Original Contributions

Prognostic Value of the Pulmonary Dead-Space Fraction During the First 6 Days of Acute Respiratory Distress Syndrome

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BACKGROUND: The ratio of pulmonary dead space to tidal volume (V_D/V_T) in acute respiratory distress syndrome (ARDS) is reported to be between 0.35 and 0.55. However, V_D/V_T has seldom been measured with consideration to the evolving pathophysiology of ARDS. METHODS: We made serial V_D/V_T measurements with 59 patients who required mechanical ventilation for $\geq$ 6 days. We measured V_D/V_T within 24 h of the point at which the patient met the American-European Consensus Conference criteria for ARDS, and we repeated the V_D/V_T measurement on ARDS days 2, 3, and 6 with a bedside metabolic monitor during volume-regulated ventilation. We analyzed the changes in V_D/V_T over the 6-day period to determine whether V_D/V_T has a significant association with mortality. RESULTS: V_D/V_T was significantly higher in nonsurvivors on day 1 (0.61 $\pm$ 0.09 vs 0.54 $\pm$ 0.08, $p < 0.05$), day 2 (0.63 $\pm$ 0.09 vs 0.53 $\pm$ 0.09, $p < 0.001$), day 3 (0.64 $\pm$ 0.09 vs 0.53 $\pm$ 0.09, $p < 0.001$), and day 6 (0.66 $\pm$ 0.09 vs 0.51 $\pm$ 0.08, $p < 0.001$). CONCLUSION: In ARDS a sustained V_D/V_T elevation is characteristic of nonsurvivors, so dead-space measurements made beyond the first 24 hours may have prognostic value. *Key words: acute respiratory distress syndrome, respiratory dead space, dead-space, dead-space-to-tidal volume ratio, expired carbon dioxide, acute lung injury.* [Respir Care 2004;49(9):1008–1014. © 2004 Daedalus Enterprises]

Introduction

Compared to pulmonary oxygen transfer function, the ratio of dead space to tidal volume (V_D/V_T) has not been widely studied with regard to acute respiratory distress syndrome (ARDS). Although V_D/V_T in ARDS general-

ly[1–6] is between 0.35 and 0.55, substantially higher V_D/V_T ($\geq$ 0.60) has been reported.[7–10] The timing of dead-space measurements may be important to understanding the pathophysiologic evolution of ARDS. Elevated V_D/V_T generally is thought to be characteristic of the subacute phase of ARDS (beginning at approximately ARDS day 5–7) when microvascular obliteration becomes a prevalent feature.[11] However, we recently reported that V_D/V_T was markedly elevated within 24 h of the onset of ARDS and was particularly elevated in nonsurvivors at that early time point.[10]

SEE THE RELATED EDITORIAL ON PAGE 1006

In previous studies the timing of dead-space measurements was not specified[1,3,7,8] or measurements were made randomly within 7 days of ARDS onset.[4,5,9] Only 2 small studies[2,6] measured V_D/V_T over the course of ARDS and related V_D/V_T changes to mortality. Therefore, we prospectively made serial V_D/V_T measurements over the first 6 days of ARDS with a subset of 59 patients from our original study[10] who required mechanical ventilation for at

least 1 week. Our primary objective was to investigate whether V_D/V_T changed during the first 6 days of ARDS. Our secondary objectives included determining whether an elevated V_D/V_T beyond the first day of ARDS was associated with higher hospital mortality and the strength of relationship between V_D/V_T and other measures of pulmonary mechanics and gas exchange function.

Methods

We made serial V_D/V_T measurements with 59 patients who met American-European Consensus Conference criteria for ARDS[12] and who required at least 6 days of mechanical ventilation. Patients with a documented history of chronic obstructive pulmonary disease were excluded from the study. The primary etiologies of ARDS were pneumonia and sepsis (Table 1). Initial dead-space measurements were made within 24 h of meeting ARDS criteria[12] and were repeated on ARDS days 2, 3, and 6. As in the earlier study,[10] dead-space measurements were made when patients were on either volume-controlled ventilation or pressure-regulated, volume-controlled ventilation, with a target V_T of 10 ± 1 mL/kg of predicted body weight. Patients were studied in the absence of nursing care activities and when they were observed to be reasonably calm and synchronous with the ventilator.

The study was approved by our committee on human research and waiver of informed consent was granted because of the noninvasive nature of dead-space measurements, as in the earlier study.[10]

The fractional concentration of expired carbon dioxide (F_{eCO_2}) and the minute production of carbon dioxide ($\dot{V}_{CO_2}$) were measured with a metabolic monitor (Deltatrac, Sensormedics, Yorba Linda, California).[13] Both gas and baro-

metric pressure calibrations were done prior to each measurement. Mean expired carbon dioxide tension (P_{eCO_2}) was determined by multiplying the F_{eCO_2} by the barometric pressure (minus water vapor pressure). We used a 5-min expired gas collection period to determine P_{eCO_2} and $\dot{V}_{CO_2}$, with an arterial blood sample obtained at the mid-point of the 5-min interval, to determine the P_{aCO_2}.[13] All arterial blood gas samples were obtained from an indwelling arterial catheter. Mean P_{eCO_2} was corrected for compression volume dilution,[14] which is a method comparable in accuracy to physical segregation of expired gases.[15] As in our original study,[10] we recorded both uncorrected and corrected V_D/V_T values. The mechanical dead-space of the ventilator circuit was minimal ($\leq$ 10 mL). V_D/V_T was calculated using the Enghoff modification[16] of the Bohr equation:

$$V_D/V_T = [P_{aCO_2} - P_{eCO_2}] \div P_{aCO_2}$$

Quasi-static respiratory system compliance was calculated as the V_T (corrected for compression volume) divided by the end-inspiratory plateau pressure minus the positive end-expiratory pressure (PEEP). Minute ventilation ($\dot{V}_E$) was calculated using the V_T corrected for compression volume loss. Pulmonary oxygen transfer function was assessed by the ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}). Mean arterial blood pressure also was measured during the expired gas collection. We also collected daily clinical data from a ventilator status check performed during a reference period between 06:00 and 10:00 hours, for comparison. Outcome is reported at discharge from the study hospital.

Data are expressed as mean ± standard deviation. Multiple comparisons were made using either 1-way analysis of variance and the Tukey-Kramer test, or the Kruskal-Wallis and Dunn's tests.[17] Paired comparisons were made using the Mann-Whitney test.[17] Mortality risk on each day was assessed with the 2-sided Fisher's exact test. The Pearson product-moment correlation coefficient was calculated to determine the strength of association between V_D/V_T and variables such as V_T and mean arterial pressure.[17] Statistical analysis was done with commercially-available software (InStat version 3.0, GraphPad Software, San Diego, California). Differences were considered statistically significant when $p < 0.05$.

Results

Hospital mortality was 51% (30/59) and all the deaths occurred in the intensive care unit. The corrected V_D/V_T was significantly higher in nonsurvivors on days 1, 2, 3, and 6 (Fig. 1). Mean uncorrected V_D/V_T was 0.04 points higher than corrected measurements. When the uncorrected V_D/V_T values were used for statistical comparisons, the results were the same as those obtained with corrected

Table 1.   Characteristics of the Study Patients

Variable	Results
Age (y, mean ± SD)	46.6 ± 14.3
APACHE II score (mean ± SD)	21.6 ± 6.0
SAPS (mean ± SD)	42.1 ± 12.8
Lung injury score (mean ± SD)	2.70 ± 0.49
	Female: 13 (22%)
	Male: 46 (78%)
Primary Etiology of ARDS	Pneumonia: 21 (36%)
	Sepsis: 19 (32%)
	Trauma: 9 (15%)
	Aspiration: 7 (12%)
	Multiple transfusions: 2 (3%)
	Inhalation injury: 1 (2%)

APACHE = Acute Physiology and Chronic Health Evaluation
SAPS = simplified acute physiology score
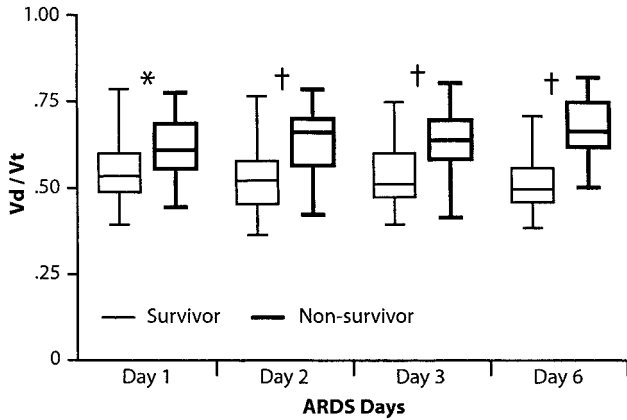ARDS = acute respiratory distress syndrome

Fig. 1. Changes in the ratio of pulmonary dead space to tidal volume (V_D/V_T) during the first 6 days of acute respiratory distress syndrome (ARDS). The boxes represent the 25–75% data interval. The horizontal lines within the boxes represent the mean V_D/V_T values. The error bars represent the 95% confidence intervals. * p < 0.05 between survivors and nonsurvivors on the same day. † = p < 0.001 between survivors and nonsurvivors on the same day.
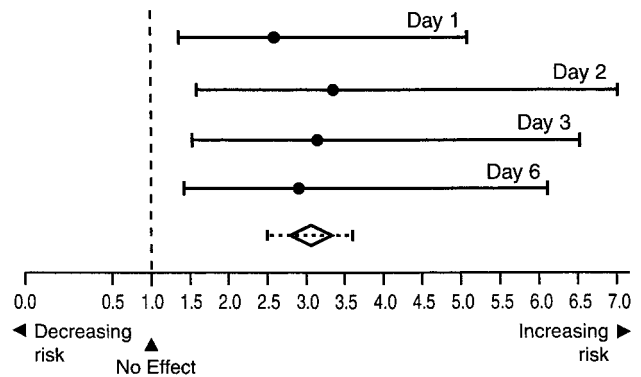

Fig. 2. Relative mortality risk on acute respiratory distress syndrome days 1, 2, 3, and 6 when the dead-space fraction (V_D/V_T) was > 0.55. The dots represent the mean odds ratios. The error bars represent the 95% confidence intervals. The diamond represents the average mortality risk, and the hatched-lined error bar represents the 95% confidence interval, during the first 6 days of acute respiratory distress syndrome.

Table 2. Differences in Dead-Space Fraction Between Survivors and Nonsurvivors by Etiology of Acute Respiratory Distress Syndrome

Category	Number of Patients	Dead-Space Fraction (mean ± SD)			
		Day 1	Day 2	Day 3	Day 6
Pneumonia S	9	0.57 ± 0.09	0.57 ± 0.08	0.57 ± 0.07	0.55 ± 0.07
Pneumonia NS	12	0.63 ± 0.09	0.64 ± 0.10	0.64 ± 0.10	0.68 ± 0.10
Sepsis S	8	0.50 ± 0.02	0.47 ± 0.04	0.47 ± 0.06	0.46 ± 0.03
Sepsis NS	11	0.61 ± 0.07*	0.63 ± 0.09*	0.64 ± 0.09	0.64 ± 0.07†
Aspiration S	2	0.50 ± 0.10	0.48 ± 0.06	0.52 ± 0.09	0.53 ± 0.09
Aspiration NS	5	0.62 ± 0.10	0.66 ± 0.04	0.62 ± 0.10	0.67 ± 0.10
Trauma S	8	0.51 ± 0.09	0.51 ± 0.09	0.52 ± 0.08	0.49 ± 0.09
Trauma NS	1	0.60	0.61	0.63	0.67

S = survivors
NS = non-survivors
*p < 0.05 compared to sepsis survivors
†p < 0.01 compared to sepsis survivors

measurements. Among nonsurvivors mean V_D/V_T was consistently > 0.60, whereas among survivors mean V_D/V_T was consistently < 0.55.

When the data were analyzed according to the primary cause of ARDS, there was no V_D/V_T difference (p = 0.08) between the patients with pneumonia (0.61 ± 0.09), sepsis (0.57 ± 0.08), aspiration (0.58 ± 0.11), and trauma (0.52 ± 0.09). In all 4 subgroups mean V_D/V_T was always > 0.60 among nonsurvivors, whereas mean V_D/V_T among survivors generally was between 0.46 and 0.53 (Table 2). The exception was survivors of pneumonia, who had a slightly higher mean V_D/V_T (0.55–0.57). However, the difference between survivors and nonsurvivors in the subgroups was significant only among patients with sepsis.

We also evaluated daily mortality risk based on a V_D/V_T cut-off value of 0.55. That value was chosen because the mean V_D/V_T among survivors was consistently < 0.55. When V_D/V_T was measured on ARDS days 1, 2, 3, and 6, the patients whose V_D/V_T was > 0.55 had significantly higher mortality risk (Fig. 2). The odds ratio for mortality was always > 2.50 in that group, and the lower boundary of the 95% confidence interval was always > 1.30.

Despite the significantly higher V_D/V_T among nonsurvivors, neither P_{aCO_2} nor $\dot{V}_E$ was different between nonsurvivors and survivors in either the acute (days 1, 2, and 3) or subacute (day 6) phase of ARDS (Fig. 3 and Table 3). However, $\dot{V}_{CO_2}$ was significantly lower among nonsurvivors on days 1, 2, and 3 (Fig. 4). Therefore, among nonsurvivors the effect of elevated V_D/V_T on $\dot{V}_E$ demand
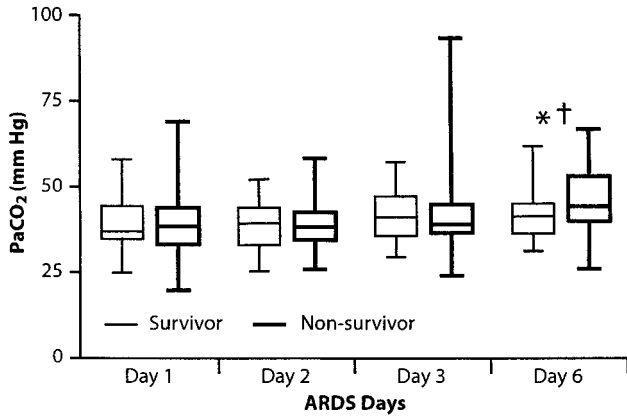
Fig. 3. P_{aCO_2} changes during the first 6 days of acute respiratory distress syndrome (ARDS). The boxes represent the 25–75% data interval. The horizontal lines within the boxes represent the mean P_{aCO_2} values. The error bars represent the 95% confidence intervals. Among nonsurvivors, an asterisk (*) signifies a p value < 0.05 when the P_{aCO_2} on day 6 is compared to day 1, whereas a dagger (†) signifies a p value < 0.01 when the P_{aCO_2} on day 6 is compared to day 2.
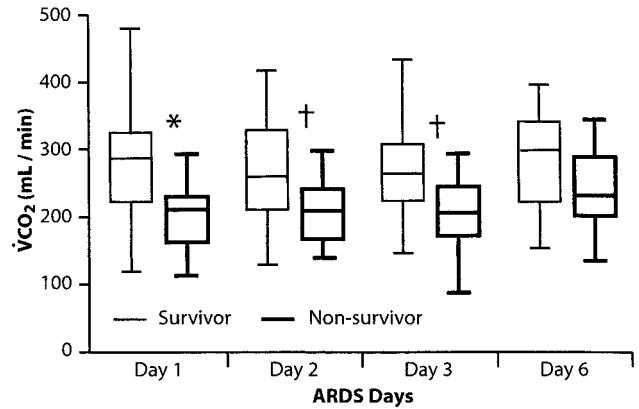

Fig. 4. Changes in the minute production of carbon dioxide ($\dot{V}_{CO_2}$) during the first 6 days of acute respiratory distress syndrome. The boxes represent the 25–75% data interval. The horizontal lines within the boxes represent the mean $\dot{V}_{CO_2}$ values. The error bars represent the 95% confidence intervals. * p < 0.05 between survivors and nonsurvivors on the same day. † = p < 0.001 between survivors and nonsurvivors on the same day.

Table 3. Differences in Pulmonary Oxygen Transfer Function and Pulmonary Mechanics: Survivors Versus Nonsurvivors of Acute Respiratory Distress Syndrome

Variable	Outcome	Day 1	Day 2	Day 3	Day 6
P_{aO_2}/F_{IO_2} (mm Hg)	S	153 ± 52	188 ± 71	177 ± 55	207 ± 43
	NS	125 ± 44	133 ± 70*	128 ± 52†	130 ± 72‡
PEEP (cm H$_2$O)	S	8.3 ± 3.3	8.7 ± 3.1	8.4 ± 3.4	7.5 ± 3.2
	NS	8.1 ± 3.1	9.5 ± 3.6	10.9 ± 3.7	11.1 ± 4.1§
P_{plat} (cm H$_2$O)	S	34.6 ± 6.6	33.7 ± 8.0	34.2 ± 7.9	29.2 ± 7.8
	NS	35.3 ± 7.2	36.7 ± 5.7	38.3 ± 7.2	37.7 ± 9.9‡
C_{RS} (mL/cm H$_2$O)	S	29.1 ± 11	32.5 ± 16.7	31 ± 12.5	34.2 ± 13.6
	NS	24.9 ± 7.3	24.5 ± 6.6	23.6 ± 12.7	26.5 ± 18.2
$\dot{V}_E$ (L/min)	S	13.3 ± 4.2	12.5 ± 3.7	12.1 ± 3.5	12.2 ± 3.6
	NS	11.3 ± 3.4	12.8 ± 3.6	12.3 ± 4.4	13.9 ± 3.6
V_T (mL/kg)	S	10.0 ± 1.6	10.0 ± 1.3	10.3 ± 1.8	9.5 ± 1.6
	NS	10.3 ± 1.6	10.3 ± 1.8	9.6 ± 2.1	9.7 ± 2.0

P_{aO_2}/F_{IO_2} = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
S = survivor
NS = nonsurvivor
P_{plat} = plateau pressure
C_{RS} = compliance of the respiratory system
$\dot{V}_E$ = minute volume
V_T = tidal volume
PEEP = positive end-expiratory pressure
*p < 0.01 compared to survivors on Day 2
†p < 0.05 compared to survivors on Day 3
‡p < 0.001 compared to survivor on Day 6
§p < 0.01 compared to survivors on Day 6

and P_{aCO_2} was offset by the corresponding decrease in $\dot{V}_{CO_2}$. By day 6 the $\dot{V}_{CO_2}$ of nonsurvivors was not different than that of the survivors. Both arterial pH and base excess were not different between the groups (Table 4).

Differences in P_{aO_2}/F_{IO_2} between nonsurvivors and survivors were not significant until day 2 (Table 3). Over the

first 6 days of ARDS the P_{aO_2}/F_{IO_2} did not change in nonsurvivors, whereas it improved significantly in survivors by day 6. PEEP was similar between nonsurvivors and survivors during the acute phase but was significantly higher in nonsurvivors by day 6. There was a moderate correlation between P_{aO_2}/F_{IO_2} and V_D/V_T (r = 0.57, p < 0.0001)

Table 4. Differences in Mean Arterial Blood Pressure and Acid-Base Balance: Survivors Versus Nonsurvivors of Acute Respiratory Distress Syndrome

Variable	Outcome	Day 1	Day 2	Day 3	Day 6
MAP (mm Hg)	S	73 ± 14	75 ± 14	76 ± 15	72 ± 14
	NS	75 ± 17	74 ± 13	77 ± 12	74 ± 14
Arterial pH	S	7.38 ± 0.07	7.39 ± 0.05	7.38 ± 0.07	7.40 ± 0.04
	NS	7.35 ± 0.11	7.35 ± 0.07	7.36 ± 0.08	7.36 ± 0.07
Base excess (mEq/dL)	S	-3.3 ± 5.5	-2.2 ± 3.6	-1.9 ± 3.2	-0.3 ± 3.7
	NS	-5.1 ± 5.0	-4.5 ± 5.0	-3.8 ± 4.3	-1.3 ± 5.5

MAP = mean arterial pressure
S = survivors
NS = non-survivors

but only a weak correlation between PEEP and V_D/V_T ($r = 0.36$, $p < 0.0001$).

Throughout the study V_T was the same both between nonsurvivors and survivors and within each subgroup over time. The V_T used to study V_D/V_T was not different from the V_T used for clinical management on day 1 (10.0 ± 1.4 vs 9.8 ± 1.5 mL/kg, respectively, $p = 0.26$). However, on study days 2, 3, and 6 the V_T used for clinical management exceeded the study V_T by approximately 1–1.5 mL/kg ($p < 0.05$).

Mean arterial pressure was indistinguishable between nonsurvivors and survivors throughout the study (Table 4) and there was only a weak correlation (-0.17, $p = 0.006$) between mean arterial pressure and V_D/V_T. Analysis by quartiles of mean arterial pressure revealed that V_D/V_T was different only between the first and fourth quartiles (0.61 ± 0.10 vs 0.56 ± 0.12, respectively, $p < 0.05$) with corresponding mean arterial pressure boundaries of 64 and 84 mm Hg.

Discussion

In this study we made serial measurements of V_D/V_T in patients with ARDS who required at least 6 days of mechanical ventilation. The V_D/V_T was markedly higher from the acute (ARDS days 1, 2, and 3) to the subacute phase (ARDS day 6) in patients who eventually died than in those who survived. That finding extends our previous finding that V_D/V_T is elevated in nonsurvivors within 24 h of ARDS onset.[10]

Only 2 studies have described the evolution of V_D/V_T over the course of ARDS. Shimada et al[2] found that peak V_D/V_T occurred by ARDS day 3 in survivors and then steadily decreased. In nonsurvivors V_D/V_T was markedly increased beginning on ARDS day 4 and remained high (≥ 0.65) until death. Valta et al[6] found that V_D/V_T was increased at ARDS onset but did not differentiate between nonsurvivors and survivors (0.56 and 0.55, respectively). However at recovery or death V_D/V_T was higher among nonsurvivors than among survivors (0.67 and 0.56, respectively). However, Shimada et al[2] described V_D/V_T changes in only 14 surgical patients, so their results probably do not represent the general ARDS population, particularly in light of the modified Consensus Conference definition.[12] Valta et al[6] measured V_D/V_T at 3 points in the disease course: onset, at the nadir of oxygen gas exchange (approximately ARDS day 3), and at the point of recovery/ death or placement on extracorporeal membrane oxygenation (ARDS days 15–25). Also, not all the patients had dead-space measurements made at each point in the study, so V_D/V_T at any particular point may not have been representative of the entire sample.

It is difficult to compare any of these studies because different techniques were used to measure dead space. Earlier studies measured mean P_{eCO_2} with the Douglas bag,[1,2,8] derived P_{eCO_2} from calculations based on the carbon dioxide content of mixed venous blood,[7] or used inert-gas ventilation-perfusion distribution data.[3] Later studies[4–6,9,10] used indirect calorimetry to calculate V_D/V_T, which is comparable to the Douglas bag technique.[13,18] However, even in some of those studies V_D/V_T was calculated indirectly, rather than using the Bohr equation.[4,5] Furthermore, some studies[2,8,10] controlled for the effects of circuit compression volume contamination (which artificially raises V_D/V_T), whereas others apparently did not.[1,4–6,9] With our patients the average difference between uncorrected and corrected V_D/V_T was 0.04.

A further uncertainty of those observational studies is that uncontrolled variables such as PEEP and V_T may have affected V_D/V_T. In previous studies V_T ranged between approximately 7 mL/kg[6,9] and 15 mL/kg.[1,8] In general, V_D/V_T is largely independent of V_T,[4,19,20] with only a slight decrease in the dead-space fraction with a higher V_T.[20] Kiiski et al[4] reported that V_D/V_T was independent of V_T when V_T was set between approximately 8 and 13 mL/kg. Yet the combination of relatively high V_T and PEEP may increase V_D/V_T, due to alterations in pulmonary perfusion,[1] either by reducing cardiac output[19] or by

causing regional pulmonary overdistention.[21,22] When PEEP is applied to acutely injured lungs, V_D/V_T decreases as the lung is recruited and increases only when the lung becomes over-distended.[1,23] We found that both V_T in mL/kg predicted body weight (r = −0.10, p = 0.10) and PEEP (r = 0.36, p < 0.0001) had only a weak correlation with V_D/V_T. Other variables that may correspond with lung over-distention, such as compliance of the respiratory system[1] (r = −0.18, p = 0.003) and end-inspiratory plateau pressure[24] (r = 0.22, p = 0.049) also had weak correlations with V_D/V_T. In contrast, there was a moderate correlation between P_{aO_2}/F_{IO_2} and V_D/V_T (r = 0.57, p < 0.0001). In part that may have reflected an overestimation of V_D/V_T in the presence of large intrapulmonary shunts, as P_{aCO_2} tends to overestimate pulmonary capillary P_{CO_2}.[25] The meaning of these relationships is a matter of conjecture, but an intriguing interpretation is that vascular-related phenomena such as microemboli or regional maldistribution of pulmonary blood flow may be more important than ventilator-related variables in determining V_D/V_T.

The fact that $\dot{V}_E$ and P_{aCO_2} were the same in both nonsurvivors and survivors during the acute phase was attributed to the lower $\dot{V}_{CO_2}$ in nonsurvivors, which probably offset the effects of elevated V_D/V_T. The clinical implication of that finding is that the presence of an abnormally high $\dot{V}_E$ and/or P_{aCO_2} should not be used to infer the presence of high V_D/V_T. Dead-space ventilation should be measured directly.

Elevated V_D/V_T in patients with ARDS probably reflects the interplay of several mechanisms. Dead space is influenced primarily by alterations in the distribution of pulmonary blood flow.[20] In patients with acute lung injury those alterations arise from 2 sources. First, shock causes either pulmonary hypoperfusion or hyperperfusion with concurrent maldistribution of pulmonary blood flow. The latter (more common in ARDS) is associated with hyperdynamic cardiovascular states (eg, severe sepsis, necrotizing pancreatitis, severe liver failure) that are known to transform substantial areas of the lung into regions of very high ventilation-to-perfusion.[7,26] Second, pulmonary vascular injury, which is a central feature of ARDS, increases pulmonary vascular resistance by causing vasoconstriction,[27] macro and micro thromboembolism from platelet and fibrin clots,[27] endothelial cell swelling,[28] mechanical compression of pulmonary capillaries from extravascular inflammation,[29] and microvascular obliteration from fibrosis.[30] All of those mechanisms can increase absolute alveolar dead space and/or convert substantial portions of the lung into zones of very high ventilation-to-perfusion. Both hemodynamic and vascular injury mechanisms would manifest as high V_D/V_T because of the crudeness of carbon dioxide dead-space measurement.[9]

When carbon dioxide is used as the tracer gas, dead space is overestimated because any degree of ventilation-perfusion imbalance lowers the P_{eCO_2}, thus increasing the calculated V_D/V_T.[31] More accurate estimates of V_D/V_T require the multiple inert gas elimination technique (MIGET) because it is sensitive enough to exclude most units of ventilation-to-perfusion mismatching (< 100/1) from the measurement.[31] MIGET, however, is complicated and clinically impractical. The few studies[3,9,31,32] that used MIGET to measure V_D/V_T in ARDS reported mean V_D/V_T of approximately 0.40 or less. The one study[9] that directly compared MIGET to the modified Bohr equation found that using carbon dioxide as the tracer-gas markedly overestimated V_D/V_T (0.37 ± 0.04 vs 0.64 ± 0.03, respectively). Therefore, elevated V_D/V_T in ARDS is properly understood as signifying a gross disturbance in pulmonary perfusion that probably represents some combination of elevated alveolar dead space as well as severe ventilation-perfusion mismatching.

Because we studied only patients who survived until at least day 6, sustained shock is unlikely to explain the association between V_D/V_T and mortality. Dead-space fraction was weakly associated with mean arterial pressure and was indistinguishable both between nonsurvivors and survivors and within each subgroup over time. However, the fact that V_D/V_T was significantly lower in the highest quartile of mean arterial pressure (≥ 84 mm Hg) suggests that some of the V_D/V_T elevation may have been related to suboptimal hemodynamics.

Early V_D/V_T elevation among nonsurvivors is consistent with other biochemical and physiologic studies of ARDS. Within 24 h of ARDS onset, markedly elevated procollagen peptide III levels have been found in the pulmonary edema fluid of nonsurvivors.[33] Procollagen peptide III, a biological marker of collagen synthesis and alveolar fibroblast activity, is thought to be an indicator of lung injury severity and probably presages fibrosing alveolitis.[33] In addition, nonsurvivors' pulmonary edema fluid has high levels of von Willebrand factor antigen (a marker of endothelial injury) at ARDS onset.[34] Pulmonary hypertension and increased pulmonary vascular resistance, primarily due to vascular obstruction,[35] have long been associated with severe ARDS and higher mortality.[29,35,36] Thus, the pronounced early V_D/V_T elevation in ARDS patients who die may be an indirect marker of the severity of pulmonary vascular injury.[10]

Conclusions

V_D/V_T was markedly elevated on the first day of ARDS in nonsurvivors and remained elevated between the acute and subacute phases of ARDS. In a univariate analysis, a V_D/V_T of > 0.55 during the first 6 days of ARDS was associated with a significantly higher mortality risk. Therefore, V_D/V_T measurements made beyond the first day of ARDS diagnosis may have prognostic value.

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