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CRITICAL CARE

Evaluation of the physiological properties of ventilatory ratio in a computational cardiopulmonary model and its clinical application in an acute respiratory distress syndrome population

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Editor's key points

- Increased dead space ventilation is associated with increased mortality in acute respiratory distress syndrome (ARDS) patients.

- Ventilatory ratio (VR) provides a simple tool to monitor dead space in critical care practice.

- In the computational model, VR was larger as dead space and $\dot{V}_{CO_2}$ increased.

- A higher VR, found in patients with more severe ARDS, was associated with an increased mortality.

- VR may have clinical utility in critical care. Further clinical studies are required.

Background. Owing to complexities of measuring dead space, ventilatory failure is difficult to quantify in critical care. A simple, novel index called ventilatory ratio (VR) can quantify ventilatory efficiency at the bedside. The study objectives were to evaluate physiological properties of VR and examine its clinical applicability in acute respiratory distress syndrome (ARDS) patients.

Methods. A validated computational model of cardiopulmonary physiology [Nottingham Physiology Simulator (NPS)] was used to evaluate VR *ex vivo* in three virtual patients with varying degrees of gas exchange defects. Arterial P_{CO_2} and mixed expired P_{CO_2} were obtained from the simulator while either dead space or CO_2 production was altered in isolation. VR and dead space fraction was calculated using these values. A retrospective analysis of a previously presented prospective ARDS database was then used to evaluate the clinical utility of VR. Basic characteristics of VR and its association with mortality were examined.

Results. The NPS showed that VR behaved in an intuitive manner as would be predicted by its physiological properties. When CO_2 production was constant, there was strong positive correlation between dead space and VR (modified Pearson's *r* 0.98, *P*<0.01). The ARDS database had a mean VR of 1.47 (standard deviation 0.58). Non-survivors had a significantly higher VR compared with survivors [1.70 *vs* 1.34, mean difference 0.35, 95% confidence interval (CI) 0.16–0.56, *P*<0.01]. VR was an independent predictor of mortality (odds ratio 3.05, CI 1.35–6.91, *P*<0.01).

Conclusions. VR is influenced by dead space and CO_2 production. In ARDS, high VR was associated with increased mortality.

Keywords: ARDS; dead space; definition; ventilatory failure

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Alveolar ventilation is the portion of the tidal volume that participates in gas exchange and defines ventilatory efficiency. It is intuitive that monitoring ventilatory efficiency will be of considerable importance in the management of mechanically ventilated patients. Dead space measurement is the most accurate surrogate for assessing ventilatory inefficiency. Increased dead space ventilation has consistently been shown to be associated with increased mortality and disease progression in patients with acute respiratory distress syndrome (ARDS).[1–5] Yet in day-to-day practice, dead space measurements are seldom performed. In the main, this is due to problems associated with measuring dead space. Volumetric capnography offers a relatively simple method of calculating dead space. Despite being available for over two decades, it has failed to gain popularity in intensive care practice. This may in part be because volumetric capnographs are not integrated as standard in most commonly used ventilators and installation incurs additional expense.[6 7] The traditional method of calculating physiological

dead space is cumbersome and requires a large chamber (Douglas Bag) for the collection of mixed expired gas. In addition, measured mixed expired P_{CO_2} requires correction for compressed ventilator gas that contaminates the expired volume.[7] For these reasons, efficiency of ventilation is seldom monitored in critically unwell patients.

The Pa_{O_2}/F_{IO_2} ratio is a widely used bedside index of adequacy of oxygenation and is the only measured variable used to categorize disease severity in ARDS. No such index of ventilatory efficiency is in common use. There is, therefore, a clinical need to develop an index that is easy to calculate and monitors ventilatory efficiency at the bedside. Ventilatory ratio (VR) has been recently described and could potentially fulfil this role. VR is a product of measured expired minute ventilation ($\dot{V}_{E\,measured}$) and measured arterial P_{CO_2} ($Pa_{CO_2\,measured}$) normalized to a preset ventilatory standard established from nomograms.[8] VR is a unitless ratio.[9] Physiological analysis shows that VR is influenced by physiological dead space fraction and CO_2 production, two variables seldom measured in intensive care units (ICUs).

The aims of this study were:

(i) to evaluate the previously described physiological properties of VR in a cardiorespiratory simulation model;
(ii) to assess the clinical applicability of VR in a database relating to patients with ARDS.

Methods

Ventilatory ratio

VR is defined as

$$VR = \frac{\dot{V}_{E\,measured} \times Pa_{CO_2\,measured}}{\dot{V}_{E\,predicted} \times Pa_{CO_2\,ideal}} \quad (1)$$

where $\dot{V}_{E\,predicted}$ is taken to be 100 ml kg^{-1} min^{-1} based on predicted body weight and $Pa_{CO_2\,ideal}$ is set at 5 kPa. Physiological analysis of VR shows that it is influenced by changes in the ventilatory efficiency and rate of CO_2 production ($\dot{V}_{CO_2}$)

$$VR = \frac{\dot{V}_{CO_2\,actual}}{E_{actual}} \times \frac{E_{predicted}}{\dot{V}_{CO_2\,predicted}} \quad (2)$$

where E is 'efficiency' described as $1 - (V_D/V_T)$. For a given individual, the predicted values would remain constant; therefore, we could restate equation (2) as:

$$VR = \frac{\dot{V}_{CO_2\,actual}}{E_{actual}} \times k \quad (3)$$

Equation (3) shows that an increase in VR would be due to either an increase in dead space, an increase in $\dot{V}_{CO_2}$, or both.

Nottingham Physiological Simulator

The Nottingham Physiological Simulator is a previously validated multi-compartment computational lung model that has previously been used for theoretical investigation of carbon dioxide production, dead space ventilation, and carbon dioxide

clearance.[10] [11] Three virtual patients were configured with normal, moderate, and severe gas exchange defects. Gas exchange defects were created by varying ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch. $\dot{V}/\dot{Q}$ mismatch was altered within the simulator by varying compartmental bronchiolar and pulmonary capillary resistance. Details of the simulator configuration of the respective bronchiolar and pulmonary capillary resistance for the three virtual patients can be found in Supplementary Appendix S1.

In all three virtual configurations, the patient settings were for a 70 kg and 170 cm individual. True series (anatomic) dead space (V_{Danat}) was configured at 147 ml, haemoglobin at 145 g litre^{-1}, and body temperature was set at 37.2°C. Volume-controlled ventilation was used in all readings. F_{IO_2} was set at 0.21 and PEEP was set at 5 cm H_2O for the normal and moderately impaired patients. For the patient with severe lung impairment, F_{IO_2} was set at 0.5 and PEEP was set at 10 cm H_2O.

Readings were taken with minute ventilation set at 7000, 6400, 5800, and 5200 ml min^{-1}. Breath frequency (F) was altered sequentially to 10, 12, and 15 bpm, while V_T was changed to keep the expired minute ventilation constant. Respiratory coefficient, dead space volume, cardiac output, shunt fraction, and PEEP were kept constant during all subsequent readings. These alterations resulted in alteration of 'E' or V_D/V_T. At each permutation of V_T/F, three separate readings were taken with $\dot{V}_{CO_2}$ levels at 150, 200, and 250 ml min^{-1}. This strategy ensured that VR was calculated for all three virtual patient configurations while either V_D/V_T or $\dot{V}_{CO_2}$ were altered in isolation. At each permutation values for Pa_{CO_2}, mixed expired P_{CO_2} (P_{ECO_2}) and percentage shunt were recorded. Pa_{CO_2} and P_{ECO_2} were used to calculate dead space fraction using Enghoff's modification of the Bohr equation. VR was calculated using expired minute ventilation and Pa_{CO_2}.

At a minute ventilation of 7000 ml min^{-1} (15 bpm with V_T of 467 ml), the configured $\dot{V}/\dot{Q}$ parameters for the patients were as follows: normal patient V_D/V_T 0.35 and shunt 2.9%; moderate impaired patient V_D/V_T 0.57 and shunt 9.1%; severely impaired patient V_D/V_T 0.66 and shunt 41.7%. Changes in Pa_{CO_2} because of pulmonary shunt (venous admixture) are modelled into the simulator. The simulator model responds to changes in the pulmonary circulation as a result of changing ventilatory pressures and as a result of hypoxic pulmonary vasoconstriction.

ARDS database

A previously presented database of ARDS patients, which had been prospectively collected by the Australian and New Zealand Intensive Care Society Clinical Trials Group was used to evaluate the characteristics and clinical utility of VR.[12] In the database, information was collected on all ICUs in three Australian States from patients requiring ventilation (invasive and non-invasive) between October and November 1999. Standard patient characteristic data were collected alongside aetiology of ARDS, ventilator settings, and respiratory and cardiovascular variables. Severity of illness scores (APACHE II and SOFA scores), Murray lung injury score, days of mechanical

ventilation, and survival outcome scores were also recorded. From the above data and arterial blood gas measurements, $Pa_{O_2}/F_{I_{O_2}}$ ratio and VR were calculated at the time of diagnosis of ARDS. One hundred and twenty-one of 168 patients from the original database were included in the data analysis. Only patients managed with invasive mechanical ventilation were included in the analysis. Where data were missing for the height of the patient ($n=26$), the mean population height specific for sex was used to calculate the ideal body weight.

Statistical analysis

Data are presented as mean and standard deviation (SD) or median with inter-quartile range, where appropriate. The un-paired *t*-test or Mann–Whitney test were used to compare groups (depending on the distribution of the data). Comparisons between multiple groups were made using one-way analysis of variance. A modified Pearson's correlation coefficient as described by Stratton and colleagues[13] was obtained to study the association between VR and V_D/V_T. The method was used to correct bias in Pearson's correlation coefficient as a result of mathematical coupling due to Pa_{CO_2} being used in the computation of both VR and V_D/V_T.

The χ^2 test for trends was used to analyse the association of mortality and ordinal groups of VR. Univariate logistic regression analysis was used to calculate odds ratios (ORs) for multiple respiratory variables to individually predict mortality. To examine the relationship of hospital mortality and VR and adjusting for confounding variables, multivariate logistic regression analysis was also performed. Statistical software STATA/IC 11.1 (StataCorp., TX, USA) was used for data analysis. Prism 5 for Mac OS X (GraphPad Software, Inc., San Diego, CA, USA, www.graphpad.com) was used to create graphs.

Results

Nottingham Physiological Simulator

The range of calculated values for VR from the three simulated patients was 0.63–2.64. The range of values for physiological dead space and shunt fraction for the three virtual configured patients were as follows: normal patient V_D/V_T 0.24–0.44, total calculated shunt 1.2–2.1% of cardiac output; moderate mismatch V_D/V_T 0.49–0.59, total calculated shunt 12–22.1% of cardiac output; and severe mismatch V_D/V_T 0.60–0.71, total calculated shunt 46.1–52.3% of cardiac output.

The mean values and range of VR in the three patients were as follows: normal 0.89 (0.63–1.35), moderate 1.37 (range 0.98–1.84), and severe 1.76 (range 1.2–2.64) (Fig. 1). VR was larger as dead space increased. Figure 2A shows the relationship of VR and V_D/V_T and the interaction of $\dot{V}_{CO_2}$ with these variables. Values of VR were larger as $\dot{V}_{CO_2}$ increased in all three patients. As predicted by the physiological analysis, the results show an asymptotic relationship between V_D/V_T and VR. When $\dot{V}_{CO_2}$ was constant, there was strong correlation between VR and $V_D/V_{T \text{ phys}}$ (modified Pearson's *r* 0.98,
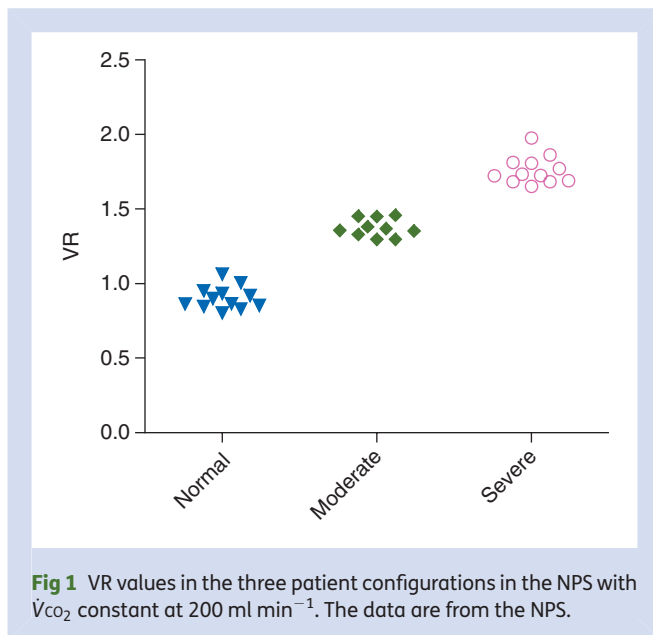

Fig 1 VR values in the three patient configurations in the NPS with $\dot{V}_{CO_2}$ constant at 200 ml min^{-1}. The data are from the NPS.
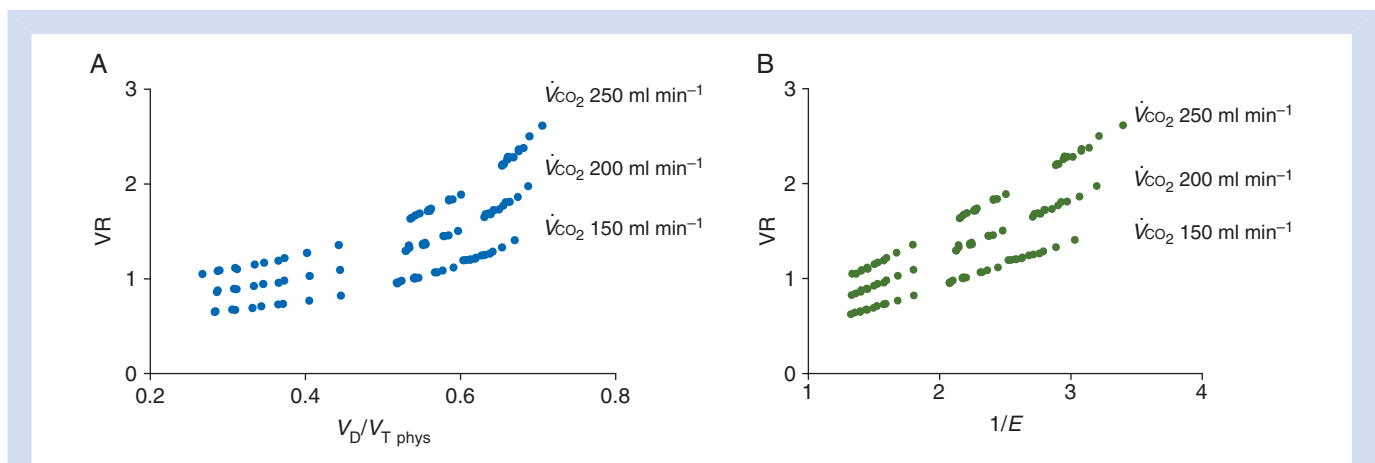

Fig 2 (A) VR plotted against $V_D/V_{T \text{ phys}}$. The isopleths represent configurations with three different rates of $\dot{V}_{CO_2}$. (B) The relationship of VR with $1/E$ at different rates of $\dot{V}_{CO_2}$. The data are from the NPS.

Table 1 Patient characteristic data and respiratory variables for the ARDS database. Mean values were analysed using the unpaired t-test. Median values were analysed using the Mann–Whitney test

	Survivor ($n=85$)	Non-survivors ($n=36$)	P-value
Age (yr)	58.6 (17–88)	66.4 (23–89)	0.04
Height (cm)	1.72 (0.1)	1.70 (0.08)	0.65
Weight (kg)	77.6 (14.3)	74.2 (15.1)	0.24
Tidal volume (ml)	647 (112)	634 (139)	0.59
Minute ventilation (ml min^{-1})	7742 (1950)	8772 (3104)	0.22
Peak pressure (cm H_2O)	27 (24–33)	29.5 (25.25–35)	0.19
Plateau pressure (cm H_2O)	22 (18–25)	20 (19.5–27)	0.97
APACHE II score	18.5 (9.1)	24.7 (9)	<0.01
$Pa_{O_2}/F_{I_{O_2}}$ ratio	24.8 (8.2)	17.5 (8.6)	<0.01
Pa_{CO_2} (kPa)	5.7 (1.5)	6.5 (2)	0.06
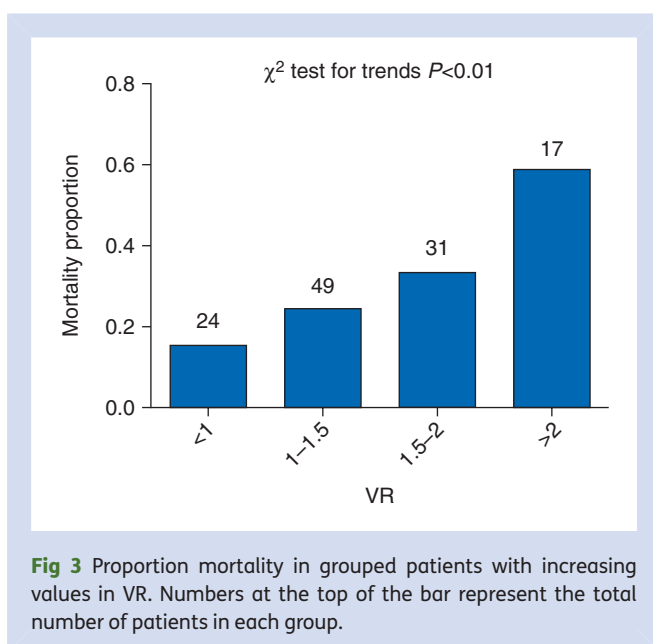
Fig 3 Proportion mortality in grouped patients with increasing values in VR. Numbers at the top of the bar represent the total number of patients in each group.

Table 2 OR derived from univariate analysis of individual respiratory variables on admission with mortality as the outcome ($n=121$)

	OR	CI	P-value
Ventilatory ratio	3.55	1.61–7.84	<0.01
Pa_{CO_2} (kPa)	1.44	1.10–1.89	<0.01
Minute ventilation (ml min^{-1})	1.00	0.99–1.01	0.08
Peak inspiratory pressure (cm H_2O)	1.03	0.97–1.10	0.29
$Pa_{O_2}/F_{I_{O_2}}$ ratio	0.89	0.85–0.95	<0.01
PEEP (cm H_2O)	1.05	0.91–1.12	0.48
APACHE II score	1.08	1.03–1.13	<0.01

$P<0.01$). VR shared a linear relationship with $1/E$ as demonstrated in Figure 2B. There was also a linear relationship between $\dot{V}_{CO_2}$ and VR when V_D/V_T was constant.

ARDS database

The baseline patient characteristics are presented in Table 1. The range of VR in this population was 0.56–3.27. The mean VR in this population was 1.47 (0.58). The mean values for VR were significantly larger in non-survivors than in survivors [1.70 vs 1.34, difference mean 0.35, 95% confidence interval (CI) 0.16–0.56, $P<0.01$]. Patients with moderate and severe ARDS had a significantly higher mean VR in comparison with those with mild ARDS (1.53 SD 0.53 vs 1.27 SD 0.46, $P=0.01$).

Increasing value of VR was associated with an increased risk for mortality (χ^2 test for trends $P<0.01$) (Fig. 3). Univariate logistic regression analysis showed that higher VR was associated with increased mortality [odds ratio (OR) 3.55, CI 1.61–7.84, $P<0.01$]. Table 2 summarizes the results of univariate logistic regression analysis of individual respiratory variables with mortality as the primary outcome. Stepwise multivariate logistic analysis showed that VR remained a significant independent predictor of mortality after the addition of APACHE II score to the baseline model (OR 3.05, 95% CI 1.35–6.91, $P<0.01$) and after addition of PEEP and PIP to the baseline model (OR 2.55, 95% CI 1.06–6.14, $P=0.02$) (Table 3).

Analysis of variance by groups based on the Murray lung injury showed that VR was significantly different in each of the groups [score <2: VR 1.21 (0.45), score 2–2.5: VR 1.37 (0.37), and score >2.5: VR 1.74 (0.62)].[14] There was weak negative correlation between $Pa_{O_2}/F_{I_{O_2}}$ ratio and VR in the population ($r=-0.4$, 95% CI -0.54 to -0.23, $P<0.01$) (Fig. 4).

Discussion

Two separate methods were chosen to evaluate the robustness, clinical applicability, and potential usefulness of VR.

The study with virtual patients using the Nottingham Physiology Simulator (NPS) demonstrated that both dead space and $\dot{V}_{CO_2}$ influences VR. Virtual patients configured to have higher V_D/V_T had higher VR. Increasing $\dot{V}_{CO_2}$, while V_D/V_T remained constant, also led to increasing values of VR. Results from the NPS confirm that VR responds to changes in physiological conditions as predicted by equations (2) and (3).

Table 3 The predictive value of VR on admission with ICU mortality as the primary outcome using logistic regression. Data presented for univariate and multivariate analysis. PEEP, positive end-expiratory pressure

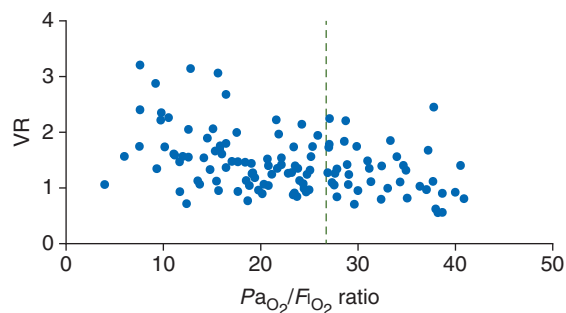| Day 1	OR	95% CI
Univariate analysis		
Ventilatory ratio	3.56	1.61–7.84
Multivariate analysis		
Base model+APACHE II score	3.05	1.35–6.91
(Base model+APACHE II score)+PEEP	3.00	1.30–6.91

Fig 4 Comparison of the relationship of VR and $Pa_{O_2}/F_{I_{O_2}}$ ratio. As the $Pa_{O_2}/F_{I_{O_2}}$ ratio decreases, there is a greater spread in the values of VR. The dotted line represents the transition point of mild and moderate-to-severe ARDS.

Figure 2 describes the relationship of V_D/V_T and VR in the NPS with the additional effect of $\dot{V}_{CO_2}$. From the various isopleths, we can observe that for a given V_D/V_T, the values of VR would depend on the rate of $\dot{V}_{CO_2}$. This relationship is akin to that described between Pa_{CO_2}, alveolar ventilation, and $\dot{V}_{CO_2}$ by Nunn.[15] The physiological properties of VR should, therefore, be intuitive to clinicians interpreting changes in its value. In patients in steady state where $\dot{V}_{CO_2}$ is likely to remain relatively stable, changes in VR would be representative of changes in physiological dead space. However, a more simplistic assessment of VR shows it to be either a marker of efficiency of CO_2 clearance or of adequacy of meeting ventilatory demands. A VR of ~1, in a clinical context, is likely to represent the lungs functioning with a reassuring degree of efficiency regardless of the dead space or $\dot{V}_{CO_2}$. While a VR of 2 would represent the inability of the lung to clear CO_2 adequately be it a manifestation of increased dead space or $\dot{V}_{CO_2}$. In patients with marked respiratory failure, an increase in ventilatory demands is most likely to be as a result of increased dead space ventilation.

From the modelling work, we estimate that 0.85 is probably closer to being near the 'normal' value for VR. Nomograms that were used as a guide to set the predicted values probably overestimate required adequate minute ventilation.[8][16] Similarly, using ideal P_{CO_2} as 5 kPa has also resulted in a small amount of inaccuracy. Part of the objective of the ratio, however, was that it should be simple to calculate at the bedside. Therefore,

a small degree of accuracy has been knowingly relinquished for the sake of ease of calculation. Given that arterial P_{CO_2} is used as a surrogate for alveolar P_{CO_2}, the contributions of intrapulmonary shunt are incorporated in VR. Therefore, changes in shunt would also influence VR. This holds true for most methods of calculating physiological dead space.[17]

In the second part of the study, VR was calculated in an existing data set of ARDS patients. The results indicate that VR has prognostic significance. Higher VR was associated with increased mortality. Mean VR was higher in non-survivors than in survivors. Patients with moderate-to-severe ARDS had higher VR than those with mild ARDS. VR was also significantly larger in groups with higher Murray lung injury scores. These results suggest a relationship between severity of lung injury and VR. Figure 3 shows that the higher ordinal groups of VR were associated with an increased risk in mortality. These findings are in keeping with the findings of other studies that have looked at ventilatory efficiency as a prognostic marker.[3][18] VR was also an independent predictor of outcome in this population after adjusting for the APACHE II score.

The $Pa_{O_2}/F_{I_{O_2}}$ ratio is the only measured respiratory variable used to define ARDS.[19] Not only is the value of the $Pa_{O_2}/F_{I_{O_2}}$ ratio as a predictor of outcome uncertain, there are also uncertainties surrounding its ability to categorize severity of disease particularly in ARDS.[20] There are also data to suggest that altering levels of PEEP and $F_{I_{O_2}}$ may manipulate the $Pa_{O_2}/F_{I_{O_2}}$ ratio and with it categories of severity of ARDS.[21][22] VR appears to increase with worsening oxygenation. Although the relationship between the $Pa_{O_2}/F_{I_{O_2}}$ ratio and VR was consistent, the correlation was weak (Fig. 4). The value of VR in addition to the $Pa_{O_2}/F_{I_{O_2}}$ ratio can be interpreted from this relationship. A tight correlation between oxygenation and ventilatory efficiency would suggest that the physiology of oxygenation and CO_2 clearance are the same. This is clearly not the case and suggests that VR provides clinicians with additional information about the state of the lung that cannot be extracted from the $Pa_{O_2}/F_{I_{O_2}}$ ratio. In theory, VR may be more robust as a marker of the pathological state of the lungs in ARDS. There are fewer variables that can be externally manipulated to alter the value of VR. Specifically, tidal volume and its ratio with the frequency of delivered breaths can be altered to change VR. Provided dead space volume is constant, a decrease in tidal volume will lead to an increase in V_D/V_T and thereby lead to an increase in VR. The magnitude of change in VR would depend on the underlying state of the lungs and the level of CO_2 production.

As seen in Figure 4, values of VR were more heterogeneous in patients with moderate-to-severe ARDS compared with those with mild ARDS. Coupled with an increased association of death with increasing values of VR, there may be biological plausibility in the addition of VR to the current definition of ARDS. The trend of increasing mortality in ordinal groups of VR (Fig. 3) substantiates the importance of ventilatory failure as a predictor of outcome. VR may be used to categorize the ARDS population into those with or without significant ventilatory failure and identify high-risk patients. In an era where extracorporeal oxygenation and CO_2 removal are increasingly being used, early recognition and categorization of ventilatory failure may trigger

instigation of these therapies at an earlier stage potentially offering more effective therapy.

There are aspects of the ratio that need further attention in terms of assessing its clinical performance. The presented ARDS database in this study was small and collected before the introduction of the widespread use of protective lung strategy. Protective lung strategies over the last decade will result in higher values of VR as a result of lower tidal volumes. Further studies are needed to evaluate the behaviour of VR in current ventilatory practice. Larger prospective studies are needed to verify the results presented here.

Summary

VR is a novel tool to monitor ventilatory efficiency at the bedside. Physiological analysis shows that VR is mainly influenced by dead space and $\dot{V}_{CO_2}$. Evaluation in a cardiorespiratory simulator confirms that VR behaves as would be anticipated by its physiological properties. Although VR may be a relatively crude marker of dead space fraction, it is easy to calculate and appears to be useful as a clinical tool for assessing disease severity and predicting mortality in patients with ARDS. It has potential for use as a tool for categorizing disease severity and monitoring disease progression.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

J.G.H. is an editor and editorial board member of the *British Journal of Anaesthesia*. All other authors: none declared.

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