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Validity of Empirical Estimates of the Ratio of Dead Space to Tidal Volume in ARDS

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BACKGROUND: The ratio of dead space to tidal volume (V_D/V_T) is a clinically relevant parameter in ARDS; it has been shown to predict mortality, and it determines the extent to which extracorporeal CO_2 removal reduces tidal volume (V_T) and driving pressure (ΔP). V_D/V_T can be estimated with volumetric capnography, but empirical formulas using demographic and physiological information have been proposed to estimate V_D/V_T without the need of additional equipment. It is unknown whether estimated and measured V_D/V_T produce similar estimates of the predicted effect of extracorporeal CO_2 removal on ΔP. METHODS: We performed a secondary analysis of data from a previous clinical trial including subjects with ARDS in whom V_D/V_T and CO_2 production ($\dot{V}_{CO_2}$) were measured with volumetric capnography. The estimated ratio of dead space to tidal volume ($V_{D,est}/V_T$) was calculated using standard empiric formulas. Agreement between measured and estimated values was evaluated with Bland-Altman analysis. Agreement between the predicted change in ΔP with extracorporeal CO_2 removal as computed using the measured ratio of alveolar dead space to tidal volume (V_{Dalv}/V_T) or estimated V_{Dalv}/V_T ($V_{Dalv,est}/V_T$) was also evaluated. RESULTS: $V_{D,est}/V_T$ was higher than measured V_D/V_T, and agreement between them was low (bias 0.05, limits of agreement –0.21 to 0.31). Differences between measured and estimated $\dot{V}_{CO_2}$ accounted for 57% of the error in $V_{D,est}/V_T$. The predicted reduction in ΔP with extracorporeal CO_2 removal computed using $V_{Dalv,est}/V_T$ was in reasonable agreement with the expected reduction using V_{Dalv}/V_T (bias –0.7 cm H_2O, limits of agreement –1.87 to 0.47 cm H_2O). In multivariable regression, measured V_D/V_T was associated with mortality (odds ratio 1.9, 95% CI 1.2–3.1, *P* = .01), but $V_{D,est}/V_T$ was not (odds ratio 1.2, 95% CI 0.8–1.8, *P* = .3). CONCLUSIONS: V_D/V_T and $V_{D,est}/V_T$ showed low levels of agreement and cannot be used interchangeably in clinical practice. Nevertheless, the predicted decrease in ΔP due to extracorporeal CO_2 removal was similar when computed from either estimated or measured V_{Dalv}/V_T. *Key words: dead space; ARDS; mechanical ventilation; volumetric capnography; extracorporeal life support; driving pressure.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

An increase in the ratio of dead space to tidal volume (V_D/V_T) is a hallmark of ARDS.[1] Alveolar flooding by protein rich fluids causes shunt and hypoxemia,[2] while an increase in dead space develops secondary to microthrombi, maldistributed hypoxic pulmonary vasoconstriction, and the collapse of small pulmonary vessels due to alveolar overdistention with positive-pressure ventilation.[3,4]

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V_D/V_T has consistently been shown to predict mortality in ARDS with greater discrimination than the severity of hypoxemia.[5-7] V_D/V_T is also important in determining the extent to which a given rate of extracorporeal CO_2 removal reduces V_T and driving pressure (ΔP).[8] V_D/V_T values may therefore play a central role in the selection of subjects for trials of ultra-protective ventilation facilitated by extracorporeal CO_2 removal.

V_D/V_T can be measured with volumetric capnography or with a dedicated metabolic monitor at the bedside.[9] However, these techniques require dedicated equipment and some expertise to ensure accurate measurements.[10] Empirical formulas using demographic and physiological information have been proposed to estimate V_D/V_T without the need of any additional equipment. Siddiki et al[11] reported that an empirically estimated V_D/V_T ($V_{D,est}/V_T$) using a modified Harris-Benedict equation (adjusting for hypermetabolic factors) correlated with mortality in a secondary analysis of 2 large prospective studies of subjects with ARDS. A larger study, however, reported that using the unadjusted Harris-Benedict equation best predicted the association between $V_{D,est}/V_T$ and mortality.[12] A smaller study ($N = 13$ subjects)[13] noted that the agreement between empirically estimated and measured values for V_D/V_T was poor; in that study, the estimated approach systematically underestimated measured V_D/V_T.

We set out to (1) quantify the agreement between measured and estimated V_D/V_T, (2) compare their relationships to clinical outcomes, and (3) assess whether the error in empirical estimates of V_D/V_T significantly modifies the predicted change in ΔP with extracorporeal CO_2 removal.

QUICK LOOK

Current knowledge

The ratio of dead space to tidal volume (V_D/V_T) is a better prognostic factor than the severity of hypoxemia in ARDS. It is also important in determining the extent to which a given rate of extracorporeal CO_2 removal reduces driving pressure. However, dedicated equipment and expertise are required for its measurement, making it infrequently available. Empiric formulas have been proposed to estimate V_D/V_T without the need of specific equipment, but there is conflicting evidence regarding the accuracy of these formulas in critically ill subjects.

What this paper contributes to our knowledge

In a secondary analysis of a randomized clinical trial, measured and estimated V_D/V_T showed low levels of agreement, suggesting that their values should not be used interchangeably. However, the predicted decrease in driving pressure from initiating extracorporeal CO_2 removal was similar using either approach, suggesting that the estimated V_D/V_T can be used to assess the potential benefit of extracorporeal CO_2 removal. This could have implications in the design of future trials of extracorporeal life support, allowing for better subject selection.

Methods

Study Population

We conducted a secondary analysis of data from the Aerosolized β_2-Agonist for Treatment of Acute Lung Injury (ALTA) trial.[14] Briefly, this multi-center, randomized clinical trial evaluated the use of aerosolized albuterol versus placebo for the treatment of ARDS. This dataset was selected for analysis because it includes V_D/V_T measurements with volumetric capnography (NM3, Philips Respironics, Philadelphia, Pennsylvania) in a well-defined cohort of subjects with ARDS. Subjects in whom V_D/V_T and CO_2 production ($\dot{V}_{CO_2}$) were measured on day 1 after randomization were included in this analysis. This study was approved by the local research ethics board at St. Michael's Hospital, Toronto, Canada (REB# 17–022).

Physiological Measurements

In the ALTA trial, V_D/V_T was measured with volumetric capnography using Enghoff's modification of Bohr's formula, where alveolar CO_2 partial pressure (P_{ACO_2}) is replaced with P_{aCO_2}[15]:

$$\frac{V_D}{V_T} = \frac{P_{aCO_2} - P_{\bar{E}CO_2}}{P_{aCO_2}}$$

where $P_{\bar{E}CO_2}$ represents the mixed exhaled pressure of CO_2. Anatomical V_D/V_T was also measured, and V_{Dalv}/V_T was calculated by subtraction of anatomical V_D/V_T from V_D/V_T (see the supplementary materials at http://www.rcjournal.com).[16]

Empirical Estimation of V_D/V_T

First, estimated $\dot{V}_{CO_2}$ ($\dot{V}_{CO_2,est}$) was calculated according to the Harris-Benedict equation[17] (see the supplementary materials at http://www.rcjournal.com). We then estimated V_D/V_T ($V_{D,est}/V_T$) by rearranging the alveolar air equation for P_{aCO_2} using $\dot{V}_{CO_2,est}$ as:

$$V_D = 1 - \frac{0.86 \times -\dot{V}_{CO_2,est}}{\dot{V}_E \times P_{aCO_2}}$$

where $\dot{V}_E$ represents minute volume and 0.86 is a standard constant necessary for converting fractional concentrations

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to pressures and correcting to standard conditions. The estimate of alveolar subcomponent ($V_{Dalv,est}/V_T$) was determined using $V_{D,est}/V_T$ and the predicted anatomical V_D/V_T (see the supplementary materials at http://www.rcjournal.com).

Predicting the Effect of Extracorporeal CO_2 Removal on ΔP

ΔP was computed as the difference between plateau pressure and PEEP. Respiratory system compliance (C_{RS}) was computed as the quotient of V_T and ΔP. The predicted change in ΔP achieved by applying extracorporeal CO_2 removal at a clearance rate of 80 mL/min ($\dot{V}_{CO_2}$) was computed from C_{RS} and V_{Dalv}/V_T following a previously described model derived from the theoretical equation used to define alveolar ventilation (see the supplementary materials at http://www.rcjournal.com).[18] This model was recently validated in a large cohort of subjects with ARDS receiving extracorporeal CO_2 removal to achieve ultra-protective mechanical ventilation.[8]

Statistical Analysis

Continuous variables are described as mean ± SD or median (interquartile range) according to their distribution, and categorical variables are described as counts and percentages. The *t* test and the Wilcoxon rank-sum test were used to analyze normally and non-normally distributed continuous variables, respectively. Analysis of variance was used to compare means across multiple groups. Categorical variables were compared using the chi-square test.

Relationships among physiological variables (P_{aO_2}/F_{IO_2}, V_D/V_T, V_{Dalv}/V_T, and C_{RS}) were compared with linear regression. Agreement between measured and estimated V_D/V_T variables and between the predicted changes in ΔP with the application of extracorporeal CO_2 removal computed using either measured or predicted V_{Dalv}/V_T was evaluated with Bland-Altman analysis. Linear regression was used to analyze the error between measured and estimated V_D/V_T, comparing the difference between V_D/V_T and $V_{D,est}/V_T$ and the difference between $\dot{V}_{CO_2}$ and $\dot{V}_{CO_2,est}$.

The association between physiological variables and the risk of death was evaluated with multivariable logistic regression. Mortality was defined as 60-d hospital mortality according to the information available in the dataset. Variables previously known to be associated with an increased risk of death (eg, V_D/V_T, P_{aO_2}/F_{IO_2}, C_{RS}, SOFA score, and age) were included in the logistic regression model. For the multivariable analysis, V_D/V_T and C_{RS} were considered the primary predictor variables. All analyses and figures were performed using RStudio 1.2.5019 (RStudio, Boston, Massachusetts).

Table 1. Baseline Characteristics of the Study Cohort*

	All Subjects	Survivors	Non-Survivors	*P*
Age, y	49 ± 16	48 ± 16	53 ± 15	.19
Female	51 (48)	52 (86)	7 (14)	.14
SOFA score	10 ± 3	10 ± 3	11 ± 4	.19
P_{aO_2}/F_{IO_2}	172 ± 72	170 ± 68	182 ± 91	.60
ΔP	14 ± 4	14 ± 5	16 ± 5	.16
V_T, mL/kg	6.7 ± 1.3	6.7 ± 2.1	6.5 ± 1.6	.68
C_{RS}	29 (23–36)	30 (23–37)	25 (22–32)	.20
Measured V_D/V_T	0.56 ± 0.11	0.54 ± 0.11	0.61 ± 0.11	.01
Measured V_{Dalv}/V_T	0.14 ± 0.09	0.14 ± 0.08	0.16 ± 0.11	.40
ARDS severity				.59
Mild	7 (7)	5 (6)	2 (10)	
Moderate	83 (78)	69 (80)	14 (70)	
Severe	17 (15)	12 (14)	5 (20)	

Data are presented as mean ± SD, *n* (%), or median (interquartile range). All Subjects: *N* = 107; Survivors: *n* = 86; Non-Survivors: *n* = 21.
* Data from Reference 14.
C_{RS} = respiratory system compliance
V_D/V_T = ratio of dead space to tidal volume
V_{Dalv}/V_T = ratio of alveolar dead space to tidal volume

Table 2. Measured and Estimated Values of Dead Space and CO_2 Elimination

	Measured	Estimated	R^2	Bias	Limits of Agreement
V_D/V_T	0.56 ± 0.11	0.61 ± 0.14	0.21	0.05	–0.21 to 0.31
V_{Dalv}/V_T	0.21 ± 0.12	0.3 ± 0.12	0.34	0.06	–0.14 to 0.28
$\dot{V}_{CO_2}$, mL/min	208 ± 66	178 ± 49	0.39	–29.7	–132 to 73

Data are presented as mean ± SD.
V_D/V_T = ratio of dead space to tidal volume
V_{Dalv}/V_T = ratio of alveolar dead space to tidal volume
V_{CO_2} = CO_2 clearance rate

Results

V_D/V_T measurements were obtained in the first 24 h after randomization in 107 (38%) of the 282 subjects. Baseline subject characteristics and demographics are described in Table 1. Overall mortality was 19%.

Measures of agreement between estimated and measured values for V_D/V_T are shown in Table 2 and Figure 1. Measured V_D/V_T and $V_{D,est}/V_T$ were moderately correlated (R^2 = 0.21, *P* < .001). $V_{D,est}/V_T$ slightly overestimated measured V_D/V_T on average (bias 0.05, limits of agreement –0.21 to 0.31), likely because $\dot{V}_{CO_2,est}$ tended to underestimate measured $\dot{V}_{CO_2}$ (bias –29.7 mL/min, limits of agreement –132 to 73 mL/min). Error in $\dot{V}_{CO_2,est}$ accounted for 57% of the error in $V_{D,est}/V_T$ (Fig. 2). Correcting $V_{D,est}/V_T$ by correcting $\dot{V}_{CO_2,est}$ using the mean bias in the estimation of $\dot{V}_{CO_2}$ (30 mL/min) reduced the bias between $V_{D,est}/V_T$

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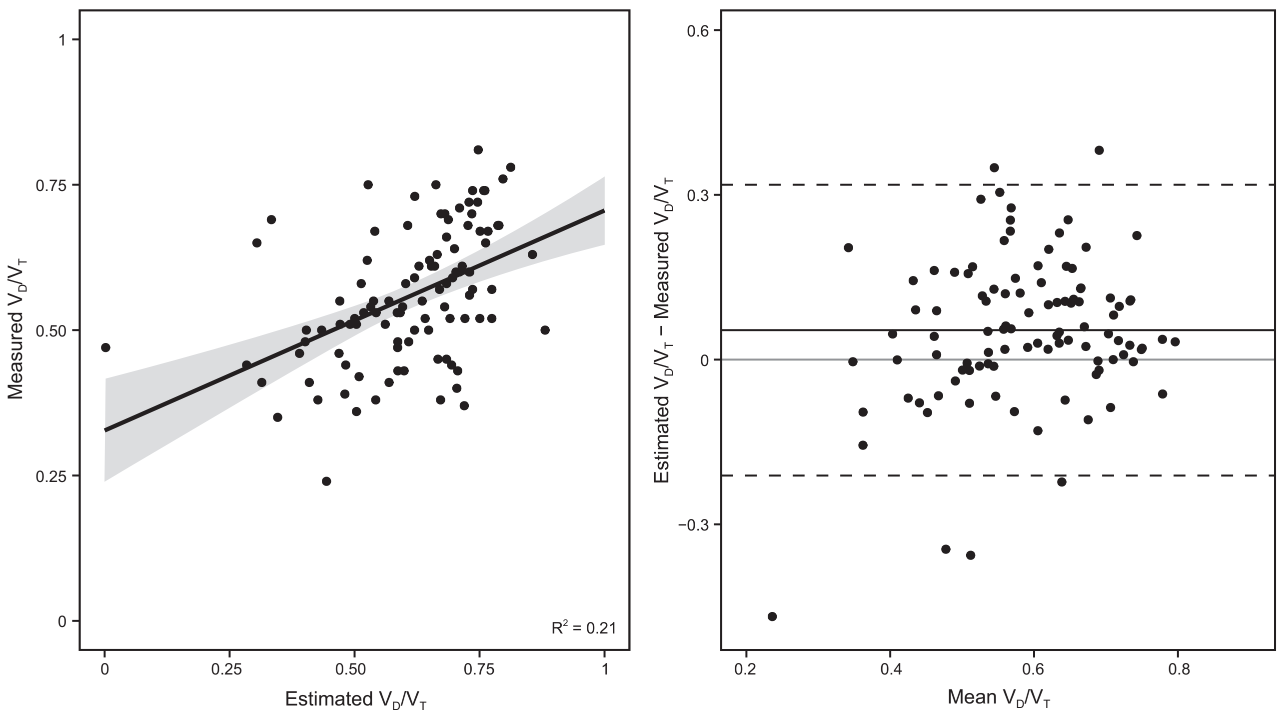

Fig. 1. Correlation and agreement between measured and estimated ratio of dead space to tidal volume (V_D/V_T) and $\dot{V}_{CO_2}$. Shaded area represents confidence 95% confidence intervals. Center line represents the mean difference between both variables. Dashed lines represent 95% limits of agreement.

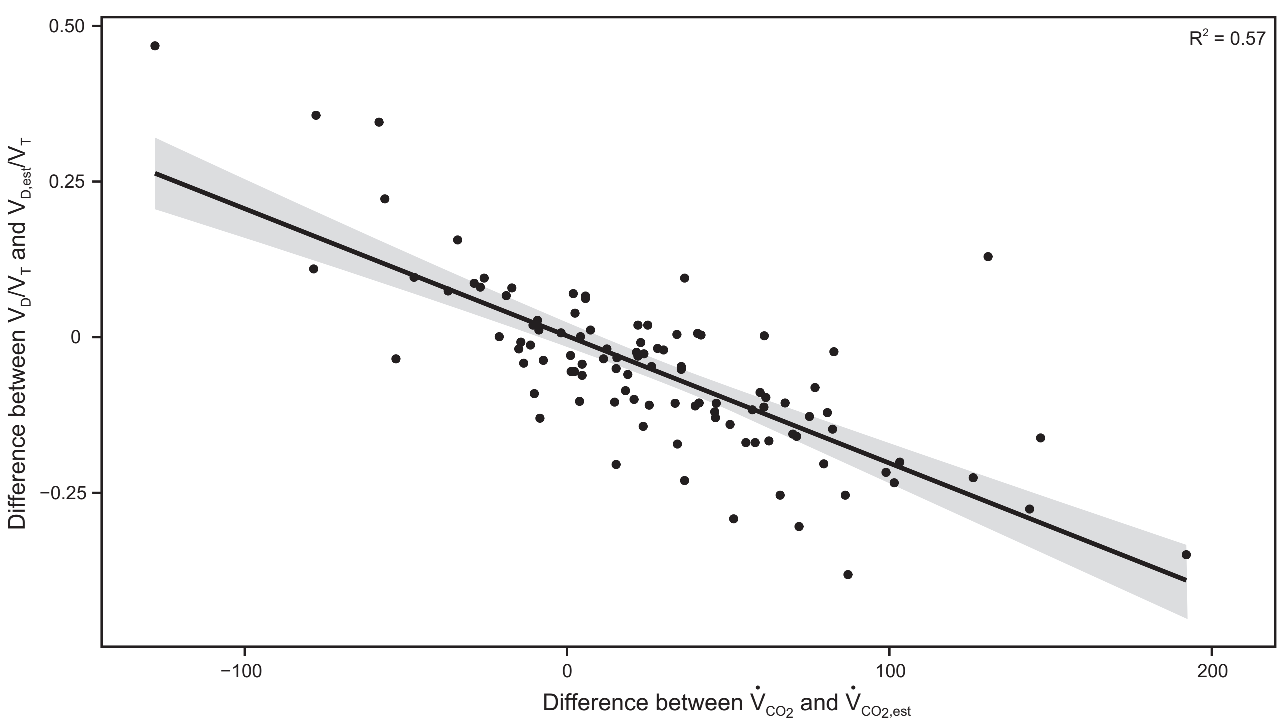

Fig. 2. Correlation between differences in measured and estimated values for physiologic dead space and CO_2 production. Error in the estimation of V_{CO_2} ($V_{CO_2,est}$) accounted for 57% of the error in the estimation of V_D/V_T ($V_{D,est}/V_T$). Shaded area represents confidence 95% confidence intervals. Center line represents the mean difference between both variables. Dashed lines represent 95% limits of agreement.

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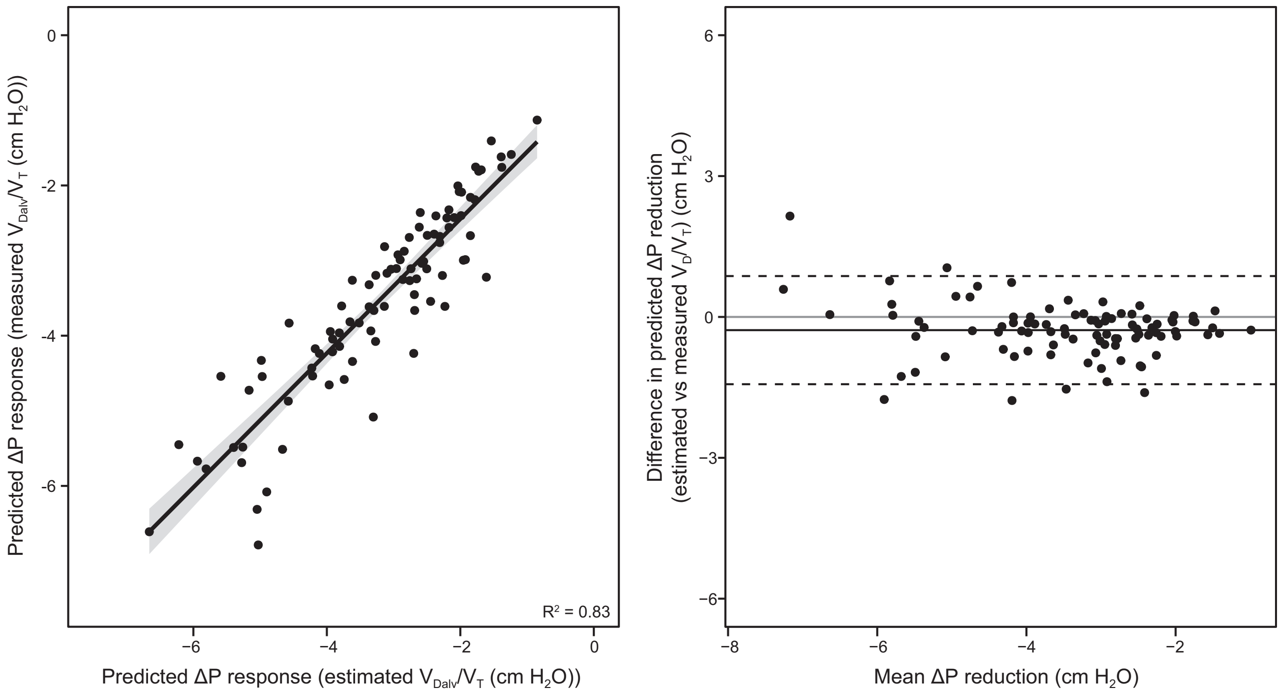

Fig. 3. Correlation and agreement analysis between the predicted change in driving pressure (ΔP) with extracorporeal carbon dioxide removal with alveolar dead space (V_{Dalv}/V_T) and estimated alveolar dead space ($V_{Dalv,est}/V_T$). The estimated approach slightly overestimated the response in ΔP. Shaded area represents confidence 95% confidence intervals. Center line represents the mean difference between both variables. Dashed lines represent 95% limits of agreement.

Table 3. Association of Physiologic Variables With 60-d Mortality

	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
V_D/V_T (per 0.1-unit increase)	1.7 (1.2–2.6)	.01	1.9 (1.2–3.1)	.01
Estimated V_D/V_T (per 0.1-unit increase)	1.3 (0.8–1.9)	.20	1.2 (0.8–1.8)	.33
P_{aO_2}/F_{IO_2} (per 25 units decrease)	1.05 (0.9–1.2)	.51	1.1 (.99–1.4)	.10
C_{RS} (per 5 mL/cm H_2O decrease)	0.9 (0.7–1.07)	.41	1.01 (0.8–1.2)	.85

V_D/V_T = ratio of dead space to tidal volume
C_{RS} = respiratory system compliance

and measured V_D/V_T (bias –0.007, limits of agreement –0.26 to 0.25).

The expected reduction in ΔP with extracorporeal CO_2 removal at 80 mL/min based on V_{Dalv}/V_T was in reasonable agreement with the value obtained using $V_{Dalv,est}/V_T$ (bias –0.3 cm H_2O, limits of agreement –1.4 to 0.8 cm H_2O) (Fig. 3). The mean ± SD predicted reductions in ΔP in the ALTA trial subjects if they were to put on extracorporeal CO_2 removal at a flow that removed 80 mL/min of CO_2 were –3.3 ± 1.5 cm H_2O and –3.5 ± 1.3 cm H_2O using the measured and estimated approaches, respectively.

Neither measured V_D/V_T nor $V_{D,est}/V_T$ were correlated with P_{aO_2}/F_{IO_2} (R^2 = 0.05 and 0.02, respectively) or C_{RS} (R^2 = 0.07 and 0.01, respectively). P_{aO_2}/F_{IO_2} also showed no correlation with C_{RS} (R^2 = 0.01). Correlation between ΔP and both V_D/V_T and $V_{D,est}/V_T$ was also low (R^2 = 0.05 and 0.03, respectively).

In univariable analysis, measured V_D/V_T, but not P_{aO_2}/F_{IO_2} or C_{RS}, was associated with mortality (Table 3). The association between measured V_D/V_T and mortality persisted in multivariable analysis after adjusting for P_{aO_2}/F_{IO_2}, C_{RS}, SOFA score, and age (odds ratio 1.9, 95% CI 1.2–3.1, P = .01). $V_{D,est}/V_T$ was not significantly associated with mortality in univariable analysis (odds ratio 1.3, 95% CI 0.8–1.9, P = .20) or in multivariable analysis (odds ratio 1.2, 95% CI 0.8–1.8, P = .33).

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Discussion

In this secondary analysis of a previous randomized trial of subjects with ARDS, we observed low agreement between measured and estimated V_D/V_T variables. Nevertheless, we observed a satisfactory level of agreement in the predicted decrease in ΔP from extracorporeal CO_2 removal between both approaches, suggesting that empiric V_D/V_T estimates can be used to evaluate the predicted response to extracorporeal CO_2 removal.

$\dot{V}_{CO_2}$ and V_D/V_T are infrequently measured with volumetric capnography in routine clinical practice because its measurement requires dedicated equipment and technical expertise to address potential subtleties of the method.[10] Considering the important prognostic information conferred by measurement of V_D/V_T, the ability to estimate $\dot{V}_{CO_2}$ and V_D/V_T based on readily available information such as age, height, weight, and sex is appealing from a clinical standpoint. In this analysis, however, estimated V_D/V_T overestimated measured values with relatively low agreement, indicating that these values should not be used interchangeably in everyday clinical practice. This is in keeping with the findings of Beitler et al.[12] Calculated values rely on the Harris-Benedict equation of resting energy expenditure, which, in the setting of critically ill subjects with elevated shunt, tends to underestimate $\dot{V}_{CO_2}$.[19] In this analysis, more than half of the observed error between measured and estimated V_D/V_T was related to differences in measured and estimated $\dot{V}_{CO_2}$.

Despite the significant differences observed between measured and estimated V_D/V_T, we found a reasonable agreement in the predicted decrease in ΔP using V_{Dalv}/V_T and $V_{Dalv,est}/V_T$. This could be explained by the fact that the formula used to predict the decrease in ΔP from extracorporeal CO_2 removal is more influenced by easily measured variables such as C_{RS}, breathing frequency, and P_{aCO_2} than by V_D/V_T. Two previous studies reported that the change in ΔP and V_T which could be achieved using extracorporeal CO_2 removal was associated with the baseline V_{Dalv}/V_T and C_{RS}, and that the change in ΔP could be predicted by integrating these parameters into an equation derived from the alveolar ventilation equation.[8,18] In subjects with a high probability of benefiting, extracorporeal CO_2 removal would permit a reduction in CO_2 to further reduce V_T and ΔP and achieve an ultra-protective ventilation strategy in a population at higher risk of developing ventilator-induced lung injury.[20,21] Our findings suggest that integrating estimated V_D/V_T values with C_{RS} in a formula to predict the expected change in ΔP would yield similar results to the use of measured V_D/V_T values. Because the predicted change in ΔP has been shown to predict the response to extracorporeal CO_2 removal, our findings suggest that estimated V_D/V_T is adequate for this purpose.[8]

Measured V_D/V_T was associated with increased odds of mortality after adjusting for confounding variables (Table 3), similar to previous studies. The relationship between measured V_D/V_T and mortality was more significant than the relationship between P_{aO_2}/F_{IO_2} and mortality, reinforcing the relative prognostic importance of V_D/V_T, as shown previously.[5,6,22,23] Estimated V_D/V_T, on the other hand, was not associated with increased risk of death, a finding that contrasts with previous observations analyzing larger cohorts.[11,12]

Interestingly, we found no correlation between V_D/V_T and P_{aO_2}/F_{IO_2} or C_{RS}. The relationship between these variables is complex. In all of the previously cited studies, as well as in our study, V_D/V_T was measured using the Enghoff modification of Bohr's original formula, using P_{aCO_2} instead of P_{ACO_2}. This approach is usually acceptable in subjects with "normal" lungs[24]; however, in subjects with increased shunt, such as subjects with ARDS, it has been suggested that P_{aCO_2} could be increased due to the shunt, therefore overestimating the true V_D/V_T.[19,25] However, correcting the Enghoff V_D/V_T using 2 different mathematical approaches to account for shunt effect failed to improve the agreement between the Enghoff modification and Bohr's original formula.[15] Thus, the lack of correlation between P_{aO_2}/F_{IO_2} and V_D/V_T observed in our study suggests that the shunt is not the primary mechanism of altered V_D/V_T in this population. The absence of correlation between V_D/V_T and C_{RS} is perhaps less surprising. As a marker of gas exchange, V_D/V_T can be affected by changes in either alveolar ventilation or perfusion. Gogniat et al[26] reported that ΔP was only correlated to V_D/V_T when C_{RS} decreased after an increase in PEEP, suggesting that a reduction in ventilation secondary to overdistention plays an important role in the relationship between V_D/V_T and lung mechanics. As such, an improvement in V_D/V_T measured using the Enghoff approach in response to increased PEEP might represent either an improvement in lung mechanics or a reduction in shunt. Aside from this specific scenario of attempted lung recruitment, V_D/V_T and C_{RS} are generally not correlated, as also shown in subjects with ARDS secondary to COVID-19.[27]

Our study has limitations. First, more than half of the subjects from the original dataset had to be removed for analysis because they had no V_D/V_T measurements on the first day. This could mean our analysis is underpowered to observe an association between P_{aO_2}/F_{IO_2} and mortality and between estimated V_D/V_T and mortality (a finding reported in 2 previous studies[11,12]). Moreover, the low overall mortality observed in this study may have further reduced statistical power. Second, we are using a theoretical model to predict the response to extracorporeal CO_2 removal, although this model was recently validated in a trial evaluating the feasibility of lung ultra-protective ventilation

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in subjects with ARDS,[8] thus enhancing the reliability of our findings.

Conclusions

We found that measured and estimated V_D/V_T values showed low levels of agreement and should not be used interchangeably in clinical practice. Nevertheless, the predicted decrease in ΔP from extracorporeal CO_2 removal was similar when using either estimated or measured V_{Dalv}/V_T. Empirical estimates of V_D/V_T can be used to predict the effect of extracorporeal CO_2 removal on driving pressure.

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