Physiological Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome

Pratik Sinha, Carolyn S Calfee, Jeremy R Beitler, Neil Soni, Kelly Ho, Michael A Matthay, and Richard H Kallet

Online Data Supplement

Supplementary Material

Physiological Analysis of Ventilatory Ratio

From equation 1 of the main body of the manuscript, we know ventilatory ratio (VR) is

$$\boldsymbol{VR} = \frac{\dot{\boldsymbol{V}}_{\boldsymbol{E}\ measured} \times \boldsymbol{Pa}_{\boldsymbol{CO_2}\ measured}}{\dot{\boldsymbol{V}}_{\boldsymbol{E}\ predicted} \times \boldsymbol{Pa}_{\boldsymbol{CO_2}\ ideal}} \qquad [1]$$

For a given individual, we know the predicted and ideal values (denominator) in VR would be constant. Therefore, we can restate equation 1 as:

$$\boldsymbol{VR} = \dot{\boldsymbol{V}}_{\boldsymbol{E\ measured}} \times \boldsymbol{Pa}_{\boldsymbol{CO_2\ measured}} \times \boldsymbol{k} \quad [2]$$

where k is the constant for predicted and ideal values. Next, we can describe alveolar ventilation ($\dot{V}_A$) as a function of $\dot{V}_E$:

$$\dot{\mathbf{V}}_{\mathbf{A}} = \dot{\boldsymbol{V}}_{\boldsymbol{E\ measured}} \times \left(\mathbf{1} - \frac{\boldsymbol{V_D}}{\boldsymbol{V_T}}\right) \quad [3]$$

rearranging equation 3:

$$\dot{\boldsymbol{V}}_{\boldsymbol{E\ measured}} = \frac{\dot{\mathbf{V}}_{\mathbf{A}}}{\left(\mathbf{1} - \frac{\boldsymbol{V_D}}{\boldsymbol{V_T}}\right)} \quad [4]$$

We also know that alveolar PCO_2 can be described as a function of CO_2 production ($\dot{V}CO_2$) and $\dot{V}_A$:

$$\boldsymbol{PA}_{\boldsymbol{CO_2}} = \frac{\dot{\mathbf{V}}\mathbf{CO_2}}{\dot{\mathbf{V}}_{\mathbf{A}}} \times \boldsymbol{k} \quad [5]$$

Substituting alveolar PCO_2 for arterial PCO_2 we can restate equation 5 as follows:

$$Pa_{CO_2\,measured} = \frac{\dot{V}CO_2}{\dot{V}_A} \times P_b \quad [6]$$

where P_b represents the barometric pressure and is constant for most individuals. Incorporating P_b into k and inserting equations 4 and 6 into equation 2, we can simplify VR as:

$$VR = \frac{\dot{V}CO_2}{1 - \frac{V_D}{V_T}} \times k \qquad [7]$$

where k is the constant for predicted values for an individual. From equation 7 we can see that an increase in pulmonary dead space $\left(\frac{V_D}{V_T}\right)$ or CO_2 production ($\dot{V}CO_2$) or both would lead to an increase in VR. In addition, the assumption of arterial PCO_2 approximating alveolar PCO_2 would also result in increased shunt leading to an increase in VR.[1]

Supplementary Methods

Primary Analysis Study Protocol

Dead-space measurements coincided with a full ventilator-systems check that included the measurement of expired tidal volume (V_T) (both in mL and relative to predicted body weight according to the ARDS Clinical Trials Network protocol),[2] end-inspiratory plateau pressure (P_{PLAT}), PEEP, mean airway pressure (P_{AW}), and minute ventilation (V_E). Consistent with protocols from prior studies,[3,4] assessments were made only when patients were observed to be calm and synchronous with the ventilator, in the absence of nursing care activities, and, unless contraindicated, studied in in the semi-recumbent position. Additional ventilatory variables recorded at this time included the fraction of inspired oxygen (FiO_2), tidal volume (V_T), minute ventilation (V_E), positive-end expiratory pressure (PEEP), mean airway pressure (P_{AW}), and plateau airway pressure (P_{plat}).

In addition, Lung Injury Score (LIS),[5] and Acute Physiology and Chronic Health Evaluation II (APACHE II)[6] score were calculated on the day that protocol management commenced as described previously.[9] Variables from these scores that were likely to impact outcomes were added to the statistical modeling used to assess mortality risk (eg. the most abnormal value for mean blood pressure, creatinine, blood urea nitrogen, total bilirubin, platelet count and white blood cell count). For quality assurance purposes mortality was assessed at the time of hospital discharge. Predicted body weight was calculated using the NHLBI ARDS network formula; female = 45.5 + 0.91* (height in cm – 152.4), male = 50 + 0.91 * (height in cm – 152.4). For transgender patients, predicted body weight was calculated using gender assigned at birth.

Logistic Regression Analysis- Approach to Variable Selection

Mortality was used as the dependent variable for all logistic regression models. For the primary dataset, aside from the APACHE II score, only respiratory variables were chosen as predictors for logistic regression modeling. Respiratory Covariates were selected via review of existing literature for relevance to risk of death in patients with ARDS.[7-9] The covariates selected included variables of impaired oxygenation (PaO_2/FiO_2), mechanical support (PEEP, driving pressure), a combination of these factors (OI), and bedside variables of impaired ventilation (VR and $V_{E\text{-}corr}$). In a regression model consisting of these six variables, VR was the only variable significantly associated with increased risk of mortality (OR 1.85, CI 1.00 – 3.49). Backward stepwise regression using these variables led to the retention of VR, PaO_2/FiO_2, PEEP, and driving pressure in the final model. This formed the basis of the primary regression analysis presented in **Table 2**. Many of these covariates are both physiologically and mathematically related (PEEP with driving pressure, PaO_2/FiO_2 with OI). Thus, to avoid inflating type II errors, successive models were run adjusting for combinations of covariates for impaired oxygenation, and mechanical support avoiding highly co-linear variables.

Supplementary Tables

Table E1 Sensitivity analysis comparing demographics, outcome, and respiratory variables between analyzed data and missing values in the primary dataset. P-values student t-test unless stated otherwise stated (* Chi-square test).

	Study Data	Missing Data	P-Value
Number of Patients	520	165	
Age (Years)	51.4±16.5	50.9±17.5	0.74
APACHE II	24.8±9.1	23.0±8.4	0.04
In-Hospital Mortality	203 (39%)	58 (35%)	0.37*
Lung Injury Score	2.87±0.52	2.76±0.52	0.02
Driving Pressure (cmH_2O)	14.4±4.4	15.8±5.1	0.0004
Plateau Pressure (cmH_2O)	25.2±5.8	25.2±5.7	0.62
PEEP (cmH_2O)	11.0±3.8	9.3±3.7	<0.0001
Respiratory Compliance (mL/ cmH_2O)	30.4±9.5	29.9±9.5	0.54
Tidal Volume (mL)	6.4±1.5	6.9±1.1	0.0001
Oxygenation Index	16.8±10.9	14.9±8.9	0.08

Table E2 Values of respiratory variables at the time of volumetric capnography measurements with stratification by ICU-mortality. All measurements are within 12 hours of initiation of ARDS network lung protective ventilation protocol. P-values student t-test unless stated otherwise stated (§ Mann-Whitney test).

	Population (n = 520)	Discharged Alive (n = 317)	Died in Hospital (n = 203)	P-Value
PaO_2 (mmHg)	97 (± 43)	104 (± 46)	86 (± 35)	< 0·001
$PaCO_2$ (mmHg)	41 (± 9)	41 (± 9)	42 (± 10)	0·046
FiO_2	0·8 (0.6 -1.0)	0·7 (0·6 – 1·0)	0·8 (0·7 – 1·0)	0·106
PaO_2/FiO_2 Ratio (mmHg)	133 (± 60)	145 (± 60)	115 (± 54)	< 0·001
Oxygenation Index	16·8 (± 11)	20·6 (± 12·7)	14·4 (± 8·9)	< 0·001
Tidal Volume (mL)	405 (± 86)	402 (± 76)	407 (± 92)	0·505
Tidal Volume (mL/Kg)	6·4 (± 1·5)	6·4 (± 1·0)	6·5 (± 2·0)	0·253
Minute Ventilation (L/min)	10·8 (± 3·0)	10·5 (± 2·9)	11·2 (± 3·1)	0·014
Plateau Pressure (cmH_2O)	25 (22 – 29)	24 (21 – 27)	26 (23 – 30)	< 0·001§
Mean Airway Pressure (cmH_2O)	17 (14 - 20)	16 (14 -19)	18 (15-22)	< 0·001§
PEEP (cmH_2O)	10 (8 – 13.5)	10 (8 -12)	10 (10 -14)	< 0·001§
Respiratory Compliance (mL/ cmH_2O)	29 (24 - 36)	31 (25 – 37)	27 (23 – 35)	0·001§
Driving Pressure	14 (11 – 16)	13 (11-16)	14 (12-18)	< 0·001§
VCO_2 (mL/min)	183 (± 65)	193 (± 65)	167 (± 61)	< 0·001
V_D/V_T	0.63 (± 0·12)	0.60 (± 0·12)	0·69 (± 0·11)	< 0·001
Ventilatory Ratio	1·9 (± 0·6)	1·75 (± 0·5)	2·02 (± 0·8)	< 0·001
V_E Corrected	11·0 (± 3·8)	10.5 (± 3·2)	11.8 (± 4·5)	< 0·001

Table E3 Odds ratio for ICU-mortality using univariate logistic regression model for key respiratory variables in the primary dataset. Odds ratio are per unit change of variable unless stated otherwise. * Odds ratio per 0.05 increase in V_D/V_T.

	Odds Ratio	95% Confidence Interval	P-value
Ventilatory Ratio	2·07	1·53 - 2·85	< 0·001
PaO_2/FiO_2 Ratio	0·99	0·98 - 0·99	< 0·001
Oxygenation Index	1·05	1·03 - 1·07	< 0·001
PEEP (cmH_2O)	1·11	1·06 - 1·17	< 0·001
Driving Pressure	1.07	1.03 - 1.12	0·002
Pulmonary Dead Space	1·37*	1·27- 1·50	< 0·001
V_E corrected	1·09	1.04 - 1·51	< 0·001

Table E4 Odds ratio for ICU-mortality using multivariate logistic regression with corrected minute ventilation as the base model in the primary dataset. Odds ratio are per unit change in V_E-corrected. PF-Ratio = PaO_2/FiO_2 Ratio, PEEP = Peak end-expiratory pressure, OI = Oxygenation Index.

	Odds Ratio	95% Confidence Interval	P-value
Univariate Analysis			
V_E corrected (Base Model)	1·09	1·04 – 1·51	< 0·001
Multivariate Analysis			
Base model + PF-Ratio	1·05	0·99 - 1·11	0·054
Base model + PF-Ratio + PEEP	1·04	0·98 - 1·09	0·198

Table E5 Odds ratio for ICU-mortality using multivariate logistic regression with ventilatory ratio as the base model in the FACTT dataset. Odds ratio are per unit change of ventilatory ratio. PF-Ratio = PaO_2/FiO_2 Ratio, PEEP = Peak end-expiratory pressure, DP = Driving Pressure, OI = Oxygenation Index.

	Odds Ratio	95% Confidence Interval	P-value
Univariate Analysis			
Ventilatory Ratio (Base Model)	1·49	1·24 - 1·89	<0·001
Multivariate Analysis			
Base model + PF-Ratio	1·45	1·18 - 1·77	<0.001
Base model + PF-Ratio + PEEP	1·45	1·18 - 1·75	<0.001
Base model + PF-Ratio + DP	1.31	1·03 - 1·67	0·030
Base model + OI	1·39	1·10 - 1·75	0·006
Base model + OI + PEEP	1·42	1·11 - 1·77	0·005
Base model + OI + DP	1·30	1·00 - 1·40	0·049
Base Model + APACHE III score	1·28	1·04 - 1·58	0·021

Supplemental Figures

Figure E1 Flowchart of screening of patients for inclusion into the primary dataset (at Zuckerberg San Francisco General Hospital).

Figure E2 Ventilatory ratio in ARDS severity categories in the primary dataset. P-value represents analysis of variance test.

Figure E3A Correlation between pulmonary dead space and ventilatory ratio in the ALTA dataset. Figure E3B Correlation between CO_2 production and ventilatory ratio in the ALTA dataset.

Figure E4 Physiological dead space in ordinal groups of VRs in the ALTA dataset. Q1: < 1.43; Q2 ≥ 1.43 - < 1.80; Q3 ≥ 1.80 - < 2.17; Q4 ≥ 2.17. P-value represents analysis of variance test.

References

1. Sinha P, Fauvel NJ, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of ventilation. *Br J Anaesth* 2009; **102**(5): 692-7.
2. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, 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): 1301-8.
3. 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): 462-7.
4. Nuckton TJ, Alonso JA, Kallet RH, 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): 1281-6.
5. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **138**(3): 720-3.
6. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**(10): 818-29.

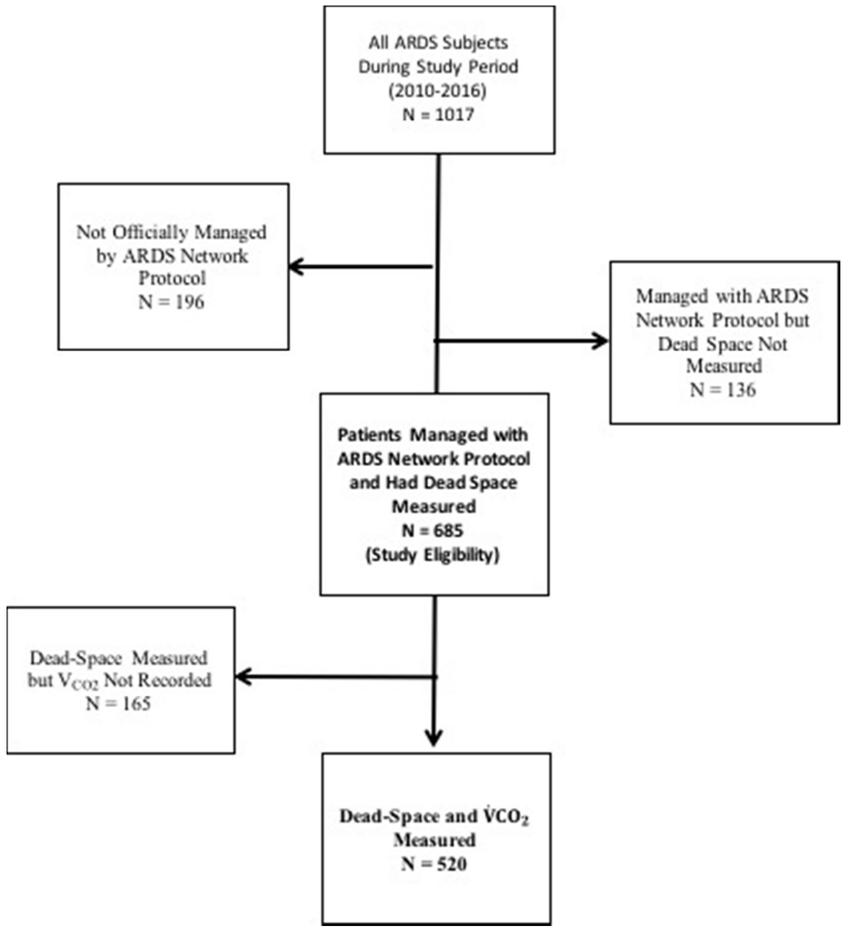

Figure E1

147x162mm (72 x 72 DPI)

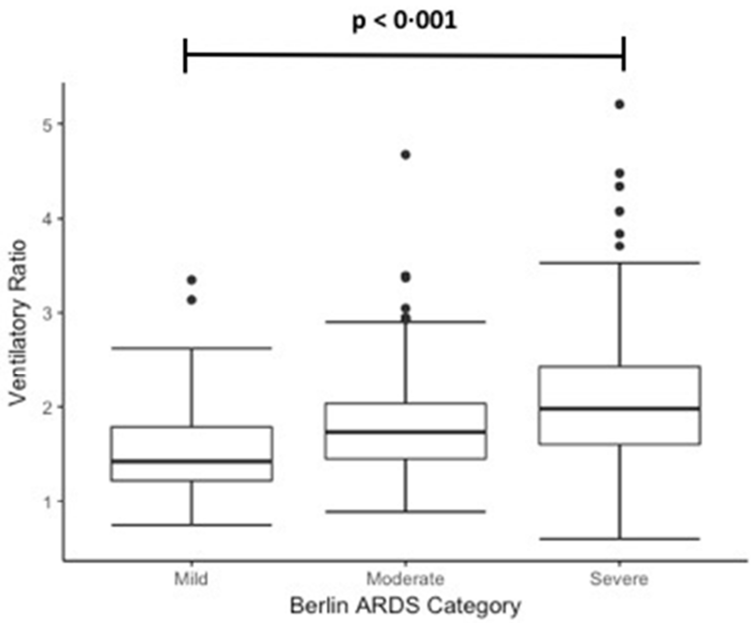

Figure E2

134x112mm (72 x 72 DPI)

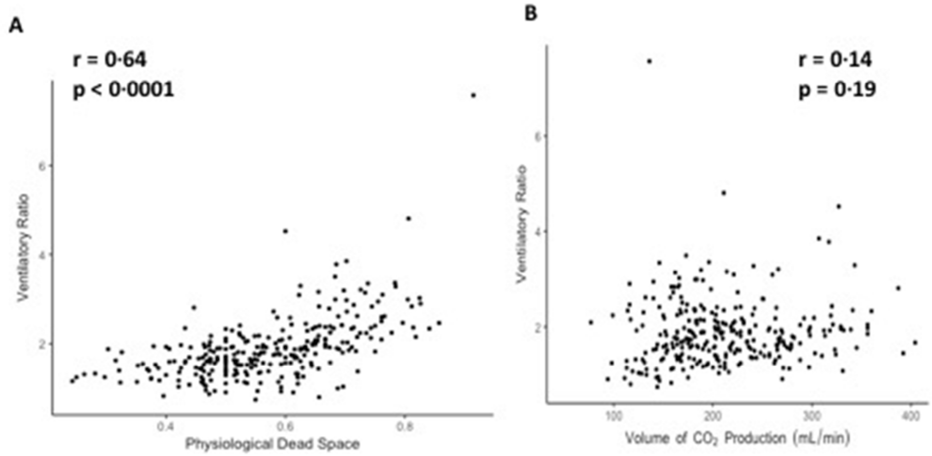

Figure E3

166x82mm (72 x 72 DPI)

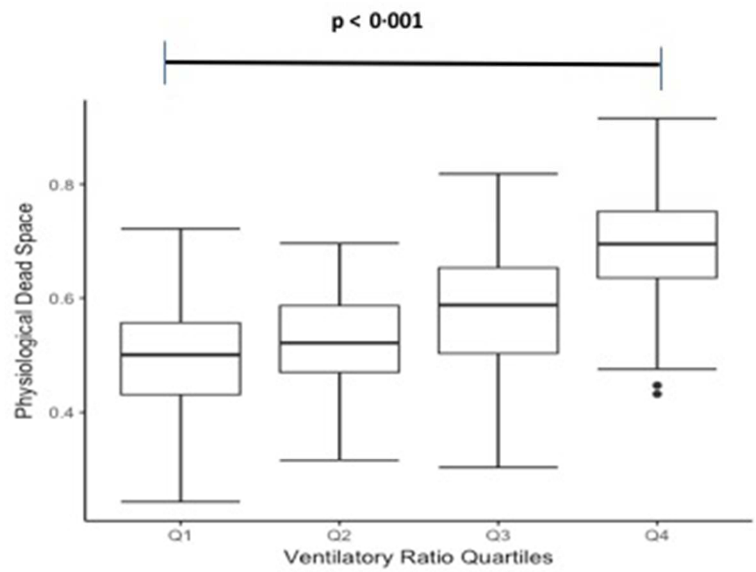

Figure E4

134x104mm (72 x 72 DPI)