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Original article

Comparison of the pulmonary dead-space fraction derived from ventilator volumetric capnography and a validated equation in the survival prediction of patients with acute respiratory distress syndrome

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ABSTRACT

Purpose: This prospective observational study aims to evaluate the accuracy of dead-space fraction derived from the ventilator volumetric capnography (volumetric CO_2) or a prediction equation to predict the survival of mechanically ventilated patients with acute respiratory distress syndrome (ARDS).
Methods: Consecutive VD/VT measurements were obtained based upon a prediction equation validated by Frankenfield et al for dead-space ventilation fraction: $VD/VT = 0.320 + 0.0106 (PaCO_2\text{-}ETCO_2) + 0.003 (RR) + 0.0015 (age)$ in adult patients who had infection-related severe pneumonia and were confirmed as having ARDS. Here $PaCO_2$ is the arterial partial pressure of carbon dioxide in mmHg; $ETCO_2$, the end-tidal carbon dioxide measurement in mmHg; RR, respiratory rate per minute; and age in years. Once the patient had intubation, positive end expiratory pressure was adjusted and after P_{high} reached a steady state, VD/VT was measured and recorded as the data for the first day. VD/VT measurement was repeated on days 2, 3, 4, 5 and 6. Meanwhile we collected dead-space fraction directly from the ventilator volumetric CO_2 and recorded it as Vd/Vt. We analyzed the changes in VD/VT and Vd/Vt over the 6-day period to determine their accuracy in predicting the survival of ARDS patients.
Results: Overall, 46 patients with ARDS met the inclusion criteria and 24 of them died. During the first 6 days of intubation, VD/VT was significantly higher in nonsurvivors on day 4 (0.70 ± 0.01 vs 0.57 ± 0.01), day 5 (0.73 ± 0.01 vs. 0.54 ± 0.01), and day 6 (0.73 ± 0.02 vs. 0.54 ± 0.01) (all $p = 0.000$). Vd/Vt showed no significant difference on days 1–4 but it was much higher in nonsurvivors on day 5 (0.45 ± 0.04 vs. 0.41 ± 0.06) and day 6 (0.47 ± 0.05 vs. 0.40 ± 0.03) (both $p = 0.008$). VD/VT on the fourth day was more accurate to predict survival than Vd/Vt. The area under the receiver-operating characteristic curve for VD/VT and Vd/Vt in evaluating ARDS patients survival was day 4 (0.974 ± 0.093 vs. 0.701 ± 0.023, $p = 0.0024$) with the 95% confidence interval being 0.857–0.999 vs. 0.525–0.841.
Conclusion: Compared with Vd/Vt derived from ventilator volumetric CO_2, VD/VT on day 4 calculated by Frankenfield et al's equation can more accurately predict the survival of ARDS patients.

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition, which presents as progressive hypoxemia and difficulty in breathing following diffuse pulmonary interstitial and alveolar edema due to pulmonary capillary endothelial cell damage. Patients with ARDS are often critical and accompanied by other diseases or major injuries, for example, severe infection, shock, trauma and burns, etc.[1] Although medical rescue is enhancing unceasingly, the mortality rate of critical patients has not been greatly decreased. Previous studies have shown the importance of physiologic dead space and its evolution in predicting mortality in critical patients.[2–6] In clinical practice, we can directly read pulmonary dead-space fraction on the ventilator screen (in this study

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we recorded it as Vd/Vt), which may change a lot and sometimes contradictory or nonsensitive due to numerous interference factors, including high positive end-expiratory pressure (PEEP), administration of sedatives or muscle relaxants, etc. Therefore its accuracy to predict survival should be studied further. The equation VD/VT = 0.320 + 0.0106 ($PaCO_2$-$ETCO_2$) + 0.003 (RR) + 0.0015 (Age) proposed by Frankenfield et al[7] (in this study we recorded it as VD/VT) has been shown to calculate pulmonary dead-space fraction precisely and without bias, eliminating the above-mentioned disturbing factors. In this study, we compared VD/VT with Vd/Vt to evaluate their prediction accuracy of survival of ARDS patients.

Methods

Patient selection

This was a prospective observational cohort study conducted in the intensive care unit (ICU) of Tianjin Third Central Hospital, Tianjin, China. All the protocols have been approved by the Institutional Committee on Human Research, and informed consents have been obtained from the patients or their relatives. All patients with ARDS admitted to the adult ICU of our hospital between January 2014 and January 2015 were eligible for this study. Inclusion criteria were adult patients (≥18 years old) who were diagnosed as having ARDS based on the Berlin Definition for ARDS[8] and required positive pressure mechanical ventilation via an endotracheal tube. Vd/Vt was directly read from the Dräger XL ventilator (Dräger Medical, Germany) volumetric CO_2. Patients were excluded if they have pulmonary thromboembolism (PTE), history of chronic obstructive pulmonary disease (COPD), bronchiectasis or interstitial lung disease. Of 58 patients with ARDS, 46 were included in this study.

Clinical data collection

Baseline characteristics, demographic data and relevant physiologic data were recorded on the first day of study (defined as the moment when PEEP has been well adjusted and P_{high} reached a steady state after intubation). Acute physiology and chronic health evaluation (APACHE) II score and lung-injury score at the time of enrollment were calculated. The primary etiology of ARDS was assessed based on a detailed review of the clinical history. Finally, we recorded the information about the survival condition of patients within 28 days.

Measurement of dead-space fraction

Initial VD/VT measurements were obtained on the first day. VD/VT was serially measured on days 2, 3, 4, 5 and 6 following the equation: VD/VT = 0.320 + 0.0106 ($PaCO_2$-$ETCO_2$) + 0.003 (RR) + 0.0015 (Age). At the same time, we recorded Vd/Vt directly from breath-by-breath volumetric CO_2. We also recorded the arterial blood gas values, PaO_2/FiO_2, PEEP and FiO_2. Breath-by-breath volumetric CO_2 and analysis of $ETCO_2$ were obtained by the mainstream CO_2 sensor of a Dräger XL ventilator based on the non-dispersive infrared absorption principle. The machine was placed between the ventilator circuit and the patient. Measurement of dead-space fraction was conducted at the same time of arterial blood sampling, which was analyzed by a Radiometer ABL800 arterial blood gas analyzer (Radiometer, Bronshøj, Denmark). Modality of mechanical ventilation of all patients were bilevel positive airway pressure. Data were read when the patient were observed to be calm with complete respiratory rhythm.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (Version 17.0, SPSS Inc, Chicago, Illinois, USA) and Med Calc statistical software (V.15.6.1). Parametric and nonparametric values were expressed as mean ± SEM, and distance between median and quartile respectively. Comparison of sampled ratios were explored by using χ^2 test. Student *t* test were used to compare mean values. Paired comparisons were conducted by using the Mann-Whitney test. Receiver operating characteristic (ROC) curves were obtained for the prognostic value of VD/VT and Vd/Vt, respectively. The area under the ROC curves of VD/VT and Vd/Vt were compared with Med Calc statistical software. A simple Pearson correlation was used to compare the relation of VD/VT to PEEP and PaO_2/FiO_2. A logistic regression was used to determine the association of VD/VT with mortality as the outcome. All tests were two sided and considered significant at $p < 0.05$.

Results

Baseline characteristics

A total of 46 patients with ARDS were enrolled in this study, including 18 females and 28 males with the mean age of (55.71 ± 3.01) years. Etiology of ARDS was pneumonia in 26 patients (57%), sepsis in 12 (25%), aspiration in 4 (9%) and trauma or others in 4 (9%). Of the 46 patients enrolled, 24 (52%) died and 22 (48%) survived. The demographics data, APACHE II score and lung-injury score are summarized in Table 1. Differences in PEEP and PaO_2/FiO_2 are summarized in Table 2. In this study, PEEP and FiO_2 were adjusted based upon a target $PaO_2 \geq 60$ mmHg and low tidal volume. PEEP showed no significant difference at the first 5 days, but it was much lower in survivors on day 6 (9.2 ± 0.10 vs. 14.3 ± 0.08, $p < 0.001$). PaO_2/FiO_2 was significantly higher among survivors on day 4 (273 ± 11 vs. 182 ± 56), day 5 (289 ± 20 vs. 172 ± 15) and day 6 (305 ± 29 vs. 174 ± 40, $p = 0.000$ for all).

Comparison of VD/VT and Vd/Vt between survivors and nonsurvivors

The mean VD/VT was significantly higher in nonsurvivors than in survivors from the fourth day of mechanical ventilation ($p < 0.05$, Fig. 1). As for Vd/Vt, nonsurvivors had a slightly higher mean value (0.40–0.47). However, the difference between two groups was significant only on day 5 and day 6. During the whole study period (6 days of mechanical ventilation), the mean Vd/Vt for all the patients was consistently lower than 0.5 (Fig. 2).

Table 1
Baseline data and clinical characteristics of 46 patients (mean ± SEM).

Group	Age (yr)	Female percentage	APACHE II score	Lung-injury score
Survivors ($n = 22$)	43.84 ± 3.35	32%	25 ± 0.5	2.60 ± 0.7
Non-survivor ($n = 24$)	66.59 ± 2.94	45%	28 ± 0.4	2.7 ± 0.6
Examining value	$t = -3.342$	$\chi^2 = 0.947$	$U = -2.846$	$U = -1.78$
p value	0.003	0.378	0.004	0.076

Table 2
Differences in PEEP and PaO_2/FiO_2 during the first 6 days between survivors ($n = 22$) and nonsurvivors ($n = 24$).

Physiologic variables	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
PEEP (cmH_2O)						
S	12.3 ± 0.06	11.6 ± 0.04	12.8 ± 0.12	11.8 ± 0.14	10.9 ± 0.04	10.2 ± 0.10
NS	12.4 ± 0.06	12.6 ± 0.06	13.2 ± 0.12	13.8 ± 0.09	13.3 ± 0.10	15.3 ± 0.08
U	−0.16	−1.53	−1.13	−1.77	−1.63	−5.50
P	0.875	0.127	0.261	0.077	0.104	< 0.001
PaO_2/FiO_2 (mmHg)						
S	166 ± 13	172 ± 26	171 ± 16	273 ± 11	289 ± 20	305 ± 29
NS	157 ± 21	161 ± 10	169 ± 22	182 ± 56	172 ± 15	174 ± 40
U	−1.22	−1.706	−0.76	−5.62	−5.77	−5.81
P	0.222	0.088	0.448	0.000	0.000	0.000

ROC curves for the prognosis of patients

The mean VD/VT was significantly higher in nonsurvivors than in survivors from the fourth day of mechanical ventilation. So VD/VT and Vd/Vt on the fourth day as a survival predictor of ARDS patients was compared using the area under the ROC curve, which showed a much larger area of VD/VT (0.974 ± 0.093, *95% CI*: 0.857–0.999) than that of Vd/Vt (0.701 ± 0.023, *95% CI*: 0.525–0.841) ($Z = 3.302$, $p = 0.0024$). Therefore, VD/VT calculated by Frankenfield et al's prediction formula has a higher prognostic value of patients with ARDS on the fourth day.

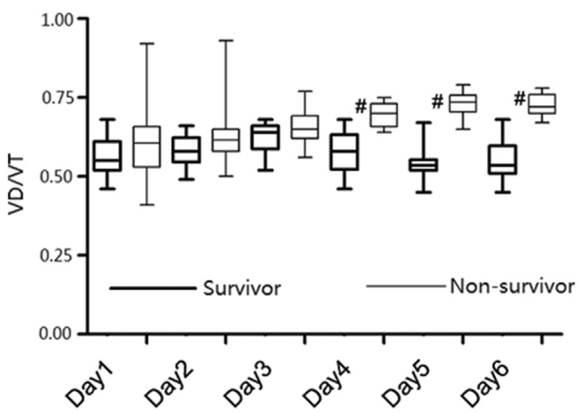

Fig. 1. Changes of VD/VT during the first 6 days of intubation. $^{\#}p < 0.001$ represents the significant differences between survivors and nonsurvivors on the same day.

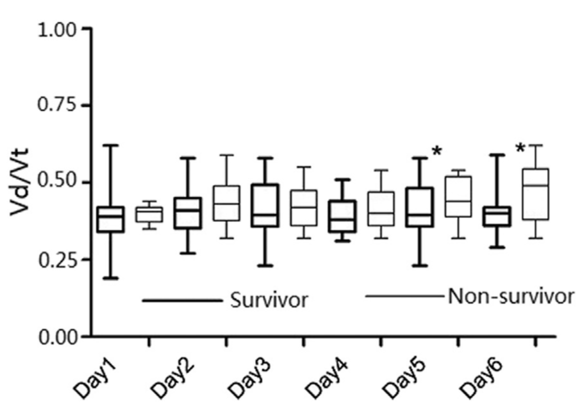

Fig. 2. Changes of Vd/Vt during the first 6 days of intubation. $^{*}p < 0.05$ represents the significant differences between survivors and nonsurvivors on the same day.

Correlation analysis between VD/VT and PEEP & PaO_2/FiO_2

VD/VT has no correlation with PEEP in statistics at the study period of mechanical ventilation ($p > 0.05$). At the first three days, there was no correlation between VD/VT and PaO_2/FiO_2 neither, but they were positively related on day 4 ($r = -0.56$, $p = 0.018$), day 5 ($r = -0.58$, $p = 0.01$), and day 6 ($r = -0.50$, $p = 0.014$). Statistic analysis was shown in Figs. 3–5.

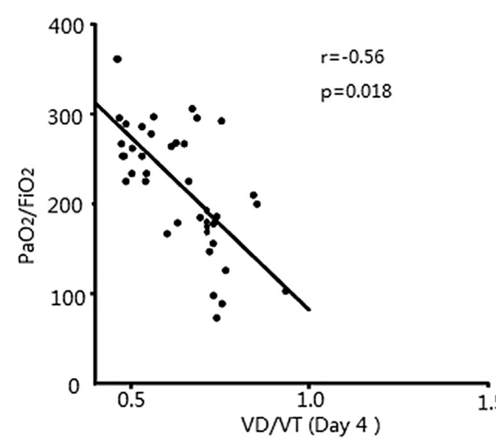

Fig. 3. Scatter plot of VD/VT and PaO_2/FiO_2 on day 4. There was statistically significant correlation between VD/VT and PaO_2/FiO_2.

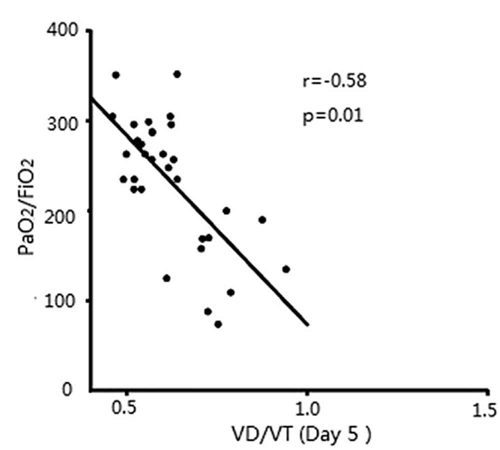

Fig. 4. Scatter plot of VD/VT and PaO_2/FiO_2 on day 5. There was statistically significant correlation between VD/VT and PaO_2/FiO_2.

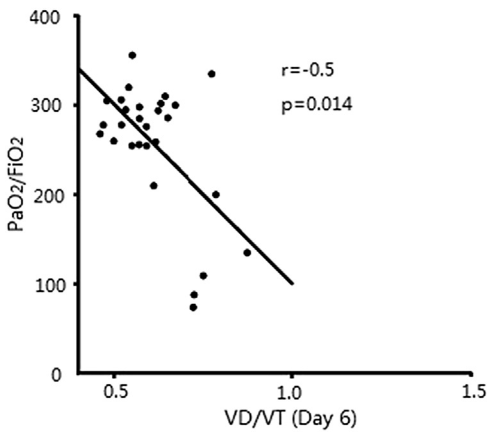

Fig. 5. Scatter plot of VD/VT and PaO_2/FiO_2 on day 6. There was statistically significant correlation between VD/VT and PaO_2/FiO_2.

The strength analysis of association between VD/VT and mortality

In the analysis of correlation between VD/VT and mortality, the odds ratio (OR) was calculated for every increase of 0.05 in VD/VT. The ORs for death in the unadjusted logistic regression model were statistical significant from day 4. They were still consistently >2.55 after the combined analysis of age, PaO_2/FiO_2, and APACHE II score. Moreover we found that age and APACHE II score were independent death risk factors ($p < 0.05$). PaO_2/FiO_2 in the adjusted logistic regression model reached statistic significance on days 4, 5 and 6. Because significant difference of VD/VT between survivors and nonsurvivors appeared on the fourth day, we only list detailed data on days 4, 5, and 6 in Table 3.

Discussion

Pulmonary dead-space ventilation i.e. the tidal volume that does not participate in gas exchange was first described and calculated by the Bohr equation in 1891. Later the Bohr's formula was simplified as dead-space fraction = $(PACO_2 - P\overline{E}\,CO_2)/PACO_2$, where $PACO_2$ represents the mean alveolar partial pressure of CO_2 during expiration[9] and $P\overline{E}\,CO_2$ is defined as mixed expired partial pressures of CO_2. In 1938, Bohr equation was modified by Enghoff. Physiologic dead-space fraction is consisted of anatomic or airway dead space and alveolar dead space.[10,11]

Recently, due to the advanced technology, the ratio of physiologic dead space to tidal volume can be obtained directly by using forced expiratory volumetric CO_2 concentration. The Dräger XL ventilator is equipped with integrated CO_2 sensor and has this capability. ARDS patients were clinically managed with lung-protective ventilation and sufficient lung recruitment maneuvers. For example, ARDS patients received a high PEEP and low tidal volume ventilation, and some of them were injected sedative drugs or muscle relaxants. In this condition, patients cannot breathe evenly or reach forced respiration, resulting in inaccurate measurement of $ETCO_{2.}$ Therefore, the concentration curve of expiratory volumetric CO_2 may have poor stability. In this study, VD/VT has a much larger areas under the ROC curve than Vd/Vt as a survival predictor on the fourth day. The result indicates that Vd/Vt may be highly variable or nonsensitive. As a result, Vd/Vt, when applied to evaluate clinical therapeutic effect and prognosis of patients, may be unreliable.

The prediction equation constructed by Frankenfield DC et al[7] for dead space fraction has been proved to be capable of avoiding the abovementioned disturbances. In fact, most pioneering studies have found that the dead space fraction can reliably predict the threshold values for prognosis (i.e. >60%).[2–4,6,12–14] However, we found that the mean Vd/Vt among survivors was volatile and consistently <0.50. From a clinical viewpoint, Vd/Vt may mislead clinicians to make inaccurate judgment. Our result indicates that VD/VT has a greater value in predicting the survival of ARDS patients than Vd/Vt. But our study is potentially limited by its relatively small size, thus requiring a larger sample clinical research for further study.

In our study, VD/VT has no correlation with PEEP during the first 6 days of ARDS. In ARDS, PEEP has a bidirectional variable influence on VD/VT: alveolar recruitment decreases dead-space while alveolar over-distension increases it.[15] It is hard to predict the effect of PEEP because both phenomena may occur at the same time. We designed the research based on previous studies and showed prognostic value of pulmonary dead-space fraction among ARDS patients by the strength analysis of relationship between VD/VT and mortality. At present, PaO_2/FiO_2 and APACHE II score have been proved to be capable of predicting mortality in ARDS patients. But because of numerous interference factors, PaO_2/FiO_2 and APACHE II score alone can not be treated as a prognostic indicator. Complications and extrapulmonary organ failure also have important influence on the prognosis of patients with ARDS.

This study is a further confirmation and supplement of Robert et al's result.[16] In conclusion, on the fourth day of mechanical ventilation for patients with ARDS, compared with Vd/Vt derived from ventilator volumetric CO_2, VD/VT calculated by a prediction equation constructed by Frankenfield et al[7] is more accurate to estimate patients' survival.

Table 3
Unadjusted and adjusted logistic analyses of VD/VT and mortality on days 4, 5 and 6.

	Day 4			Day 5			Day 6		
	OR	*95% CI*	*p*	*OR*	*95% CI*	*p*	*OR*	*95% CI*	*p*
Unadjusted model									
VD/VT	3.06	1.77–5.3	0.000	3.23	1.82–5.61	0.000	5.37	1.83–15.69	0.002
Adjusted model									
VD/VT	2.82	1.35–5.88	0.006	3.02	1.63–5.29	0.028	5.52	1.16–26.22	0.031
PaO_2/FiO_2	0.98	0.97–1	0.044	0.97	0.96–1.00	0.034	0.97	0.94–1.003	0.037
Age	1.08	1.01–1.16	0.025	1.07	0.98–1.16	0.086	1.07	0.99–1.16	0.087
APACHE II score	2.18	1.19–3.98	0.011	2.23	1.15–4.08	0.013	2.55	1.09–5.94	0.03

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