Prognostic Value of the Pulmonary Dead-Space Fraction During the Early and Intermediate Phases of Acute Respiratory Distress Syndrome

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BACKGROUND: Little is known about the alveolar dead-space fraction after the first week of acute respiratory distress syndrome (ARDS). We measured the dead-space fraction in the early phase (first week) and the intermediate phase (second week) of ARDS, and evaluated the association of dead-space fraction with mortality. METHODS: We prospectively measured dead-space fraction and other variables in 80 intubated patients during the early phase of ARDS and in 49 patients during the intermediate phase. We used multiple logistic regression analysis to evaluate data. The primary outcome was in-hospital mortality. RESULTS: In the early and intermediate phases the dead-space fraction was higher in patients who died than among those who survived (dead-space fraction 0.64 ± 0.09 vs 0.53 ± 0.11, *P* < .001, and 0.62 ± 0.09 vs 0.50 ± 0.10, *P* < .001, respectively). In both the early and intermediate phases the dead-space fraction was independently associated with a greater risk of death. For every dead-space-fraction increase of 0.05 the odds of death increased by 59% in the early phase (odds ratio 1.59, 95% confidence interval 1.18–2.16, *P* = .003) and by 186% in the intermediate phase (odds ratio 2.87, 95% confidence interval 1.36–6.04, *P* = .005). Age and Sequential Organ Failure Assessment score were also independently associated with a greater risk of death in both phases. CONCLUSIONS: Increased alveolar dead-space fraction in the early and intermediate phases of ARDS is associated with a greater risk of death. *Key words: acute respiratory distress syndrome; ARDS; respiratory dead space; mechanical ventilation; survival.* [Respir Care 2010;55(3):282–287.

Introduction

The acute respiratory distress syndrome (ARDS) is physiologically characterized by a right-to-left intrapulmonary shunt, which leads to hypoxemia,[1] and by an early increased physiologic dead-space fraction, which impairs carbon dioxide excretion.[2,3] Though the level of hypoxemia is not always correlated with mortality,[2,4-7] an early increase in dead-space fraction is a risk factor associated with higher mortality in ARDS patients.[2,4,5,8]

Approximately 60% of patients with ARDS fail to clinically improve and deteriorate after 1 week of mechanical ventilation.[9] Dead-space fraction remains elevated during the first week of ARDS[10,11] (the early phase), but little is known about dead-space and its relationship to outcome during the second week of ARDS (the intermediate phase). Only 2 studies (which included a small number of patients) have measured dead-space fraction over the course of ARDS and related it to mortality.[12,13]

We speculated that the measurement of dead-space fraction during the second week of ARDS could be useful as

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The authors have disclosed no conflicts of interest.

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a marker of the evolution of the illness. We measured the dead-space fraction in the early and intermediate phases of ARDS and evaluated its association with mortality.

Methods

Patients

We studied 80 patients with ARDS admitted to the intensive care unit of our tertiary-care center (Son Dureta University Hospital, Palma de Mallorca, Spain) from October 2005 to May 2008. The study protocol was approved by our institutional review board. Because the measurements were noninvasive, the informed-consent requirement was waived.

The inclusion criteria were: $\geq$ 18 years old, endotracheally intubated, receiving mechanical ventilation, and meeting the American-European Consensus Conference criteria for ARDS[14] (ratio of P_{aO_2} to fraction of inspired oxygen [F_{IO_2}] $\leq$ 200 mm Hg, bilateral opacities on chest radiograph, and either a pulmonary-artery wedge pressure of $\leq$ 18 mm Hg or absence of clinical evidence of left-atrial hypertension). The exclusion criteria were: obstructive or interstitial lung disease, pulmonary vascular disease, pleural drainage, and air leak.

Measurement of Dead-Space Fraction

Dead-space fraction was measured within 3 days of ARDS onset, and again on one of days 8–10, in those patients who remained mechanically ventilated.

The dead-space measurement was made on volume-controlled or pressure-support ventilation, while the patient was at rest and observed to be reasonably calm and synchronous with the ventilator. We measured the partial pressure of mixed expired carbon dioxide ($P_{\bar{E}CO_2}$) by collecting expired gas in a Douglas bag for 5 minutes, during which we also drew an arterial blood sample to measure P_{aCO_2}. We measured $P_{\bar{E}CO_2}$ and P_{aCO_2} with a blood gas analyzer (IL-1650, Instrument Laboratory, Izasa, Spain). We used a previously described method to correct the $P_{\bar{E}CO_2}$ for ventilator circuit compressible volume.[15,16] The compressible volume value applied to correct $P_{\bar{E}CO_2}$ was 2 mL/cm H_2O (measured compressible volume was 1.9–2.1 mL/cm H_2O). Tidal volume (V_T) was not adjusted for the measurement of dead space (V_D). We then calculated the dead-space fraction with the Enghoff modification[17] of the Bohr equation:

$$V_D/V_T = (P_{aCO_2} - P_{\bar{E}CO_2})/P_{aCO_2}$$

Low V_T was used in all patients, by adjusting V_T to achieve a plateau pressure < 33 cm H_2O.

Minute volume was measured with a Wright spirometer. Quasistatic respiratory compliance was calculated with standard methods from measurements made during the collection of expired carbon dioxide. It was calculated as the value obtained by dividing the difference between the V_T (in mL) and the volume compressed in the ventilator circuit (in mL) by the difference between the plateau pressure (in cm H_2O) and the positive end-expiratory pressure (in cm H_2O).

Carbon dioxide production per minute was calculated by multiplying the measured mixed expired carbon dioxide fraction ($F_{\bar{E}CO_2}$) by the minute volume. F_{eCO_2} was calculated as:

$$F_{\bar{E}CO_2} = P_{\bar{E}CO_2}/(\text{barometric pressure} - H_2O \text{ vapor pressure})$$

Data Collection

The following data were recorded: age, sex, weight, height, and severity of illness, evaluated with the Simplified Acute Physiology Score II (SAPS II) during the first day of intensive care unit stay,[18] the Sequential Organ Failure Assessment (SOFA) score,[19] and the Lung Injury Score[20] on the day of dead-space measurement. We also recorded comorbidities, such as diabetes, cirrhosis, chronic alcohol abuse, malignancy, and immunodeficiency (including human immunodeficiency virus infection or immunosuppressive therapy), the etiology of the ARDS, respiratory parameters of interest, use of vasopressors, and the use of activated protein C (in patients with septic shock). According to the etiology of ARDS, the lung injury may be direct, as occurs in pneumonia, aspiration of gastric contents, or near-drowning; or indirect, as occurs in sepsis, pancreatitis, or severe trauma.[21]

Statistical Analysis

Categorical data are expressed as numbers and percentages. Measurements and other recorded values are expressed as mean ± standard deviation. Differences between groups were compared with the independent Student's *t* test or the Mann-Whitney test for continuous data, and with the chi-square or 2-sided Fisher's exact tests for categorical data. Differences in dead-space fraction between the early and intermediate phases in patients treated with activated protein C were compared with the Wilcoxon rank test.

We used receiver-operating-characteristic curve analysis to assess the dead-space fraction as a sole predictor of survival/death. The threshold value was selected according to the minimum sum of false positive and false negative test results.[22] The accuracy of the threshold value was analyzed for sensitivity, specificity, positive predictive

Table 1. Clinical Characteristics of 80 Patients With Acute Respiratory Distress Syndrome

Age (mean ± SD y)	51 ± 18
Male (*n*, %)	54 (68)
Weight (mean ± SD kg)	76 ± 19
Ideal body weight (mean ± SD kg)	63 ± 11
Height (mean ± SD cm)	168 ± 10
SAPS II score (mean ± SD)	45 ± 16
SOFA score (mean ± SD)	9.6 ± 3.4
Lung injury score (mean ± SD)	2.8 ± 0.5
P_{aO_2}/F_{IO_2} (mean ± SD mm Hg)	153 ± 55
Direct lung injury (*n*, %)	66 (82)
Cause of ARDS (*n*, %)*	
Pneumonia	55 (69)
Aspiration	7 (9)
Sepsis	11 (14)
Trauma, or other	7 (9)
Comorbidities (*n*, %)	
Diabetes	15 (19)
Cirrhosis	10 (12)
Chronic alcohol abuse	18 (22)
Malignancy	15 (19)
Immunodeficiency	16 (20)

SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment
ARDS = acute respiratory distress syndrome
F_{IO_2} = fraction of inspired oxygen
* Percentages do not sum to 100 because of rounding.

Table 2. Variables Associated With a Greater Risk of Death in the Early Phase of Acute Respiratory Distress Syndrome

	Survivors (*n* = 45)	Non-survivors (*n* = 35)	*P*
Age (mean ± SD y)	44 ± 16	59 ± 17	< .001
SAPS II (mean ± SD)	39 ± 15	52 ± 16	< .001
SOFA score (mean ± SD)	8.4 ± 3.1	11.3 ± 3.2	< .001
Use of vasopressors (*n*, %)	30 (67)	29 (83)	.10
Use of activated protein C (*n*, %)	8 (18)	2 (6)	.17
Lung injury score (mean ± SD)	2.7 ± 0.5	2.9 ± 0.5	.22
PEEP (mean ± SD cm H_2O)	9.4 ± 3.7	10.0 ± 3.6	.50
Tidal volume (mean ± SD mL/kg IBW)	7.9 ± 2.6	7.7 ± 1.7	.76
Minute volume (mean ± SD L/min)	10.8 ± 2.8	11.5 ± 3.2	.28
Plateau pressure (mean ± SD cm H_2O)	26.3 ± 4.5	28.2 ± 6.4	.15
Quasistatic respiratory compliance (mean ± SD mL/cm H_2O)	30.5 ± 10.2	29.8 ± 12.1	.79
pH (mean ± SD)	7.39 ± 0.09	7.34 ± 0.10	.03
P_{aCO_2} (mean ± SD mm Hg)	42 ± 15	45 ± 8	.20
P_{aO_2}/F_{IO_2} (mean ± SD mm Hg)	162 ± 61	141 ± 44	.09
Dead-space fraction (mean ± SD)	0.53 ± 0.11	0.64 ± 0.09	< .001
CO_2 production (mean ± SD mL/min/kg of body weight)	3.4 ± 0.9	3.0 ± 0.8	.08

SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment
PEEP = positive end-expiratory pressure
IBW = ideal body weight

value, and negative predictive value. To determine the relationship between in-hospital mortality (dependent variable) and dead-space fraction (independent variable), we used a multiple logistic regression model to control for the effects of confounding variables. The logistic regression analysis results are reported as adjusted odds ratios with 95% confidence intervals (CIs). The variables included in the logistic regression were those with significance levels of $P < .20$ in the univariate analysis. We chose the variables on the basis of prior studies of outcomes in ARDS.[2,4,5,23] We performed the statistical analysis with statistics software (SPSS 15.0, SPSS, Chicago, Illinois).

Results

We collected the first measurements from 80 subjects within a mean 1.5 ± 0.8 days (range 1–3 days) of the onset of ARDS (Table 1). Forty-nine of those 80 subjects were subsequently measured again, at a mean 9.0 ± 1.1 days (range 8–10 days) after ARDS onset. The second set of measurements was not performed in 31 patients because the acute respiratory failure had resolved and they had been extubated (14 patients) or they had died (17 patients). Overall, 35 (44%) of the 80 subjects died (95% CI 33–55%). Eighteen of the 49 (37%) subjects studied in the intermediate phase died (95% CI 23–51%).

In the early phase of ARDS, age, SAPS II score, SOFA score, pH, and dead-space fraction were associated with a greater risk of death (Table 2 and Fig. 1). The early-phase dead-space fraction was independently associated with a greater risk of death in the multiple-regression analysis (Table 3). For every dead-space-fraction increase of 0.05, the odds of death increased by 59% (odds ratio 1.59, 95% CI 1.18–2.16, $P = .003$). Age and SOFA score were also independently associated with a greater risk of death (see Table 3). The Hosmer-Lemeshow test indicated that the model had good fit ($P = .64$). There were no interactions between or non-linearity in the continuous variables. The other variables (SAPS II, use of vasopressors or activated protein C, plateau pressure, pH, P_{aO_2}/F_{IO_2}, and CO_2 production) were not significant in the multiple logistic-regression model.

The area under the receiver-operating-characteristic curve of the dead-space fraction in the early phase to discriminate between non-survivors and survivors was 0.78 (95% CI 0.67–0.86). The early-phase dead-space threshold value with the fewest false classifications was 0.58, yielding a sensitivity of 80% (95% CI 70–88), a specific-

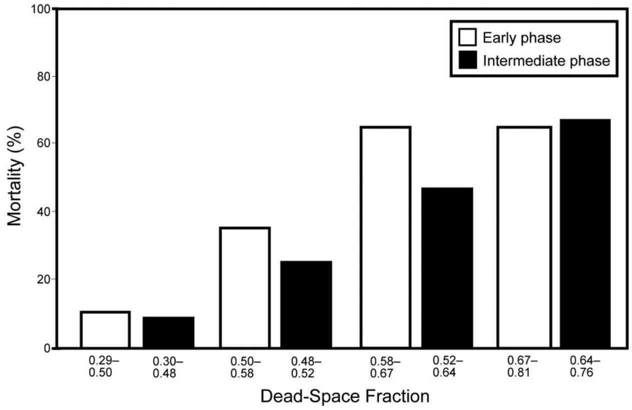

Fig. 1. Mortality according to the quartiles of dead-space fraction in 80 patients with early-phase acute respiratory distress syndrome and 49 patients with intermediate-phase acute respiratory distress syndrome.

Table 3. Odds Ratios for Variables Independently Associated With a Greater Risk of Death in the Early Phase of Acute Respiratory Distress Syndrome

	Odds Ratio	95% CI	*P*
Dead-space fraction, per increase of 0.05	1.59	1.18–2.16	.003
Age, per 1-year increase	1.06	1.02–1.10	.004
SOFA, per 1-point increase	1.44	1.17–1.77	.001

CI = confidence interval
SOFA = Sequential Organ Failure Assessment

ity of 69% (95% CI 58–79), a positive predictive value of 67%, and a negative predictive value of 82%.

In the intermediate phase, age, SAPS II, SOFA score, use of vasopressors, pH, P_{aCO_2}, and dead-space fraction were associated with a greater risk of death (Table 4 and Fig. 1). The intermediate-phase dead-space fraction was independently associated with a greater risk of death in the multiple-regression analysis (Table 5). For every dead-space-fraction increase of 0.05, the odds of death increased by 186% (odds ratio 2.87, 95% CI 1.36–6.04, $P = .005$). Age and SOFA score were also independently associated with a greater risk of death (see Table 5). The Hosmer-Lemeshow test indicated that the model had good fit ($P = .88$). There were no interactions between or non-linearity in the continuous variables. The other variables (SAPS II, use of vasopressors, lung injury score, pH, P_{aCO_2}, P_{aO_2}/F_{IO_2}, and CO_2 production) were not significant in the multiple logistic-regression model.

The area under the receiver-operating-characteristic curve of the dead-space fraction in the intermediate phase to discriminate between non-survivors and survivors was 0.80 (95% CI 0.66–0.90). The intermediate-phase dead-space threshold value with the fewest false classifications

Table 4. Variables Associated With a Greater Risk of Death in the Intermediate Phase of Acute Respiratory Distress Syndrome

	Survivors ($n = 31$)	Non-survivors ($n = 18$)	*P*
Age (mean ± SD y)	46 ± 17	59 ± 19	.02
SAPS II (mean ± SD)	39 ± 15	50 ± 12	.02
SOFA score (mean ± SD)	6.7 ± 3.2	10.5 ± 2.6	< .001
Use of vasopressors (*n*, %)	11 (36)	12 (67)	.04
Use of activated protein C (*n*, %)	4 (13)	0 (0)	.28
Lung injury score (mean ± SD)	2.5 ± 0.6	2.8 ± 0.7	.14
PEEP (mean ± SD cm H_2O)	8.5 ± 3.8	9.7 ± 4.0	.33
Tidal volume (mean ± SD mL/kg IBW)	7.6 ± 1.5	7.3 ± 1.5	.32
Minute volume (mean ± SD L/min)	11.7 ± 2.8	11.4 ± 3.1	.69
Plateau pressure (mean ± SD cm H_2O)	25.4 ± 4.4	27.7 ± 6.2	.24
Quasistatic respiratory compliance (mean ± SD mL/cm H_2O)	31.8 ± 9.7	27.6 ± 14.2	.24
pH (mean ± SD)	7.45 ± 0.06	7.38 ± 0.09	.003
P_{aCO_2} (mean ± SD mm Hg)	39 ± 10	47 ± 10	.008
P_{aO_2}/F_{IO_2} (mean ± SD mm Hg)	205 ± 76	169 ± 77	.13
Dead-space fraction (mean ± SD)	0.50 ± 0.10	0.62 ± 0.09	< .001
CO_2 production (mean ± SD mL/min/kg of body weight)	3.6 ± 0.8	3.2 ± 1.0	.14

SAPS = simplified acute physiology score
SOFA = sequential organ failure assessment
PEEP = positive end expiratory pressure
IBW = ideal body weight

Table 5. Odds Ratios for Variables Independently Associated With a Greater Risk of Death in the Intermediate Phase of Acute Respiratory Distress Syndrome

	Odds Ratio	95% CI	*P*
Dead-space fraction, per increase of 0.05	2.87	1.36–6.04	.005
Age, per 1-year increase	1.09	1.01–1.18	.03
SOFA, per 1-point increase	2.35	1.22–4.53	.01

CI = confidence interval
SOFA = sequential organ failure assessment

was 0.62, yielding a sensitivity of 61% (95% CI 46–75), specificity of 84% (95% CI 71–93), a positive predictive value of 69%, and a negative predictive value of 79%.

We found no significant differences in dead-space fraction between direct and indirect lung injury in the early phase (0.58 ± 0.11 and 0.55 ± 0.10, respectively, $P = .41$) or the intermediate phase (0.54 ± 0.11 and 0.55 ± 0.10, respectively, $P = .98$). The dead-space in the 4 patients treated with activated protein C and with 2 measurements (Table 4) was 0.64 ± 0.07 in the early phase and 0.59 ± 0.15 in the intermediate phase (P = .27).

Discussion

In this study, an increased physiologic dead-space fraction in the early and intermediate phases of ARDS was associated with a higher risk of death. Our results are consistent with the findings of Nuckton et al,[2] who measured dead space on the first day, and Kallet et al,[10] who measured dead space during the first 6 days of ARDS. We analyzed dead-space fraction and mortality at fixed time points. Our results must be considered in light of the fact that our first analysis applies only to intubated patients surviving at ARDS day 3, and the second analysis applies only to intubated patients surviving at ARDS days 8–10. We considered the early phase the first week of ARDS and the intermediate phase the second week, as defined by Gattinoni et al,[24] but this indicates only arbitrary time progress, and not pathophysiologic evolution, because the evolution of diffuse alveolar damage is highly variable, and fibroproliferation occurs early in ARDS.[25]

Our dead-space-fraction threshold values to discriminate survivors and non-survivors are in accordance with other studies that suggest that a dead-space fraction of ≥ 0.60 is associated with more severe lung injury[24,26,27] and that a sustained dead-space elevation is characteristic in non-survivors.[10,12,13] The area under the receiver-operating-characteristic curve of dead-space fraction to discriminate survivors and non-survivors was similar in the early phase and intermediate phase of ARDS.

Similar to a study by Cepkova et al,[8] we did not find differences between dead-space fraction in patients with direct and indirect lung injury. In 4 patients with concomitant septic shock and receiving treatment with activated protein C we found a trend toward a reduced dead-space fraction, similar to Liu et al.[11]

The increase in physiologic dead-space in ARDS could be due to injury of pulmonary capillaries by thrombotic and inflammatory mechanisms,[28,29] obstruction of pulmonary blood flow in the extra-alveolar pulmonary circulation,[30,31] and areas with a high ventilation/perfusion ratio, which may impair carbon dioxide clearance.[27,32] The measurement of dead-space fraction could be of interest because it may reflect the extent of pulmonary vascular injury in patients with ARDS.[2] Respiratory compliance was non-significantly lower in non-survivors, which is contrary to the results of Nuckton et al,[2] but similar to the findings of other studies.[4,5,23]

Limitations

First, we studied a relatively small number of patients, so the coefficients of the regression model may be biased, due to the few events per predictor variable present in our data.[33]

Second, under optimal conditions, measurement of dead-space has a precision of 0.05.[34] The precision of physiologic dead-space measurement makes detection of changes less than 0.05 difficult.

Third, 43% of the subjects (11 who survived and 10 who died) were treated with corticosteroids for septic shock, and it is not known whether or not corticosteroids affect the course of dead-space-fraction changes. Some patients were also treated with activated protein C, which can reduce dead-space fraction by its anticoagulant and profibrinolytic properties.[11]

Fourth, several factors can affect the dead-space-fraction measurement. To calculate the dead-space fraction we used the Enghoff modification[15] of the Bohr equation, corrected for the dilution of expired gas by the compressible volume of the ventilator circuit.[16] This fact should not influence the measurement, since this method is comparable to physical segregation of expired gases.[17] In our study the mean difference between the corrected and uncorrected dead-space values was 0.05 (data not shown), which is similar to the study by Nuckton et al.[2] Other possible causes were an uncontrolled variability of V_T and positive end-expiratory pressure, but they were similar in the survivors and the non-survivors. Moreover, dead-space fraction is independent of V_T,[35] particularly when V_T is set in the narrow range of the lung-protective strategy.[36] Also, changes in the positive end-expiratory pressure usually do not significantly change the dead-space fraction.[37,38]

Conclusions

Our findings are consistent with results from previous studies and confirm that a higher alveolar dead-space fraction in early and intermediate phases of ARDS is associated with a greater risk of death.

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