

## PULMONARY DEAD-SPACE FRACTION AS A RISK FACTOR FOR DEATH IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

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### ABSTRACT

**Background** No single pulmonary-specific variable, including the severity of hypoxemia, has been found to predict the risk of death independently when measured early in the course of the acute respiratory distress syndrome. Because an increase in the pulmonary dead-space fraction has been described in observational studies of the syndrome, we systematically measured the dead-space fraction early in the course of the illness and evaluated its potential association with the risk of death.

**Methods** The dead-space fraction was prospectively measured in 179 intubated patients, a mean ( $\pm$ SD) of  $10.9 \pm 7.4$  hours after the acute respiratory distress syndrome had developed. Additional clinical and physiological variables were analyzed with the use of multiple logistic regression. The study outcome was mortality before hospital discharge.

**Results** The mean dead-space fraction was markedly elevated ( $0.58 \pm 0.09$ ) early in the course of the acute respiratory distress syndrome and was higher among patients who died than among those who survived ( $0.63 \pm 0.10$  vs.  $0.54 \pm 0.09$ ,  $P < 0.001$ ). The dead-space fraction was an independent risk factor for death: for every 0.05 increase, the odds of death increased by 45 percent (odds ratio, 1.45; 95 percent confidence interval, 1.15 to 1.83;  $P = 0.002$ ). The only other independent predictors of an increased risk of death were the Simplified Acute Physiology Score II, an indicator of the severity of illness (odds ratio, 1.06; 95 percent confidence interval, 1.03 to 1.08;  $P < 0.001$ ) and quasistatic respiratory compliance (odds ratio, 1.06; 95 percent confidence interval, 1.01 to 1.10;  $P = 0.01$ ).

**Conclusions** Increased dead-space fraction is a feature of the early phase of the acute respiratory distress syndrome. Elevated values are associated with an increased risk of death. (N Engl J Med 2002;346:1281-6.)

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**T**HE acute respiratory distress syndrome is an important cause of acute respiratory failure and has a high mortality rate.<sup>1-5</sup> Despite 30 years of research into the causes and consequences of the acute respiratory distress syndrome, efforts to identify a reliable, pulmonary-specific risk factor for death have been disappointing. Variables that are independently associated with mortality are qualitative or not specific to abnormalities of pulmo-

nary pathophysiology, such as sepsis, nonpulmonary organ system dysfunction, age, and cirrhosis.<sup>4-7</sup> Although indexes of hypoxemia, such as the partial pressure of arterial oxygen ( $\text{PaO}_2$ ), the fraction of inspired oxygen ( $\text{FiO}_2$ ), and the ratio of  $\text{PaO}_2$  to  $\text{FiO}_2$ , were initially thought to have prognostic value,<sup>3,8</sup> subsequent studies established that these variables were not independently associated with the risk of death when they were measured early in the course of the acute respiratory distress syndrome.<sup>4-6</sup>

Abnormalities of pulmonary blood flow and injury to the microcirculation are characteristic features of clinical lung injury.<sup>9-11</sup> If, as a result, pulmonary blood flow is compromised to lung regions that remain well ventilated, the expected consequence would be an increase in the physiological dead space. Pulmonary dead space is the component of ventilation that is wasted because it does not participate in gas exchange, and an increase in dead space represents an impaired ability to excrete carbon dioxide. Other investigators have reported an increase in the dead-space fraction in patients with the acute respiratory distress syndrome,<sup>12-14</sup> but the measurements were not all made early in the clinical course, the number of patients studied was small, and the relation with mortality was not examined. Therefore, in this large prospective study, we collected data on several pulmonary physiological variables, including the dead-space fraction, to test for independent associations with mortality.

### METHODS

#### Patients

Patients were studied at the University of California Moffitt-Long Hospital, a tertiary university referral center, and at San Francisco General Hospital, a large, inner-city hospital and trauma center, from January 1998 through April 2000. The protocol was approved by the institutional review board of the University of California, San Francisco. Given the noninvasive nature of the measurement of the dead-space fraction and the routine use of similar procedures for nutritional assessment, the requirement for informed consent was waived by the institutional review board.

Patients who were at least 18 years of age, intubated, and re-

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ceiving positive-pressure ventilation were eligible if they met the American–European consensus definition of the acute respiratory distress syndrome<sup>15</sup>: a PaO<sub>2</sub>:FiO<sub>2</sub> ratio of 200 or less, bilateral opacities on the chest radiograph, and either a pulmonary-artery wedge pressure of 18 mm Hg or less or the absence of clinical evidence of left atrial hypertension. Patients who were known to have obstructive lung disease, interstitial lung disease, pulmonary vascular disease, or a history of more than 60 pack-years of smoking were excluded. Patients were enrolled a mean (±SD) of 10.9±7.4 hours after they met the inclusion criteria.

### Measurement of Dead-Space Fraction

To calculate dead space, the mean expired carbon dioxide fraction was measured with a bedside metabolic monitor (Deltatrac, Sensor-Medics, Yorba Linda, Calif.). Metabolic monitoring is noninvasive, is used widely for metabolic and nutritional assessment,<sup>16,17</sup> and is as accurate as other methods of the measurement of expired carbon dioxide.<sup>18,19</sup> Expired gas was collected for five minutes, during which time an arterial blood gas measurement was made. The dead-space fraction was calculated with use of the Enghoff modification of the Bohr equation<sup>20–22</sup>: dead-space fraction = (PaCO<sub>2</sub>–PECO<sub>2</sub>) ÷ PaCO<sub>2</sub>, where PECO<sub>2</sub> is the partial pressure of carbon dioxide in mixed expired gas and is equal to the mean expired carbon dioxide fraction multiplied by the difference between the atmospheric pressure and the water-vapor pressure. The dead-space fraction is considered to be normal if it does not exceed 0.3.<sup>22</sup> Dead space per kilogram of ideal body weight was calculated by multiplying the dead-space fraction by the ratio of the tidal volume to the ideal body weight.<sup>2</sup>

Standard disposable ventilator circuits were used (compressible volume, 2.5 to 2.8 ml per centimeter of water). Initial calculated values of the dead-space fraction included the compressible volume of the circuit. Corrected estimates for compressible volume were also made, with the use of previously described methods.<sup>23</sup> Tidal volumes were standardized with the use of volume-controlled modes of ventilation, with or without pressure regulation. Since prior studies have indicated that dead-space measurements can be altered by different tidal volumes,<sup>24–26</sup> expired carbon dioxide was collected at a standard tidal volume (mean, 10.0±1.4 ml per kilogram). Thus, the tidal volumes for some patients were altered 10 minutes before and during the measurement of expired carbon dioxide; the original tidal volume was then resumed. Although the respiratory rate was adjusted to maintain minute ventilation if the tidal volume was changed, no changes in positive end-expiratory pressure or in other ventilator settings were made.

Quasistatic respiratory compliance was calculated from measurements obtained at the time of the collection of expired carbon dioxide with the use of standard methods. The quasistatic respiratory compliance was calculated as the value obtained by dividing the difference between the tidal volume (in milliliters) and the volume compressed in the ventilator circuit (in milliliters) by the difference between the plateau pressure (in centimeters of water) and the positive end-expiratory pressure (in centimeters of water).

### Statistical Analysis

The outcome variable was death before a patient was discharged from the hospital and was breathing without assistance, as in a recent clinical trial.<sup>2</sup> SAS computer software (SAS Institute, Cary, N.C.) was used for the analysis.

Logistic-regression analysis was used to examine multiple variables individually for a possible association with mortality. A complete list is provided in the Supplementary Appendix, available with the full text of this article at <http://www.nejm.org>. Variables were chosen on the basis of prior studies of outcomes in the acute respiratory distress syndrome<sup>4–6,27–30</sup> and potential clinical and physiological significance. The Simplified Acute Physiology Score II (SAPS II) was used to assess the severity of illness. This score is com-

posed of 17 variables, including the reason for admission (scheduled surgery, unscheduled surgery, or medical care), the presence or absence of underlying diseases, and laboratory measurements. Scores can range from 0 to 163, and higher scores indicate a higher risk of death. This instrument was designed specifically for the assessment of patients in the intensive care unit<sup>28</sup> and was independently predictive of the risk of death in a prior study of the acute respiratory distress syndrome.<sup>6</sup> Pearson product-moment and Spearman rank correlations were used to examine the relation between the dead-space fraction and other variables, and unpaired t-tests were used to compare mean values between survivors and patients who died.

Multiple logistic regression was used to identify the variables that were independently associated with death. Each variable with a significant association (P<0.05) and additional variables that were not significant but had potential clinical importance (Table 1)

**TABLE 1. CLINICAL CHARACTERISTICS OF 179 PATIENTS WITH THE ACUTE RESPIRATORY DISTRESS SYNDROME.\***

CHARACTERISTIC	VALUE
Age — yr	48±15
PaO <sub>2</sub> :FiO <sub>2</sub>	147±61
SAPS II†	47±17
Clinical disorder associated with the acute respiratory distress syndrome — no. of patients (%)	
Sepsis	45 (25)
Aspiration	19 (11)
Pneumonia	55 (31)
Trauma, overdose, fat emboli, or idiopathic	60 (34)
Reason for admission — no. of patients (%)	
Scheduled surgery	10 (6)
Unscheduled surgery	67 (37)
Medical	102 (57)
Underlying medical illness — no. of patients (%)	
Acquired immunodeficiency syndrome	27 (15)
Metastatic carcinoma (solid tumor)	5 (3)
Hematologic cancer	13 (7)
Liver transplantation	11 (6)
Bone marrow transplantation	9 (5)
Diabetes mellitus	26 (15)
Cirrhosis	28 (16)
Low-volume ventilation protocol — no. of patients (%)‡	31 (17)
Tidal volume — ml/kg of ideal body weight§	10.0±1.4
Quasistatic respiratory compliance — ml/cm of water	30.9±11.1
Minute ventilation — liters/min	12.1±4.3
Dead-space fraction¶	0.58±0.10
Absolute dead space — ml/kg of ideal body weight¶	6.5±1.4

\*Plus–minus values are means ±SD. Because of rounding, not all percentages total 100. PaO<sub>2</sub> denotes the partial pressure of arterial oxygen, and FiO<sub>2</sub> the fraction of inspired oxygen.

†The Simplified Acute Physiology Score II (SAPS II)<sup>28</sup> was used to assess the severity of illness. Possible scores range from 0 to 163, with higher scores indicating more severe impairment.

‡The low-volume ventilation protocol used a tidal volume of 6 ml per kilogram of ideal body weight, which has previously been shown to be beneficial.<sup>2</sup>

§The standardized tidal volume that was used for the measurement of the dead-space fraction was not necessarily the tidal volume used for patient care.

¶The measurement includes the compressible volume of the ventilator circuit.

were introduced into a forward, stepwise, logistic-regression model. The variables of the dead-space fraction and the dead space per kilogram of ideal body weight were modeled separately, and the odds ratio for death was calculated for increments of 0.05 in the dead-space fraction. For simplicity, values for dead-space fraction and dead space per kilogram of ideal body weight included the compressible volume of the ventilator circuit. The multiple logistic-regression analysis was also repeated with the use of the dead-space fraction corrected for the compressible volume of the ventilator circuit. To determine whether the relation between the dead-space fraction and the risk of death was different in patients who received a low tidal volume as part of a lung-protection strategy,<sup>2</sup> a test for interaction was done. The goodness of fit of the logistic-regression model was assessed with the Hosmer–Lemeshow test.<sup>31</sup>

## RESULTS

A diverse group of 179 patients with various clinical disorders associated with the development of the acute respiratory distress syndrome was studied a mean of  $10.9 \pm 7.4$  hours after meeting the inclusion criteria (Table 1). The dead-space fraction was markedly elevated in these patients ( $0.58 \pm 0.10$ ).

Overall, 75 of 179 patients died (42 percent; 95 percent confidence interval, 35 to 49 percent). Several of the base-line variables were associated with an increased risk of death (Table 2). All variables listed in Table 2 were introduced into the forward, stepwise, multiple logistic-regression model. Other variables, including minute ventilation, the respiratory rate, the tidal volume, and the positive end-expiratory pressure, were not significant in single-variable models and were not introduced into the multiple logistic-regression model.

The mean dead-space fraction was significantly higher in patients who died than in those who survived ( $0.63 \pm 0.09$  vs.  $0.54 \pm 0.09$ ,  $P < 0.001$ ). The risk of death increased as the dead-space fraction increased (Fig. 1). The observed mortality according to the quintile of the dead-space fraction was similar to the mortality predicted by logistic regression, and the Hosmer–Lemeshow test indicated that the fit of the model was good ( $P = 0.44$ ). Most important, the dead-space fraction was independently associated with an increased risk of death in the multiple-regression analysis (Table 3). For every increase of 0.05 in the dead-space fraction, the odds of death increased by 45 percent (odds ratio, 1.45; 95 percent confidence interval, 1.15 to 1.83;  $P = 0.002$ ).

The mean positive end-expiratory pressure was similar among patients who died and those who survived ( $8.8 \pm 3.4$  and  $8.2 \pm 3.2$  cm of water, respectively). The dead-space fraction was only weakly associated with the level of positive end-expiratory pressure ( $r = 0.22$ ,  $P = 0.003$ ) and the level of peak inspiratory pressure ( $r = 0.27$ ,  $P < 0.001$ ), and it was not associated with the time from the diagnosis of the acute respiratory distress syndrome to the measurement of the dead-space fraction ( $r = -0.05$ ,  $P = 0.48$ ). The pos-

**TABLE 2.** VARIABLES ASSOCIATED WITH AN INCREASED RISK OF DEATH.\*

VARIABLE	PATIENTS WHO SURVIVED (N=104)	PATIENTS WHO DIED (N=75)	P VALUE†
PaO <sub>2</sub> :FiO <sub>2</sub>	163±63	123±51	<0.001
pH	7.41±0.07	7.36±0.12	<0.001
Quasistatic respiratory compliance — ml/cm of water	33.6±12.0	27.2±8.5	<0.001
Lung-injury score‡	2.2±0.6	2.6±0.6	<0.001
Oxygenation index§	11.4±6.1	17.2±10.8	<0.001
SAPS II¶	41±15	55±15	<0.001
Acquired immunodeficiency syndrome — no. of patients (%)	8 (8)	19 (25)	0.002
Sepsis — no. of patients (%)	32 (31)	38 (51)	0.008
Medical reason for admission — no. of patients (%)	52 (50)	50 (67)	0.03
Use of vasopressors — no. of patients (%)**	23 (23)	36 (48)	<0.001
Low-volume ventilation protocol — no. of patients (%)††	24 (23)	7 (9)	0.02
Nonpulmonary organ system dysfunction‡‡			
No. of organ systems involved	1.1±1.2	1.5±1.2	0.04
Dysfunction of any organ system	65 (62)	57 (76)	0.06
Hepatic dysfunction	17 (16)	21 (28)	0.06
Hematologic dysfunction	30 (29)	31 (41)	0.08
Neurologic dysfunction	21 (20)	24 (32)	0.07
Cirrhosis — no. of patients (%)	12 (12)	16 (21)	0.08
Dead-space fraction§§	0.54±0.09	0.63±0.09	<0.001
Absolute dead space — ml/kg of ideal body weight§§	6.0±1.3	7.2±1.3	<0.001

\*Plus-minus values are means ±SD. PaO<sub>2</sub> denotes the partial pressure of arterial oxygen, and FiO<sub>2</sub> the fraction of inspired oxygen.

†P values were obtained by bivariate logistic-regression analysis.

‡The lung-injury score can range from 0 to 4, with higher values indicating more severe injury.

§The oxygenation index was calculated with use of the following equation: (mean airway pressure × FiO<sub>2</sub> × 100) ÷ PaO<sub>2</sub>.

¶The Simplified Acute Physiology Score II (SAPS II)<sup>28</sup> was used to assess the severity of illness. Possible scores range from 0 to 163, with higher scores indicating more severe impairment.

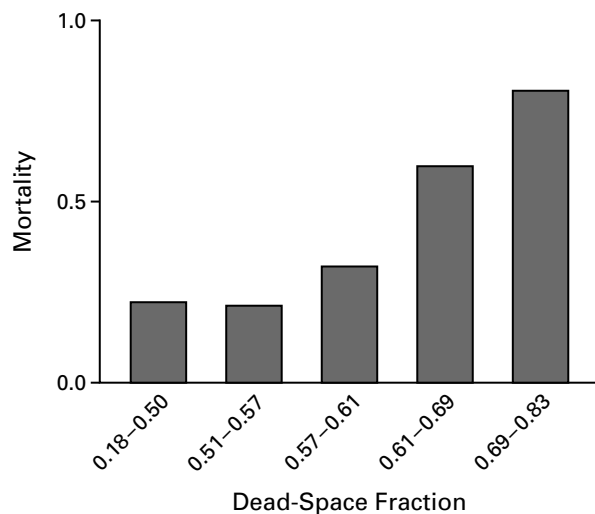
||Sepsis was also classified independently from the analysis of the primary cause of the acute respiratory distress syndrome and was based on a previously used definition.<sup>4</sup>

\*\*Data were missing for two patients who survived.

††The low-volume ventilation protocol used a tidal volume of 6 ml per kilogram of ideal body weight, which has previously been shown to be beneficial.<sup>2</sup>

‡‡Nonpulmonary organ system dysfunction included hepatic, renal, hematologic, central nervous system, and cardiac dysfunction (see Supplementary Appendix 1). The values for cardiac and renal dysfunction did not approach statistical significance ( $P = 0.71$  and  $P = 0.62$ , respectively).

§§The measurements include the compressible volume of the ventilator circuit.



**Figure 1.** The Observed Mortality According to the Quintile of Dead-Space Fraction in 179 Patients with the Acute Respiratory Distress Syndrome.

The quintiles were derived from the logistic-regression analysis. The observed mortality was similar to the mortality predicted by logistic regression; the Hosmer–Lemeshow test indicated that the fit of the model was good ( $P=0.44$ ). The overlap in the dead-space–fraction values is related to rounding and to the fact that the values were identical in some patients.

itive end-expiratory pressure was not associated with an increased risk of death (odds ratio, 1.06; 95 percent confidence interval, 0.97 to 1.16;  $P=0.23$ ), nor was the time from diagnosis to the measurement of the dead-space fraction (odds ratio, 0.99; 95 percent confidence interval, 0.96 to 1.04;  $P=0.76$ ). The association between the dead-space fraction and an increased risk of death was not affected by the use of a low tidal volume as a lung-protection strategy<sup>2</sup> ( $P$  for interaction = 0.46).

The substitution of the dead space per kilogram of ideal body weight for the dead-space fraction in the multiple logistic-regression model yielded similar results (odds ratio, 1.69; 95 percent confidence interval, 1.23 to 2.32;  $P=0.001$ ). When the measurements of the dead-space fraction were corrected for the compressible volume of the circuit, the mean dead-space fraction was  $0.53 \pm 0.11$ . An analysis that used the corrected values for the dead-space fraction yielded only minor differences in the results (odds ratio, 1.39; 95 percent confidence interval, 1.14 to 1.71;  $P=0.002$ ).

SAPS II<sup>28</sup> and quasistatic respiratory compliance were the only other variables that were independently associated with an increased risk of death. The odds

**TABLE 3.** ODDS RATIOS FOR VARIABLES INDEPENDENTLY ASSOCIATED WITH AN INCREASED RISK OF DEATH.\*

VARIABLE	ODDS RATIO (95% CI)	P VALUE
Dead-space fraction (per increase of 0.05)†	1.45 (1.15–1.83)	0.002
SAPS II (per 1-point increase)	1.06 (1.03–1.08)	<0.001
Quasistatic respiratory compliance (per decrease of 1 ml/cm of water)	1.06 (1.01–1.10)	0.01

\*Results were calculated with the use of stepwise, forward, multiple-logistic regression. The odds of death increased as the dead-space fraction and the Simplified Acute Physiology Score II (SAPS II) increased and as quasistatic respiratory compliance decreased. CI denotes confidence interval.

†Measurements of the dead-space fraction include the compressible volume of the ventilator circuit.

of death increased as the SAPS II increased and as compliance decreased (Table 3).

## DISCUSSION

Classically, right-to-left intrapulmonary shunt leading to arterial hypoxemia has been considered the primary physiological abnormality in early acute lung injury.<sup>1,32,33</sup> However, our findings indicate that a substantial increase in alveolar dead space occurs very early in the course of the acute respiratory distress syndrome, to an extent not previously appreciated. Possible mechanisms include injury of pulmonary capillaries by thrombotic and inflammatory mechanisms,<sup>10,11,34</sup> obstruction of pulmonary blood flow in the extraalveolar pulmonary circulation,<sup>9</sup> and areas with a high ratio of ventilation to perfusion, which may impair the excretion of carbon dioxide.<sup>13,33</sup> A recent study showed that patients with the acute respiratory distress syndrome who died, as compared with those who survived, had higher levels of von Willebrand factor antigen,<sup>35</sup> a marker of endothelial injury,<sup>27</sup> in pulmonary edema fluid and plasma. Thus, the increase in the dead-space fraction may reflect the extent of pulmonary vascular injury. Regardless of the mechanism, it is now clear that both altered excretion of carbon dioxide and impaired oxygenation are characteristic physiological abnormalities of the early phase of this syndrome.

The association of dead space with the risk of death was similar whether dead space was expressed as the dead-space fraction or as the dead space per kilogram of ideal body weight. The use of either variable is acceptable, provided that a standard tidal volume is used during measurements of expired carbon dioxide. Correction of the measured dead-space fraction for the compressible volume of the ventilator circuit did not substantially alter the results. Thus, the

use of uncorrected values (which involve fewer calculations) may be simpler to implement in clinical settings and is adequate for measuring the dead-space fraction, provided that a standard circuit is used.

In some experimental studies of acute lung injury, positive end-expiratory pressure improved the elimination of carbon dioxide and decreased the dead-space fraction.<sup>36,37</sup> In subsequent studies in animals and humans, however, incremental changes in the positive end-expiratory pressure did not result in significant or consistent changes in the dead-space fraction.<sup>13,38</sup> We found that the positive end-expiratory pressure was not associated with an increased risk of death and was minimally associated with the dead-space fraction. Thus, the level of positive end-expiratory pressure did not have an important effect on either the measurements of the dead-space fraction or the association of the dead-space fraction with an increased risk of death.

For every increase of 0.05 in the dead-space fraction, the odds of death increased by 45 percent. Data from prior observational studies suggest that a value of 0.60 or higher may be associated with more severe lung injury.<sup>12-14</sup> In our study, the mortality was highest in the three highest quintiles of the dead-space fraction ( $\geq 0.57$ ), although this study was not designed to evaluate a specific cutoff value.

We found that respiratory compliance and the SAPS II were also predictive of an increased risk of death. In prior studies, respiratory compliance has not been independently predictive when it was measured early in the acute respiratory distress syndrome.<sup>4-6</sup> Our finding may be explained in part by the use of a standardized tidal volume. From a mechanistic perspective, respiratory compliance may be significantly lower in patients with higher mortality because patients with less compliant lungs may have more severe pulmonary edema and reduced concentrations of functional surfactant.

Beside measurement of the dead-space fraction at the time of the diagnosis of the acute respiratory distress syndrome may provide clinicians with useful prognostic information early in the course of illness and may be particularly valuable given that the American-European consensus definition of the acute respiratory distress syndrome<sup>15</sup> is based on variables that do not predict the risk of death.<sup>39-43</sup> Measurement of the dead-space fraction could help clinical investigators identify the patients who may benefit most from a particular therapeutic intervention. The dead-space fraction could also be used prospectively in future clinical trials, particularly when the goal is to evaluate the benefit of a treatment in the most severely ill patients.

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