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BJA

British Journal of Anaesthesia, 130 (3): 360–367 (2023)

doi: 10.1016/j.bja.2022.10.035
Advance Access Publication Date: 2 December 2022
Respiration and the Airway

RESPIRATION AND THE AIRWAY

Ventilatory ratio, dead space, and venous admixture in patients with acute respiratory distress syndrome

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Abstract

Background: Ventilatory ratio (VR) has been proposed as an alternative approach to estimate physiological dead space. However, the absolute value of VR, at constant dead space, might be affected by venous admixture and CO_2 volume expired per minute (VCO_2).

Methods: This was a retrospective, observational study of mechanically ventilated patients with acute respiratory distress syndrome (ARDS) in the UK and Italy. Venous admixture was either directly measured or estimated using the surrogate measure Pa_{O2}/FiO_2 ratio. VCO_2 was estimated through the resting energy expenditure derived from the Harris–Benedict formula.

Results: A total of 641 mechanically ventilated patients with mild (n=65), moderate (n=363), or severe (n=213) ARDS were studied. Venous admixture was measured (n=153 patients) or estimated using the Pa_{O2}/FiO_2 ratio (n=448). The VR increased exponentially as a function of the dead space, and the absolute values of this relationship were a function of VCO_2. At a physiological dead space of 0.6, VR was 1.1, 1.4, and 1.7 in patients with VCO_2 equal to 200, 250, and 300, respectively. VR was independently associated with mortality (odds ratio [OR]=2.5; 95% confidence interval [CI], 1.8–3.5), but was not associated when adjusted for V_D/V_{Tphys}, VCO_2, Pa_{O2}/FiO_2 (OR_{adj}=1.2; 95% CI, 0.7–2.1). These three variables remained independent predictors of ICU mortality (V_D/V_{Tphys} [OR_{adj}=17.9; 95% CI, 1.8–185; P<0.05]; VCO_2 [OR_{adj}=0.99; 95% CI, 0.99–1.00; P<0.001]; and Pa_{O2}/FiO_2 (OR_{adj}=0.99; 95% CI, 0.99–1.00; P<0.001]).

Conclusions: VR is a useful aggregate variable associated with outcome, but variables not associated with ventilation (VCO_2 and venous admixture) strongly contribute to the high values of VR seen in patients with severe illness.

Keywords: ARDS; dead space; mechanical ventilation; venous admixture; ventilatory ratio

Received: 16 August 2022; **Accepted:** 13 October 2022

Editor's key points

- The use of ventilatory ratio to quantify physiological dead space is potentially limited by venous admixture and CO_2 volume expired per minute.
- The authors examined data from patients mechanically ventilated with ARDS.
- Ventilatory ratio increased exponentially as a function of the dead space.
- Ventilatory ratio was associated with mortality, but non-ventilatory variables were the chief contributors to high ventilatory ratio values associated with severe illness.

The physiological dead space (V_D/V_{Tphys}) reflects the severity of lung injury[1] and is a powerful prognostic factor in acute respiratory distress syndrome (ARDS).[2–4] Its use, however, is uncommon, as it requires measurement of mixed expired CO_2 and the simultaneous arterial blood sample to determine Pa_{CO2}. The ventilatory ratio (VR) has recently emerged as an alternative measure of ventilatory efficiency.

VR correlates strongly with V_D/V_{Tphys},[5] does not require measurement of mixed expired CO_2, and can be easily calculated from a few routinely collected variables.[6] In addition, the unitless VR is easy to interpret, as it is normalised to a predefined 'standard' and quantifies the degree of impaired CO_2 elimination in relation to an expected reference value. However, VR may be affected by factors such as venous admixture (Q_{va}/Q) and CO_2 volume expired per minute (VCO_2), which can alter the absolute value of VR despite an unchanged dead space ventilation. The potential effects of these two factors on VR, in particular Q_{va}/Q, have been described but not quantified.[7] Specifically, there are no clinical data that establish the relative importance of measured Q_{va}/Q on VR, nor the relative importance of VCO_2 on VR when the V_D/V_{Tphys} is adjusted for the degree of Q_{va}/Q. These considerations are particularly important in patients with more severe disease, in whom the assumption that virtually all of the variations in VR are attributable to an increased V_D/V_{Tphys}[8] may be confounded by the effect of larger venous admixture.

We compared VR and V_D/V_{Tphys} in a large cohort of ventilated patients with ARDS, aiming to: (1) define the effect of Q_{va}/Q and VCO_2 on VR; (2) examine the relationship between mortality and VR corrected for physiological confounders; (3) provide theoretical models to explain the variations in VR which may occur for the same V_D/V_{Tphys}.

Methods

Study design

This was a multicentre, retrospective, observational study including 641 patients with ARDS (448 patients admitted to Guy's & St Thomas' NHS Foundation Trust, London, UK, from March 2020 to March 2021; and 193 admitted to San Paolo Hospital in Milan, Italy, from 2003 to 2018). All patients present in the databases were included into the analysis, except for seven patients who underwent extra-corporeal support. The study was approved by the institutional review board of each hospital, and written informed consent was obtained according to the national regulations of the participating institutions (see Supplementary material for details). All patients met ARDS criteria, according to the Berlin definition.[9]

Variables

The following variables were collected contemporaneously at the time of lowest Pa_{O2}/FiO_2 ratio during the first 24 h of mechanical ventilation: minute ventilation (VE), tidal volume (VT), ventilatory frequency, and arterial PCO_2 ($P_{a_{CO_2}}$). VCO_2 was estimated in all 641 patients using the Harris–Benedict formula[10] and mixed-expired P_{CO2} ($PECO_2$) was computed using the estimated VCO_2/VE ratio. In 129 patients, both VCO_2 and $PECO_2$ were directly measured with capnometry. A subgroup of patients with normal Pa_{CO2} (4.5–6 kPa) and V_D/V_{Tphys} <0.35 was used to calculate the theoretical reference VE needed to estimate the VR.

Modelling of ventilatory ratio

To understand the relationships between V_D/V_{Tphys}, VR, and venous admixture, we created a model as a function of their independent determinants: VCO_2, minute ventilation (VE), venous admixture (Q_{va}/Q), cardiac output (Qt), and arterial CO_2 tension (Pa_{CO2}). The model derivation described in the supplement, shows that the V_D/V_{Tphys} utilising arterial P_{CO2} as a surrogate of alveolar P_{CO2} depends on the alveolar/total ventilation ratio (Supplementary material, equation [6]) and the Q_{va}/Q (Supplementary material, equation [8]). In addition, the VR depends both on V_D/V_{Tphys} and VCO_2 (Supplementary material, equation [15]).

Definition of dead space

Physiological dead space (V_D/V_{Tphys}) was defined as the dead space calculated using the Bohr–Enghoff formula, which assumes a Q_{va}/Q of zero (i.e. arterial P_{CO2} is equal to the alveolar P_{CO2}).

Corrected dead space (V_D/V_{Tcorr}) was defined as V_D/V_{Tphys} corrected for the Q_{va}/Q using the Kuwabara equation[11] and its modification using CO_2 content in the blood,[12] rather than the CO_2 pressure. As the dead space fraction obtained with both methods were similar, we have used the classical Kuwabara equation for simplicity.

Quantitative computed tomography

Quantitative chest CT was performed as previously described using a dedicated software (Maluna).[13,14] We estimated lung weight, gas volume, and the amount of well-aerated, poorly aerated, and non-aerated tissues.

Statistical analysis

All continuous data are presented as means (standard deviation [SD]) with comparisons between two means performed using with Student's *t*-test, and with analysis of variance (ANOVA) between more values. Categorical data were presented as counts and percentages, with comparisons between categories made using χ^2 tests. Linear regression was used to test associations among variables.

The association between VR and ICU mortality was examined through univariable and multivariable logistic regression models. To assess the association of VR with mortality when adjusted for covariates which could have a contribution to the VR, we performed a multivariable logistic regression including VCO_2, Pa_{O2}/FiO_2, and V_D/V_{Tphys}. To make an additional

comparison of the ORs, we standardised all covariates by subtracting the mean and dividing by their SD. After standardisation, the ORs refer to a unit change in SD of each covariate – therefore giving all covariates numerically similar scales. Model coefficients are reported for standardised and non-standardised data. The aim of this multivariable analysis was not to find a model which included all the factors potentially associated to outcome (i.e. age, mechanical power), but to explore the effects of the physiological variables which contribute to the VR and its association to outcome once adjusted by these physiological confounders.

Two-tailed *P*-values <0.05 were considered statistically significant. All analyses were performed with R for Statistical Computing 4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Table 1 shows the characteristics of the study cohort (n=641) at baseline, with ARDS severity categorised according to the Berlin definition.[9] COVID-19 was the aetiology in 70% of the population (see Supplementary material for details). Patients with more severe ARDS had higher BMI, VE, Pa_{CO_2}, and VR, and driving pressure and mechanical power; and lower $P_{end\text{-}tidal CO_2}$ ($P_{et CO_2}$) to Pa_{CO_2} ratio. ICU mortality increased with severity from 18% in mild, to 31% in moderate, and 46% in severe ARDS.

Calculation of ventilatory ratio

The reference value used for VR computation was 5.3 kPa 0.1 L min^{-1} kg^{-1}, derived from patients during anaesthesia,[15] where 0.1 L min^{-1} kg^{-1} is assumed as the normal VE. To assess whether a similar reference value can be applied to critically ill patients, we selected among our 641 ICU patients 26 patients with 'normal' Pa_{CO_2} and V_D/V_{Tphys}. The characteristics of this ARDS reference cohort are reported in Supplementary Table E1. The measured VE averaged 0.1 L min^{-1} kg_{PBW}^{-1} and Pa_{CO_2} averaged 5.3 kPa (0.4) – which were similar to those found in patients undergoing anaesthesia[5,15] and led to identical VR.

Quantitative chest CT scan and contemporaneous arterial and central venous blood gas samples were available in 153 patients (Table 2), allowing for the calculation of Q_{va}/Q and determination of its effects on the V_D/V_{Tphys} and VR. Q_{va}/Q increased from 0.31 (0.15) in mild ARDS, and to 0.39 (0.11) and 0.61 (0.12), respectively, for moderate and severe ARDS, likely reflecting the increase in the non-aerated tissue fraction. The V_D/V_{Tphys} in this cohort also increased with disease severity, increasing from 0.54 (0.13) in mild disease, to 0.57 (0.12) in moderate disease, and 0.65 (0.11) in severe disease (P<0.001). However, the physiological dead space corrected (V_D/V_{Tcorr}) for Q_{va}/Q was similar in all patients across severity categories.

Relationship between dead space, VCO_2, and ventilatory ratio

The theoretical relationship between VR and V_D/V_{Tphys} demonstrates that VR increases asymptotically with V_D/V_{Tphys}, and its value depends on VCO_2 (Fig 1a). VRs <1 (0.86 [0.11], n=71), between 1 and 2 (1.44 [0.27], n=484) and >2 (2.41 [0.52], n=86) were respectively associated (Fig 1b) with V_D/V_{Tphys} of 0.32 (0.11), 0.55 (0.1), and 0.73 (0.07). This exponential relationship was shifted on the vertical axis (VR) depending on VCO_2. Patients with VCO_2 values exceeding the median (208 [29] ml min^{-1}) had a higher VR than patients with VCO_2 below the median for the same calculated V_D/V_{Tphys}. In both the theoretical (Fig 1a) and the actual cohort (Fig 1b), remarkably different VRs were associated with the same V_D/V_{Tphys}, depending on the VCO_2.

Effects of venous admixture on physiological dead space and ventilatory ratio

Venous admixture and physiological dead space

Figure 2 shows the relationship between V_D/V_{Tcorr} and V_D/V_{Tphys} in our theoretical model (panel a) and in the subgroup of 153 patients in whom the computation of the V_D/V_{Tcorr} for Q_{va}/Q was

Table 1 Demographic data of the whole study cohort. All data are presented as means (standard deviation). Analysis of variance (ANOVA) was used to analyse mean values. *Data presented as absolute and relative frequencies (%).

	Overall (n=641)	Mild (n=65; 10.1%)	Moderate (n=363; 56.6%)	Severe (n=213; 33.2%)	*P*-value
Age (yr)	58 (17–88)	55 (18–84)	59 (17–88)	58 (19–86)	0.138
Female (%)*	195 (30.5)	24 (37)	108 (39)	63 (30)	0.485
Height (cm)	171 (8.9)	172 (8.7)	171 (9)	171 (8.9)	0.541
Actual weight (kg)	83 (20.8)	78 (19.4)	82 (19.5)	88 (22.9)	<0.001
BMI (kg m^{-2})	28.4 (6.7)	26.2 (5.5)	27.8 (5.9)	30.1 (7.9)	<0.001
Pa_{O_2}/FiO_2 (kPa)	17.2 (6.9)	32 (4.4)	18.4 (3.5)	10.5 (1.8)	<0.001
Minute ventilation (L min^{-1})	8.7 (2.3)	8.3 (2.1)	8.5 (2.2)	9.0 (2.6)	0.007
Respiratory rate (bpm)	18 (4.3)	17 (4.6)	18 (4.2)	19 (4.3)	<0.001
Tidal volume kg_{PBW}^{-1} (ml kg^{-1})	7.4 (1.6)	7.7 (1.6)	7.3 (1.5)	7.4 (1.7)	0.349
VCO_2 (ml min^{-1})	116.9 (34)	114.2 (33.2)	114.1 (32.1)	122.4 (36.8)	0.012
Pa_{CO_2} (kPa)	6.1 (1.2)	5.6 (0.9)	6 (1.2)	6.3 (1.3)	<0.001
Physiological dead space	0.55 (0.15)	0.69 (0.13)	0.72 (0.12)	0.72 (0.13)	0.225
Ventilatory ratio	1.51 (0.50)	1.32 (0.37)	1.47 (0.46)	1.63 (0.57)	<0.001
$P_{end\text{-}tidal CO_2}/Pa_{CO_2}$	0.79 (0.16)	0.88 (0.14)	0.81 (0.14)	0.73 (0.16)	<0.001
Mechanical power	17 (7)	15 (7)	16 (6)	18 (8)	0.002
Driving pressure (mm H_2O)	14 (4)	13 (4)	14 (4)	15 (4)	<0.001
ICU mortality (%)*	224 (35%)	12 (18%)	114 (31%)	98 (46%)	<0.001

Table 2 Demographic data of the subgroup with chest computed tomography and paired central venous and arterial gases. All data are presented as means (standard deviation). Analysis of variance (ANOVA) was used to analyse mean values. *Data presented as absolute and relative frequencies.

	Overall (n=153)	Mild (n=27)	Moderate (n=97)	Severe (n=29)	P-value
Age (yr)	59 (18–88)	54 (18–84)	60 (21–88)	61 (19–86)	0.226
Female (%)*	49 (33%)	11 (41%)	30 (31%)	8 (28%)	0.533
Height (cm)	170 (9.5)	171 (9.5)	170 (9.9)	171 (7.9)	0.785
Actual weight (kg)	77 (21.3)	75 (18.1)	75 (20.8)	85 (29.3)	0.056
BMI (kg m^{-2})	26.3 (6.4)	25.7 (5.6)	25.8 (5.8)	28.8 (9.1)	0.059
Pa_{O2}/FiO_2 (kPa)	20 (7.6)	32.4 (4.1)	19.5 (3.7)	10 (2.1)	<0.001
Venous admixture	0.42 (0.15)	0.31 (0.15)	0.39 (0.11)	0.61 (0.12)	<0.001
Minute ventilation (L min^{-1})	8.7 (2.1)	8.4 (1.6)	8.6 (2.1)	9.7 (2.3)	0.032
Ventilatory frequency (bpm)	17 (4.5)	16 (5.1)	16 (4.3)	19 (4.8)	0.062
Tidal volume/kg_{PBW} (ml kg^{-1})	8.3 (1.4)	8.6 (1.4)	8.6 (1.4)	8.1 (1.3)	0.485
VCO_2 (ml min^{-1})	180 (39.8)	180 (40.1)	176 (36.7)	191 (47.5)	0.148
Pa_{CO2} (kPa)	45.2 (7.7)	42.1 (5.4)	44.4 (7.6)	50.6 (7.7)	<0.001
Physiological dead space	0.58 (0.12)	0.54 (0.13)	0.57 (0.12)	0.65 (0.11)	<0.001
True dead space	0.53 (0.13)	0.51 (0.15)	0.53 (0.13)	0.53 (0.27)	0.199
Ventilatory ratio	1.54 (0.45)	1.38 (0.39)	1.49 (0.45)	1.86 (0.39)	<0.001
Mechanical power	19 (7)	20 (8)	18 (7)	21 (8)	0.002
Driving pressure	14 (4)	14 (3)	14 (4)	15 (4)	<0.001
Lung tissue mass (g)	1480 (504)	1234 (186.1)	1429 (481)	1894 (565.2)	<0.001
Lung gas volume (ml)	1141 (635)	1192 (489)	1173 (657)	977 (673)	0.319
Non-aerated tissue fraction (%)	42.6 (15.5)	36.2 (13)	41.5 (15.1)	52.7 (14.8)	<0.001
Poorly aerated tissue fraction (%)	31.1 (11.3)	30.6 (10.8)	31.5 (11.8)	30.1 (10.1)	0.830
Normally aerated tissue fraction (%)	25.9 (13.3)	32.9 (11.5)	26.7 (12.9)	16.8 (11.3)	<0.001
ICU mortality (%)*	63 (41%)	7 (26%)	34 (36%)	22 (75%)	<0.001

possible (panel b). As shown, the relationship between V_D/V_{Tcorr} and V_D/V_{Tphys} was linear but shifted to the right with higher Q_{va}/Q. Figure 2 shows that V_D/V_{Tphys}, as measured in clinical practice, corresponds to V_D/V_{Tcorr} only if Q_{va}/Q is zero, that is the alveolar P_{CO2} equals the arterial P_{CO2}. With increasing Q_{va}/Q (Fig 2a), V_D/V_{Tcorr} was remarkably lower than V_D/V_{Tphys}. The difference between physiological and V_D/V_{Tcorr} as a function of Q_{va}/Q is reported in Supplementary Figure E1, panel A.

Venous admixture and ventilatory ratio

In Fig 3 we report the differences between VR and the VR corrected for Q_{va}/Q in mild, moderate, and severe ARDS. The difference between VR and VR corrected for Q_{va}/Q becomes progressively larger with greater disease severity at different levels of V_D/V_{Tphys} (Supplementary Figure E1, panel B).

Associations of dead space and ventilatory ratio with mortality

In the entire cohort, V_D/V_{Tphys}, Pa_{O2}/FiO_2, and VR were independently associated with mortality. The OR for mortality of VR and V_D/V_{Tphys} were respectively 2.5 (95% CI, 1.8–3.5) and 7.04 (95% CI, 1.9–27.7). The area under the receiver operating characteristic (ROC) curve was 0.64 (95% CI, 0.59–0.68) for VR and 0.66 (95% CI, 0.62–0.71) for V_D/V_{Tphys}. When the effect of VR on mortality was adjusted – in a multivariable model – for variables proven to affect VR in the physiological modelling (i.e. V_D/V_{Tphys}, VCO_2, Pa_{O2}/FiO_2), VR was no longer independently associated with mortality, OR_{adj}=1.2 (95% CI, 0.7–2.1).

On the contrary, V_D/V_{Tphys} (OR_{adj}=17.9; 95% CI, 1.8–185; P<0.05); VCO_2 (OR_{adj}=0.99; 95% CI, 0.99–1.00; P<0.001); and Pa_{O2}/FiO_2 (OR_{adj}=0.99; 95% CI, 0.99–1.00; P<0.001) remained independent predictors of ICU mortality. To further investigate the relative association of each covariate on mortality, we used a standardised model including the same variables so that the resulting adjusted ORs refer to a unit change in SD – regardless of the real units, therefore giving all covariates similar numerical scale. Using this model, the standardised adjusted OR ($OR_{st\text{-}adj}$) for mortality were 1.09 (95% CI, 0.8–1.5), 1.5 (95% CI, 1.1–2.1; P<0.05); 0.71 (95% CI, 0.58–0.87; P<0.001), 0.67 (95% CI, 0.55–0.81; P<0.001) for VR, V_D/V_{Tphys}, VCO_2, and Pa_{O2}/FiO_2, respectively, all independently associated with mortality. These results indicate that variations in VCO_2 and Pa_{O2}/FiO_2 have a similar and important independent association with mortality and affect the prognostic prediction of VR.

Discussion

The main results of this study are: (1) the effect of Q_{va}/Q on absolute VR becomes larger with increasing V_D/V_{Tphys}; (2) the effect of VCO_2 is also of major significance, particularly when VR is corrected for Q_{va}/Q; (3) VR is a useful aggregate variable associated with outcome; however, it does not only reflect V_D/V_{Tphys} but also important contributions from VCO_2 (Fig 1) and Q_{va}/Q, reflected by Pa_{O2}/FiO_2 (Supplementary Figure E2). These data suggest that VCO_2 and Q_{va}/Q contribute to the high values of VR seen in the most severe categories of patients.

The CO_2-related variables are strongly related with structural lung changes in ARDS[1] and in COVID-19 pneumonia.[16] In the Bohr's formulation,[17] V_D/V_{Tphys} was measured as the difference between alveolar and mixed expired CO_2 normalised to the alveolar P_{CO2} (Supplementary material, equation [1]).

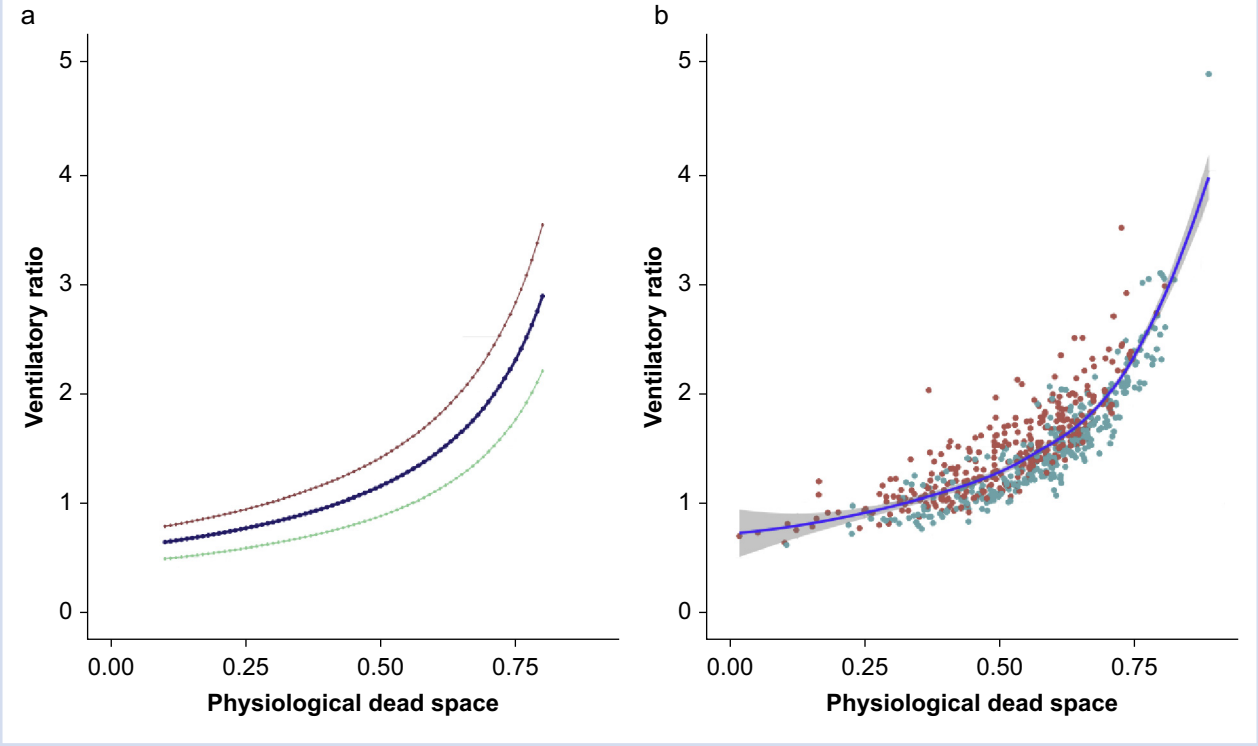

Fig 1. (a) Theoretical model: ventilatory ratio as a function of the physiological dead space at VCO_2 equal to 186 ml min^{-1} (median of the clinical cohort – blue line), 228 ml min^{-1} (50% above the median – red line), and 142 ml min^{-1} (50% below the median). (b) Clinical cohort (n=641): ventilatory ratio as a function of physiological dead space. Patients with VCO_2 higher than median (186 ml min^{-1}) are represented by red points (average VCO_2 equal to 208 (29) ml min^{-1}); patients with VCO_2 below the median are represented by green points (average VCO_2 equal to 164 (17) ml min^{-1}).

The alveolar P_{CO_2}, according to Riley and colleagues,[18] is the pressure present continuously and uniformly in functioning alveoli, assuming that the quantity of CO_2 exchanged from blood to alveoli occurs in equal proportion to the VCO_2 measured in the expired air (Supplementary material, equation [2]). The dead space fraction computed in this model depends on the ratio between alveolar ventilation and minute ventilation, regardless of oxygenation status or VCO_2. The measurement of alveolar P_{CO_2}, however, is complex and not easily performed in clinical practice; therefore, V_D/V_{Tphys} is estimated using the Enghoff modification, where alveolar P_{CO_2} is assumed equal to arterial P_{CO_2}.[19] The dead space computed in this way was defined as 'physiological', as during health, the alveolar P_{CO_2} and arterial P_{CO_2} differ only by 0.1–0.4 kPa. In ARDS, however, the arterial P_{CO_2} may substantially exceed the alveolar P_{CO_2}, because of the effect of Q_{va}/Q. Indeed, the difference between arterial and alveolar P_{CO_2} increases with Q_{va}/Q and VCO_2, whereas it decreases with cardiac output (Supplementary Figure E3). Therefore, the substitution of alveolar with the arterial P_{CO_2} overestimates the true dead space. To correct for the Q_{va}/Q effect, Kuwabara and Duncalf[11] proposed an equation based on the mass conservation principle:

$$CaCO_2 = CcCO_2 * \left(1 - \frac{Q_{va}}{Q}\right) + CvcCO_2 * \frac{Q_{va}}{Q}$$

where $CaCO_2$, $CcCO_2$, and $CvcCO_2$ are the CO_2 contents in arterial, pulmonary (ventilated) capillary, and mixed venous blood, respectively. Kuwabara and Duncalf[11] assumed that tensions and contents are in equilibrium and vary proportionately, and therefore the formula to correct dead space for shunt uses gas tensions instead of their contents. Although this assumption is not strictly accurate, using CO_2 contents or tensions provided similar results (see supplement). Therefore, despite its limitations, the Kuwabara equation is the best available option to correct the dead space. The impact of Q_{va}/Q on V_D/V_{Tphys} may be relevant at Q_{va}/Q>0.2–0.3 (Supplementary Fig. E1, panel A). Indeed, the 'physiological' dead space in pathological conditions represents the entirety of the gas exchange dysfunction, as it is influenced both by wasted ventilation (dead space ventilation) and wasted perfusion (Q_{va}/Q).

VR has been proposed by Sinha and colleagues[5] as an estimate of ventilatory efficiency. A theoretical analysis[8] indicated that VCO_2 and V_D/V_{Tphys} are both determinants of VR. VR uses as a reference the product of 'standard' VE and the 'standard' P_{aCO_2}. The standard VE was derived, more than five decades ago, from normal subjects undergoing anaesthesia.[15] Interestingly, we found similar values (0.1 kg_{PBW}^{-1}) in our subgroup of ARDS patients. VR values in the literature range from <1 in the anaesthetised cohorts (indicating the effects of normal V_D/V_{Tphys} and Q_{va}/Q and reduced VCO_2) to >5 in ICU patients. The largest values of VR are unlikely to reflect the magnitude of dead space ventilation alone, and it is therefore unclear whether the higher absolute value of VR observed in severe ARDS reflects a worse dead space or the

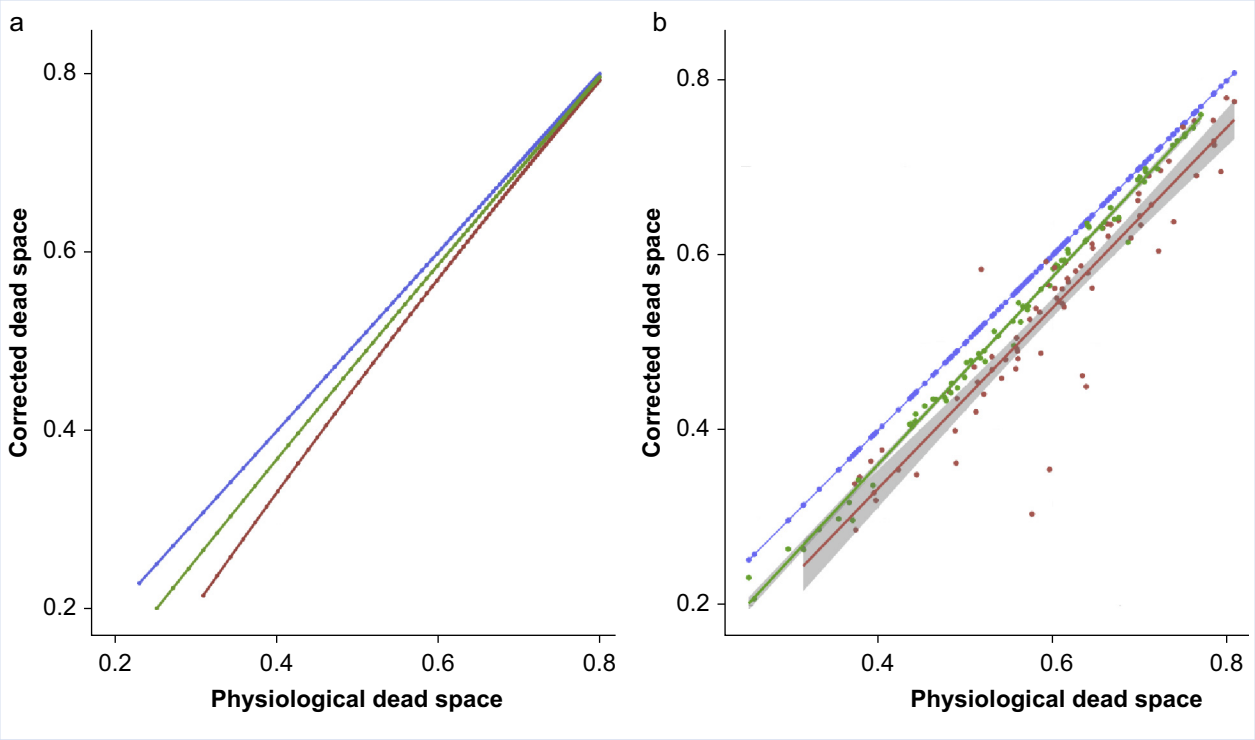

Fig 2. (a) Theoretical model: the true physiological dead space as a function of physiological dead space at different venous admixture. The blue line is the identity line (venous admixture equal to zero), green line denotes venous admixture equals to 0.31, whereas the red line has venous admixture equal to 0.48. (b) Corrected dead space as a function of the physiological dead space in the clinical cohort of patients in which venous admixture was available. The venous admixture levels were the average above the median (0.31 [0.07]) and below the median (0.48 [0.13]).

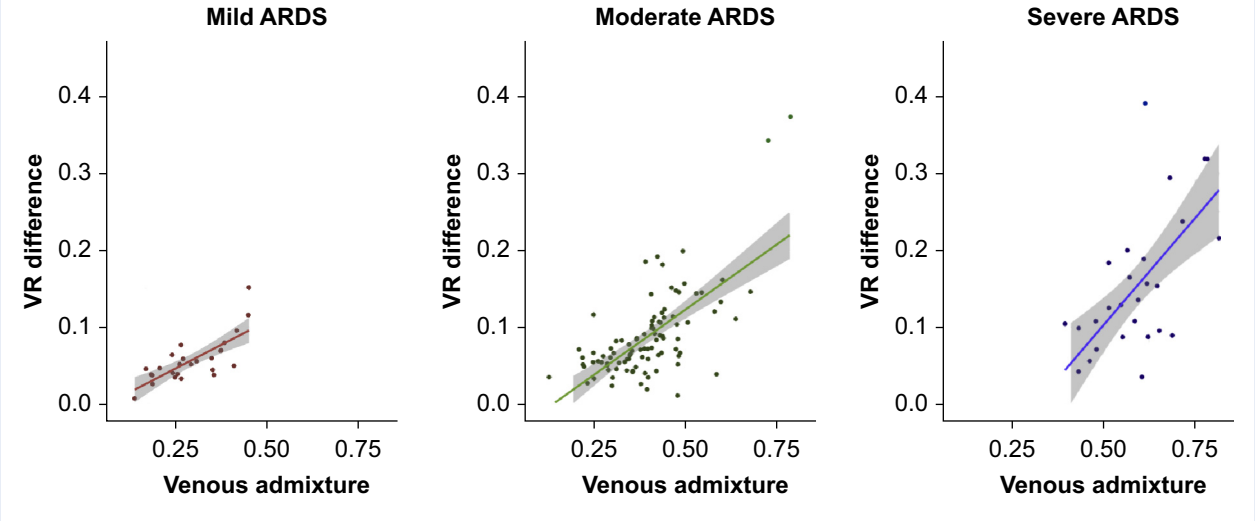

Fig 3. Effect of the venous admixture, measured as difference between ventilatory ratio and ventilatory ratio corrected for venous admixture, in different classes of ARDS severity. The greater is the venous admixture, the higher is its effect on the difference between measured and corrected ventilatory ratios. ARDS, acute respiratory distress syndrome; VR, ventilatory ratio.

greater contribution of the Q_{va}/Q. Our multivariable logistic regression indicates that VR alone is a useful aggregate variable associated with outcome with odds ratios similar to other studies.[7] Because of the relationship between VR and Pa_{O2}/FiO_2 ratio, particularly in severe disease, VR should be interpreted accordingly and not considered a bedside index to estimate purely dead space. The physiological dead space and VR have a near-exponential relationship whose level depends on VCO_2. Indeed, we found higher VR in patients with higher VCO_2 (Fig 1).

Sinha and colleagues[7] found weak and non-significant association between VCO_2 and VR. They attributed this to the smaller and short-lived variation in VCO_2 compared with the larger variations of V_D/V_{Tphys}. However, we found that the effects of VCO_2 are more marked when VR is corrected for Q_{va}/Q. The recognition that venous admixture (Q_{va}/Q) and VCO_2 can change the absolute value of VR despite an unchanged dead space ventilation has several potential implications: (1) Changes in VR may not be attributed to a change in V_D/V_T if there are associated variations in oxygenation or VCO_2. This may affect the interpretation of the effect of therapeutic manoeuvres such as prone position, PEEP selection, or pulmonary vasodilators on the change in V_D/V_T. In these examples, changes in VR may be determined by a variable combination of reduction in Q_{va}/Q and V_D/V_T – but not necessarily exclusively in V_D/V_T. (2) In patients with more severe disease, the variations in VR may be confounded by the effect of larger Q_{va}/Q. In this case, interventions that affect Q_{va}/Q may disproportionally affect VR and affect the assumption of the underlying pathophysiological mechanisms. (3) Prediction models using VR as a proxy of V_D/V_T can inflate the range and its prognostic effect. (4) Although VCO_2 disparities may appear a minor problem in general cohort, the VR dependency on this variable makes its use misleading in cases of abnormal VCO_2 or during extracorporeal support, where a substantial portion of CO_2 may be cleared by the membrane lung. In that setting, V_D/V_{Tphys} fully reflects the lung status, whereas VR may appear normal or even low.

The major limitation of this work, beyond its retrospective design, is that VCO_2 was estimated rather than measured. The computation relies on the Harris–Benedict equation, which estimates the 'standard' VCO_2 production based on age, height, and weight (Supplementary material, equation [19]). In ICU patients, we may expect remarkable discrepancies between the actual and the predicted VCO_2. Yet, in the 176 patients in which VCO_2 was measured, the relationship with the computed VCO_2 was acceptable and the bias between measured and computed VCO_2 was −22 (48) ml, despite the large variability of their absolute values (Supplementary Fig. E4). Any inaccuracy of VCO_2 estimation should affect the V_D/V_T (Supplementary material, Equation [2]), whereas it would not affect the calculation of VR. The measured and estimated V_D/V_{Tphys} values computed in 176 individuals, however, were similar (0.65 [0.13] and 0.59 [0.12], respectively).

In conclusion, our data suggest that: (1) if one aims to strictly determine the true dead space in ARDS, the V_D/V_{Tphys} must be corrected for Q_{va}/Q; (2) the V_D/V_{Tphys} is an estimate of the overall gas exchange (oxygenation and CO_2 clearance) and, as such, a powerful clinical tool to assess the severity of the lung impairment; (3) ventilatory ratio alone is a useful variable associated with outcome; however, ventilatory ratio, as V_D/V_{Tphys}, does not only reflect ventilated regions alone but also the important contributions of VCO_2 and Q_{va}/Q.

Authors' contributions

Study concept and design: LG, LC, JM, MQ, KM
Acquisition, analysis, or interpretation of data: RM, PP, LG, LC, OM, MB, SG, CZ, RD, MV, FR
First drafting of manuscript-writing committee: RM; PP, LG, FR, LC, BS, JM, MQ
Critical revision for important intellectual content and final approval of manuscript: LC, JM, MQ, RM, LC, JM, MQ, JW, DC
Statistical analysis: BS, JW, RM
Paper review and modifications: all authors
Administrative, technical or material support: KM, OM, PH

Declaration of Interest

LG reports a consultancy for General Electric and SIDAM. He also receives lecture fees from Estor and Mindray.

Funding

Sartorius AG (Göttingen, Germany) for an unrestricted grant for lung injury-related research to the Department of Anesthesiology of Göttingen University Medical Center; Klaus-Tschira Stiftung gGmbH, Heidelberg (development of the software for CT analysis).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.10.035.

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Handling editor: Gareth Ackland