End-Tidal-to-Arterial P_{CO_2} Ratio as Signifier for Physiologic Dead-Space Ratio and Oxygenation Dysfunction in Acute Respiratory Distress Syndrome

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BACKGROUND: The ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 (P_{ETCO_2}/P_{aCO_2}) was recently suggested for monitoring pulmonary gas exchange in patients with ARDS associated with COVID-19, yet no evidence was offered supporting that claim. Therefore, we evaluated whether P_{ETCO_2}/P_{aCO_2} might be relevant in assessing ARDS not associated with COVID-19. METHODS: We evaluated the correspondence between P_{ETCO_2}/P_{aCO_2} and the ratio of dead space to tidal volume (V_D/V_T) measured in 561 subjects with ARDS from a previous study in whom P_{ETCO_2} data were also available. Subjects also were analyzed according to 4 ranges of P_{ETCO_2}/P_{aCO_2} representing increasing illness severity (≥ 0.80, 0.6–0.79, 0.50–0.59, and < 0.50). Correlation was assessed by either Pearson or Spearman tests, grouped comparisons were assessed using either ANOVA or Kruskal-Wallis tests and dichotomous variables assessed by Fisher Exact tests. Normally distributed data are presented as mean and standard deviation(SD) and non-normal data are presented as median and inter-quartile range (IQR). Overall mortality risk was assessed with multivariate logistic regression. Alpha was set at 0.05. RESULTS: P_{ETCO_2}/P_{aCO_2} correlated strongly with V_D/V_T (r = –0.87 [95% CI –0.89 to –0.85], $P < .001$). Decreasing P_{ETCO_2}/P_{aCO_2} was associated with increased V_D/V_T and hospital mortality between all groups. In the univariate analysis, for every 0.01 decrease in P_{ETCO_2}/P_{aCO_2}, mortality risk increased by ~1% (odds ratio 0.009, 95% CI 0.003–0.029, $P < .001$) and maintained a strong independent association with mortality risk when adjusted for other variables (odds ratio 0.19, 95% CI 0.04–0.91, $P = .039$). $P_{ETCO_2}/P_{aCO_2} < 0.50$ was characterized by very high mean $\pm$ SD value for V_D/V_T (0.82 $\pm$ 0.05, $P < .001$) and high hospital mortality (70%). CONCLUSIONS: Using P_{ETCO_2}/P_{aCO_2} as a surrogate for V_D/V_T may be a useful and practical measurement for both management and ongoing research into the nature of ARDS. *Key words: ARDS; ratio of arterial-to-alveolar oxygen tension; ratio of dead space to tidal volume; end-tidal carbon dioxide pressure.* [Respir Care 2021;66(2):263–268. © 2021 Daedalus Enterprises]

Introduction

The seminal study by Nuckton and colleagues[1] demonstrated that the ratio of physiologic dead space to tidal volume (V_D/V_T) at ARDS onset was a strong, independent predictor of mortality risk. Since then, numerous studies have confirmed and expanded these findings.[2-9] Others have demonstrated the value of using V_D/V_T measurements to detect lung recruitment and de-recruitment,[10-14] as well as insight into the effects of pharmacologic therapies for ARDS.[15-17]

Unfortunately, it has been our perception that, despite both the clinical value of V_D/V_T and wide access to indirect

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calorimetry and volumetric capnography monitors, measuring V_D/V_T has not been universally embraced by the larger critical care community.[18,19] Surrogate measures for estimating V_D/V_T now are commonly utilized and include versions of the Harris-Benedict or other equations.[20,21] Another is the ventilatory ratio, which compares arterial partial pressure of CO_2 (P_{aCO_2}) and minute ventilation to corresponding "ideal" and "predicted" values as a signifier for V_D/V_T.[22] In the absence of bedside capnography, these substitutes serve an important function.

Despite the general lack of enthusiasm for measuring V_D/V_T, bedside capnography is much more widely used to measure end-tidal CO_2 pressure (P_{ETCO_2}). Given this backdrop amid the current COVID-19 pandemic, Gattinoni and colleagues[23] offered the ratio of P_{ETCO_2}/P_{aCO_2} to evaluate pulmonary gas exchange dysfunction. Specifically, they stated that $P_{ETCO_2}/P_{aCO_2} < 1$ "suggests" the presence of elevated intrapulmonary shunt fraction and V_D/V_T. With few exceptions (eg, differences in how P_{aCO_2} and expired P_{CO_2} are measured, or the effect of prolonged expiratory time constants on P_{ETCO_2}), there is always a positive difference between P_{aCO_2} and P_{ETCO_2}. Therefore, P_{ETCO_2}/P_{aCO_2} will always be < 1, regardless of the severity of gas-exchange dysfunction. Therefore, without citing supportive evidence, the suggestion is not particularly informative.

We were intrigued by the possibility that P_{ETCO_2}/P_{aCO_2} might be a meaningful signifier for pulmonary gas exchange dysfunction in ARDS in general. Because P_{ETCO_2}/P_{aCO_2} is easily calculated with readily available technology at the bedside, it may be useful both for patient management and ongoing research into the course of ARDS. It may also obviate the need for calculating surrogate measures when basic capnography is available at the bedside. Therefore, we retrospectively studied the association between P_{ETCO_2}/P_{aCO_2} and measurements of gas exchange dysfunction in a large number of ARDS subjects.

Methods

Data were abstracted from a previous study of V_D/V_T using volumetric capnography in subjects with early ARDS.[3] Briefly, contemporaneous measurements of expired gas and arterial blood gases along with full ventilator systems checks were made early in the course of ARDS (99% within 48 h of syndrome onset) via volumetric capnopgraphy.[3] These subjects were managed with the National Institutes of Health ARDS Clinical Trials Network ventilator protocol, which was adopted for clinical management in 2000.[24,25] In 2010, the wide availability of volumetric capnography at San Francisco General Hospital allowed us to incorporate V_D/V_T measurements into our routine assessment and clinical management of ARDS. Between 2010 and 2017, 561 of the

QUICK LOOK

Current knowledge

The ratio of dead space to tidal volume (V_D/V_T) increases with ARDS severity and is strongly associated with increasing intrapulmonary shunt and mortality. Assessing each of these variables requires additional data collection or calculations that are not widely performed in clinical practice. In contrast, basic bedside capnography is widely practiced. Both increasing dead-space ventilation and oxygenation dysfunction are associated with an increased difference between arterial partial pressure of CO_2 (P_{aCO_2}) and end-tidal CO_2 pressure (P_{ETCO_2}).

What this paper contributes to our knowledge

In ARDS, a strong association exists between an increasing V_D/V_T and a decreasing P_{ETCO_2}/P_{aCO_2} ratio, with only a moderate association with increasing oxygenation dysfunction. The use of ratio cutoff values representing increasing severity of P_{ETCO_2}/P_{aCO_2} was significantly associated with an increasing V_D/V_T, oxygenation dysfunction, illness severity scores, and mortality, and this might be a convenient and useful measurement for both clinical management and research into the nature and progression of ARDS.

original 685 subjects (82%) from the previous study also had paired measurements for P_{ETCO_2} and P_{aCO_2} available for analysis.[3] As detailed in the previous study, illness severity scores were calculated on the day of ARDS onset along with basic demographic information and status at hospital discharge.

We assessed oxygenation using the ratio of arterial-to-alveolar oxygen tension (P_a/A_{O_2}) because it is a more precise physiologic measure of pulmonary oxygen diffusion as it accounts for alveolar P_{CO_2},[26] and thus the effects of permissive hypercapnia during lung-protective ventilation. In addition, P_a/A_{O_2} values < 0.50 are associated with high degrees of intrapulmonary shunt, particularly at $F_{IO_2} \geq 0.50$.[26-28] We also used the formula $(P_{aCO_2} - P_{ETCO_2}) \div P_{aCO_2}$ because it reflects both alveolar and shunt-associated dead space.

Data are reported as either mean $\pm$ SD or median and interquartile range (IQR). Correlation between variables were assessed with Pearson or Spearman tests. Comparisons between groups were made using one-way analysis of variance and Tukey-Kramer multiple comparison tests, or with Kruskal-Wallis multiple comparisons test and Dunn post-test. Paired comparisons were made using either unpaired t test or the Mann-Whitney test. Dichotomous variables were assessed with the

Table 1. Gas Exchange and Illness Severity Characteristics Across Ranges of P_{ETCO_2}/P_{aCO_2}

	P_{ETCO_2}/P_{aCO_2} Range			
	≥ 0.80	≥ 0.60	≥ 0.50	< 0.50
Subjects, n	170	238	86	67
P_{ETCO_2}/P_{aCO_2}*†	0.89 ± 0.06	0.70 ± 0.06	0.55 ± 0.03	0.39 ± 0.08
V_D/V_T*†	0.51 ± 0.08	0.64 ± 0.07	0.73 ± 0.06	0.82 ± 0.05
V_D/V_T alv-shunt*†	0.11 ± 0.07	0.30 ± 0.06	0.45 ± 0.03	0.61 ± 0.08
P_a/A_{O_2}*‡	0.26 ± 0.09	0.21 ± 0.09	0.16 ± 0.06	0.14 ± 0.06
Ventilatory ratio*	1.56 (1.31–1.79)	1.76 (1.45–2.03)§	2.0 (1.65–2.39)§‖	2.6 (2.1–3.01)§¶
Oxygen index*†	9.8 (7.5–14)	13.6 (9.4–20.3)	20 (13.4–26.5)	24.4 (17–32.6)
Respiratory system compliance, mL/cm H_2O*	31 (25–39)	29 (23–37)	30 (24–35)	26 (21–31)§
APACHE II score*	20 (15–25)	24 (18–31)§	28 (22–35)§‖	42 (32–54)§¶
SAPS II score*	42 (32–54)	50 (39–63)§	57 (43–70)§**	65 (55–74)§¶

P_{ETCO_2}/P_{aCO_2} = ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 pressure
P_a/A_{O_2} = ratio of arterial to alveolar oxygen pressure
V_D/V_T = ratio of dead space to tidal volume
$V_D/V_{T-alv-shunt}$ = alveolar and shunt associated ratio of dead space to tidal volume
APACHE = Acute Physiology and Chronic Health Evaluation
SAPS = Simplified Acute Physiology Score
* $P < .001$ by one-way analysis of variance or Kruskal-Wallis test
† $P < .001$ for all inter-group comparisons
‡ $P < .001$ for all inter-group comparisons except for range 0.50–0.59 vs range < 0.50 ($P = .63$)
§ $P < .001$ vs range ≥ 0.80
‖ $P = .006$ vs range ≥ 0.60
¶ $P < .001$ vs range ≥ 0.60
** $P = .045$ vs range ≥ 0.60

Fisher exact test. Data were analyzed using PRISM 8.4 (GraphPad, La Jolla, California). Alpha was set at 0.05. Use of this database was approved by the University of California, San Francisco Committee on Human Research.

Data were analyzed in 3 ways. First, the correlation between P_{ETCO_2}/P_{aCO_2} with V_D/V_T and P_a/A_{O_2} was assessed. Second, data were categorized into ranges of P_{ETCO_2}/P_{aCO_2} that represent increasing severity of CO_2 excretion dysfunction. Because the data were skewed toward values suggesting less severe dysfunction (ie, 73% were ≥ 0.60), we divided P_{ETCO_2}/P_{aCO_2} data into 4 groups that would facilitate clinical apprehension: ≥ 0.80, 0.6–0.79, 0.50–0.59, and < 0.50. Within these groupings, we also included variables previously shown to be associated with hospital mortality in other studies[3,22,29,30]: Acute Physiology and Chronic Health Evaluation score (APACHE II),[31] Simplified Acute Physiology Score (SAPS II),[32] age, presence of sepsis, enrollment eligibility criteria used by the ARDS Clinical Trials Network,[25] cutoff values signifying organ dysfunction (eg, platelets $< 150 \times 10^3/mm^3$, total bilirubin > 2 mg/dL), ventilatory ratio, oxygenation index, respiratory system compliance, and driving pressure. Third, we performed step-wise, backward, logistical regression modeling using the variables described above. Variables with a P value < .10 were entered into the final model. Model goodness of fit was assessed with the Hosmer-Lemeshow test.

Results

A strong negative relationship was found between P_{ETCO_2}/P_{aCO_2} and V_D/V_T: r = –0.87 (95% CI –0.89 to –0.85), $P < .001$ (Fig. 1). In contrast, only a moderate relationship was found with P_a/A_{O_2}: r = 0.46 (95% CI 0.38–0.52), $P < .001$. Analyzing subjects by group revealed that decreasing P_{ETCO_2}/P_{aCO_2} coincided with elevated V_D/V_T and ventilatory ratio, decreasing P_a/A_{O_2}, increasing oxygenation index, and increasing APACHE II and SAPS II scores (Table 1). All comparisons between variables across groups were statistically significant. Values of P_{ETCO_2}/P_{aCO_2} < 0.50 coincided with very high V_D/V_T and low P_a/A_{O_2} (ie, only 14% of alveolar partial pressure of O_2 was reflected in arterial partial pressure of O_2). The mortality risk was significant between all 4 groups. As P_{ETCO_2}/P_{aCO_2} decreased, hospital mortality increased from 20% at values ≥ 0.80 to 70% when P_{ETCO_2}/P_{aCO_2} fell to < 0.50 (Table 2, Fig. 2). All measures of gas exchange dysfunction distinguished survivors from non-survivors (Table 3).

In the univariate analysis, for every 0.01 increase in P_{ETCO_2}/P_{aCO_2}, mortality risk decreased by ~1% (odds ratio 0.009, 95% CI 0.003–0.029, $P < .001$) (Fig. 3). In multivariate logistic regression modeling, both P_{ETCO_2}/P_{aCO_2} and ventilatory ratio remained independent predictors of mortality after controlling for other variables (Table 4). Area under the receiver operating characteristic curve was 0.84 (95% CI 0.81–0.87), $P < .001$.

Discussion

The primary finding of our study is that, during lung-protective ventilation, decreasing P_{ETCO_2}/P_{aCO_2} in early ARDS is associated with increasing V_D/V_T, oxygenation dysfunction, illness severity scores, and mortality. Moreover, P_{ETCO_2}/P_{aCO_2} is independently associated with mortality risk after adjusting for variables known to increase mortality in ARDS. Our findings were similar to those that we previously reported for ventilatory ratio, which is another surrogate for V_D/V_T.[22] Therefore, P_{ETCO_2}/P_{aCO_2} is a convenient and elegant surrogate for V_D/V_T that can be used to assess both pulmonary function and mortality risk in ARDS.

As implied in the methods section, P_{ETCO_2}/P_{aCO_2} is derived from an equation often used for estimating alveolar dead space: $(P_{aCO_2} - P_{ETCO_2}) \div P_{aCO_2}$. However, accurate measurement of alveolar dead space requires volumetric capnography (ie, the ability to measure the slope of phase III in the capnograph).[33] $P_{aCO_2} - P_{ETCO_2}$ itself is an unreliable indicator of true alveolar dead space.[34] This stems from the fact that, like the Enghoff modification of the Bohr equation, utilizing P_{aCO_2} introduces the alveolar-capillary interface as a factor.[35] In the presence of increased intrapulmonary shunt, as occurs in ARDS, rising P_{aCO_2} coincides with decreasing P_{ETCO_2}.[36] Considerable intrapulmonary shunting accounts for 20–33% of alveolar dead space in animal models.[37] In our study, alveolar and shunt-associated dead space accounted for over half of the measured physiologic dead space as P_{ETCO_2}/P_{aCO_2} fell to < 0.60.

As mentioned earlier, despite 2 decades of research demonstrating the value of directly measuring V_D/V_T in patients with ARDS, adoption of this measurement as part of routine clinical management remains relatively sparse. This has motivated others to find alternative signifiers of dead space, particularly for evaluating mortality in large databases rather than evaluating the effects of therapy per se.

Estimating V_D/V_T based upon approximations of resting energy expenditure to calculate CO_2 production substantially underestimates measured V_D/V_T, with reported
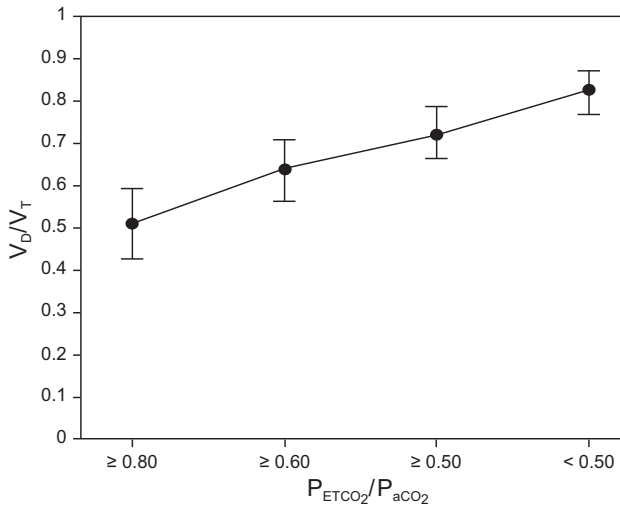

Fig. 1. Relationship between groupings of the ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 pressure (P_{ETCO_2}/P_{aCO_2}) by severity and corresponding ratio of physiologic dead space to tidal volume (V_D/V_T).
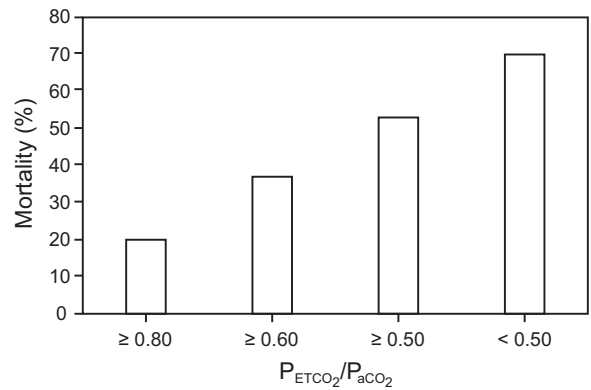

Fig. 2. Relationship between groupings of the ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 pressure (P_{ETCO_2}/P_{aCO_2}) by severity and corresponding hospital mortality.

Table 2. Hospital Mortality Across Ranges of P_{ETCO_2}/P_{aCO_2}

	P_{ETCO_2}/P_{aCO_2}			
	≥ 0.80	≥ 0.60	≥ 0.50	< 0.50
Mortality	20%	37%*	53%*†	70%*‡§
Odds ratio vs > 0.80		2.35 (1.47–3.75)	4.6 (2.60–8.06)	9.4 (4.9–17.8)
Odds ratio vs > 0.60			1.96 (1.21–3.21)	4.01 (2.23–7.20)
Odds ratio vs > 0.50				2.04 (1.03–4.05)

* $P < .001$ vs range ≥ 0.80
† $P = .01$ vs range ≥ 0.60
‡ $P < .001$ vs range ≥ 0.60
§ $P = .045$ vs range ≥ 0.50
P_{ETCO_2}/P_{aCO_2} = ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 pressure

Table 3. Differences Between Survivors and Non-Survivors in Measures of Gas Exchange Dysfunction

	Survivors	Non-Survivors	P
P_{ETCO_2}/P_{aCO_2}	0.75 ± 0.16	0.62 ± 0.17	< .001
Ventilatory ratio	1.71 (1.40–2.04)	1.90 (1.56–2.44)	< .001
V_D/V_T	0.60 ± 0.12	0.69 ± 0.11	< .001
P_a/A_{O_2}	0.21 (0.015–0.30)	0.15 (0.12–0.23)	< .001

P_{ETCO_2}/P_{aCO_2} = ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 pressure
V_D/V_T = ratio of dead space to tidal volume
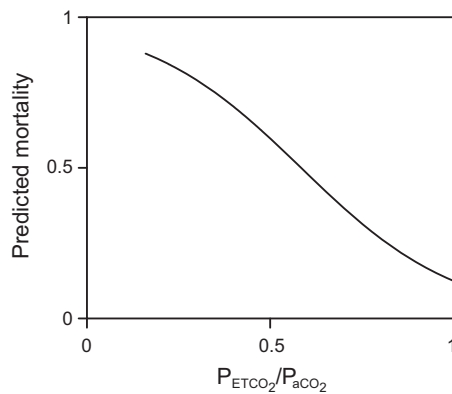P_a/A_{O_2} = ratio of arterial to alveolar oxygen pressure

Fig. 3. Univariate analysis of the ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2 pressure (P_{ETCO_2}/P_{aCO_2}) and mortality risk.

Table 4. Mortality as a Function of P_{ETCO_2}/P_{aCO_2}

	Odds Ratio (95% CI)	P
Unadjusted model		
P_{ETCO_2}/P_{aCO_2}	0.009 (0.003–0.029)	<.001
Adjusted model		
P_{ETCO_2}/P_{aCO_2}	0.19 (0.04–0.91)	.039
Ventilatory ratio	1.63 (1.06–2.53)	.03
Eligible for randomized controlled trial	0.48 (0.31–0.73)	< .001
Oxygen index	1.04 (1.01–1.07)	.002
Age	1.05 (1.03–1.06)	< .001
APACHE II score	1.05 (1.03–1.08)	< .001
Platelets $< 150 \times 10^3/mm^3$	2.64 (1.61–4.37)	< .001
Total bilirubin > 2.0 mg/dL	2.42 (1.42–4.19)	< .001

P_{ETCO_2}/P_{aCO_2} = ratio of end-tidal CO_2 pressure to arterial partial pressure of CO_2
APACHE = Acute Physiology and Chronic Health Evaluation

bias ranging from –0.16 to –0.32.[13,38] Nonetheless, in non-survivors all estimates of V_D/V_T have been reported to be significantly higher compared to estimates in survivors.[38] In particular, an unadjusted estimate of V_D/V_T in both survivors and non-survivors (eg, those not correcting resting energy expenditure for body temperature) were very close to those in whom V_D/V_T was measured.[38]

Likewise, we previously reported that ventilatory ratio is moderately correlated with V_D/V_T (r = 0.66, P < .001) and was independently associated with mortality both in univariate and multivariate analyses at 2.07 (95% CI 1.53–2.85, P < .001) and 1.59 (95% CI 1.15–2.32, P = .004), respectively.[22] In our study, which consisted of a large subset of data from a previous study, we found a moderate but slightly weaker correlation between ventilatory ratio and V_D/V_T (r = 0.55, P < .001) and a modestly higher mortality association in both the univariate and multivariate analyses at 2.25 (95% CI 1.68–3.07, P < .001) and 1.63 (95% CI 1.06–2.53, P = .03).

Ventilatory ratio is a less unwieldly method for evaluating the relationship between CO_2 excretion dysfunction and ARDS compared to derivations based upon the Harris-Benedict and other equations. Thus, it is perhaps ideal for use in large observational or interventional studies when capnography is not widely used. Nonetheless, ventilatory ratio itself is somewhat unwieldly for clinical use compared to P_{ETCO_2}/P_{aCO_2}. In particular, it does not translate as easily when evaluating interventions such as PEEP titration, prone positioning, or recruitment maneuvers. Regardless of these small differences, when direct measurement of V_D/V_T is unavailable, either method is a suitable substitute.

Conclusions

Our analysis suggests that P_{ETCO_2}/P_{aCO_2} can be used as a surrogate for both V_D/V_T and oxygenation dysfunction in patients with ARDS. Similar to elevated V_D/V_T in early ARDS, decreasing P_{ETCO_2}/P_{aCO_2} is also associated with increasing illness severity and mortality risk. Although P_{ETCO_2}/P_{aCO_2} was recently proposed specifically for monitoring patients with ARDS associated with COVID-19, currently there are no data available to evaluate its potential relevance or utility.

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