatory mechanisms, that cause pulmonary vascular injury and increase in pulmonary vascular resistance (70, 73-77). Multiple factors can contribute to the increase in pulmonary vascular resistance in ARDS, such as pulmonary vasoconstriction, macro and micro emboli formation, endothelial cell swelling, mechanical compression of pulmonary capillaries and microvascular changes from fibrosis (56, 78-81).

Another reason for increased physiological dead space in ARDS is intra-pulmonary shunt (5, 82), as diffuse endothelial and epithelial lung injury cause alveolar flooding (83-86), impairment of alveolar ventilation, inactivation of surfactant and worsening of V/Q distribution (65). Furthermore, ventilation strategies involving higher tidal volume and high positive end-expiratory pressure can over-distend lung regions, creating high V/Q regions and an increase in dead space to tidal volume ratio (5).

Prognostic significance of V_D/V_T

Dead space to tidal volume ratio is an important respiratory parameter that provides an insight into ventilation/perfusion relationship and the extent of carbon dioxide clearance (87, 88). Many studies have looked into the association between dead space ventilation and prognosis in critically ill patients (18, 26, 89). Some important studies that show an association between dead space fraction and prognosis are described in the following section.

Nuckton et al.

In 2002, Nuckton et al. published an important paper in which they measured dead space fraction in patients with ARDS (18). They collected data from 179 adult intubated patients who were diagnosed with ARDS according to the American-European consensus definition of ARDS. They used a metabolic monitor to measure mean expired PCO_2 and calculated dead space fraction by the Bohr-Enghoff equation of dead space. They found that mean dead-space fraction was significantly higher among non-survivors vs. survivors (0.63 ± 0.09 vs. 0.54 ± 0.09 , $P < 0.001$). Multiple regression analysis showed that dead space fraction was independently associated with increased risk of death and for every 0.05 increase in V_D/V_T , the odds of death increased by 45%. They concluded that dead space fraction is increased

in early phase of ARDS and it is independently associated with mortality.

Lucangelo et al.

Lucangelo et al. conducted an observational study to find an association between V_D/V_T and mortality in mechanically ventilated patients (25). Thirty six mechanically ventilated patients with Murray lung injury score ≥ 1 and $PaO_2/FiO_2 < 300$ were included in the study. Lung-protective mechanical ventilation strategies were used and data was collected at 24 hours and 48 hours of ICU admission. Capnographic indices of dead space that they measured included Bohr dead space, physiologic dead space, expired normalized CO_2 slope, carbon dioxide output and the alveolar ejection volume/tidal volume ratio (V_{AE}/V_T). They found that higher dead space was associated with poor outcomes in ARDS patients and V_{AE}/V_T was more accurate in determining prognosis.

Kallet et al.

Kallet et al. conducted a study to observe changes in dead space fraction during first 6 days of ARDS (70). The data was collected from 59 patients who were mechanically ventilated for at least one week. They used a metabolic monitor to measure V_D/V_T . Dead space to tidal volume ratio was calculated within 24 hours

of the onset of ARDS and the measurements were repeated on day 2, day 3 and day 6. Patients were on either volume-controlled ventilation or pressure-regulated, volume-controlled ventilation, with a target of tidal volume of 10 ± 1 ml/kg. They found that V_D/V_T was significantly higher among non-survivors on day 1 than survivors (0.61 ± 0.09 vs. 0.54 ± 0.08 , $p < 0.05$) and it remained higher on day 2, day 3 and day 6. They also found that there was no significant difference in PaO_2/FiO_2 ratio among survivors vs. nonsurvivors until day 2. They concluded that dead space ratio is increased early in ARDS and V_D/V_T value > 0.55 during the first 6 days of ARDS was associated with significantly higher mortality in patients with ARDS.

In another recent retrospective study Kallet et al. examined the impact of ARDS aetiology on dead space fraction and mortality in patients with ARDS (24). They measured V_D/V_T in 685 patients undergoing lung-protective mechanical ventilation. Subjects were classified as mild, moderate and severe ARDS according to the Berlin definition of ARDS. They measured V_D/V_T , respiratory system compliance, oxygenation index, simplified acute physiology score (SAPS II) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Dead space fraction was measured by volumetric capnography and measurements were taken within 48 hours of onset of

ARDS. They found that magnitude of V_D/V_T varies by aetiology of ARDS and V_D/V_T was significantly higher when primary causes of ARDS were aspiration and pneumonia than non-pulmonary sepsis and trauma. Another important finding was that although was almost similar in pneumonia and aspiration (i.e. 67% and 66% respectively) but mortality was substantially lower in pneumonia than aspiration (34% vs. 47% respectively) and this difference was attributed to high lung injury score in patients with aspiration. They concluded that V_D/V_T is strongly associated with mortality in patients with ARDS.

Zhang et al.

Zhang et al. conducted a study to compare the accuracy of dead space fraction measured by the two different methods in determining prognosis of patients with ARDS (90). First, they measured V_D/V_T by volumetric capnography. Second, dead space fraction was estimated by the Frankenfield equation of dead space. Forty six ARDS patients were recruited and dead space measurements were taken on Day 1 and were repeated on day 2-6. They found that dead space estimated by the Frankenfield equation of dead space on day 4 was significantly higher among patients who died than who survived. There was no significant difference in dead space fraction measured by volumetric capnography until day 5 and day 6. They concluded

that the Frankenfield equation of dead space is more accurate than dead space measured by the conventional method in predicting prognosis of patients with ARDS.

Raurich et al.

Raurich et al. conducted an observational study to find an association between dead space fraction and mortality in patients with ARDS (64). They measured dead space fraction during the early phase (first week) and the intermediate phase (second week) of ARDS. Data was collected from 80 intubated patients with $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 and they were classified as ARDS according to the American-European Consensus Conference definition for ARDS. Dead space fraction was measured by the Douglas bag and data was collected within 3 days of ARDS onset. Dead space measurements were repeated at day 8-10 in 49 out of 80 subjects who remained mechanically ventilated. They found that elevated dead space fraction in both phases of ARDS was associated with poor outcomes and for every 0.05 increase of V_D/V_T odds of death increased by 59% in the early phase and by 186% in the intermediate phase of ARDS. They concluded that increased dead space fraction in the early and the intermediate phase of ARDS is independently associated with mortality.

Estimates of Dead Space

Recent literature emphasizes measuring dead space along with other physiological variables (4, 8, 87, 91, 92). Because of the technical difficulties in measuring dead space to tidal volume ratio by the conventional method different methods are used for the estimation of dead space fraction (10, 63, 91, 93-95). Different authors have proposed various equations for the estimation of dead space to tidal volume ratio (63, 93, 96). The section below describes few methods proposed by researchers for the estimation of dead space ventilation.

The Siddiki et al. estimate

Siddiki et al. conducted secondary analysis of data from two previous studies of ALI/ARDS patients (97). They rearranged alveolar gas equation and derived the following equation for the estimation of dead space fraction (97).

$$V_D/V_T = 1 - ((0.86 \times V_{CO_{2est}}) / (V_E \times Pa_{CO_2})) \text{ (equation 4)}$$

$$V_{CO_{2est}} = (HB_{pred} \times hf \times 0.8) / 6.8644 \text{ (equation 5)}$$

V_E is minute ventilation and $V_{CO_{2est}}$ is estimated metabolic production of carbon dioxide calculated from the Harris-Benedict equation. HB_{pred} is the predicted resting energy

expenditure which is gender specific and *hf* are hypermetabolic factors.

Multiple logistic regression was used to determine prognostic value of the Siddiki et al. estimate. They found that estimated dead space to tidal volume ratio predicted hospital mortality. They concluded that elevated dead space fraction is an independent predictor of mortality and the proposed estimate may be used for the estimation of dead space to tidal volume ratio at the bedside in patients with ARDS (97).

The Tyburski et al. estimate

Tyburski et al. examined the prognostic value of an estimate of alveolar dead space to tidal volume ratio in trauma patients. They estimated alveolar dead space to tidal volume ratio by the arterial to end-tidal PCO₂ difference divided by Pa_{CO₂} i.e. $(Pa - E'CO_2)/Pa_{CO_2}$ (30). Alveolar dead space to tidal volume ratio was measured at 3 phases: (a) initial phase which included data on arrival of patients in the operating room; (b) postresuscitation phase which included data after bleeding was controlled and resuscitation efforts were clinically adequate; and (c) final phase which included data obtained at final intraoperative arterial blood gas analysis. The results showed that there was a significant difference in the estimated alveolar dead space ratio and the arterial to end-tidal PCO₂ difference among survivors

and non-survivors. The associated mortality rate at final stage 3 for $(Pa-E'CO_2)/Pa_{CO_2}$ value of ≥ 0.21 was 44% and for $(Pa-E'CO_2)/Pa_{CO_2}$ value of ≤ 0.20 was 3% ($p < 0.001$). They found that the estimated alveolar dead space ratio and end-tidal PCO_2 derived values strongly correlate with outcomes in trauma patients.

The Hardman and Aitkenhead estimate

Hardman et al. examined the relationship between $(Pa-E'CO_2)/Pa_{CO_2}$ and alveolar dead space to alveolar tidal volume ratio $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$ and they devised an equation for the estimation of dead space fraction (equation 6) (91). Three virtual patients with small, moderate and large ventilation/perfusion mismatch were created within the Nottingham Physiology Simulator (NPS). They examined the effects of variations in CO_2 production (V_{CO_2}), anatomical dead space and pulmonary shunt fraction on the relationship between $(Pa-E'CO_2)/Pa_{CO_2}$ and $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$. The results showed that there is a linear relationship between $(Pa-E'CO_2)/Pa_{CO_2}$ and $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$. They found that variations in V_{CO_2} and pulmonary shunt fraction caused similar changes in $(Pa-E'CO_2)/Pa_{CO_2}$ and $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$, whereas variations in anatomical dead space caused slightly

larger variations in $(Pa-E'CO_2)/Pa_{CO_2}$. They proposed that the following equation may be used for the estimation of alveolar dead space to alveolar tidal volume ratio at the bedside (98).

$$(VD_{alv}/VT_{alv})_{Bohr-Fowler} = 1.14 \times (Pa-E'CO_2)/Pa_{CO_2} - 0.005$$

(equation 6)

The Sinha et al. estimate

Sinha et al. developed a simple index termed as 'ventilatory ratio' (VR) to monitor the efficiency of ventilation (99). It is a ratio of product of measured minute ventilation (V_E) and Pa_{CO_2} to product of predicted V_E and Pa_{CO_2} , with normal value close to 1 (equation 7). Ventilatory efficiency and CO_2 production influence ventilatory ratio. An increasing value of VR represents worsening of ventilation and/or increase in CO_2 production. In another investigation, they examined the influence of changes in dead space to tidal volume ratio and V_{CO_2} on VR in three virtual patients. Virtual patients were created with normal, moderate and severe gas exchange defects using the Nottingham Physiology Simulator (100). They found that at constant V_{CO_2} , there was a strong correlation between V_D/V_T and VR (modified Pearson's r 0.98, $P < 0.01$). They showed that an increase in CO_2 production, at constant V_D/V_T , resulted in increase in VR value in all three virtual patients. They also

carried out a retrospective analysis of ARDS database to determine prognostic significance of ventilatory ratio. The results showed that VR was significantly higher among non-survivors than survivors (1.70 vs. 1.34, 95% confidence interval (CI) 0.16–0.56, $P < 0.01$) and VR was independently associated with mortality (100). The ventilatory ratio is mentioned below.

$$VR = (V_{E_{\text{measured}}} \times Pa_{CO_{2\text{measured}}}) / (V_{E_{\text{predicted}}} \times Pa_{CO_{2\text{predicted}}})$$

(equation 7)

$$V_{E_{\text{predicted}}} = 100 \text{ mlkg}^{-1}\text{min}^{-1}$$

$Pa_{CO_{2\text{predicted}}}$ is ideal Pa_{CO_2} defined as 5 kPa.

The Frankenfield et al. estimate

Frankenfield et al. also utilized the arterial to end-tidal PCO_2 difference and developed an equation for the estimation of dead space to tidal volume ratio (equation 8) (101). The study was divided into phases. First, they measured V_D/V_T in 135 mechanically ventilated patients by the Bohr-Enghoff dead space equation and constructed an equation by regression analysis. In the second phase, they validated the derived equation in a separate data set of 50 patients and the equation performed well in estimating dead space fraction (95% confidence interval -0.18 to 0.06). They proposed that the

equation may be used for the bedside estimation of dead space from routinely measured clinical variables. The equation is as follows:

$$V_D/V_T = 0.320 + 0.0106 (\text{Pa-E}'\text{CO}_2) + 0.003 (\text{RR}) + 0.0015(\text{age}) \quad (\text{equation 8})$$

In a subsequent investigation, they examined the prognostic significance of the estimate of dead space fraction (63). They compared V_D/V_T between survivors and non-survivors. There was a significant difference in V_D/V_T among survivors and non-survivors (56.5% vs. 71.2%, respectively). They concluded that the proposed equation correlates with mortality in mechanically ventilated patients (63, 101).

The Jones et al. estimate

Jones et al. examined the relationship between Pa_{CO_2} and $\text{E}'\text{CO}_2$ during exercise and developed a regression equation for the estimation of Pa_{CO_2} from $\text{E}'\text{CO}_2$ and tidal volume (102). In another investigation, researcher utilized the equation for the estimation of dead space to tidal volume ratio in morbidly obese patients (103). They measured dead space fraction at rest and during exercise by 3 different equations. First, they measured dead space to tidal volume ratio by the conventional Bohr-Enghoff equation. Then, $\text{E}'\text{CO}_2$ and P_jCO_2 were substituted

independently for Pa_{CO_2} in the subsequent two equations as mentioned below:

$$V_D/V_T \text{ (arterial)} = (Pa_{CO_2} - P\bar{E}_{CO_2})/Pa_{CO_2} - V_{DM}/V_T \quad \text{(equation 9)}$$

$$V_D/V_T \text{ (Jones)} = (P_{J_{CO_2}} - P\bar{E}_{CO_2})/P_{J_{CO_2}} - V_{DM}/V_T \quad \text{(equation 10)}$$

$$V_D/V_T \text{ (end-tidal)} = (E'CO_2 - P\bar{E}_{CO_2})/Pa_{CO_2} - V_{DM}/V_T$$

(equation 11)

V_{DM}/V_T is a correction factor for apparatus dead space.

They found that at rest there was no significant difference between the three equations while at exercise V_D/V_T estimated by $E'CO_2$ was significantly higher than the other two equations. They also found that the arterial to end-tidal PCO_2 difference was closely related to dead space to tidal volume ratio. They concluded that the Jones et al. equation is a better estimate of Pa_{CO_2} than $E'CO_2$ during exercise in morbidly obese patients (103).

The Beitler et al. estimate

Beitler et al. conducted a study to compare dead space fraction measured by volumetric capnography and equations for estimation of dead space fraction (4). They proposed a new equation for the estimation of dead space fraction by routinely

measured physiological variables (equation 12). Dead space fraction was estimated by 4 different equations for the estimation of dead space. Firstly, dead space fraction was measured by the unadjusted Harris-Benedict estimate. Secondly, dead space was measured by the Siddiki et al. estimate of dead space. Thirdly, dead space was measured by the Penn State estimate. Fourthly, dead space was measured by the Beitler et al. estimate of dead space. The study was divided into two phases and data was collected from previously published ARDS clinical trials. In the first phase, the accuracy of the four equations to predict dead space measured by the volumetric capnography was evaluated in 210 patients. In the second phase, they assessed the accuracy of the estimating equations in predicting the association between dead space fraction and mortality in patients with ARDS. They showed that the unadjusted Harris-Benedict estimate of dead space and the Beitler et al. estimate of dead space performed best in determining measured dead space fraction and the Siddiki estimate of dead space was least accurate in predicting measured dead space fraction. They also found that dead space to tidal volume ratio measured by the volumetric capnography was independently associated with mortality and for every 0.05 increase in dead space fraction, odds of death increased by 36%. The unadjusted Harris-Benedict estimate of dead space

was most accurate in determining the association between measured dead space fraction and mortality. They devised the following equation:

$$V_D/V_T = 0.1726 + 0.0059 (RR) + 0.0293 (LIS) + 0.0036 (Pa_{CO_2} \times V_E) + 0.000057 (Pa_{CO_2} \times \text{age}) \quad (\text{equation 12})$$

where, RR is respiratory rate and LIS is Murray lung injury score.

Chapter 3

Performance of Clinical Estimates of Dead Space in Multiple Ventilation/Perfusion Relationships within a Computer Model

Introduction

Dead space is a part of tidal volume that does not take part in gas exchange and is wasted (104, 105). An increase in dead space leads to gas exchange impairment, increase in the work of breathing and decrease in efficiency of ventilation (91). High dead space to tidal volume ratio (V_D/V_T) has conclusively been shown to be associated with mortality in patients with acute respiratory distress syndrome (ARDS) (18, 25, 64). It has been found to predict success or failure of weaning from mechanical ventilation (106-108) and a few studies have also investigated its relation to prognosis following therapeutic interventions (34, 42, 109, 110).

Ventilation perfusion mismatch is the main cause of high dead space ventilation (111). Normal regional distribution of ventilation (V) and perfusion (Q) can be altered by mechanisms such as variation in time constants of respiratory system, changes in intrathoracic pressure and pattern of breathing (112, 113). Quantification of dead space by the original Bohr's equation requires measuring mean alveolar pressure of CO_2 and mixed expired partial pressure of CO_2 (6, 114). Because of the difficulties and technical issues related with measuring $P_{A_{CO_2}}$ and $P_{\bar{E}_{CO_2}}$, alternative methods have been proposed for the estimation of dead space (97, 98, 115).

The classical 3-compartment lung model of Riley and Cournand divides alveoli according to V/Q ratios into three units i.e. unit A with $V/Q = 0$, unit B with $V/Q = 1$ and unit C with $V/Q = \infty$ (88, 116-118). There can be a wide variety of V/Q ratios between zero and infinity in a diseased lung (88, 119-121). Our aim in this investigation was to determine the performance of clinical estimates of dead space in multiple V/Q relationships.

Objectives

This was a computer simulation study and our specific objectives were to analyse:

1. The performance of the available methods of estimating dead space in lungs with heterogeneous ventilation/perfusion distributions.
2. Variation in the performance of these methods of estimating dead space upon varying relevant physiological factors.

Methods

The computational model

The computational model used in this study is a mathematical simulation of an integrated cardio-respiratory system named the Nottingham Physiology Simulator (NPS) (122). The detailed construction and validation of the simulator has been described

previously (123-128). Concisely, it is a multi-compartment model and configures the lung as a combination of 500 alveolar compartments (91). Each modelled alveolar compartment contains parameters that can be adjusted to vary the ventilation and perfusion of the compartment. This allows for configuration of a lung with a wide distribution of V/Q ratios (122). Basic model settings were: weight 70 kg, height 1.73 m, inspired oxygen fraction 0.21, inspired gas temperature 37 °C, oxygen consumption ($\dot{V}_{O_2}$) 250 ml/min, carbon dioxide production ($\dot{V}_{CO_2}$) 200 ml/min, respiratory exchange ratio (RQ) 0.8, anatomical dead space ($V_{d_{anat}}$) 60 ml, anatomical shunt 1%, tidal volume 400 ml, minute ventilation 5000 ml/min, positive end-expiratory pressure (PEEP) 0 cm H₂O and constant inspiratory flow pattern. Hypoxic pulmonary vasoconstriction (HPV) was disabled.

Two separate studies were devised to investigate each of our objectives. The first study objective was the calculation of V_D/V_T ratios in multiple ventilation/perfusion mismatch patterns using different methods for estimation of dead space ventilation. In second study, relevant physiological factors were varied to observe the effect of these changes on estimated V_D/V_T ratios calculated by the various methods of estimating dead space ventilation.

Origins of dead space

Six origins of pulmonary dead space were configured within the model (Fig. 3). In each configuration alveolar dead space fraction $(V_{Dalv}/V_{T_{alv}})_{Bohr-Fowler}$ was set to 25% as a result of a specific V/Q ratio distribution pattern. $(V_{Dalv}/V_{T_{alv}})_{Bohr-Fowler}$ was calculated from the NPS output as $((1 - (P_{\bar{E}_{CO_2}}/P_{a_{CO_2}}) * V_{T_{exh}}) - V_{d_{anat}}) / (V_{T_{exh}} - V_{d_{anat}})$, where $V_{T_{exh}}$ is exhaled tidal volume. The origins of dead space were defined according to their V/Q ratios distribution as follows:

Narrow and deep dead space: This dead space was configured as 20% of alveoli with very high V/Q and remaining of the lung with normal distribution of V/Q ratios (Fig. 1).

Wide and shallow dead space: This configuration had 50% of alveoli with $V/Q = 7.0$ and 50% of alveoli with normal V/Q ratios distribution.

Variable dead space 1 (VDS1): The vascular resistance was set that all alveoli had different V/Q ratios. There was little variation in time constants of alveolar compartments and airway resistance was increased from 7.9 to 11.1 cm H₂O.s/l.

Variable dead space 2 (VDS2): This configuration had same pattern of V/Q distribution as VDS1 but there was a wide

variation in time constants of alveolar compartments. The compliance was reduced to 50% of normal.

Variable dead space 3 (VDS3): The pattern of V/Q distribution was configured as 20% of alveoli with normal distribution of V/Q ratios, 40% of alveoli with varying V/Q ratios and rest 40% of alveoli with high V/Q ratios.

Venous admixture: This was modelled as 20% of alveoli with shunt and 20 percent of alveoli with dead space. Twenty percent of alveoli had a very low VQ of 0.072, twenty percent of alveoli had $VQ = 3.0$ and remaining 60% of alveolar compartments had varying VQ ratios. The mechanical characteristics of the six origins of dead space are described in table 1.

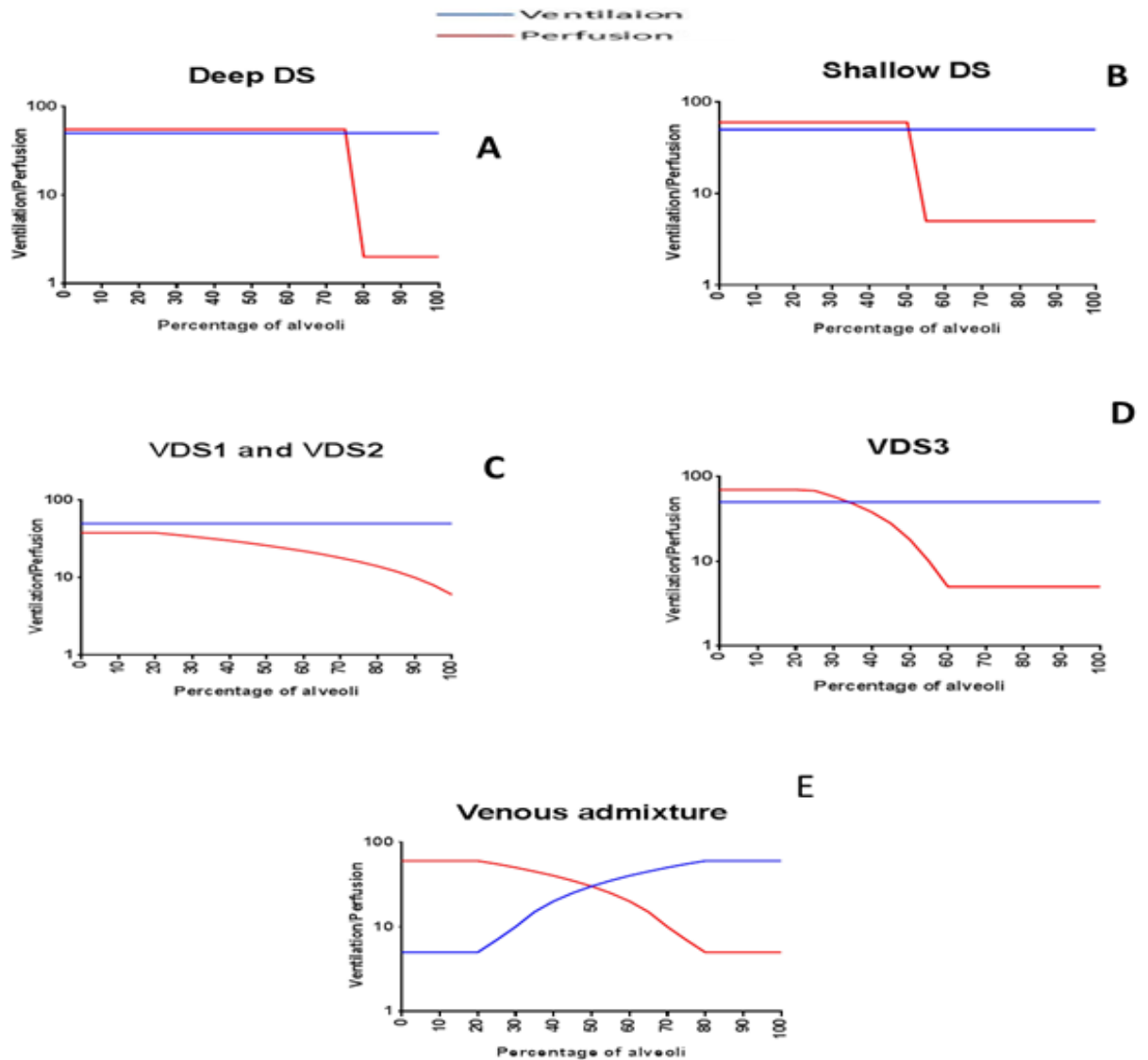


Figure 3: Pulmonary configurations of 6 origins of dead space

A) Narrow and deep DS: This pattern of V/Q mismatch was reproduced by increasing vascular resistance of 20 % of the alveolar compartment of NPS by 40 times than normal. B) Shallow DS: The vascular resistance was increased 13 times than normal in 50% of the alveolar compartments of NPS. C & D) Variable DS: Dead space with all alveoli having varying V/Q ratios. E) Pulmonary shunt: The airway resistance was increased to 50 times than normal in a 20% of alveoli.

Table 1: Alveolar and airway pressure of 6 origins of dead space

	Deep DS	Shallow DS	VDS1	VDS2	VDS3	Shunt
Alveolar pressure						
Mean	3.9	3.9	5.4	7.3	4.6	5.9
Peak	5.4	5.4	6.9	8.8	6.2	7.4
Airway pressure						
Mean	3.9	3.9	5.4	7.5	4.7	6.1
Peak	13.3	13.3	18	26.1	15.7	20.6
Compliance (ml/cm H₂O)	30	30	22	15	25	19

Estimation of V_D/V_T ratios

Multiple methods have been proposed for estimation of dead space ventilation (63, 97, 98, 102, 129, 130). In this study, V_D/V_T ratios were calculated by 5 different estimates of dead space ratio, as outlined below:

The Hardman and Aitkenhead estimate

V_D/V_T was calculated by an estimate proposed by Hardman and Aitkenhead (98). They examined the relationship between $(V_{Dalv}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ and arterial to end-tidal PCO_2 divided by arterial PCO_2 and developed the following equation for estimation of dead space:

$$(V_{Dalv}/V_{T_{alv}})_{\text{Bohr-Fowler}} = 1.14 \times (P_a - E'CO_2)/P_{aCO_2} - 0.005$$

(equation 13)

The Jones et al. estimate

V_D/V_T was derived from Jones et al. equation (102). The equation was proposed as an estimate of P_{aCO_2} during exercise, from end-tidal PCO_2 and tidal volume. It corrects for overestimation of P_{aCO_2} from end-tidal PCO_2 . Jones et al. corrected partial pressure of carbon dioxide (P_jCO_2) was substituted for P_{aCO_2} in the Bohr-Enghoff equation as follows:

$$V_D/V_T \text{ (Jones)} = (P_{J_{CO_2}} - P_{\bar{E}_{CO_2}})/P_{J_{CO_2}} - V_{DM}/V_T \quad (\text{equation 14})$$

$$P_{J_{CO_2}} = 5.5 + 0.9 \times E'_{CO_2} - 0.0021 \times V_T \quad (\text{equation 15})$$

The Frankenfield et al. estimate

Third, dead space to tidal volume ratio was measured by Frankenfield's equation of dead space (63). The equation is based on arterial to end-tidal PCO₂ gradient and is described below.

$$V_D/V_T = 0.320 + 0.0106 (P_a - E'_{CO_2}) + 0.003 (RR) + 0.0015 (\text{age}) \quad (\text{equation 16})$$

The Siddiki et al. estimate

Fourth, V_D/V_T was calculated by Siddiki et al. equation for quantification of dead space (97). The equation is derived from alveolar gas equation and involves calculation of estimated carbon dioxide production ($V_{CO_{2es}}$) using the Harris-Benedict equation.

$$V_D/V_T = 1 - ((0.86 \times V_{CO_{2est}}) / (V_E \times P_{a_{CO_2}})) \quad (\text{equation 17})$$

$$V_{CO_{2est}} = (HB_{pred} \times hf \times 0.8) / 6.8644 \quad (\text{equation 18})$$

HB_{pred} is predicted resting energy expenditure and was calculated as $66.45 + (13.75 \times 70 \text{ (wt)}) + (5 \times 175 \text{ (Ht)}) - (6.76 \times 40 \text{ (age)})$.

The Kuwabara and Duncalf estimate

Last, V_D/V_T was measured by the Kuwabara and Duncalf correction factor (129) for effect of shunt on the Bohr-Engelhof equation. They used pulmonary capillary PCO₂ (Pc_{CO₂}) as surrogate for P_ACO₂ and derived the following equation:

$$V_D / V_T = (P_{cCO_2} - P_{\bar{E}CO_2}) / P_{cCO_2} \quad (\text{equation 19})$$

$$P_{cCO_2} = P_{vCO_2} - (P_{vCO_2} - P_{aCO_2}) / (1 - Q_s/Q_t) \quad (\text{equation 20})$$

Variations in the physiological factors

Previous research has shown that changes in certain factors, such as tidal volume (113), breathing pattern (113), lung volume (105), FiO₂ (105), shunt percentage (43, 91), V_{CO₂} (91, 131), V_{O₂} (131), body surface area (88), inspiratory flow patterns (6, 88), V/Q distribution (43) and positive end expiratory pressure (PEEP) (88) can all effect dead space. The second aim of this study was to investigate the effects of variations in four physiological factors (anatomical dead space, V_{CO₂}, V_{O₂}, shunt fraction) on the estimations of V_D/V_T given by each method. Each factor was varied independently in the

six origins of dead space configurations and V_D/V_T ratios were calculated by the methods for estimation of V_D/V_T . The estimates of dead space were noted at following values of the physiological factors.

1. Anatomical dead space (ml): 30, 50 and 80.
2. Carbon dioxide production (ml/min): 150, 200 and 250.
3. Oxygen consumption (ml/min): 200, 250 and 300.
4. Shunt fraction (%): 0, 5 and 10.

Results

Estimation of V_D/V_T ratios

The performance of 5 estimates of dead space ratio in estimating $(V_{Dalv}/V_{T_{alv}})_{Bohr-Fowler}$ is shown in figure 4. The Hardman and Aitkenhead estimate, the Siddiki et al. estimate and the Jones et al. estimate performed well in estimating $(V_{Dalv}/V_{T_{alv}})_{Bohr-Fowler}$. V_D/V_T estimated by the Hardman and Aitkenhead estimate was 0.24 in deep dead space and shallow dead space. V_D/V_T estimated by the Siddiki et al. estimate was 0.23 and the performance of this equation was consistent across 6 origins of dead space. The Frankenfield estimate of dead space overestimated alveolar dead space ratio and had same value for 6 origins of dead space. In venous admixture, the Kuwabara and Duncalf estimate measured 0.26 and was the most accurate

estimate of $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ in this pulmonary configuration.

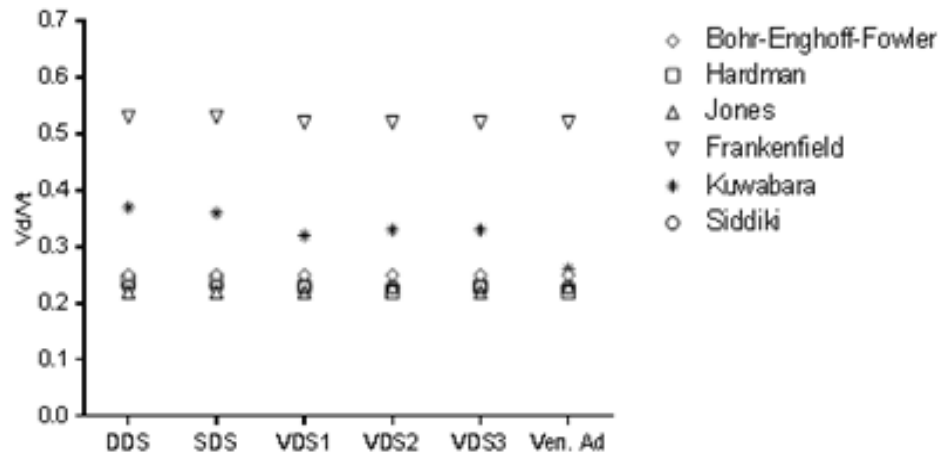


Figure 4: Performance of the estimates of V_D/V_T

This figure shows performance of six estimates of V_D/V_T across 6 pulmonary configurations. DDS is narrow and deep dead space. SDS is shallow dead space. VDS1, VDS2 and VDS3 represent pulmonary configuration with variable dead space. Ven. Ad is pulmonary configuration with shunt.

Variations in the physiological factors

The variation in each estimate of dead space ratio was calculated as $(\max - \min) / \text{mean}$, where max is maximum V_D/V_T upon varying a physiological factor. The average variation in each estimate across 6 origins of dead space, upon varying following physiological factors is represented in figure 5 and described briefly below:

$V_{d_{anat}}$: Variations in $V_{d_{anat}}$ had similar effect on $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ and on the Hardman and Aitkenhead estimate. The average variations in the Kuwabara and Duncalf estimate, the Jones et al. estimate and Siddiki et al. estimate upon varying $V_{d_{anat}}$ were markedly higher than $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$.

V_{CO_2} : Variations in V_{CO_2} had same effect on $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ and upon the Frankenfield equation of dead space. When V_{CO_2} was decreased to 150 ml/min, dead space ratio calculated by the Siddiki et al. estimate was negative across all origins of dead space. Thus, the average variation in this estimate upon varying V_{CO_2} was greater than 200%.

V_{O_2} : The changes in V_{O_2} caused similar change in $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ and the Jones et al. estimate of V_D/V_T . The average variation in the Hardman and Aitkenhead estimate upon varying V_{O_2} was higher than $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$.

Shunt fraction: Changes in anatomical shunt had similar effect on $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ and the Hardman and Aitkenhead equation and the Siddiki et al. equation. Detailed description of the performance of each method upon varying the physiological factors is provided in figure 6-11.

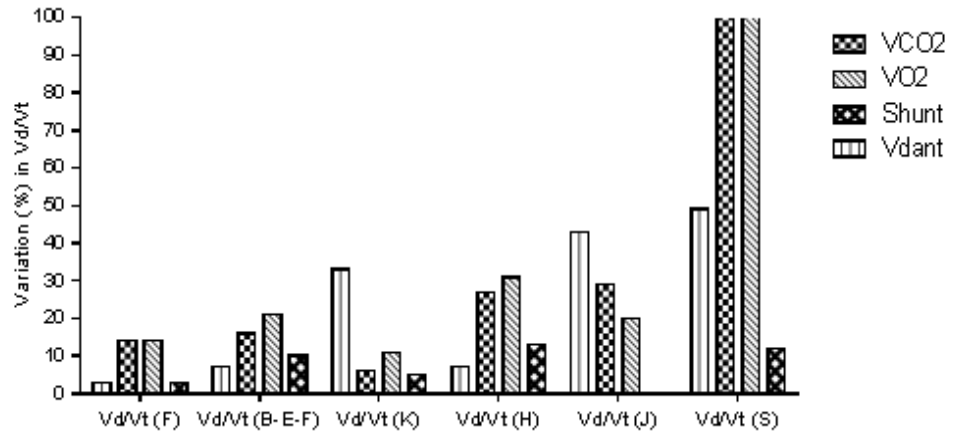


Figure 5: Average variation across pulmonary configurations

This graph represents the mean variation in VD/VT ratios across 6 origins of dead space, calculated by 5 methods of estimating VD/VT upon varying the physiological factors. A robust method is less likely to be varied by changes in the external physiological factors. VD/VT (F): The Frankenfield et al. estimate of dead space: VD/VT (B-E-F): Alveolar dead space to tidal volume ratio: VD/VT (K): The Kuwabara and Duncalf estimate of dead space: VD/VT (H): The Hardman and Aitkenhead estimate of dead space: VD/VT (J): The Jones et al. estimate of dead space. Average variation in VD/VT (F) across 6 origins of dead space was less than average variation in VD/VT (B-E-F) upon varying all 4 physiological factors. VD/VT (K) also varied less than VD/VT (B-E-F) upon varying the physiological factors except for Vdant that induced significantly higher variation in VD/VT (K). VD/VT (J) varied by 43% upon variation in anatomical dead space.

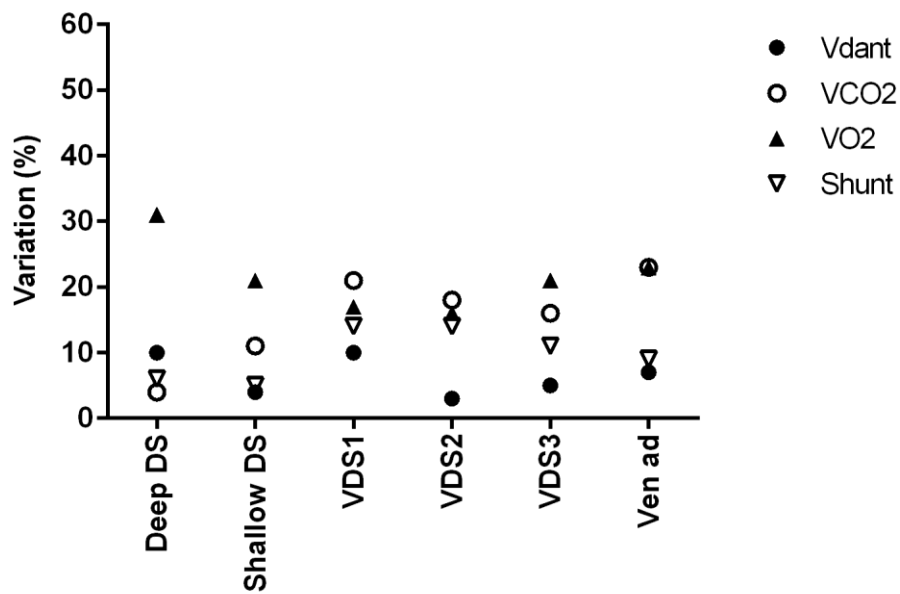


Figure 6: Percentage variation in $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$

This figure shows percentage variation in $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$ upon varying 4 physiological factors. Shallow DS is wide and shallow dead space. VDS1, VDS2 and VDS3 are variable dead space having alveoli with varying V/Q ratios and Ven Ad is dead space with shunt. All external factors caused variation in $(VD_{alv}/VT_{alv})_{Bohr-Fowler}$. Alterations in anatomical shunt caused maximum variation of 14% in VDS1 and VDS2.

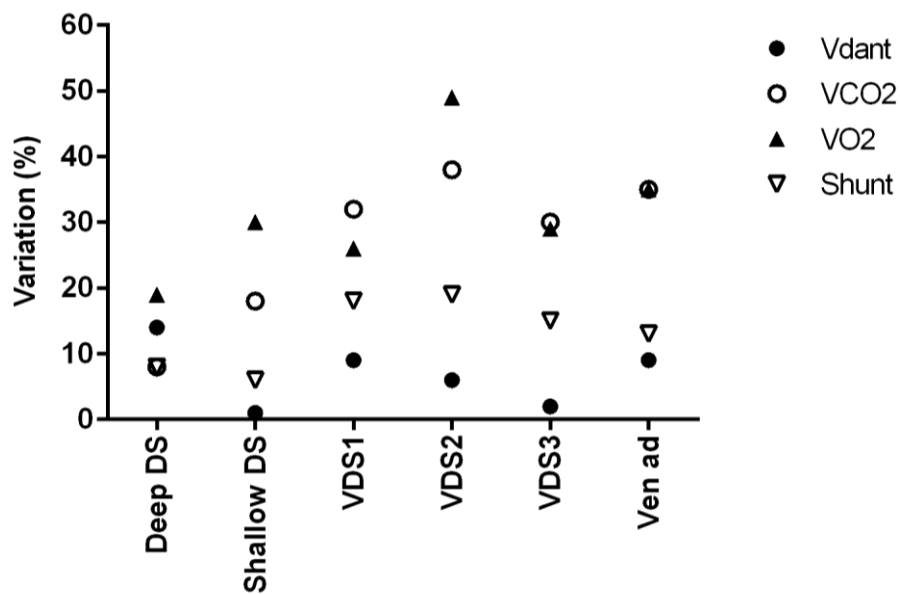


Figure 7: Percentage variation in the Hardman and Aitkenhead estimate

This figure shows percentage variation in the Hardman and Aitkenhead estimate of V_D/V_T upon varying 4 physiological factors. Deep DS is narrow and deep dead space. Shallow DS is wide and shallow dead space. VDS1, VDS2 and VDS3 are variable dead space having alveoli with varying V/Q ratios. Ven Ad is dead space with shunt. All external factors caused variation in the Hardman and Aitkenhead estimate. Maximum variations were observed upon varying carbon dioxide production and oxygen consumption. Variation in anatomical dead space caused little variation across 6 origins of dead space, except in deep dead space that showed 14% variation.

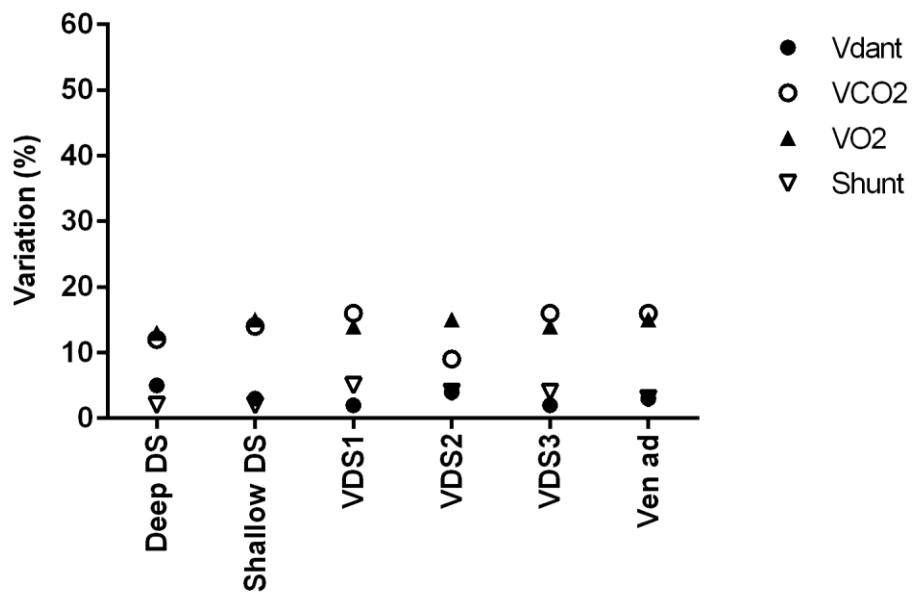


Figure 8: Percentage variation in the Frankenfield et al. estimate

This figure shows percentage variation in the Frankenfield et al. estimate of V_D/V_T upon varying 4 physiological factors. Deep DS is narrow and deep dead space. Shallow DS is wide and shallow dead space. VDS1, VDS2 and VDS3 are variable dead space having alveoli with varying V/Q ratios. Ven Ad is dead space with shunt. This equation showed little variation than the other estimates of dead space upon varying the external physiological factors. Maximum variations were observed upon varying carbon dioxide production and oxygen consumption. The variations in this method, upon varying anatomical shunt percentage were less than 6% across all origins of dead space.

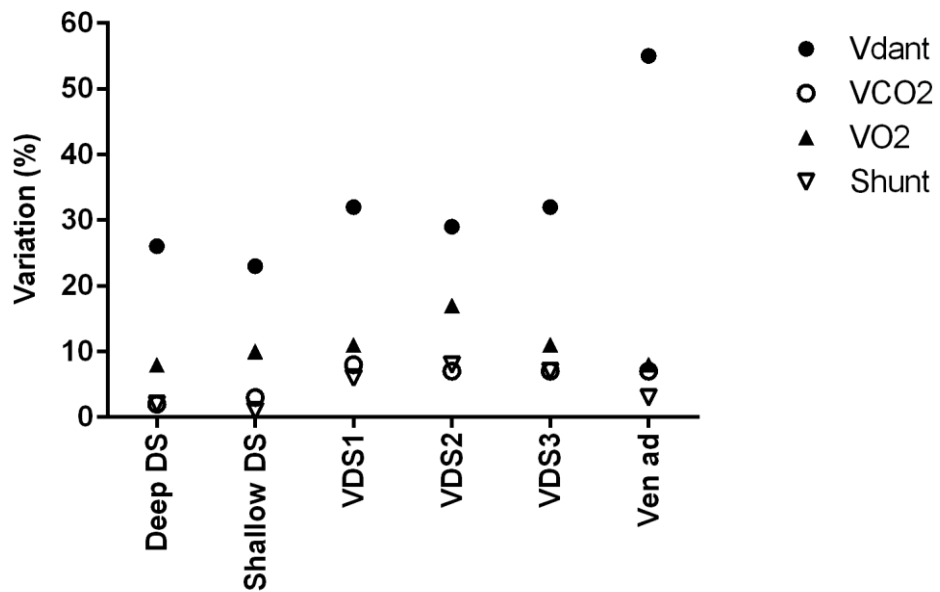


Figure 9: Percentage variation in the Kuwabara and Duncalf estimate

This figure shows percentage variation in the Kuwabara and Duncalf estimate of V_D/V_T upon varying 4 physiological factors. Deep DS is narrow and deep dead space. Shallow DS is wide and shallow dead space. VDS1, VDS2 and VDS3 are variable dead space having alveoli with varying V/Q ratios. Ven Ad is dead space with shunt. Alterations in anatomical dead space caused huge variations in this method. Variation in anatomical shunt caused little across 6 origins of dead space with maximum variation of 8% in VDS2.

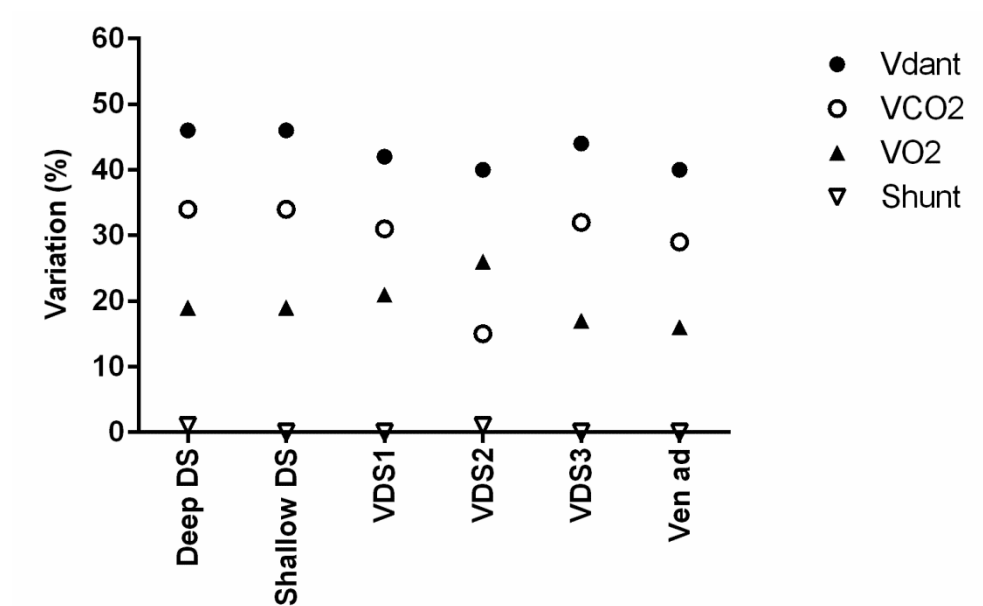


Figure 10: Percentage variation in the Jones et al. estimate

This figure shows percentage variation in the Jones et al. estimate of V_D/V_T upon varying 4 physiological factors. Deep DS is narrow and deep dead space. Shallow DS is wide and shallow dead space. VDS1, VDS2 and VDS3 are variable dead space having alveoli with varying V/Q ratios. Ven Ad is dead space with shunt. Changes in all external factors, except anatomical shunt, caused high variations in this method. Alterations in anatomical dead space fraction caused more than 40% variation across all origins of dead space. The variation in the method upon varying carbon dioxide production was almost 30% across all origins of dead space except VDS2. In VDS2, variation in V_{CO_2} caused 15% variation.

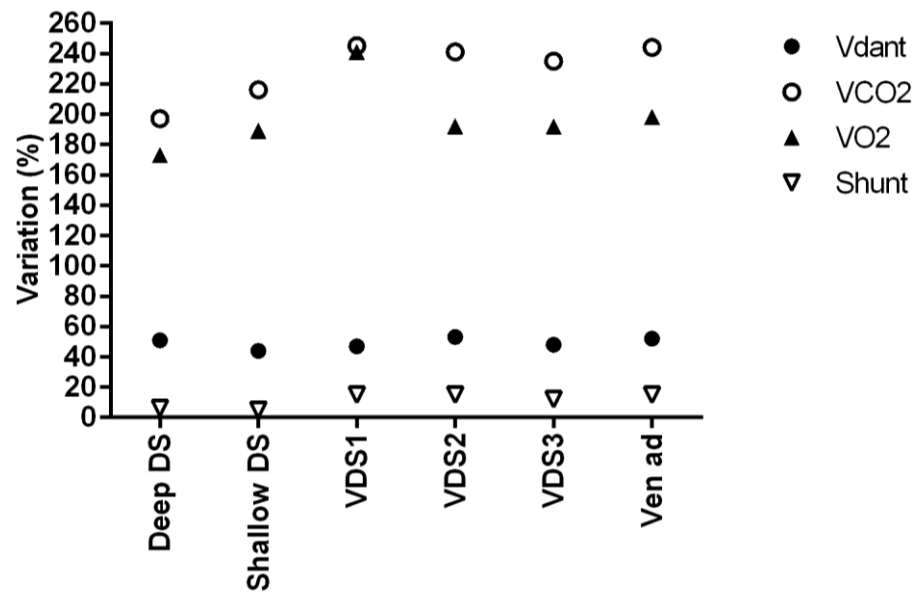


Figure 11: Percentage variation in the Siddiki et al. estimate

This figure shows percentage variation in the Siddiki et al. estimate of V_D/V_T upon varying 4 physiological factors. Deep DS is narrow and deep dead space. Shallow DS is wide and shallow dead space. VDS1, VDS2 and VDS3 are variable dead space having alveoli with varying V/Q ratios. Ven Ad is dead space with shunt. Changes in all external factors, except anatomical shunt, caused high variations in this method. Upon varying carbon dioxide production and oxygen consumption, the variations rose up to 200 percent. This was the only estimate of dead space that had negative value for dead space to tidal volume ratio, upon varying V_{CO_2} . In all variable origins of dead space, there was almost 15% variation upon varying anatomical shunt fraction.

Discussion

This study shows that the clinical estimates of dead space perform different than $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ across 6 modelled origins of dead space. We found that the Kuwabara and Duncalf equation perform differently than $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ across all origins of dead space, except venous admixture. We have shown that the Siddiki et al. equation might be an inaccurate estimate of V_D/V_T in clinical situations when there are changes in metabolic states.

Figure 2 represents the performance of the estimates of V_D/V_T in six V/Q patterns. A young healthy lung has bell-shaped V/Q distribution (132). In lung diseases normal regional V/Q distribution is altered (120, 125, 133-137). Abnormal V/Q distribution increase measured alveolar dead space ratio due to shunting of Pa_{CO_2} from low V/Q regions and/or dead space from high V/Q units (43). For instance, pulmonary embolism results in non-perfused lung units, thus, increased alveolar dead space fraction (42, 132, 138, 139). We have demonstrated that in clinical conditions with complete vascular obstruction of pulmonary compartments or in low pulmonary blood flow states, $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ can be estimated precisely by the Hardman and Aitkenhead estimate. By contrast, in these two origins of dead space, the Frankenfield equation of dead space

might overestimate $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$. Similarly, previous simulation studies for estimation of $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ by $Pa-E'CO_2$ reported that $(Pa-E'CO_2)/Pa_{CO_2}$ is better correlated with $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ instead of $(Pa-E'CO_2)/Pa_{CO_2}$ (91, 98). Dead space calculated by the Kuwabara and Duncalf estimate was also higher than $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ in the two origins of dead space. Suarez-Sipmann Fernando also showed that Kuwabara and Duncalf's equation overestimates dead space ratio measured by the original Bohr equation in the range of ventilation/perfusion defects (104). One possible explanation for this might be that our investigation involves inhomogeneous lung whereas Kuwabara and Duncalf assumed homogenous lung configuration. We found that dead space to tidal volume ratio estimated by the Frankenfield equation overestimates $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ across all 6 origins of dead space. On the other hand, the equation had less variations than $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ upon varying the external physiological factors.

Increased VQ heterogeneity and shunt fraction influence the estimates of dead space ventilation (104, 130, 140). The relationship between the estimates of dead space and prognosis in patients with ARDS has been widely investigated (18, 22, 63, 97, 100, 141). We found that Kuwabara and Duncalf's equation

was accurate in estimating alveolar dead space ratio in presence of both intrapulmonary shunt and increased V/Q heterogeneity. The computer model study of Tang and colleagues also showed the accuracy of this equation to determine dead space ratio in presence of pulmonary shunt (43). It may however be noted that this estimate requires pulmonary artery catheterization for quantification of dead space. Alternatively, dead space ratio can be determined by the Siddiki et al., the Hardman and Aitkenhead estimate and the Jones et al. estimate in this origin of dead space.

In the second part of this investigation, we found that the performance of the estimates of dead space is influenced by changes in the external physiological factors. The changes in $V_{d_{anat}}$ caused expected variation in $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ and the Hardman and Aitkenhead estimate. This finding is similar to previous simulation study of dependence of alveolar dead space on anatomical dead space (127). Both the Jones et al. and the Siddiki et al. estimates were shown to be inaccurate when there are changes in $V_{d_{anat}}$. So, the two estimates might be unreliable when there are changes in apparatus dead space, such as, when heat and moisture exchanger (HME) (142) is used in a ventilator circuit.

The results show that estimation of V_D/V_T without measuring $Pa-E'CO_2$ and/or $P\bar{E}_{CO_2}$ may be prone to error when there are variations in V_{O_2} or V_{CO_2} , as shown by huge variations that were observed in the Siddiki et al. estimate upon varying V_{CO_2} and V_{O_2} . This result can be explained by the fact that we varied V_{CO_2} and V_{O_2} in isolation while $V_{CO_{2est}}$ did not change upon varying the physiological factors. Similarly, Beitler et al. showed that the Siddiki equation is an inaccurate estimate of measured dead space fraction and this inaccuracy may be due to the effect of hypermetabolic factors on $V_{CO_{2est}}$ (4). Furthermore, this estimate includes calculation of $V_{CO_{2est}}$ by the Harris-Benedict equation, whose use in a critically ill patient has been questioned by other researchers (5, 21, 40).

Although our configurations simulate a heterogeneous patient population, the major limitation of this study is the use of a physiology simulator and not clinical data. Secondly, we did not study the effect of changes in ventilatory pattern on the methods of estimating dead space. A brief comparison of the methods for estimation of dead space to tidal volume ratio is provided in table 2.

Table 2: Comparison of the estimates of V_D/V_T

Methods	Parameters	Advantages	Limitations
Bohr-Enghoff-Fowler ($V_{D_{alv}}/V_{T_{alv}}$)	Represents efficient part of alveolar tidal volume. P_{aCO_2} instead of P_ACO_2 .	Index of efficiency of gas exchange that can be measured easily.	Invasive Effect of shunt on Bohr-Enghoff equation.
Hardman and Aitkenhead	Estimation of alveolar dead space fraction from $(P_a - E'CO_2)/P_aCO_2$	Simple method. Monitor changes in dead space with time.	Invasive
Jones et al.	Estimation of P_{aCO_2} from $E'CO_2$	Does not require arterial sample.	Varies with the physiological factors.
Frankenfield et al.	Use of $P_a - E'CO_2$ for dead space fraction	Simple bedside method. Showed little variation with external factors.	Invasive Over-estimated dead space.
Kuwabara and Duncalf	P_cCO_2 for P_aCO_2 for Bohr-Enghoff equation.	Correction factor for effect of shunt on Bohr-Enghoff equation.	Invasive Complex calculation inaccurate in correcting shunt effect.
Niklason et al.	P_cCO_2 for P_aCO_2 in the Bohr-Enghoff equation.	Correction factor for effect of shunt on the Bohr-Enghoff equation.	Invasive Complex method
Siddiki et al.	Harris-Benedict' equation and alveolar gas equation.	Does not require mixed expired gas analysis can be calculated by daily measured variables	Invasive Accuracy of the Harris-Benedict equation in critically ill patient uncertain

Conclusion

This study has demonstrated that the methods of estimating dead space ventilation perform differently in lungs with heterogeneous ventilation-perfusion distributions and are prone to vary upon variation in relevant physiological factors. These findings have significant implications for understanding of how effectively various methods of estimating dead space ventilation can be employed in clinical settings. For instance, in diseases with intrapulmonary shunt the alveolar dead space ratio can be estimated precisely by the Kuwabara and Duncalf estimate. However, the performance of this estimate is uncertain in situations when there are changes in configuration of a breathing system. The Siddiki et al. estimate might be unreliable in critically ill patients when there are changes in metabolic stress, such as, patients with burns or major trauma. By contrast, the Frankenfield equation of dead space may prove a better surrogate of alveolar dead space ratio in critically ill patients when there are changes in respiratory quotient. Future clinical studies are required to validate our findings in a clinical population.

Chapter 4

Evaluation of Clinical Estimates of Dead Space in Acute Respiratory Distress Syndrome

Introduction

The estimated incidence of acute respiratory distress syndrome (ARDS) is 1 case per 10,000 people every year (143) with mortality rate of 30-40 % (144). Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$), which is used to classify gas exchange impairment in patients with ARDS (59, 60, 145), has been shown to inconsistently correlate with prognosis (4, 18, 68, 146). Although $\text{PaO}_2/\text{FiO}_2$ and other measures of oxygenation have been extensively used in determining prognosis and response following medical interventions (147-151), it is equally important to assess ventilatory efficiency (21, 40, 100). Dead space to tidal volume ratio defines efficiency of ventilation and carbon dioxide excretion (5, 6). In 2002, Nuckton et al. reported that v_D/v_T is an independent predictor of mortality in ARDS patients (18). Since then, a strong relationship between v_D/v_T and outcomes of ARDS has been repeatedly reported in literature (22, 64), yet it is not a routinely measured parameter in clinical settings (4).

The quantification of dead space to tidal volume ratio by the original Bohr equation of dead space is technically challenging (4). Scholars have proposed alternative equations for estimation of v_D/v_T (4, 63, 91, 97, 104).

Primary objective

The primary objective of this study was to assess the performance of clinical estimates of V_D/V_T in patients with acute respiratory distress syndrome.

Methods

We configured 19 virtual ARDS patients within the Nottingham Physiology Simulator (123). Initially, alveolar dead space to alveolar tidal volume ratio $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ was calculated from the NPS output as $((1 - (P_{\bar{E}CO_2}/Pa_{CO_2}) * V_{T_{exh}}) - V_{d_{anat}}) / (V_{T_{exh}} - V_{d_{anat}})$, where $V_{T_{exh}}$ is exhaled tidal volume. Then, V_D/V_T was determined in 19 ARDS subjects by following 5 equations for quantification of dead space ventilation.

The Hardman and Aitkenhead estimate

Previous studies have shown that changes in alveolar dead space correlated with changes in arterial to end-tidal PCO_2 difference (91, 113, 141, 152). Hardman and Aitkenhead devised an equation for estimation of alveolar dead space to alveolar tidal volume based on arterial to end-tidal PCO_2 gradient divided by arterial PCO_2 as follows (98):

$$(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler} = 1.14 \times (Pa - E'CO_2)/Pa_{CO_2} - 0.005$$

(equation 21)

The Jones et al. estimate

Jones et al. proposed an equation for estimation of PaCO₂ from end-tidal and tidal volume (102). We substituted Jones et al. corrected partial pressure of carbon dioxide (P_JCO₂) for PaCO₂ in the Bohr-Enghoff dead space equation as follows:

$$V_D/V_T \text{ (Jones)} = (P_{J_{CO_2}} - P_{\bar{E}_{CO_2}})/P_{J_{CO_2}} - V_{DM}/V_T \quad (\text{equation 22a})$$

$$P_{J_{CO_2}} = 5.5 + 0.9 \times E'CO_2 - 0.0021 \times V_T \quad (\text{equation 23})$$

The Frankenfield et al. estimate

This equation also estimates dead space to tidal volume by arterial to end-tidal PCO₂ gradient and is describe below (63).

$$V_D/V_T = 0.320 + 0.0106 (Pa-E'CO_2) + 0.003 (RR) + 0.0015 (\text{age}) \quad (\text{equation 24})$$

The Siddiki et al. estimate

Siddiki et al. rearranged alveolar gas equation and proposed a new formula for quantification of V_D/V_T in patients with ARDS. This equation utilizes the Harris-Benedict equation for calculation of dead space ventilation as follows:

$$V_D/V_T = 1 - ((0.86 \times V_{CO_{2est}}) / (V_E \times Pa_{CO_2})) \quad (\text{equation 25})$$

$$V_{CO_{2est}} = (HB_{pred} \times hf \times 0.8) / 6.8644 \quad (\text{equation 26})$$

HB_{pred} is predicted resting energy expenditure and hf are hypermetabolic factors described as 1.13 per °C over 37 °C, 1.2 for minor surgery, 1.35 for major trauma and 1.6 for severe infection (97).

The Kuwabara and Duncalf estimate

Kuwabara and Duncalf corrected the Bohr-Enghoff equation for effect of shunt and proposed pulmonary capillary PCO_2 as a surrogate for arterial PCO_2 for estimating dead space to tidal volume ratio (129).

$$V_D / V_T = (P_{cCO_2} - P\bar{E}_{CO_2}) / P_{cCO_2} \quad (\text{equation 27})$$

$$P_{cCO_2} = P_{vCO_2} - (P_{vCO_2} - P_{aCO_2}) / (1 - Q_s/Q_t) \quad (\text{equation 28})$$

Results

Figure 12 compares the performance of the methods of estimating dead space ventilation in virtual ARDS subjects. Across 19 ARDS subjects minimum $(V_{Dalv}/V_{Tlv})_{Bohr-Fowler}$ was 0.11 and maximum was 0.55. The Frankenfield equation of dead space had same value i.e. 0.4 across 19 ARDS subjects. The Hardman and Aitkenhead equation underestimated $(V_{Dalv}/V_{Tlv})_{Bohr-Fowler}$ across 19 ARDS subjects. Beside 2 ARDS subjects, the Jones et al. equation also underestimated $(V_{Dalv}/V_{Tlv})_{Bohr-Fowler}$. The performance of the Siddiki et al.

estimate was inconsistent and it measured same as $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ in 2 ARDS subjects. When $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ was 55% all methods of estimating dead space to tidal volume ratio underestimated $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$. The performance of each estimate of dead space is illustrated in figure 13-17 by constructing 95% limits of agreement.

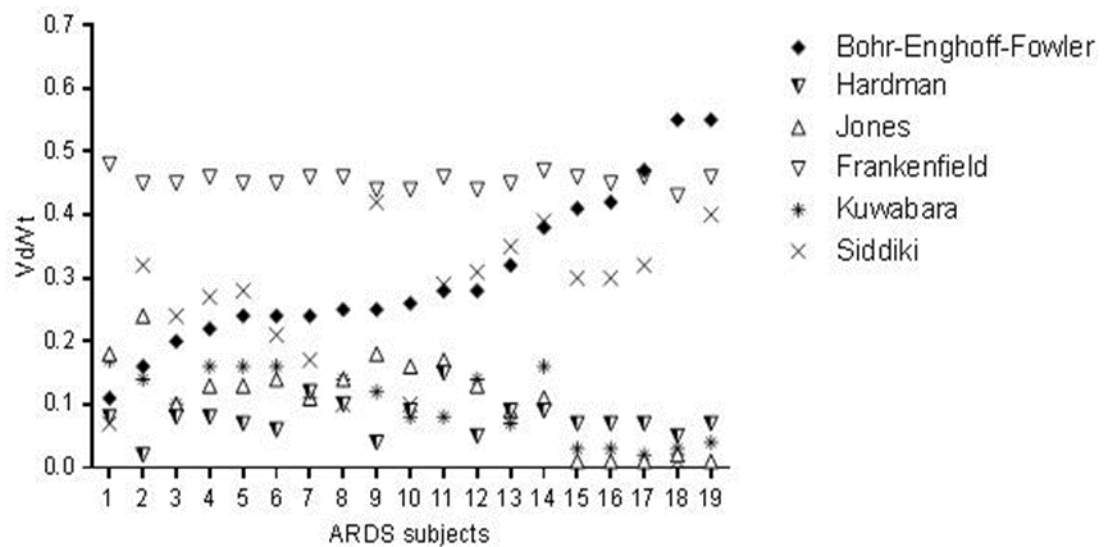


Figure 12: Performance of 6 estimates of V_D/V_T in ARDS subjects

This figure shows dead space to tidal volume ratio measured by 6 estimates of dead space in 19 virtual ARDS subjects. The Frankenfield estimate of dead space had almost same value of V_D/V_T across all ARDS subjects. The Siddiki et al. estimate measured same as $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ in 2 ARDS subjects.

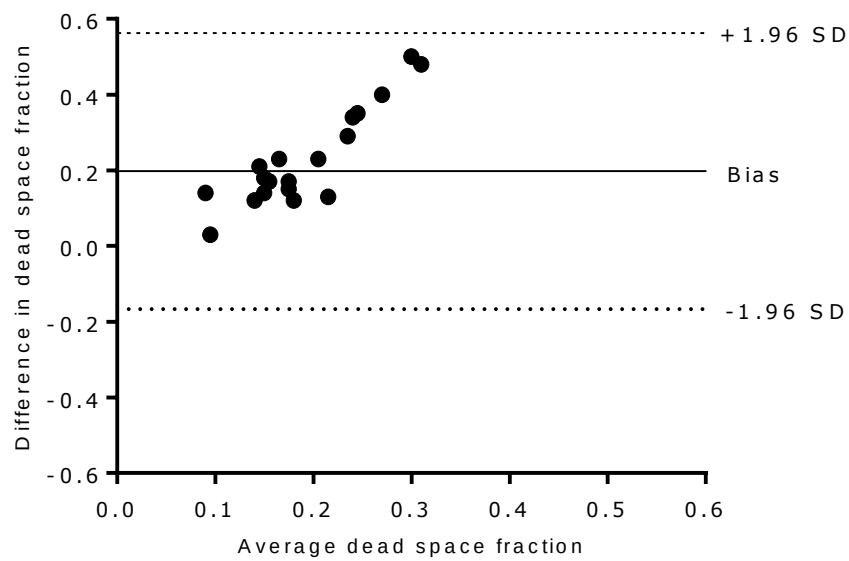


Figure 13: Bland-Altman plot for the Hardman and Aitkenhead estimate

Plot of difference between $(V_{Dalv}/V_{Talv})_{\text{Bohr-Fowler}}$ and the Hardman et al. estimate of dead space vs. the mean of two measurement across 19 ARDS subjects with representation of upper and lower 95% limits of agreement.

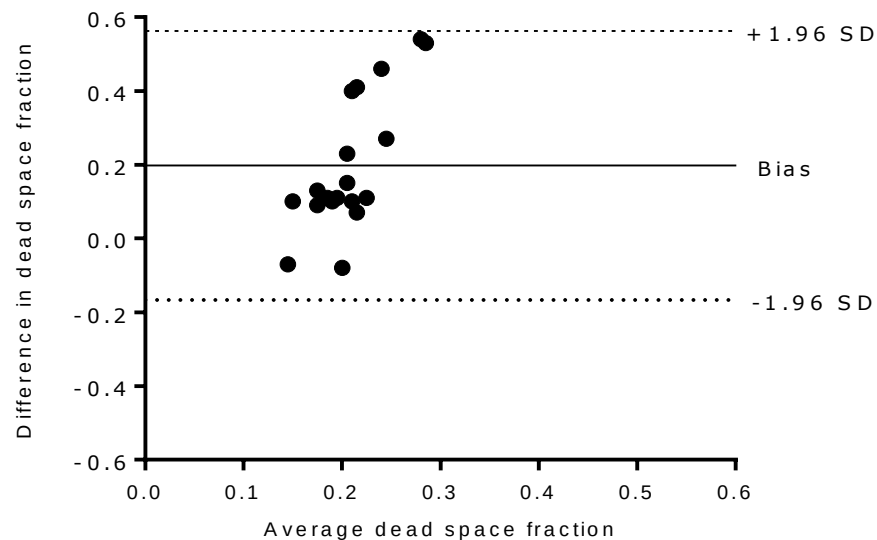


Figure 14: Bland-Altman plot for the Jones et al. estimate

Plot of difference between $(V_{Dalv}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ and the Jones et al. estimate of dead space vs. the mean of two measurement across 19 ARDS subjects with representation of upper and lower 95% limits of agreement.

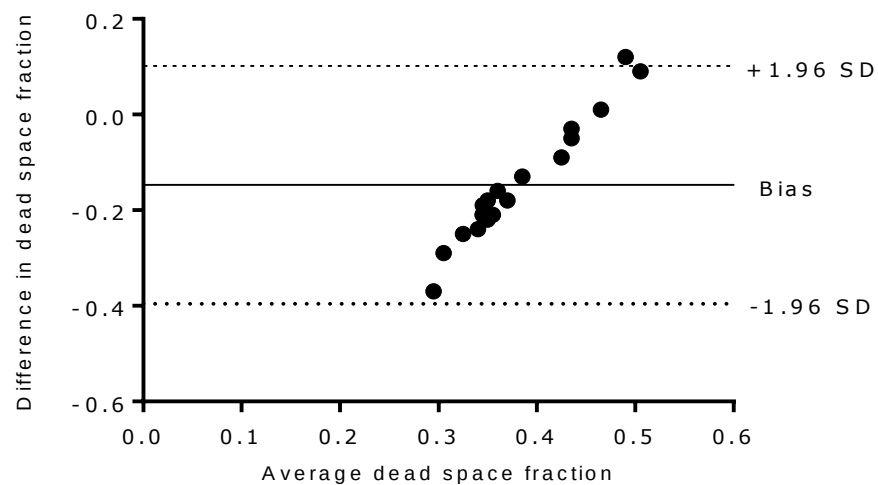


Figure 15: Bland-Altman plot for the Frankenfield et al. estimate

Plot of difference between $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ and the Frankenfield et al. estimate of dead space vs. the mean of two measurement across 19 ARDS subjects with representation of upper and lower 95% limits of agreement.

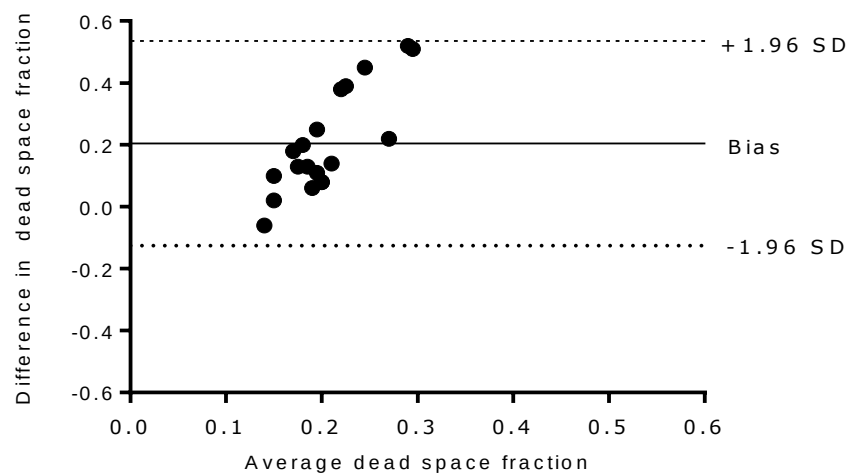


Figure 16: Bland-Altman plot for the Kuwabara and Duncalf estimate

Plot of difference between $(V_{D_{alv}}/V_{T_{alv}})_{Bohr-Fowler}$ and the Kuwabara et al. estimate of dead space vs. the mean of two measurements across 19 ARDS subjects with representation of upper and lower 95% limits of agreement.

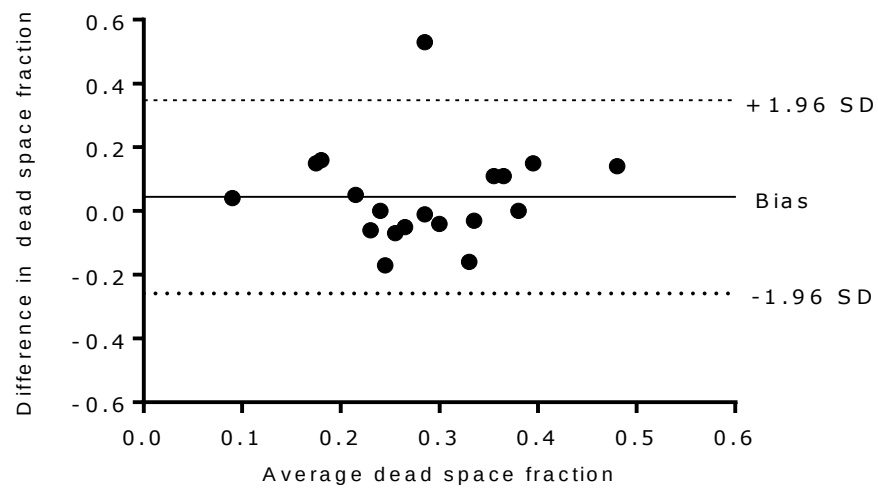


Figure 17: Bland-Altman plot for the Siddiki et al. estimate

Plot of difference between $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ and the Siddiki et al. estimate of dead space vs. the mean of two measurements across 19 ARDS subjects with representation of upper and lower 95% limits of agreement.

Discussion

The pathophysiological changes in ARDS impair normal ventilation/perfusion matching and results in lung regions with high and low V/Q ratios (8, 73, 82, 153, 154). The measurement of dead space ventilation is important because it reflects ventilation/perfusion inhomogeneity and lung structural changes in ARDS (8, 118, 155-158). There can be many causes of increase in dead space in ARDS. Firstly, it could be due to true alveolar dead space from non-perfused or poorly perfused lung regions (5). Secondly, presence of intra-pulmonary shunt will also increase measured dead space to tidal volume ratio (43, 159, 160). Thirdly, it can be result of mechanical ventilation strategies leading to over-distension of normally perfused lung regions (5).

Increase in dead space ventilation increases the gradient between Pa_{CO_2} and end-tidal PCO_2 (132). Previous research has shown that end-tidal PCO_2 is not an accurate estimate of Pa_{CO_2} in a diseased lung (5, 161). Substituting end-tidal PCO_2 for Pa_{CO_2} for estimating V_D/V_T might be inaccurate in patients with ARDS, as shown by dead space to tidal volume ratio estimated by the Jones et al. method. This finding is consistent with Robin et al. who showed that the Jones et al. method underestimates arterial PCO_2 (162). In a recent investigation by Tariq Yousaf et

al. they also found that end-tidal PCO_2 is not a reliable estimate of PaCO_2 in ARDS patients and arterial to end-tidal PCO_2 gradient increases with disease progression (161).

The arterial to end-tidal PCO_2 gradient reflects dead space ventilation and is influenced by changes in regional V/Q ratios, shunt percentage (163), VCO_2 , pulmonary time constant (163), age (163, 164), posture (165, 166), FiO_2 (167), cardiac output, tidal volume (168) and ventilatory frequency (168). We found that the Hardman et al. equation and the Frankenfield et al. equation did not perform well in estimating $(\text{VD}_{\text{alv}}/\text{VT}_{\text{alv}})_{\text{Bohr-Fowler}}$ in ARDS patients. These results are contrary to previous studies which have shown that the arterial to end-tidal PCO_2 gradient correlates with alveolar dead space fraction (63, 91, 98, 101, 132). We found that the Frankenfield equation of dead space overestimates $(\text{VD}_{\text{alv}}/\text{VT}_{\text{alv}})_{\text{Bohr-Fowler}}$ in virtual ARDS patients. This equation has been shown to predict prognosis in critically ill patients (63) and there was a significant difference in mean $\text{V}_\text{D}/\text{V}_\text{T}$ among survivors and non-survivors (63). Yu-Jiao Zhang et al. compared prognostic accuracy of the Frankenfield equation with $\text{V}_\text{D}/\text{V}_\text{T}$ measured from ventilator volumetric capnography. They concluded that this equation is more strongly related to prognosis of patients with ARDS than $\text{V}_\text{D}/\text{V}_\text{T}$ measured by volumetric capnography (90). We found that the

Frankenfield equation of dead space had same value across 19 ARDS subjects. A possible explanation of this is that the equation involves age and respiratory rate. Ten out of 19 ARDS patients had same respiratory rate. The arterial to end-tidal PCO_2 gradient is influenced by changes in FiO_2 and this might be another reason for overestimation of $(\text{V}_{\text{Dalv}}/\text{V}_{\text{Talv}})_{\text{Bohr-Fowler}}$. Out of 19 ARDS subjects, 14 had $\text{FiO}_2 \geq 0.60$, whereas the equation was constructed from mechanically ventilated patients with $\text{FiO}_2 \leq 0.60$ (101).

We found that the Kuwabara and Duncalf equation underestimate $(\text{V}_{\text{Dalv}}/\text{V}_{\text{Talv}})_{\text{Bohr-Fowler}}$. This finding is contrary to Suarez-Sipmann Fernando who found that this equation overestimates dead space to tidal volume ratio in surfactant-depleted pigs (104). Our results support the idea that use of the Harris-Benedict equation for predicting energy expenditure might be inaccurate in ARDS patients (5, 40), as shown by dead space to tidal volume ratio measured by the Siddiki et al. method. This method has been shown to underestimate dead space to tidal volume ratio in ARDS patients (4, 40). Beitler et al. also showed that the Siddiki et al. method did not perform well in estimating $\text{V}_{\text{D}}/\text{V}_{\text{T}}$ in ARDS patients and this could be due to the effect of hypermetabolic factors on estimated V_{CO_2} (4).

Conclusion

The results of this investigation show that the estimates of dead space to tidal volume ratio measure different than $(V_{D_{alv}}/V_{T_{alv}})_{\text{Bohr-Fowler}}$ in ARDS patients. The major limitation of this study is that we have used the physiological simulator and not clinical data. The Nottingham Physiology Simulator have been used and validated previously to study multiple research questions in patients with ARDS (100, 122, 143, 148). One source of weakness in this study was that anatomical dead space was not same across all simulated patients. Four out of 19 ARDS subjects had anatomical dead space greater than 200 ml and this may have influenced the estimates of dead space fraction. Another limitation of this study is that a large minute ventilation i.e. up to 12000 ml/min was used in few ARDS patients and this may have affected the estimates of dead space fraction.

Chapter 5

Effects of Lung Recruitment Manoeuvres on Dead Space Ventilation in ARDS Patients

Introduction

Acute respiratory distress syndrome is a life-threatening disease with high morbidity and mortality (3, 169-175). It is characterized by varying degree of alveolar collapse and pulmonary oedema (110). In ARDS, normal alveolar ventilation is impaired, ventilation/perfusion matching is disturbed, intrapulmonary shunt is increased, lung compliance is decreased and dead space to tidal volume ratio is increased (65). Mechanical ventilation is implemented to treat hypoxaemia (176, 177). A recent literature review reports that up to 25% of mechanically ventilated intensive care patients have ARDS (178). Mortality rates for patients with ARDS have decreased due to life-sustaining interventions (144, 179-181) and improvements in mechanical ventilation strategies (182-185).

Lung recruitment is a process of re-opening collapsed lung units by the application of high airway pressure (186-188). Recruitment manoeuvres can reduce atelectasis and increase end-expiratory lung volume in patients with ARDS (189-192). Different types of recruitment manoeuvres are used, such as sustained inflation (122, 193-195), incremental PEEP (196), maximal recruitment strategy (197), intermittent sigh (196, 198), high pressure controlled ventilation (196) and prolonged

recruitment manoeuvre (199). $\text{PaO}_2/\text{FiO}_2$ ratio and oxygenation indices are mainly monitored during the application of recruitment manoeuvres (177, 200-204). Previous studies have shown that dead space to tidal volume ratio (109, 182, 205) and arterial to end-tidal PCO_2 gradient changes following recruitment manoeuvres and it can help in making decision for the selection of optimum positive end-expiratory pressure (206-208).

Objectives

The main objectives of this study were:

- To observe changes in dead space to tidal volume ratio following recruitment manoeuvres in patients with ARDS.
- To observe changes in $(\text{Pa}-\text{E}'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ following recruitment manoeuvres in patients with ARDS.

Methods

Six virtual ARDS patients were created within the NPS. Three RMs, namely maximal recruitment strategy, prolonged recruitment manoeuvre and sustained inflation were implemented in six virtual ARDS patients and these are described in detail in a previous NPS investigation (122). Briefly, before executing recruitment manoeuvres all in-silico ARDS patients were subjected to identical end-expiratory pressures

(10 cm H₂O) and identical inspiratory pressure (15 cm H₂O above PEEP). Then, recruitment manoeuvres were implemented. Following recruitment manoeuvres, the inspiratory pressure was maintained at 15 cm H₂O above PEEP while PEEP was set to either 5 cm H₂O or 10 cm H₂O. Physiological dead space to tidal volume ratio ($V_{d_{phys}}/V_t$), PaO_2/FiO_2 , dynamic lung compliance, pulmonary shunt fraction (Q_s/Q_t) and $(Pa-E'CO_2)/Pa_{CO_2}$ were monitored during the recruitment manoeuvres.

Maximal Recruitment Strategy (MRS)

The manoeuvre comprises of PEEP adjustment in pressure-controlled mode, with a fixed driving pressure of 15 cm H₂O (above PEEP) (197, 198). During the recruitment phase, PEEP was increased from 10 cm H₂O to a maximum of 45 cm H₂O in steps of 5 cm H₂O, with each step lasting 2 minutes. During the PEEP-titration phase, the PEEP is set to 25 cm H₂O and then reduced by 5 cm H₂O in steps to the end-manoeuve PEEP, with each step lasting 5 minutes. The PEEP titration was stopped when the percentage of recruited lung fell by more than 2% from maximal recruitment achieved during the recruitment phase.

Sustained Inflation (SI)

This was simulated as a sustained pulmonary inflation manoeuvre, with a positive ventilator pressure of 40 cm H₂O applied for 40 seconds (193). The end-manoeuve PEEP was set to 10 cm H₂O.

Prolonged Recruitment Manoeuvre (PRM)

In this manoeuvre, inspiratory pressure was progressively increased every 2 minutes in steps of 5 cm H₂O from 15 cm H₂O to 25 cm H₂O, above a fixed PEEP of 15 cm H₂O (199). The end-manoeuve PEEP was set to 5 cm H₂O.

Results

Patient A: This patient had PaO₂/FiO₂ ratio of 70 mmHg, and was classified as severe ARDS (Fig. 18). During the application of the MRS, PaO₂/FiO₂ ratio increased up to 340 mmHg and it remained higher than 250 mmHg after the MRS. The PaO₂/FiO₂ ratio increased from 70 mmHg to approximately 110 mmHg during the SI and dropped again to 80 mmHg at the end-PEEP setting of 10 cm H₂O. The PRM resulted in an increase in PaO₂/FiO₂ ratio up to 180 mmHg and the end-PEEP setting of 5 cm H₂O caused a sharp decrease in the PaO₂/FiO₂ ratio to the baseline value.

Physiological dead space to tidal volume ratio ($V_{d_{phys}}/V_t$) decreased from 0.6 to 0.25 during the application of the MRS, and it remained at 0.4 after the manoeuvre. The SI resulted in a sharp decrease in $V_{d_{phys}}/V_t$ during the manoeuvre from 0.6 to up to 0.2, but it returned to the baseline value after the manoeuvre. $V_{d_{phys}}/V_t$ fluctuated during PRM and it returned to the baseline value after the manoeuvre.

Pulmonary shunt decreased during the MRS and it remained significantly lower after the application of the MRS. Dynamic compliance increased from 50 ml mbar⁻¹ up to 85 ml mbar⁻¹ during the MRS and remained 80 ml mbar⁻¹ after the manoeuvre. There was a slight decrease in $(Pa-E'CO_2)/Pa_{CO_2}$ after the application of the MRS. $(Pa-E'CO_2)/Pa_{CO_2}$ returned to the baseline value following the SI and PRM.

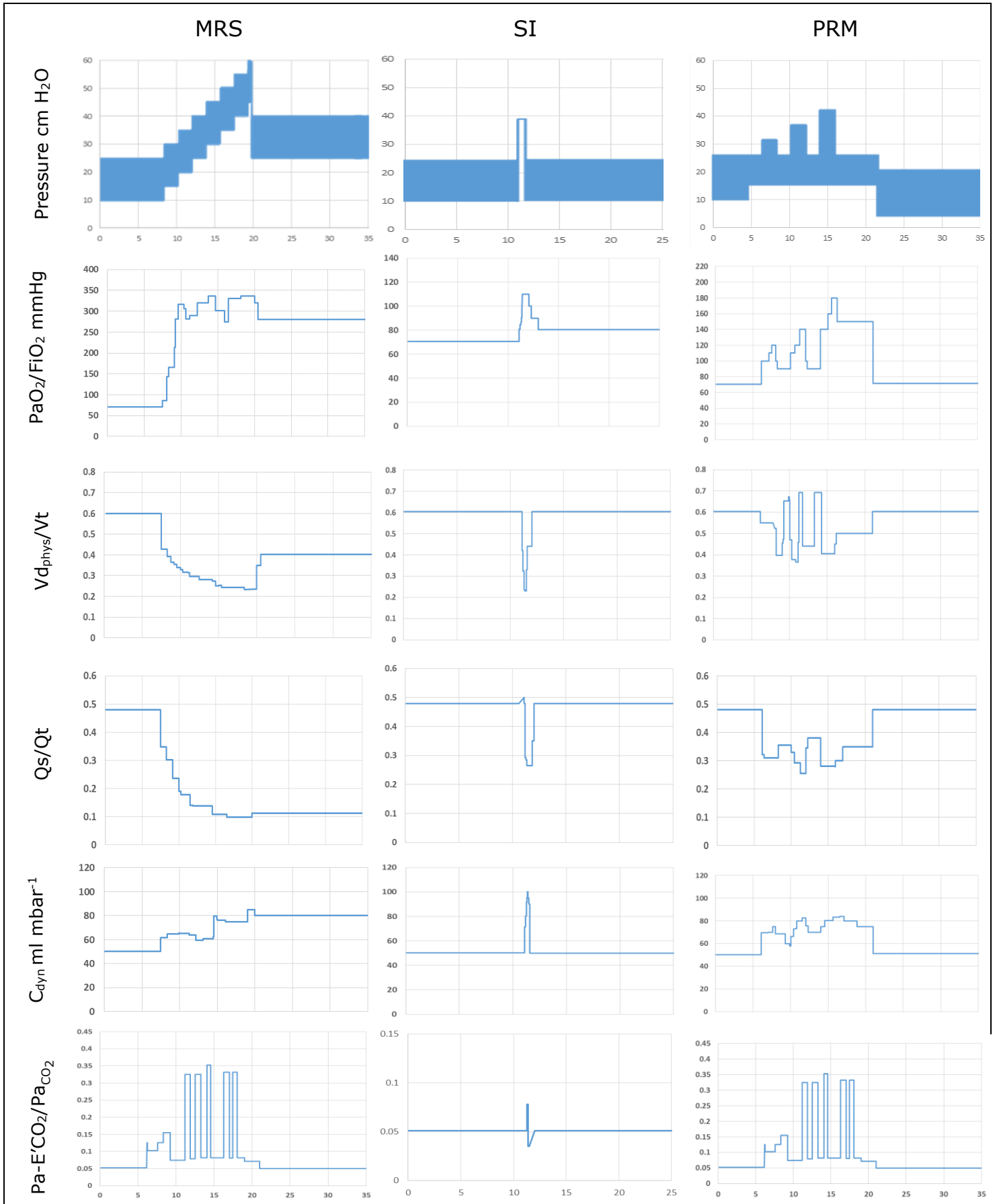


Figure 18: NPS output following application of RMs in patient A

This figure shows application of MRS, SI and PRM in patient A. x-axis shows time in minutes.

Patient B: This patient had $\text{PaO}_2/\text{FiO}_2$ ratio of 190 mmHg, and was classified as moderate ARDS (Fig. 19). The MRS resulted in an increase in the $\text{PaO}_2/\text{FiO}_2$ ratio up to 350 mmHg, and it was maintained at 340 mmHg after the manoeuvre. The SI also increased the $\text{PaO}_2/\text{FiO}_2$ ratio up to 300 mmHg and the end-PEEP setting of 10 cm H_2O maintained the $\text{PaO}_2/\text{FiO}_2$ ratio at 300 mmHg. The PRM resulted in an increase in the $\text{PaO}_2/\text{FiO}_2$ up to 300 mmHg during the manoeuvre but it returned to the baseline value after the manoeuvre.

The MRS resulted in decrease in $\text{Vd}_{\text{phys}}/\text{Vt}$ from 0.4 to 0.2, and it remained at 0.30 after the manoeuvre. There was a sharp decrease in $\text{Vd}_{\text{phys}}/\text{Vt}$ during the application of the SI from 0.4 to 0.1, and it remained at 0.35 after the manoeuvre. $\text{Vd}_{\text{phys}}/\text{Vt}$ fluctuated during the application of the PRM and it returned to the baseline value after the end of manoeuvre.

Pulmonary shunt decreased significantly during the application of the MRS and it remained considerably lower than the initial value after the application of the MRS. The SI resulted in a sharp decrease in Q_s/Q_t from 0.32 to 0.15, and it was maintained at 0.15 with the end-PEEP setting of 10 cm H_2O . The PRM resulted in drop in Q_s/Q_t during the manoeuvre but it returned to the baseline value after the application of the manoeuvre. Dynamic compliance increased during the PRM and it returned to the

baseline value after the manoeuvre. $(Pa-E'CO_2)/Pa_{CO_2}$ was lower than the baseline value after the application of the MRS and SI. Large fluctuations were observed in $(Pa-E'CO_2)/Pa_{CO_2}$ during the application of the PRM and it returned to the baseline value after the end of manoeuvre.

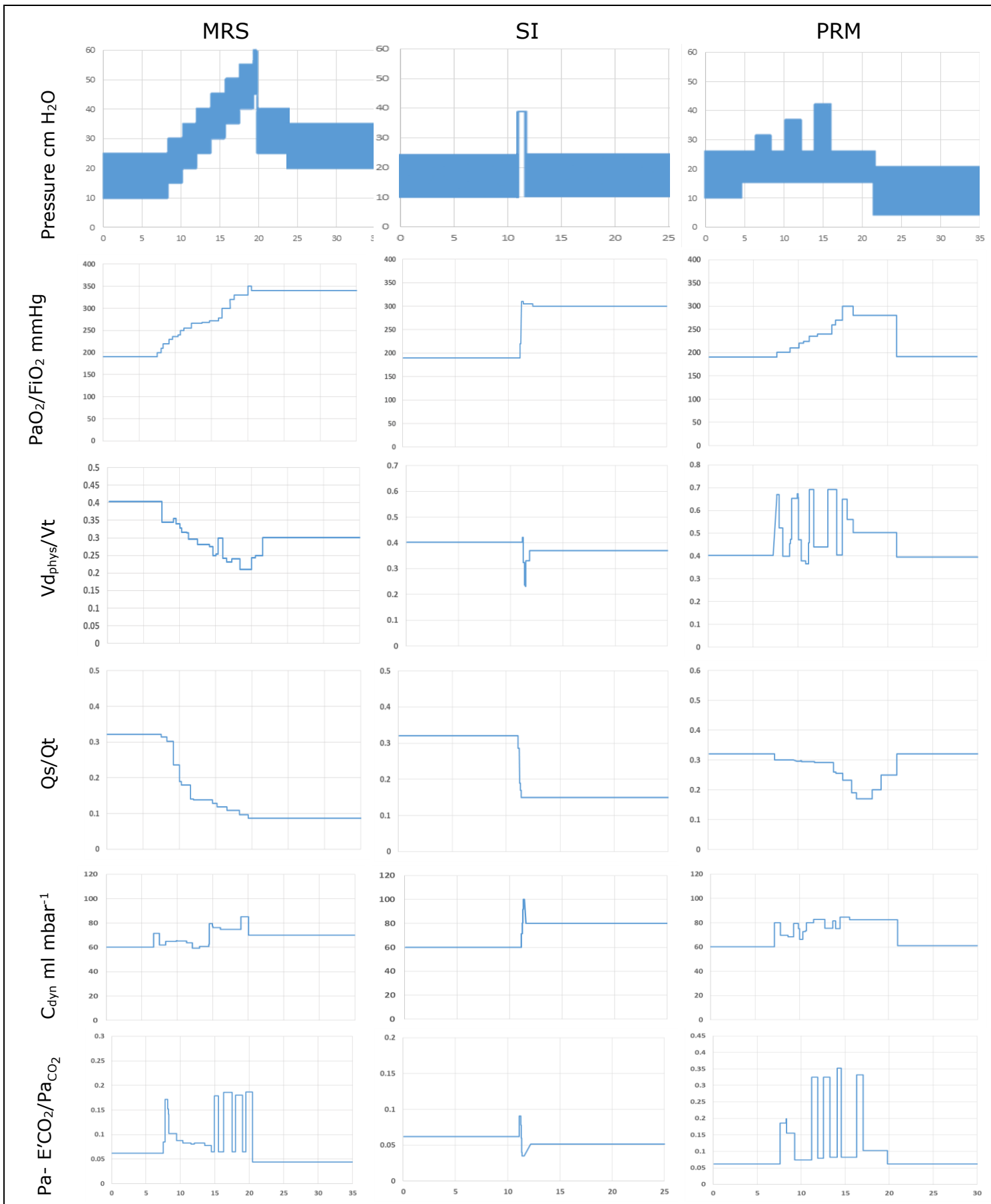


Figure 19: NPS output following application of RMS in patient B

This figure shows application of MRS, SI and PRM in patient B. x-axis shows time in minutes.

Patient C: This patient had $\text{PaO}_2/\text{FiO}_2$ of 75 mmHg, and was classified as severe ARDS (Fig. 20). During MRS $\text{PaO}_2/\text{FiO}_2$ ratio increased up to 340 mmHg and it remained higher than 300 mmHg after the manoeuvre. The SI resulted in an increase in $\text{PaO}_2/\text{FiO}_2$ ratio up to 110 mmHg and it dropped to 100 mmHg with the end-PEEP setting of 10 cm H_2O . The $\text{PaO}_2/\text{FiO}_2$ ratio returned to the baseline value following the PRM.

The application of the MRS resulted in a decrease in $\text{Vd}_{\text{phys}}/\text{Vt}$ from 0.5 to 0.25, and it was maintained at 0.25 after the manoeuvre. $\text{Vd}_{\text{phys}}/\text{Vt}$ returned to the baseline value after the application of the SI and PRM. Pulmonary shunt decreased during the MRS from 0.44 to approximately 0.1, and it remained at 0.14 after the application of the manoeuvre. It returned to the baseline value following the SI and PRM.

The MRS resulted in an increase in the dynamic compliance from the baseline value of 60 ml mbar^{-1} to 75 ml mbar^{-1} after the manoeuvre. $(\text{Pa}-\text{E}'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ decreased slightly after the application of the MRS. $(\text{Pa}-\text{E}'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ returned to the baseline value following the SI and PRM.

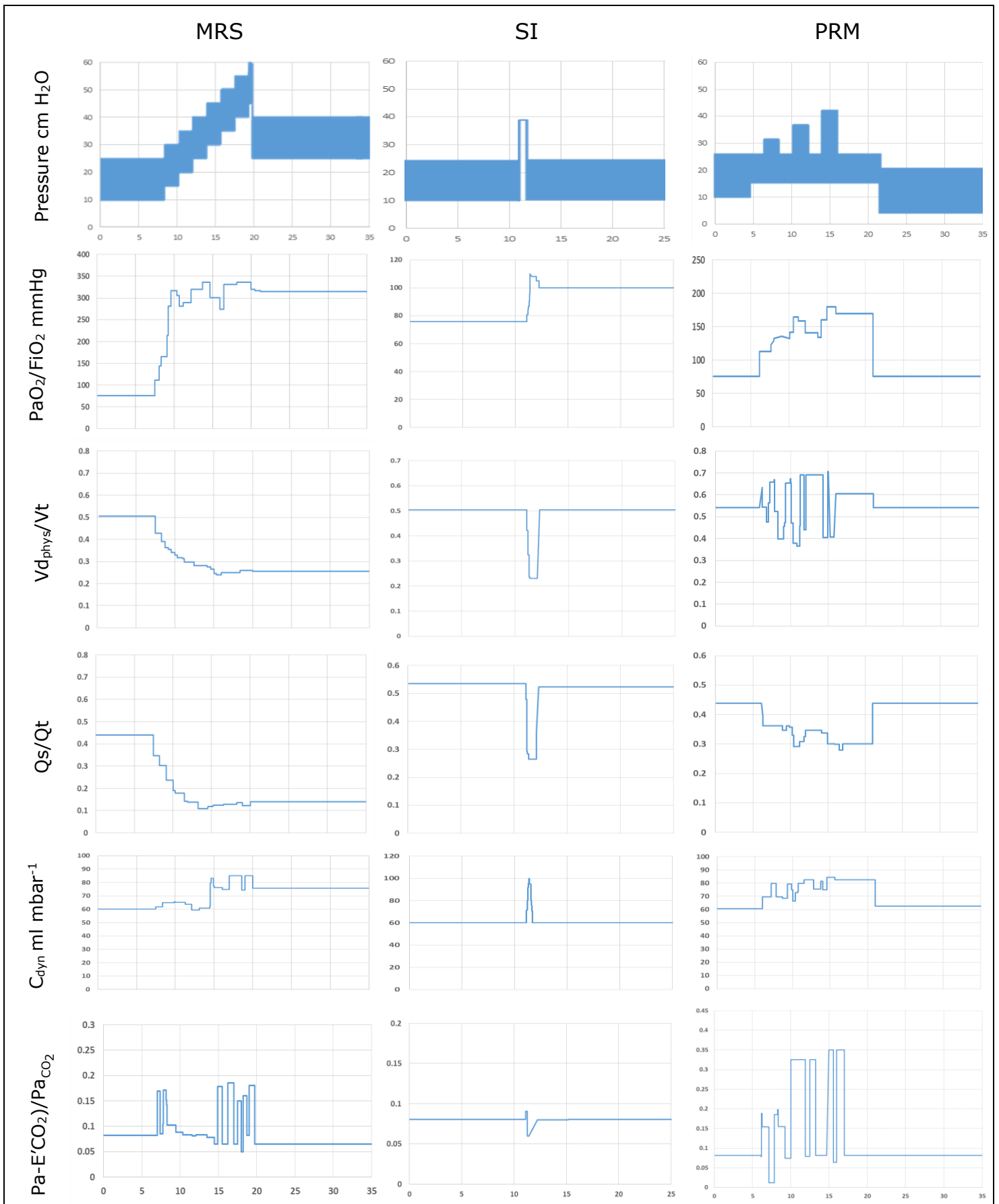


Figure 20: NPS output following application of RMs in patient C

This figure shows application of MRS, SI and PRM in patient C. x-axis shows time in minutes.

Patient D: This patient had $\text{PaO}_2/\text{FiO}_2$ ratio of 50 mmHg, and was classified as severe ARDS (Fig. 21). The application of the MRS resulted in an increase in $\text{PaO}_2/\text{FiO}_2$ ratio from 50 mmHg to approximately 340 mmHg, and it was maintained at 290 mmHg after the manoeuvre. $\text{PaO}_2/\text{FiO}_2$ returned to almost the baseline value after the application of the SI and PRM.

$\text{Vd}_{\text{phys}}/\text{Vt}$ decrease during the MRS from 0.3 to 0.12 and it was maintained at 0.15 after the manoeuvre. SI resulted in a sharp decrease in $\text{Vd}_{\text{phys}}/\text{Vt}$ during the manoeuvre, but it returned to the baseline value after the manoeuvre with the end-PEEP setting of 10 cm H_2O . $\text{Vd}_{\text{phys}}/\text{Vt}$ fluctuated during the PRM and it returned to the baseline value after the manoeuvre.

Q_s/Q_t decreased significantly following the MRS, and it returned to the baseline value after the application of the SI and PRM. The dynamic compliance increased from 50 ml mbar^{-1} to 90 ml mbar^{-1} during the MRS and it remained 80 ml mbar^{-1} after the manoeuvre. The SI resulted in a slight increase in the dynamic lung compliance from 50 ml mbar^{-1} to 60 ml mbar^{-1} . The dynamic compliance returned to almost the baseline value after the application of the PRM. $(\text{Pa}-\text{E}'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ decreased significantly following the MRS. The SI and PRM did not result in improvement of $(\text{Pa}-\text{E}'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$.

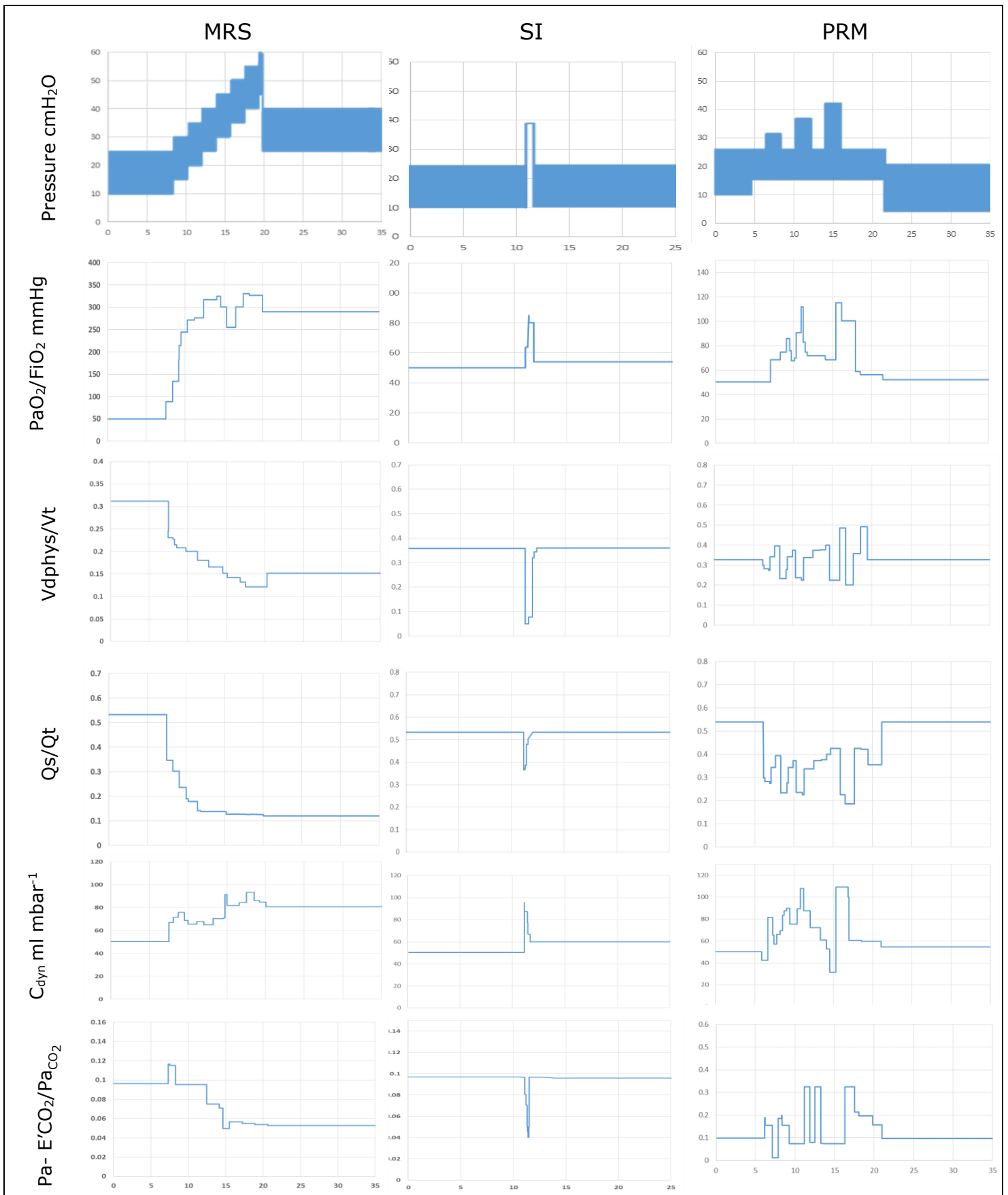


Figure 21: NPS output following application of RMs in patient D

This figure shows application of MRS, SI and PRM in patient D. x-axis shows time in minutes.

Patient E: This patient had $\text{PaO}_2/\text{FiO}_2$ ratio of 50 mmHg, and was classified as severe ARDS (Fig. 22). The MRS resulted in an increase in the $\text{PaO}_2/\text{FiO}_2$ ratio from the baseline value to 340 mmHg. The SI resulted in a slight increase in the $\text{PaO}_2/\text{FiO}_2$ ratio with the end-PEEP setting of 10 cm H_2O . The $\text{PaO}_2/\text{FiO}_2$ ratio returned to the baseline value with the end-PEEP setting of 5 cm H_2O .

$\text{Vd}_{\text{phys}}/\text{Vt}$ decreased significantly during the MRS from 0.41 to up to 0.15, and it was maintained at 0.2 after the manoeuvre. $\text{Vd}_{\text{phys}}/\text{Vt}$ returned to the baseline value after the application of the SI and PRM. Pulmonary shunt decreased greatly during the MRS from the baseline value of 0.52 to approximately 0.1, and it remained at 0.11 after the manoeuvre. Q_s/Q_t decreased sharply during the application of the SI and it returned to the baseline value after the manoeuvre. Q_s/Q_t did not improve after the application of the PRM.

The MRS resulted in an increase in dynamic compliance from 42 ml mbar^{-1} to 95 ml mbar^{-1} during the manoeuvre, and it was maintained at 80 ml mbar^{-1} after the manoeuvre. The SI with the end-PEEP setting of 10 cm H_2O did not maintain the increase in the dynamic lung compliance and it returned to the baseline value. The dynamic lung compliance fluctuated during the PRM and it returned to the baseline value after the manoeuvre. (Pa-

$E'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ decreased slightly after the application of the MRS. $(\text{Pa}-E'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ did not improve following the SI and it returned to the baseline value with the end-PEEP setting of 10 cm H₂O. $(\text{Pa}-E'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ fluctuated during the PRM and it returned to the baseline value with the end-PEEP setting of 5 cm H₂O.

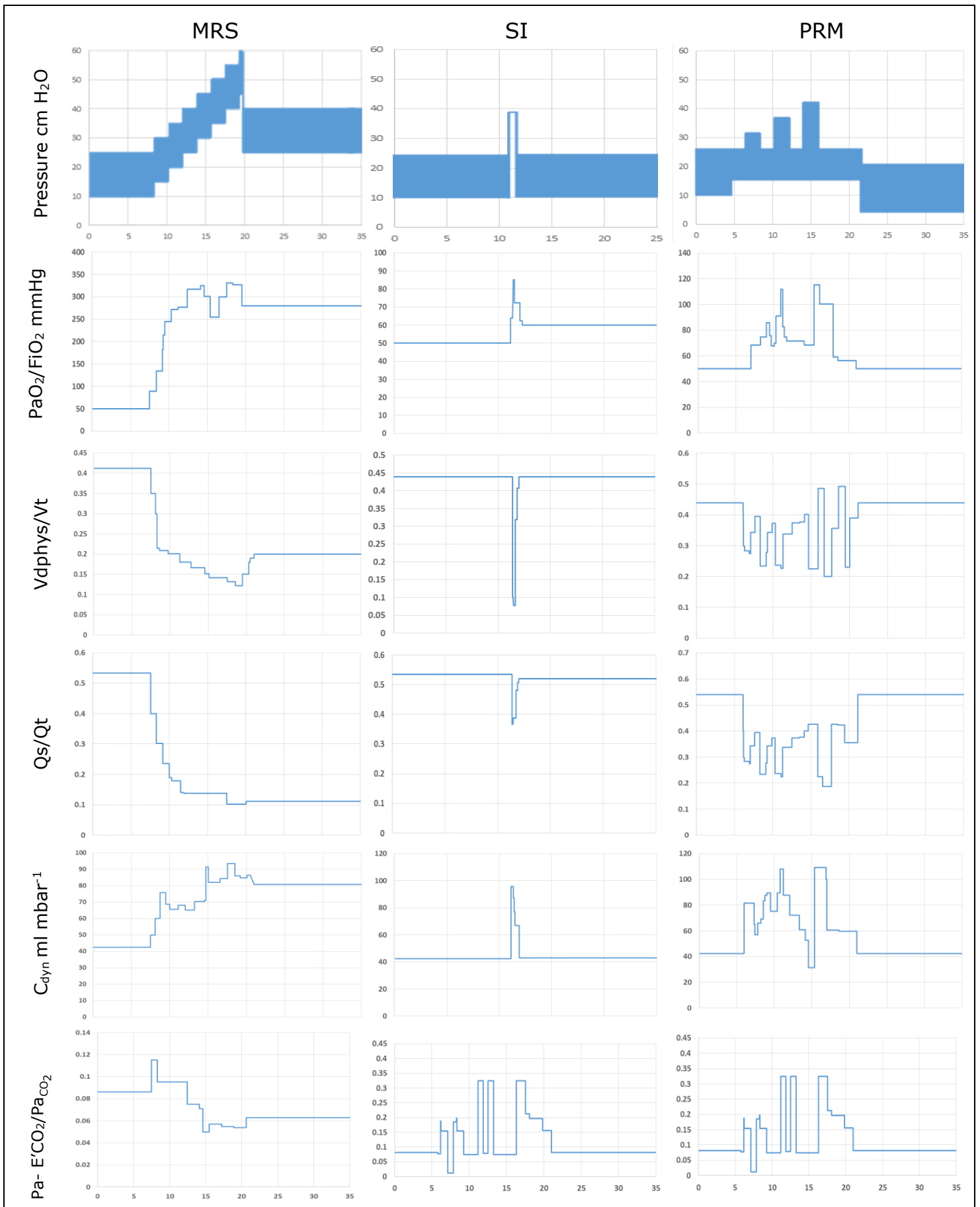


Figure 22: NPS output following application of RMs in patient E.

This figure shows application of MRS, SI and PRM in patient E. x-axis shows time in minutes.

Patient F: This patient had $\text{PaO}_2/\text{FiO}_2$ ratio of 50 mmHg, and it was classified as severe ARDS (Fig. 23). The MRS resulted in a marked increase in the $\text{PaO}_2/\text{FiO}_2$ from 50 mmHg to approximately 350 mmHg during the manoeuvre, and it remained at 250 mmHg after the manoeuvre. The SI resulted in a slight increase in $\text{PaO}_2/\text{FiO}_2$ ratio after the end of the manoeuvre. $\text{PaO}_2/\text{FiO}_2$ ratio fluctuated during the PRM and it returned to the baseline value at the end-PEEP setting of 5 cm H_2O .

The MRS resulted in a decrease in $\text{Vd}_{\text{phys}}/\text{Vt}$ from 0.37 to 0.2. $\text{Vd}_{\text{phys}}/\text{Vt}$ returned to the baseline value after the application of the SI with the end-PEEP setting of 10 cm H_2O . $\text{Vd}_{\text{phys}}/\text{Vt}$ fluctuated during the PRM and it did not improve after the manoeuvre. Pulmonary shunt decreased from 0.52 to 0.1 after the application of the MRS. Q_s/Q_t returned to the baseline value after the application of the SI and PRM.

The MRS resulted in an increase in the dynamic compliance from 40 ml mbar^{-1} to 95 ml mbar^{-1} after the manoeuvre. The SI with the end-PEEP setting of 10 cm H_2O did not maintain the increase in the dynamic compliance and it returned to the baseline value. The dynamic compliance fluctuated during the PRM and it returned to the baseline value after the manoeuvre. $(\text{Pa}-\text{E}'\text{CO}_2)/\text{Pa}_{\text{CO}_2}$ decreased slightly after the application of the MRS.

The SI did not improve $(Pa-E'CO_2)/Pa_{CO_2}$ and it returned to the baseline value with the end-PEEP setting of 10 cm H₂O. $(Pa-E'CO_2)/Pa_{CO_2}$ fluctuated during the PRM and it returned to the baseline value with the end-PEEP setting of 5 cm H₂O.

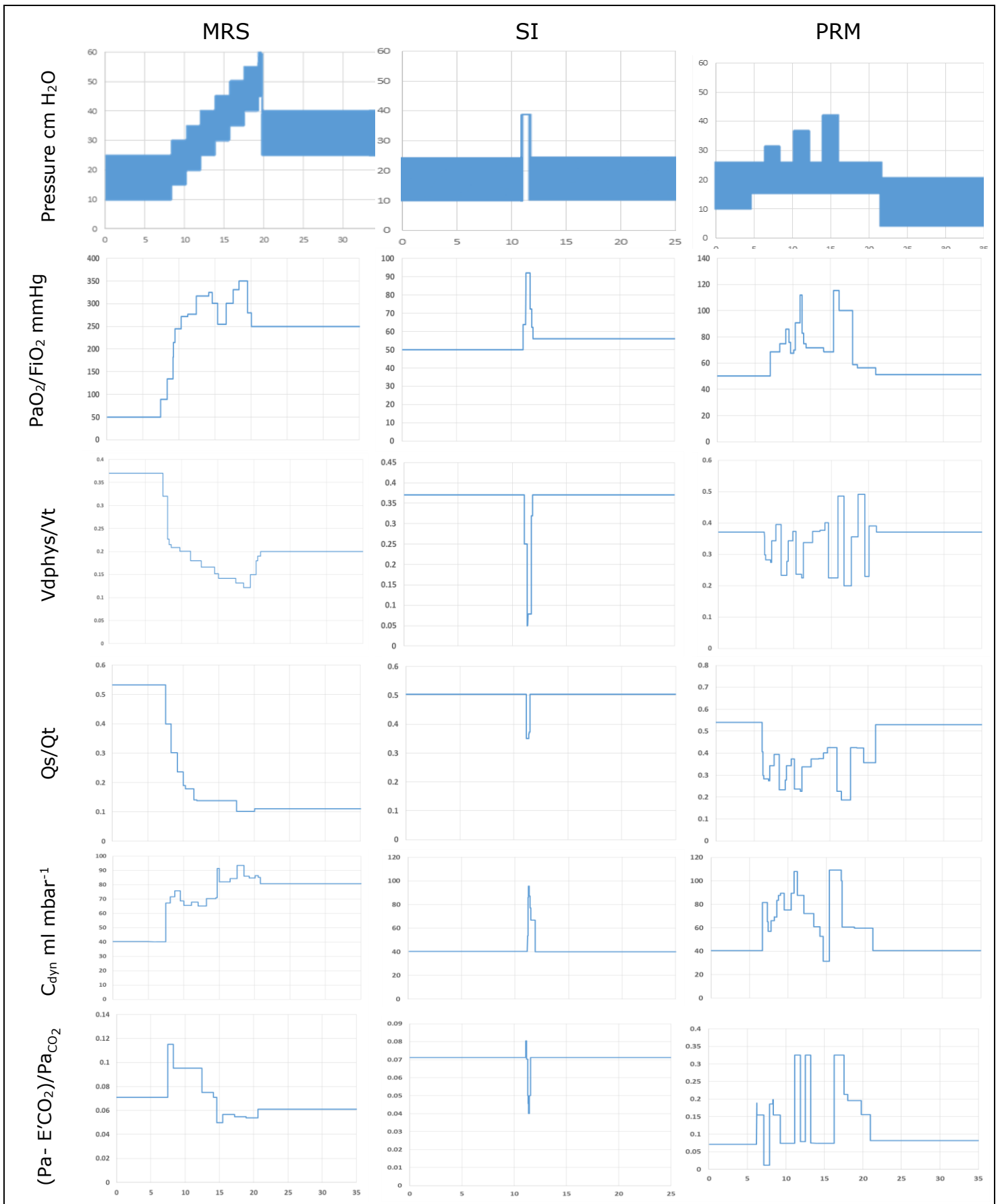


Figure 23: NPS output following application of RMs in patient F

This figure shows application of MRS, SI and PRM in patient F. x-axis show time in minutes.

Discussion

Major findings of this study are summarized below:

- a) $\text{PaO}_2/\text{FiO}_2$ ratio increased significantly after the application of the MRS across all in-silico ARDS subjects. The SI resulted in improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio only in moderate ARDS subject. The $\text{PaO}_2/\text{FiO}_2$ ratio returned to the baseline value in all ARDS subjects following the application of the PRM.
- b) $\text{Vd}_{\text{phys}}/\text{Vt}$ decreased after the application of the MRS across all in-silico ARDS subjects. $\text{Vd}_{\text{phys}}/\text{Vt}$ decreased following the SI only in moderate ARDS subject. $\text{Vd}_{\text{phys}}/\text{Vt}$ returned to the baseline value after the application of the PRM.
- c) Pulmonary shunt decreased following the application of the MRS across 6 ARDS subjects. The SI resulted in the decrease in Q_s/Q_t only in moderate ARDS subject. It returned to the baseline value in all ARDS subjects after the application of the PRM.
- d) Dynamic compliance increased after the application of MRS in all ARDS subjects. SI resulted in a slight increase in the dynamic compliance in only two ARDS subjects. It returned to the baseline value in all ARDS subject after the application of the PRM.

e) $(Pa-E'CO_2)/Pa_{CO_2}$ improved slightly after the application of the MRS. SI resulted in a slight improvement in $(Pa-E'CO_2)/Pa_{CO_2}$ only in moderate ARDS subject. It returned to the baseline value in all 6 ARDS subjects after the application of the PRM.

A number of techniques (209-213) and different physiological parameters are being used to monitor the efficacy of lung recruitment manoeuvres (RMs), and for the selection of optimal positive end-expiratory pressure in ARDS patients (190, 214-217). For example, PaO_2 (212, 218, 219), stress index (220-222), volume-pressure curve analysis (223-227), respiratory system compliance (215, 228, 229), oxygen delivery (230, 231), dead space fraction (229, 232, 233), end-expiratory transpulmonary pressure (234) and driving pressure (235). RMs improve gas exchange (122, 190, 197, 206, 236, 237) and the selection of an appropriate PEEP is crucial following the application of RMs to stabilize recruited alveoli (201) and to prevent alveolar over-distension (200, 238). PaO_2/FiO_2 -PEEP tables are generally used for the selection of an appropriate PEEP level (177, 230). A number of studies have shown that dead space fraction has a close relationship with alveolar collapse-recruitment phenomenon and it could be a useful parameter for the titration of PEEP following RMs (110, 206,

207). We have shown that the application of RMs induce significant changes in dead space fraction and $(Pa-E'CO_2)/Pa_{CO_2}$ in ARDS subjects.

Recruitment manoeuvres improve ventilation/perfusion matching in lung units and cause better elimination of CO_2 (223, 239-241). However, higher airway pressure may cause lung over-distension (223, 242), hemodynamic abnormalities (198, 243), reduction in cardiac output (78, 198, 244) and retention of carbon dioxide (239, 245, 246). Suter et al. monitored respiratory system compliance, changes in oxygen delivery and dead space fraction during changes in positive end-expiratory pressure (229). They showed that oxygen delivery was maximum and dead space fraction was lowest when respiratory system compliance was maximum. We found that after the application of the MRS PaO_2/FiO_2 was increased and dead space fraction was reduced, indicating better ventilation/perfusion matching. Fengemi et al. also studied the effects of SI, followed by decremental PEEP trial, on dead space fraction (206). They demonstrated that the optimum PEEP value was closely related with highest compliance and lowest Vd_{phys}/Vt , and dead space fraction was helpful in selecting open-lung PEEP following the recruitment maneuver. The current study showed that in contrast to the SI and PRM, the application of the MRS resulted

in better outcome in all ARDS subjects. This finding is similar to a previous NPS investigation of evaluation of lung recruitment manoeuvres which showed that the implementation of the MRS in ARDS subjects resulted in better outcome than the SI and PRM (122).

This investigation showed that changes in $(Pa-E'CO_2)/Pa_{CO_2}$ were closely related with changes in dead space fraction. Our results support previous research that the arterial to end-tidal PCO_2 gradient, along with PaO_2/FiO_2 and other physiological variables, might be used as a simple bedside tool for titration of PEEP after the application of RMs (110, 207, 239). Similarly, Tusman et al. monitored changes in dead space fraction and the arterial to end-tidal PCO_2 gradient during recruitment and PEEP titration in lung-lavaged pigs (110). They showed that dead space fraction and the arterial to end-tidal PCO_2 gradient were closely correlated with PaO_2 and atelectatic areas on CT scan.

Conclusion

We compared efficacy of three RMs and have shown that dead space fraction exhibits close relationship with alveolar recruitment-collapse phenomena. Changes in the arterial to end-tidal PCO_2 gradient were closely related with changes in dead space fraction and it might be used as a simple bedside

tool to monitor the efficacy of lung recruitment manoeuvres along with other physiological parameters. This study has some limitations. The model used in this study does not include the effects of alveolar over-distension and assume constant cardiac output (122). Pathophysiological changes due to damage of alveolar capillary membrane are not currently included in the model (122). Furthermore, we have configured only one moderated ARDS subject and have focused on the effect of RMs in patients with severe ARDS.

Chapter 6

Summary and Conclusion

Measurement of dead space to tidal volume ratio is important for multiple reasons (247-249). It has been shown as an independent predictor of outcomes in patients with ARDS (18, 26, 64, 97, 250). It has been used for monitoring the effects of lung recruitment manoeuvres and response of PEEP titration (36, 205, 251, 252). It has been used for diagnosis of pulmonary embolism (253), as a predictor of extubation failure (47, 254), to monitor response following changes in mechanical ventilation strategies and therapeutic interventions (40, 44, 109). Several methods exist for the estimation of pulmonary dead space ventilation (4, 63, 97-99, 102, 103, 208), this thesis attempts to explore the performance of some methods proposed for the estimation of dead space to tidal volume ratio in different pulmonary configurations and clinical scenarios.

$\text{PaO}_2/\text{FiO}_2$ and other indices of oxygenation are commonly monitored in critical care settings (68, 148). However, far too little attention has been paid to the measures of ventilatory efficiency (5). Dead space is an important marker of ventilatory efficiency (5). It is particularly important to measure dead space fraction in an era of lung-protective mechanical ventilation strategies. A few studies have shown that dead space fraction is a better predictor of prognosis than oxygenation indices in critically ill patients (40, 255). Initially, high dead space fraction

in mechanically ventilated ARDS patients was attributed to poorly perfused or non-perfused lung regions (18). However, a number of pathophysiological mechanisms that can contribute to increase in measured dead space fraction include ventilation/perfusion heterogeneity, shunt, diffusion impairment and alveolar over-distension due to mechanical ventilation strategies (5).

In our first study, we compared the performance of 5 different methods for the estimation of dead space ventilation with the gold standard method in multiple ventilation/perfusion relationships. Six pulmonary configurations all with same alveolar dead space fraction of 0.25, but with different specific pattern of ventilation/perfusion distribution were created within the NPS. Next, variations in the methods of estimating dead space ventilation upon varying four physiological factors were analysed. We concluded that the estimation of alveolar dead space ratio by 5 methods of estimating dead space is influenced by pattern of ventilation/perfusion distribution and alterations in the relevant physiological factors. This study demonstrated the limitations of the methods proposed for the estimation of dead space ventilation. An estimate of alveolar dead space to tidal volume ratio that performs well in a certain clinical

scenario, may not be a suitable estimate of alveolar dead space to tidal volume ratio in another clinical scenario.

In our second study, we further analysed performance of 5 methods for estimating dead space ratio in patients with ARDS. ARDS subjects were created within the NPS and alveolar dead space fraction was measured by the gold standard method. Then, dead space fraction was determined by 5 different methods for estimating dead space fraction. We found that the estimates of dead space fraction measure different than the conventional equation in ARDS patients.

In our third computer model study, we compared efficacy of three lung recruitment maneuvers in patients with ARDS. Six virtual ARDS patients were created and changes in dead space fraction, $(Pa-E'CO_2)/Pa_{CO_2}$ and other parameters were observed following the recruitment manoeuvres. The results of this study showed that changes in $(Pa-E'CO_2)/Pa_{CO_2}$ closely relate with changes in dead space to tidal volume ratio. These findings suggest that in clinical settings where it is not possible to measure dead space fraction, a simple estimate of dead space to tidal volume ratio may be used to monitor the efficacy of lung recruitment manoeuvres and titration of PEEP. We also found that the outcomes of the maximal recruitment strategy were better than the sustained inflation across all ARDS subjects. This

result supports the idea that stepwise approaches for lung recruitment are better than the sustained inflation.

These findings have a number of practical implications for future practice. Dead space to tidal volume ratio is not a routinely measured physiological variable at the bedside. Volumetric capnography is required for measuring dead space fraction and it is not available in every clinical setup. Estimation of dead space using routinely available data may allow widespread use of this important physiological parameter. For example, arterial PCO_2 and end-tidal PCO_2 are routinely measured in clinical setups. Arterial to end-tidal PCO_2 difference is minimal in normal lung. In the presence of dead space ventilation, this gradient is increased and it may be used as a simple index of alveolar dead space fraction. In this thesis, we have analysed the performance of few estimates of dead space fraction based on arterial to end-tidal PCO_2 difference, such as the Frankenfield equation of dead space and the Hardman and Aitkenhead estimate of dead space ventilation. Simplified approaches for the estimation of dead space may allow increase use of dead space fraction for diagnostic and prognostic purposes in critical care settings. Repeated measurements of V_D/V_T in patients with ARDS at the bedside may be used for classifying disease severity, for monitoring the effects of therapeutic strategies and

interventions. For example, monitoring of dead space fraction during spontaneous breathing trial may help earlier identification of patients that will require prolong mechanical ventilation.

The major limitation of this thesis is that we have used a mathematical model. In our first study, pulmonary configurations represent heterogeneous group of patients and future clinical studies are required to validate our results. We studied only a few methods for the estimation of dead space. More broadly, a detailed comparative investigation may be carried out in future evaluating other methods, such as ventilatory ratio and the Beitler et al. estimate, that are being proposed for the estimation of dead space fraction. Also, we did not study the effects of changes in mechanical ventilation strategies on the estimates of dead space ventilation. A future study could assess the effects of changes in tidal volume, respiratory rate, inspiratory time and pattern on the estimates of dead space fraction. A study on the effects of different modes of mechanical ventilation on the estimates of dead space may be carried out in future. Another clinical investigation on the effects of therapeutic interventions that are being used for the management of critically ill patients, on the estimates of dead space ventilation may also be conducted in future (256, 257).

In addition, another computer model study may also be devised to observe the performance of clinical estimates in situations that lead to negative arterial to end-tidal PCO₂ gradient.

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