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# END-TIDAL-TO-ARTERIAL PCO<sub>2</sub> RATIO AS SIGNIFIER FOR PHYSIOLOGIC DEAD-SPACE RATIO AND OXYGENATION DYSFUNCTION IN ACUTE RESPIRATORY DISTRESS SYNDROME

<https://doi.org/10.4187/respcare.08061>

**Cite as:** RESPCARE 2020; 10.4187/respcare.08061

Received: 12 May 2020

Accepted: 2 July 2020

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*This Fast Track article has been peer-reviewed and accepted, but has not been through the composition and copyediting processes. The final version may differ slightly in style or formatting and will contain links to any supplemental data.*

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## **END-TIDAL-TO-ARTERIAL PCO2 RATIO AS SIGNIFIER FOR PHYSIOLOGIC DEAD-SPACE RATIO AND OXYGENATION DYSFUNCTION IN ACUTE RESPIRATORY DISTRESS SYNDROME**

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**Key Words:** Acute respiratory distress syndrome, arterial-to-alveolar oxygen tension ratio, physiologic dead-space ratio, end-tidal carbon dioxide pressure,

**Word Count:**

Abstract: 246

Manuscript: 1692

**COI:** Mr. Kallet has received honoraria for lectures on ARDS from Nihon Kohden in the past 2years. Dr. Lipnick has no COI to declare.

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**Abstract**

**Background:** The ratio of end-tidal-to-arterial carbon dioxide tension ( $P_{ETCO_2}/P_{aCO_2}$ ) was recently suggested for monitoring pulmonary gas exchange in subjects with COVID-19 associated ARDS.

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  $V_D/V_T$  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 four categories representing increasing severity of  $P_{ETCO_2}/P_{aCO_2}$  ( $\geq 0.80$ , 0.61 to 0.79, 0.50-0.59 and  $< 0.50$ ). Correlation was assessed by either Pearson Spearman tests, group comparisons were assessed using either ANOVA or Kruskal-Wallis tests, and dichotomous variables assessed by Fisher Exact test. Overall mortality risk was assessed by multivariate logistic regression. Alpha was set at 0.05.

**Results:**  $P_{ETCO_2}/P_{aCO_2}$  correlated strongly with  $V_D/V_T$  ( $R = -0.87 [-0.89, -0.85]$   $P < 0.001$ ).

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% (OR: 0.009 [0.003-0.029]  $P < 0.001$ ), and maintained a strong independent association with mortality risk when adjusted for other variables: 0.19 (0.04-0.91)  $P = 0.039$ .  $P_{ETCO_2}/P_{aCO_2} < 0.50$  was characterized both by very high  $V_D/V_T$  ( $0.82 \pm 0.05$ ,  $P < 0.001$ ) and hospital mortality (70%).

**Conclusion:**  $P_{ETCO_2}/P_{aCO_2}$  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.

## Introduction

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

Unfortunately, it has been our perception that despite both its clinical value and wide access to indirect calorimetry and volumetric capnography monitors,<sup>18, 19</sup> measuring  $V_D/V_T$  has not been universally embraced by the larger critical care community. Surrogate measures for estimating  $V_D/V_T$  now are commonly utilized and include versions of the Harris-Benedict or other equations.<sup>20, 21</sup> Another is the ventilatory ratio (VR) that compares arterial carbon dioxide tension ( $P_{aCO_2}$ ) and minute ventilation to corresponding “ideal” and “predicted” values as a signifier for  $V_D/V_T$ .<sup>22</sup> 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 carbon dioxide tension ( $P_{ETCO_2}$ ). Given this backdrop amid the current COVID-19 pandemic, Gattinoni and colleagues offered the ratio of  $P_{ETCO_2}$  to  $P_{aCO_2}$  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 physiologic dead-space ratio ( $V_D/V_T$ ).<sup>23</sup> 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 gradient 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.<sup>3</sup> In brief, contemporaneous measurements of expired gas and arterial blood gases along with full ventilator systems check were made early in the course of ARDS (99% within 48h of syndrome onset) using volumetric capnography.<sup>18</sup> These subjects were managed with the NIH ARDS Clinical Trials Network ventilator protocol which was adopted for clinical management in 2000.<sup>24</sup> 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 2010-2017, 561 of the original 685 subjects (82%) from the previous study also had paired measurements for  $P_{ETCO_2}$  and  $P_{aCO_2}$  available for analysis.<sup>25</sup> As detailed in the previous study illness severity scores were calculated

on the day of ARDS onset along with basic demographic information as well as status at hospital discharge.

We assessed oxygenation using the ratio of arterial-to-alveolar oxygen tension ( $P_{a/AO_2}$ ) because it is a more precise physiologic measure of pulmonary oxygen diffusion as it accounts for alveolar  $P_{CO_2}$ ,<sup>26</sup> and thus the effects of permissive hypercapnia during lung protective ventilation. In addition,  $P_{a/AO_2}$  ratios  $< 0.50$  are associated with high degrees of intrapulmonary shunt, particularly at  $F_{IO_2}$  of  $\geq 0.50$ .<sup>26-28</sup> We also used the formula  $(P_{aCO_2} - P_{ETCO_2}) \div P_{aCO_2}$  as it reflects both alveolar and shunt-associated dead-space ( $V_D/V_{T-alv-shunt}$ ).

Data are reported as either mean and standard deviation or median and interquartile range. Correlation between variables were assessed either by Pearson or Spearman tests. Comparisons between groups were made using either one-way analysis of variance (ANOVA) and Tukey-Kramer multiple comparison test, or Kruskal-Wallis multiple comparisons test and Dunn's post-test. Paired comparisons were made using either unpaired t-test or Mann Whitney test. Dichotomous variables were assessed by Fisher Exact test. Data were analyzed using the software program PRISM v8.4 (GraphPad, La Jolla CA.). 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 three ways. First, the correlation between  $P_{ETCO_2}/P_{aCO_2}$  with  $V_D/V_T$  and  $P_{a/AO_2}$  was assessed. Second, data were categorized into four groups of  $P_{ETCO_2}/P_{aCO_2}$  representing increasing severity of  $CO_2$  excretion dysfunction. Because the data were skewed towards values suggesting less severe dysfunction (73% were  $\geq 0.60$ ), we divided  $P_{ETCO_2}/P_{aCO_2}$

data into groups that would facilitate clinical apprehension, these being:  $\geq 0.80$ , 0.6 to 0.79, 0.50 to 0.59 and  $< 0.50$ . Within these groupings we also included variables previously shown to be associated with hospital mortality in other studies.<sup>3, 22, 29,30</sup> These included Acute Physiology and Chronic Health Evaluation score (APACHE II) and Simplified Acute Physiology Score (SAPS II),<sup>31, 32</sup> age, presence of sepsis, enrollment eligibility criteria used by the ARDS Clinical Trials Network,<sup>25</sup> cut-off values signifying organ dysfunction (eg. platelets  $< 150 \times 10^3/\text{mm}^3$ , total bilirubin  $> 2 \text{ mg/dL}$ ), 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  $< 0.10$  were entered into the final model. Model goodness of fit was assessed by Hosmer-Lemeshow test.

## Results

A strong negative relationship was found between  $P_{\text{ETCO}_2}/P_{\text{aCO}_2}$  and  $V_D/V_T$ :  $R = -0.87$  ( $-0.89, -0.85$ ),  $P < 0.001$ . In contrast, only a moderate relationship was found with  $P_{\text{a}/\text{AO}_2}$  ( $R = 0.46$  [ $0.38, 0.52$ ]  $P < 0.001$ ). Analyzing subjects by group revealed that decreasing  $P_{\text{ETCO}_2}/P_{\text{aCO}_2}$  coincided with elevated  $V_D/V_T$  and ventilatory ratio, decreasing  $P_{\text{a}/\text{AO}_2}$ , increasing OI and increasing APACHE II and SAPS II scores (**Table 1**). All comparisons between variables across groups were statistically significant. Values of  $P_{\text{ETCO}_2}/P_{\text{aCO}_2} \leq 0.50$  coincided with very high  $V_D/V_T$  and low  $P_{\text{a}/\text{AO}_2}$  (ie. only 13% of  $P_{\text{AO}_2}$  was reflected in  $P_{\text{aO}_2}$ ) (**Fig 1**). The mortality risk was significant between all four groups. As  $P_{\text{ETCO}_2}/P_{\text{aCO}_2}$  decreased hospital mortality increased from 20% at values  $\geq 0.80$  to 70% when  $P_{\text{ETCO}_2}/P_{\text{aCO}_2}$  fell below 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% (OR: 0.009 [0.003-0.029]  $P < 0.001$ ) (**Fig 3**). In multivariate logistic regression modeling both  $P_{ETCO_2}/P_{aCO_2}$  and ventilator ratio remained independent predictors of mortality after controlling for other variables (**Table 3**). Area under the receiver operating curve was 0.84 (0.81-0.87),  $P < 0.001$ ,

### Discussion

The primary finding of our study was 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 VR: another surrogate for  $V_D/V_T$ .<sup>22</sup> 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,  $P_{ETCO_2}/P_{aCO_2}$  is a derivative of 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).<sup>33</sup>  $P_{aCO_2} - P_{ETCO_2}$  itself is an unreliable indicator of true alveolar dead-space.<sup>34</sup> This stems from the fact that like the Enghoff modification of the Bohr equation, utilizing  $P_{aCO_2}$  introduces the alveolar-capillary interface as factor.<sup>35</sup> In the presence of increased intrapulmonary shunt (as occurs in ARDS), rising  $P_{aCO_2}$  coincides with decreasing  $P_{ETCO_2}$ .<sup>36</sup>

Considerable intrapulmonary shunting has been demonstrated to account for 20-33% of alveolar dead-space in animal models.<sup>37</sup> In our study,  $V_D/V_{T\text{-alv-shunt}}$  accounted for over half of the measured physiologic dead-space as  $P_{\text{ETCO}_2}/P_{\text{aCO}_2}$  fell below 0.60.

As mentioned earlier despite two 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 dead-space signifiers: 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  $\text{CO}_2$  production substantially underestimate measured  $V_D/V_T$  with reported bias ranging from -0.16 to -0.32.<sup>13, 38</sup> Nonetheless, in non-survivors all estimates of  $V_D/V_T$  have been found to be significantly higher compared to survivors.<sup>38</sup> 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.<sup>38</sup>

Likewise, we previously reported that VR is moderately correlated with  $V_D/V_T$  ( $R = 0.66$ ,  $P < 0.001$ ) and was independently associated with mortality both in univariate and multivariate analyses: 2.07 (1.53-2.85)  $P < 0.001$  and 1.59 (1.15-2.32)  $P = 0.004$  respectively. In the current study (which consisted of a large subset of the previous study data) we found a moderate but slightly weaker correlation between VR and  $V_D/V_T$  ( $R = 0.55$ ,  $P < 0.001$ ) but a modestly higher mortality association in both the univariate and multivariate analyses: 2.25 (1.68-3.07),  $P < 0.001$  and 1.63 (1.06-2.53),  $P = 0.028$ .

VR is a less unwieldy method for evaluating the relationship between CO<sub>2</sub> 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, VR itself is somewhat unwieldy 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. Irrespective of these small differences, when direct measurement of  $V_D/V_T$  is unavailable, either method is a suitable substitute.

In summary, 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  $P_{ETCO_2}/P_{aCO_2}$  also is associated with increasing illness severity and mortality risk. Although  $P_{ETCO_2}/P_{aCO_2}$  was recently proposed specifically for monitoring COVID-19 associated ARDS, currently there is no data available to evaluate its potential relevance or utility.

## References

1. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;346(17):1281-1286.
2. Kallet RH, Alonso JA, Pittet JF, Matthay MA. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. *Respir Care* 2004;49(9):1008-1014.
3. Kallet RH, Zhuo H, Ho K, Lipnick MS, Gomez A, Matthay MA. Lung Injury Etiology and Other Factors Influencing the Relationship Between Dead-Space Fraction and Mortality in ARDS. *Respir Care* 2017;62(10):1241-1248.
4. Raurich JM, Vilar M, Colomar A, Ibanez J, Ayestaran I, Perez-Barcena J, et al. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. *Respir Care* 2010;55(3):282-287.
5. Cepkova M, Kapur V, Ren X, Quinn T, Zhuo H, Foster E, et al. Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. *Chest* 2007;132(3):836-842.
6. Phillips CR, Chesnutt MS, Smith SM. Extravascular lung water in sepsis-associated acute respiratory distress syndrome: indexing with predicted body weight improves correlation with severity of illness and survival. *Crit Care Med* 2008;36(1):69-73.
7. Lucangelo U, Bernabe F, Vatua S, Degrassi G, Villagra A, Fernandez R, et al. Prognostic value of different dead space indices in mechanically ventilated patients with acute lung injury and ARDS. *Chest* 2008;133(1):62-71.
8. Kallet RH, Zhuo H, Liu KD, Calfee CS, Matthay MA, National Heart L, et al. The association between physiologic dead-space fraction and mortality in subjects with ARDS enrolled in a prospective multi-center clinical trial. *Respir Care* 2014;59(11):1611-1618.
9. Kallet RH, Ho K, Lipnick MS, Matthay MA. Pulmonary mechanics and gas exchange characteristics in uncommon etiologies of acute respiratory distress syndrome. *J Thorac Dis* 2018;10(8):5030-5038.
10. Fengmei G, Jin C, Songqiao L, Congshan Y, Yi Y. Dead space fraction changes during PEEP titration following lung recruitment in patients with ARDS. *Respir Care* 2012;57(10):1578-1585.
11. Bohm SH, Maisch S, von Sandersleben A, Thamm O, Passoni I, Martinez Arca J, et al. The effects of lung recruitment on the Phase III slope of volumetric capnography in morbidly obese patients. *Anesth Analg* 2009;109(1):151-159.
12. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, et al. Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. *Anesth Analg* 2008;106(1):175-181.
13. Charron C, Repesse X, Bouferrache K, Bodson L, Castro S, Page B, et al. PaCO<sub>2</sub> and alveolar dead space are more relevant than PaO<sub>2</sub>/FiO<sub>2</sub> ratio in monitoring the respiratory response to prone position in ARDS patients: a physiological study. *Crit Care* 2011;15(4):R175.
14. Unzueta C, Tusman G, Suarez-Sipmann F, Bohm S, Moral V. Alveolar recruitment improves ventilation during thoracic surgery: a randomized controlled trial. *Br J Anaesth* 2012;108(3):517-524.
15. Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. *Am J Respir Crit Care Med* 2008;178(6):618-623.
16. Kallet RH, Jasmer RM, Pittet JF. Alveolar dead-space response to activated protein C in acute respiratory distress syndrome. *Respir Care* 2010;55(5):617-622.

17. Raurich JM, Ferreruela M, Llopart-Pou JA, Vilar M, Colomar A, Ayestaran I, et al. Potential effects of corticosteroids on physiological dead-space fraction in acute respiratory distress syndrome. *Respir Care* 2012;57(3):377-383.
18. Kallet RH, Daniel BM, Garcia O, Matthay MA. Accuracy of physiologic dead space measurements in patients with acute respiratory distress syndrome using volumetric capnography: comparison with the metabolic monitor method. *Respir Care* 2005;50(4):462-467.
19. Doorduyn J, Nollet JL, Vugts MP, Roesthuis LH, Akankan F, van der Hoeven JG, et al. Assessment of dead-space ventilation in patients with acute respiratory distress syndrome: a prospective observational study. *Crit Care* 2016;20(1):121.
20. Siddiki H, Kojicic M, Li G, Yilmaz M, Thompson TB, Hubmayr RD, et al. Bedside quantification of dead-space fraction using routine clinical data in patients with acute lung injury: secondary analysis of two prospective trials. *Crit Care* 2010;14(4):R141.
21. Pais FM, Sinha P, Liu KD, Matthay MA. Influence of Clinical Factors and Exclusion Criteria on Mortality in ARDS Observational Studies and Randomized Controlled Trials. *Respir Care* 2018;63(8):1060-1069.
22. Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, et al. Physiologic Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med* 2019;199(3):333-341.
23. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020;24(1):154.
24. Kallet RH, Jasmer RM, Pittet JF, Tang JF, Campbell AR, Dicker R, et al. Clinical implementation of the ARDS network protocol is associated with reduced hospital mortality compared with historical controls. *Crit Care Med* 2005;33(5):925-929.
25. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-1308.
26. Gilbert R, Auchincloss JH, Jr., Kuppinger M, Thomas MV. Stability of the arterial/alveolar oxygen partial pressure ratio. Effects of low ventilation/perfusion regions. *Crit Care Med* 1979;7(6):267-272.
27. Doyle DJ. Arterial/alveolar oxygen tension ratio: a critical appraisal. *Can Anaesth Soc J* 1986;33(4):471-474.
28. Bredenberg CE, James PM, Collins J, Anderson RW, Martin AM, Jr., Hardaway RM, 3rd. Respiratory failure in shock. *Ann Surg* 1969;169(3):392-403.
29. Seeley E, McAuley DF, Eisner M, Miletin M, Matthay MA, Kallet RH. Predictors of mortality in acute lung injury during the era of lung protective ventilation. *Thorax* 2008;63(11):994-998.
30. Kallet RH, Lipnick MS, Zhuo H, Pangilinan LP, Gomez A. Characteristics of Nonpulmonary Organ Dysfunction at Onset of ARDS Based on the Berlin Definition. *Respir Care* 2019;64(5):493-501.
31. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13(10):818-829.
32. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270(24):2957-2963.
33. Fletcher R, Jonson B, Cumming G, Brew J. The concept of deadspace with special reference to the single breath test for carbon dioxide. *Br J Anaesth* 1981;53(1):77-88.
34. Hardman JG, Aitkenhead AR. Estimation of alveolar deadspace fraction using arterial and end-tidal CO<sub>2</sub>: a factor analysis using a physiological simulation. *Anaesth Intensive Care* 1999;27(5):452-458.
35. Kallet RH. Measuring dead-space in acute lung injury. *Minerva Anesthesiol* 2012;78(11):1297-1305.

36. Tang Y, Turner MJ, Baker AB. Effects of alveolar dead-space, shunt and V/Q distribution on respiratory dead-space measurements. *Br J Anaesth* 2005;95(4):538-548.
37. Severinghaus JW, Stupfel M. Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries. *J Appl Physiol* 1957;10(3):335-348.
38. Beitler JR, Thompson BT, Matthay MA, Talmor D, Liu KD, Zhuo H, et al. Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. *Crit Care Med* 2015;43(5):1026-1035.

**Figure Legends**

**Fig 1.** Relationship between groupings of end-tidal to arterial carbon dioxide tension ratio ( $P_{ETCO_2}/P_{aCO_2}$ ) by severity and corresponding physiologic dead-space to tidal volume ratio ( $V_D/V_T$ ).

**Fig 2.** Relationship between groupings of end-tidal to arterial carbon dioxide tension ratio ( $P_{ETCO_2}/P_{aCO_2}$ ) by severity and corresponding hospital mortality.

**Fig 3.** Univariate analysis of end-tidal to arterial carbon dioxide tension ratio ( $P_{ETCO_2}/P_{aCO_2}$ ) and mortality risk.

**Quick Look**

Current Knowledge: Physiologic dead-space fraction increases with ARDS severity and is strongly associated with increasing intrapulmonary shunt as well as mortality. Assessing each of these variables requires additional data collection or calculations not widely performed in clinical practice. In contrast, basic bedside capnography is widely practiced. Both increasing dead-space ventilation and oxygenation dysfunction also are associated with an increased gradient between arterial and end-tidal  $P_{CO_2}$ .

What This Paper Contributes to Our Knowledge: In ARDS a strong association exists between increasing dead-space ratio and decreasing ratio of end-tidal to arterial  $P_{CO_2}$  but only a moderate association with increasing oxygenation dysfunction. Using ratio cut-off values representing increasing severity of  $P_{ETCO_2}/P_{aCO_2}$  is significantly associated with increasing dead-space ratio, oxygenation dysfunction, illness severity scores, and mortality that might be a convenient and useful measurement both for clinical management and research into the nature and progression of ARDS in general.

**Table 1.** Gas exchange and illness severity characteristics across ranges of end-tidal to arterial  $P_{CO_2}$  ratio.

$P_{ETCO_2}/P_{aCO_2}$ Range	$\geq 0.80$	$\geq 0.60$	$\geq 0.50$	$< 0.50$
N	170	238	86	67
$P_{ETCO_2}/P_{aCO_2}^{**}$	$0.89 \pm 0.06$	$0.70 \pm 0.06$	$0.55 \pm 0.03$	$0.39 \pm 0.08$
$V_D/V_T^{**}$	$0.51 \pm 0.08$	$0.64 \pm 0.07$	$0.73 \pm 0.06$	$0.82 \pm 0.05$
$V_D/V_{T\text{ alv-shunt}}^{**}$	$0.11 \pm 0.07$	$0.30 \pm 0.06$	$0.45 \pm 0.03$	$0.61 \pm 0.08$
$P_a/A_{O_2}^{**}$	$0.26 \pm 0.09$	$0.21 \pm 0.09$	$0.16 \pm 0.06$	$0.14 \pm 0.06$
VR*	1.56 (1.31-1.79)	1.76 (1.45-2.03) <sup>§</sup>	2.0 (1.65-2.39) <sup>§  </sup>	2.6 (2.1-3.01) <sup>§¶</sup>
OI**	9.75 (7.5-14)	13.6 (9.4-20.3)	20 (13.4-26.5)	24.4 (17-32.6)
$C_{RS}$ (mL/cmH <sub>2</sub> O)*	31 (25,39)	29 (23,37)	30 (24-35)	26 (21-31) <sup>§</sup>
APACHE II*	20 (15-25)	24 (18-31) <sup>§</sup>	28 (22-35) <sup>§  </sup>	42 (32-54) <sup>§¶</sup>
SAPS II*	42 (32-54)	50 (39-63) <sup>§</sup>	57 (43-70) <sup>§**</sup>	65 (55-74) <sup>§¶</sup>

**Key:** APACHE = Acute Physiology and Chronic Health Evaluation,  $P_{a/AO_2}$  = arterial-alveolar oxygen tension ratio,  $C_{RS}$  = respiratory system compliance, OI = Oxygenation Index,  $P_{ETCO_2}/P_{aCO_2}$  = end-tidal-to-arterial carbon dioxide tension, SAPS = Simplified Acute Physiology Score,  $V_D/V_T$  = physiologic dead-space fraction,  $V_D/V_{T\text{ alv-shunt}}$  = alveolar and shunt associated dead-space fraction, VR = ventilatory ratio, \* $P < 0.001$  by one-way ANOVA or Kruskal-Wallis test, <sup>†</sup> $P < 0.001$  for all inter-group comparisons, <sup>‡</sup> $P < 0.001$  for all inter-group comparisons except for Range 0.50-0.59 vs. Range  $< 0.50$  ( $P = 0.63$ ), <sup>§</sup> $P < 0.001$  vs. Range  $\geq 0.80$ , <sup>||</sup> $P = 0.006$  vs. Range  $\geq 0.60$ , <sup>¶</sup> $P < 0.001$  vs. Range  $\geq 0.60$ , <sup>\*\*</sup> $P = 0.009$  vs. Range  $\geq 0.60$ , <sup>\*\*</sup> $P = 0.045$  vs. Range  $\geq 0.60$ ,

**Table 2.** Hospital mortality across ranges of end-tidal to arterial P<sub>CO2</sub> ratio

P <sub>ETCO2</sub> /P <sub>aCO2</sub>	≥ 0.80	≥ 0.60	≥ 0.50	< 0.50
Mortality	20%	37%*	53%* <sup>†</sup>	70%* <sup>‡§</sup>
OR vs. ≥ 0.80		2.35 (1.47-3.75)	4.6 (2.60-8.06)	9.4 (4.9-17.8)
OR vs. ≥ 0.60			1.96 (1.21-3.21)	4.01 (2.23-7.20)
OR vs. ≥ 0.50				2.04 (1.03-4.05)

**Key:** \*P < 0.001 vs. Range ≥ 0.80, <sup>†</sup>P = 0.01 vs. Range ≥ 0.60, <sup>‡</sup>P < 0.001 vs. Range ≥ 0.60, <sup>§</sup>P = 0.045 vs. Range ≥ 0.50.

**Table 3.** Differences between survivors and non-survivors in measures of gas exchange dysfunction.

	Survivors	Non-Survivors	P
P <sub>ETCO2</sub> /P <sub>aCO2</sub>	0.75 ± 0.16	0.62 ± 0.17	< 0.001
VR	1.71 (1.40-2.04)	1.90 (1.56-2.44)	< 0.001
V <sub>D</sub> /V <sub>T</sub>	0.60 ± 0.12	0.69 ± 0.11	< 0.001
P <sub>a/AO2</sub>	0.21 (.015-0.30)	0.15 (0.12-0.23)	< 0.001

**Key:** P<sub>ETCO2</sub>/P<sub>aCO2</sub> = end-tidal-to-arterial carbon dioxide tension, P<sub>a/AO2</sub> = arterial-alveolar oxygen tension ratio, VR = ventilatory ratio, V<sub>D</sub>/V<sub>T</sub> = physiologic dead-space fraction

**Table 4.** Mortality as a function of end-tidal to arterial  $P_{CO_2}$  ratio by both unadjusted and adjusted analyses.

Model	OR	95%CI	P
Unadjusted			
$P_{ETCO_2}/P_{aCO_2}$	0.009	0.003-0.029	<0.001
Adjusted Model			
$P_{ETCO_2}/P_{aCO_2}$	0.19	0.04-0.91	0.039
VR	1.63	1.06-2.53	0.028
RCT Eligible	0.48	0.31-0.73	< 0.001
OI	1.04	1.01-1.07	0.002
Age	1.05	1.03-1.06	< 0.001
APACHE II	1.05	1.03-1.08	< 0.001
Platelets < 150 x10 <sup>3</sup> /mm <sup>3</sup>	2.64	1.61-4.37	< 0.001
Total Bilirubin > 2.0 mg/dL	2.42	1.42-4.19	<0.0013

**Key:** APACHE = Acute Physiology and Chronic Health Evaluation, OI = oxygenation index, RCT = randomized controlled trial,  $P_{ETCO_2}/P_{aCO_2}$  = end-tidal-to-arterial carbon dioxide tension, VR = ventilatory ratio)

Fig 1

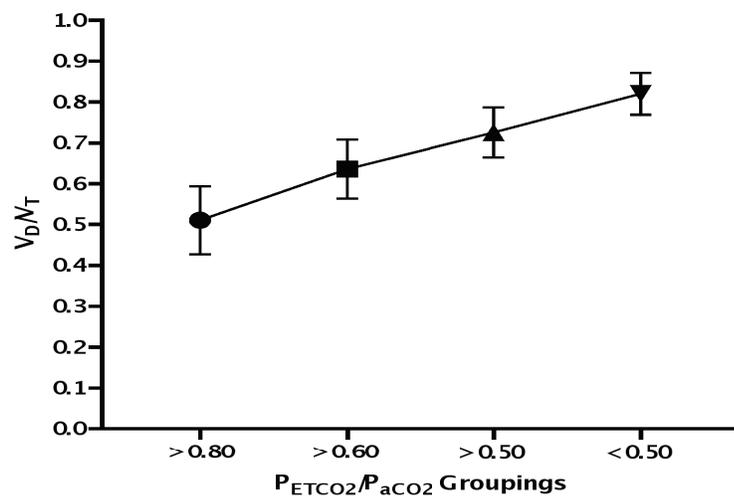


Fig 2

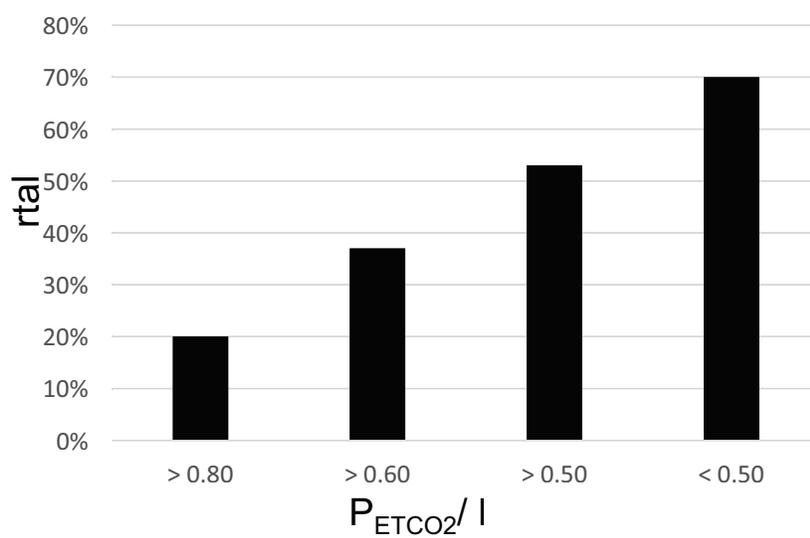


Fig 3

