Prognostic Value of Pulmonary Dead-Space Fraction and other Physiological Parameters in Patients with the Acute Respiratory Distress Syndrome

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Abstract
Background: *Physiologic dead-space fraction (DSF) (ratio of dead space to tidal volume [VD/VT]) is the portion of tidal volume that does not participate in gas exchange. Newer evidence indicates that VD/VT is markedly elevated within 24 h of acute respiratory distress syndrome (ARDS) onset and is significantly elevated in non-survivors. Moreover, sustained elevation of VD/VT in ARDS has been associated with higher mortality.*
Objectives: *to study the physiological dead space fraction and various physiological parameters in mortality prediction for patients with ARDS.*
Methods: *The study included 30 patients admitted to the ICU with ARDS. All patients were subjected to Full medical history, general examination, arterial blood gases, laboratory investigations, chest imaging, echocardiography and assessment by Acute physiology and chronic health evaluation (APACHE II) and Lung injury scoring. Patients were followed up until ICU discharge or demise. Various physiological parameters including dead space fraction, airway resistance, static and dynamic pulmonary compliance, peak inspiratory pressure and positive end-expiratory pressure were measured.*
Results: *The overall mortality was 60%. The mean dead-space fraction was significantly higher in patients who died than in those who survived (0.67±0.08 vs. 0.57±0.09, P<0.001) (table 3). The risk of death increased as the dead-space fraction increased. The dead-space fraction was also independently associated with an increased risk of death in the multiple-regression analysis. For every increase of 0.05 in the dead-space fraction, the odds of death increased by 65 percent (odds ratio, 1.65; 95 percent confidence interval, 1.25 - 1.79; P=0.001) (table 4). Decreased both static and dynamic compliance as well as PaO_2/FiO_2 were independently associated with unfavorable outcome. The odds of death increased as the APACHE II and Lung injury scores increased and as compliance and PaO_2/FiO_2 decreased. The positive end expiratory pressure was not associated with an increased mortality (odds ratio, 1.05; 95 percent confidence interval, 0.95 to 1.19; P=0.23). There was significant negative correlation between DSF on admission and static compliance (r= -0.43, P value 0.01), dynamic compliance (r= -0.47, P value 0.01)and PaO_2/FiO_2 (r=0.73, P value 0.001).*
Conclusion: *Measurement of the dead-space fraction at an early time of the diagnosis of the acute respiratory distress syndrome is a feasible , reliable in providing clinicians with more useful diagnostic and prognostic information early in the course of illness than the other physiological parameters. Measurement of the dead-space fraction could help clinical investigators to identify the patients who may benefit most from a particular tailoring of therapeutic intervention.*
Keywords: *ARDS, dead space fraction , mortality predictors.*

Introduction

The acute respiratory distress syndrome is an important cause of acute respiratory failure which carries a high mortality rate [1-5] .Variables that are independently associated with mortality are qualitative or not specific to abnormalities of pulmonary pathophysiology, such as age, nonpulmonary organ system dysfunction, sepsis and cirrhosis [4-7]. Although indexes of hypoxemia commonly measured for monitoring respiratory functions in the critical situations, such as the partial pressure of arterial oxygen (PaO2), the fraction of inspired oxygen (FiO2), and the ratio of PaO2 to FiO2, are thought to have considerable prognostic value [3,8], recent studies strongly suggest that these variables are not independent mortality predictors when they were measured early in the course of the acute respiratory distress syndrome [4-6]

Physiologic dead-space fraction is the ratio of dead space to tidal volume [VD/VT]. It is the portion of tidal volume that does not participate in gas exchange and hence consists of expired gas without carbon dioxide. Historically, elevated VD/VT in patients with ARDS was thought to be a late-occurring phenomenon associated with the fibroproliferative stage of injury (1). However, newer evidence indicates that VD/VT is markedly elevated within the first 24 h of ARDS and is particularly elevated in non-survivors [2-8] and its sustained elevation is associated with higher mortality [5,6].

In this study, we aimed to study the physiological dead space fraction and other physiological parameters in mortality prediction for patients with ARDS.

Patients and Methods

Patients

The present study was conducted in the general ICU of Fayoum University Hospital and the respiratory ICU of El-Minia University Hospital from December 2013 to November 2015. The study included 30 critically-ill patients admitted to the ICU and met the diagnostic criteria of ARDS after having consent from the patients or their relatives. All ages and both sexes were included.

ARDS was diagnosed when subjects had to meet all 3 American-European Consensus Conference criteria: (1) PaO2/FIO2 $\leq$ 300, (2) bilateral infiltrates on chest radiograph during invasive mechanical ventilation, (3) the absence of evidence of elevated left atrial pressures) within the same 24-h period [9].

Patients with one or more of the following criteria were excluded from the study: clinical or radiological evidence of chronic lung disease, history of more than 60 pack-years of smoking, history or current treatment of hypertension, any primary cardiac disease or any systemic disease which can affect the heart e.g. autoimmune disorders, severe pulmonary hypertension with mean PAP > 40 mm Hg, or ventilator dependence, severe morbid obesity, diffuse alveolar hemorrhage from vasculitis, and patient survival less than 48 h.

All patients were thoroughly examined and subjected to the following:

(1) Arterial blood gases (ABG) analysis on admission and regularly as needed for patient diagnosis and follow up.

(2) Chest imaging including plain x ray chest. CT chest was done for selected cases for tailoring patient management and to exclude other associated pulmonary comorbidities.

(3) Laboratory investigations including sputum examination and cultures, CBC (complete blood count), coagulation profile (PT, PC, INR and PTT), liver function tests, kidney function tests, blood sugar, serum electrolytes including Na, K and calcium. Other laboratory investigations according to the patient condition were done both on admission and then as needed.

(4) Standard echo Doppler study.

- **APACHE II score:** All patients were evaluated according to the acute physiology and chronic health evaluation (APACHE II) scoring system at the time of admission [25]. The APACHE II score contains

three components: age, acute physiologic score (APS), and chronic health. The total APACHE II score ranges from 0 to 71 and the higher scores imply a less favorable outcome. The acute physiologic score includes Glasgow Coma Score (GCS) as well as other physiologic variables. The 11 physiologic variables in the acute physiologic score contribute up to 4 points for each parameter. The patient's Glasgow Coma Score can add a further 15 points. Patients with severe organ system insufficiency and imuno-compromised patients receive 5 points for chronic health [10].

Lung Injury Score (LIS)

The Lung Injury Score was used to assess the studied patients at the first 10 hours of diagnosis of ARDS. LIS assess 4 risk parameters: (1) chest X-ray evaluated for alveolar consolidation (2) PaO2/FIO2 (3) PEEP level in ventilated patients (4) respiratory compliance if known. Each parameter is given 0-4 score. The total ALI score ranges from 0 to 16. A higher score implies a less favorable prognosis [11].

Measuring of airway resistance

The airflow resistance during inspiration was determined by dividing the peak inspiratory flow rate (Vinsp) into the pressure which is needed to overcome the resistance to airflow (PIP-Pplat) [12]:

$$Rinsp = PIP\text{-}Pplat \ / \ Vinsp$$

Where: PIP: peak inspiratory pressure, Pplat: plateau pressure, Rinsp: airway resistance during inspiration, Vinsp: peak inspiratory flow rate, [12]

Measurement of compliance during MV

Static compliance (Cst) is calculated as the ratio between VT and plateau pressure minus PEEP whether external applied or auto PEEP. The delivered tidal volume was corrected by subtracting the non-compressible volume of the tubing system that connects the patients to the mechanical ventilator. Auto-PEEP was assessed by airway occlusion at end expiration and subtracting PEEP from the end-expiratory alveolar pressure [12].

Measurement of Dead-Space Fraction:

For calculating the dead space, the mean expired carbon dioxide fraction was measured with a bedside metabolic monitor (Cap-ONE CO2 Sensor, TG-920; Nihon Kohden, Japan). The expired gas was measured for five minutes during which arterial blood gas measurement was made at the same time. The dead-space fraction was calculated with use of the Enghoff modification of the Bohr equation [13,14]: dead-space fraction = (PaCO2-PECO2) ÷ PaCO2, where PECO2 is the partial pressure of carbon dioxide in mixed expired gas. The dead-space fraction is considered to be normal if it does not exceed 0.3 [13,14].

Patients were followed up until ICU discharge or demise. Type and duration of ventilatory support, development of complications during ICU stay, length of ICU stay and cause of death were recorded.

Statistical analysis

All statistical analyses were performed using SPSS statistics for Windows, version 17.0. Data were expressed as the mean ± standard deviation for continuous variables and the number with percentage for categorical data. Comparisons between two categorical variables were made with chi-square. Continuous data were tested with Student's t-test. P values below 0.05 were taken to indicate statistical significance. All of the variables attaining a value < 0.05 in the univariate analysis were included in the multiple logistic regression analysis models with a stepwise forward selection.

Results

Patient Characteristics

The present study included 30 ICU admitted patients who met the all 3 American-European Consensus Conference criteria of ARDS. The main baseline patient characteristics and underlying conditions are listed in table 1. Male sex represented 60 % of the patients and the mean age was 53.0 ± 13.8 years. The most frequent cause of ARDS was severe pneumonia (33.3%), followed by sepsis (23.3%). Sixty per cent of the patients were admitted for pure medical reasons whereas 40% were related to surgical scheduled causes.

The mean dead space fraction was 0.63 ± 0.09 (range: $0.51 - 0.73$). Absolute dead space was 6.1 ± 1.8 ml/kg of ideal body weight (mean $\pm$ SD, range : 4.1-8.2)

APACHE II score, PaO2:FiO2 and ALI score were listed in table (1).

Table (1): Patient characteristics and the co-morbid conditions:

Patients (n: 30) **Males**	18 (60 %)
Age (years) (mean $\pm$ SD) Clinical disorder associated with the acute respiratory distress syndrome (no. of patients &%)	53.0 ± 13.8
Sepsis	7 (23.3 %)
Aspiration	3 (10 %)
Pneumonia	10 (33.3 %)
Trauma, overdose, or idiopathic:	10 (33.3 %)
APACHE II score (mean $\pm$ SD) on admission	27.4 ± 8.2
PaO2:FiO2 (mean $\pm$ SD) on admission	176 ± 32.2
Lung injury score (mean $\pm$ SD) on admission	10.2 ± 1.9
Reason for admission (no. of patients &%) Scheduled surgery	12 (40%)
Medical	18 (60%)
Dead space fraction	0.63 ± 0.09
Absolute dead space (ml/kg of ideal body weight)	6.1 ± 1.8

Mortality predictors in patients with ARDS

The overall mortality rate was 60 % among studied patients. Comparison between non-survivors and survivors was studied regarding patient characteristics and different parameters on admission including vital signs and laboratory findings.

The non-survivors had a significantly higher mean age than the survivors. They had also significantly higher APACHE II and ALI scores, higher heart rate, as well as lower systolic and diastolic blood pressure on admission than the survivor group. The non-survivors showed also significantly lower mean platelet count than survivors. The mean total leucocytic count, CRP, blood urea and serum creatinine were significantly higher in non-survivors compared to survivors. The duration of MV was significantly higher in non-survivors.

Table (2): Comparison of different prognostic factors in surviving and non-surviving patients with ARDS

	Non-survivors (n:18)	Survivors (n:12)	p-value
Age (year)	56.2 ± 8.5	51.5 ± 12.9	0.01
Vital signs on admission			
HR (beats/m)	125.4 ± 22.1	112.2 ± 11.0	0.09
Temperature ºC	38.2 ± 1.1	37.3 ± 0.8	0.5
SBP mmHg	82.5 ± 15.2	93.2 ± 16.1	0.01
DBP mmHg	47.9 ± 8.6	51.9 ± 12.1	0.01
APACHE II score on admission	27.1 ± 5.9	16.5 ± 2.9	0.001
ALI score on diagnosis	12.7 ± 2.2	8.3 ± 3.2	0.005
Lab investigation on diagnosis			
Hemoglobin g/dl	11.1 ± 2.3	10.2 ± 2.2	0.1
Total Leukocyte count (x 10^9/L)	14.4 ± 5.4	10.4 ± 2.1	0.01
Platelets (x 10^9/L)	165 ± 57	265 ± 38	0.01
CRP mg/l	65 ± 21	45 ± 11	0.01
Serum sodium (mmol/l)	139.5 ± 2.7	138.2 ± 1.6	0.2
Serum potassium (mmol/l)	3.7 ± 1.2	3.9 ± 1.1	0.6
Serum urea (mg/dl)	42 ± 12	28 ± 5.5	0.02
Serum creatinine (mg/dl)	2.8 ± 1.2	1.1 ± 1.5	0.01
Duration MV (day)	13.2 ± 6.3	8.1 ± 2.9	0.01
Length of ICU stay (day)	13.4 ± 5.1	14.3 ± 6.2	0.5

Prognostic factors of DSF and other lung mechanics in ARDS

The mean dead-space fraction was significantly higher in non-survivors than in survivors (0.67±0.08 vs. 0.57±0.09, P<0.001) (table 3). The risk of death increased as the dead-space fraction increased. In the multiple-regression analysis, the dead-space fraction was also independently associated with an increased mortality risk. For every increase of 0.05 in the dead-space fraction, the risk of death increased by 65 percent (odds ratio, 1.65; 95 percent confidence interval, 1.25 - 1.79; P=0.001) (table 4) . The mean positive end-expiratory pressure was similar among patients who died and those who survived (10.2±3.1 and 10.0±3.5 cm of water, respectively).

Both static and dynamic compliance as well as PaO_2/FiO_2 were independently associated with an increased risk of death. The odds of death increased as the APACHE II and Lung injury scores increased and as compliance and PaO_2/FiO_2 decreased. The positive end expiratory pressure was not associated with an increased risk of death (odds ratio, 1.05; 95 percent confidence interval, 0.95 to 1.19; P=0.23), and also not with 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) (Table 4).

Table (3): Comparison of DSF, PaO_2/FiO_2 and lung mechanics between surviving and non-surviving patients with ARDS

Parameters studied	Non-survivors (n:18)	Survivors (n:12)	p-value
DSF	0.67±0.08	0.57±0.09	0.001
PaO_2/FiO_2 (mmHg)	158 ± 57	192 ± 48	0.04
Cst (ml/cmH2O)	31.03 ± 11.78	35.63 ± 13.41	0.03
Cdyn (ml/cmH2O)	16.62 ± 7.57	22.47 ± 8.21	0.05
Raw (cmH2O/l/s	11.17 ± 6.01	10.99 ± 18.7	0.11
ETCO2 (mmHg)	54.69 ± 23.51	53.39 ± 19.49	0.21

DSF : dead space fraction , Cdyn: dynamic compliance; Cst, static compliance; Raw: airway resisirance;
ETCO2: end-tidal carbon dioxide.

Table (4): Odds Ratios for variables independently associated with increased risk of death

Parameters studied	Odds ratio	95% confidence interval	p-value
DSF (per 0.05 increase)	1.75	1.27 - 1.82	0.001
APACHE II (per 5 point increase)	1.28	1.15 - 1.55	0.04
LIS (per 1 point increase)	1.26	1.15 - 1.54	0.03
Cst (ml/cmH2O) (per decrease of 1 ml/cm of water)	1.35	1.22 - 1.58	0.04
Cdyn (ml/cmH2O) (per decrease of 1 ml/cm of water)	1.28	1.19 - 1.45	0.05
PaO_2/FiO_2 (per decrease of 10 ml/cm of water)	1.32	1.15 - 1.62	0.01
PEEP (per increase of 1 ml/cm of water)	1.05	0.95 - 1.19	0.23

DSF : dead space fraction , Cdyn: dynamic compliance; Cst, static compliance; Raw: airway resisirance; ETCO2: end-tidal carbon dioxide, LIS : lung injury score, APACHE II: acute physiology and chronic health evaluation PEEP : positive end-expiratory pressure

Correlation between DSF and APACHE II and LIS

Correlation of DSF on admission and APACHE II and LIS were tested in all studied patients. There was a statistically significant positive correlation between DSF and APACHE II score (r=0.53, P value 0.001) as well as LIS (r=0.47, P value 0.01).

Correlation between DSF and other physiological parameters

DSF on admission had a significant negative correlation with the static compliance (r= -0.43, P value 0.01), dynamic compliance   (r= -0.47, P value 0.01)and PaO_2/FiO_2 (r=0.73, P value 0.001).

The dead-space fraction was found to be weakly associated with the level of positive end-expiratory pressure (r=0.24, P=0.01) and the level of peak inspiratory pressure (r=0.23, P<0.01), and it was not associated with the time from the diagnosis of the ARDS to the measurement of the dead-space fraction (r=‹0.05, P=0.48).

Discussion

ARDS is characterized by a non-cardiogenic pulmonary edema with significant impairment of gas exchange. The increases in the right-to-left intrapulmonary shunt and the low ventilation-to-perfusion ratio lead to hypoxemia, whereas the increase in pulmonary dead space reduces CO2 removal [15,16]. The increase in pulmonary dead space is due mainly to alterations in pulmonary blood flow distribution that results from vascular obstruction, regional overdistension of ventilated alveoli induced by positive end-expiratory pressure (PEEP) as well as by the reduction in cardiac output [17-19].

In this study, we aimed to study the physiological dead space fraction and other lung mechanics in mortality prediction for patients with ARDS.

The present study showed that the mean dead space fraction was 0.63 ± 0.09 (range: 0.51 − 0.73). Absolute dead space was 6.1 ± 1.8 ml/kg of ideal body weight (mean ± SD, range : 4.1-8.2). The mean dead-space fraction was significantly higher in non-survived patients (0.67±0.08 vs. 0.57±0.09, P<0.001). The risk of death increased as the dead-space fraction increased. The dead-space fraction was also independently associated with an increased risk of death in the multiple-regression analysis. For every increase of 0.05 in the dead-space fraction, the odds of death increased by 65 percent.

This comes in accordance with a recent study [13] who tested the association between pulmonary dead-space fraction and mortality in subjects with ARDS according to Berlin definition (PaO2/FIO2< 300 mm Hg; PEEP > 5 cmH2O) in   126 patients and found that non-survivors had higher VD/VT compared with

survivors (0.62 _ 0.11 vs 0.56 _ 0.11, respectively, and the association between VD/VT and mortality was significant on study day 1.

Our results also comes in agreement with another study (14) in which DSF was tested in 179 subjects with ARDS and showed increased DSF in non-survivors compared to survivors (0.63 ± 0.10 vs. 0.54 ± 0.09, P<0.001). they also showed that the DSF was an independent risk factor for death: for every 0.05 increase, the odds of death increased by 45 percent .

The present results revealed that DSF was negatively correlated with both static and dynamic compliance as well as PaO_2/FiO_2 whereas a weak positive correlation was found with PEEP as well as peak inspiratory pressure. DSF showed a positive correlation with both APACHE II and lung injury scores on admission This comes in agreement with other recent studies [20-26]

The present study tested other physiological parameters as predictors of mortality. It was found that both static and dynamic compliance as well as PaO_2/FiO_2 were independently associated with an increased risk of death. However, change of DSF was comparably associated of higher mortality risk than static and dynamic compliance and PaO_2/FiO_2. On the other hand, PEEP was not associated with an increased risk of death. This comes in partial agreement with Kallet et al [13] and Nukton et al [14] studies. On the other hand, other studies revealed that respiratory compliance was not independently predictive when it was measured early in the acute respiratory distress syndrome [27-29]. However, From a mechanical perspective, respiratory compliance is expected to be more deteriorated in more severely affected patients with less favorable outcome as patients with less compliant lungs may have more severe pulmonary edema and reduced concentrations of functional surfactant [14].

It is concluded that, bedside measurement of the dead-space fraction at the time of the diagnosis of the acute respiratory distress syndrome is a feasible, reliable in providing clinicians with useful diagnostic prognostic information early in the course of illness than the other physiological parameters. Measurement of the dead-space fraction could help clinical investigators identify the patients who may benefit most from a particular therapeutic intervention. We recommend the clinical use of the dead-space fraction in future clinical trials to evaluate the benefit of tailoring therapies in critically ill patients with ARDS.

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