Potential Effects of Corticosteroids on Physiological Dead-Space Fraction in Acute Respiratory Distress Syndrome

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BACKGROUND: Increased dead-space fraction is common in patients with persistent acute respiratory distress syndrome (ARDS). We evaluated the changes in the oxygenation and dead-space fraction in patients with persistent ARDS after corticosteroid therapy. METHODS: This was a non-randomized non-placebo, controlled observational study including 19 patients with persistent ARDS treated with corticosteroids. We measured P_{aO_2}/F_{IO_2} and dead-space fraction at days 0, 4, and 7 after corticosteroids treatment (methylprednisolone) initiation. Patients were classified in intermediate group when corticosteroids were initiated between days 8–14 after ARDS onset, and in late group when initiated after 14 days. RESULTS: Mean time from the diagnosis of the ARDS to methylprednisolone treatment was 11 ± 2 days in the intermediate group (10 patients) and 21 ± 8 days in the late group (9 patients). When comparing days 0, 4, and 7 after methylprednisolone treatment, we found an increase in the P_{aO_2}/F_{IO_2} (145 ± 64 mm Hg, 190 ± 68 mm Hg, and 226 ± 84 mm Hg, respectively, $P < .001$) and a decrease in the physiological dead-space fraction (0.66 ± 0.10, 0.58 ± 0.12, and 0.53 ± 0.11, respectively, $P < .001$). No differences were found between the intermediate and late groups. CONCLUSIONS: In patients with persistent ARDS, the increase in oxygenation was accompanied by a decrease in the dead-space fraction after a few days of corticosteroid treatment. To confirm potential benefit of corticosteroids on physiological parameters and mortality will require a powered randomized placebo controlled trial. *Key words: acute respiratory distress syndrome; ARDS; mechanical ventilation; dead space; corticosteroids; methylprednisolone.* [Respir Care 2012;57(3):377–383. © 2012 Daedalus Enterprises]

Introduction

Acute respiratory distress syndrome (ARDS) is a complex inflammatory lung injury associated with pulmonary microcirculation abnormalities and capillary thrombosis.[1–5] Abnormal physiological responses in ARDS include an increase in right-to-left intrapulmonary shunt, an increase in total dead-space fraction, and a reduction of lung compliance.[1–5] The clinical consequence of these diverse injury responses is impaired oxygenation and ventilation. Persistent ARDS, also known as unresponding ARDS, is characterized by ongoing inflammation and disorganized fibrosis. Clinical manifestations include ongoing hypoxemia, bilateral opacities on the chest radiograph, fever, and leukocytosis, without evidence of infection for 7 or more days after ARDS onset.[2,6,7]

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The increase in the dead-space fraction is a risk factor associated with increased mortality during the early and intermediate phases of ARDS.[5,8–11] However, such association was controversial when evaluating the level of hypoxemia and mortality in early ARDS. While some studies

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showed no association,[5,12,13] others found an association of the level of hypoxemia with mortality.[14–16]

Despite the difficulty to translate into survival benefit or long-term ventilator-free days benefit when treatments that improve oxygenation are evaluated,[17] changes in physiological dead-space fraction may be useful in assessing the effectiveness of pharmacologic therapies aimed at reducing inflammation and reversing pulmonary capillaries thrombosis in ARDS. The effect of corticosteroid therapy (an anti-inflammatory agent) on the dead-space fraction of patients with ARDS has not yet been evaluated, despite the fact that this therapy showed a beneficial effect in the oxygenation and a controversial beneficial effect on mortality in the intermediate and late phases of ARDS patients.[7,18] It has to be noted that similar studies evaluating the potential effect of the administration of activated protein C, which would improve the lung microcirculation and therefore decrease the dead-space fraction in ARDS patients, did not translate into an improvement in survival.[19,20] This should be the ideal clinical studies end point.

The aim of this study was to evaluate the changes in oxygenation and dead-space fraction in persistent ARDS patients after corticosteroid therapy initiated during the intermediate and late phases.

QUICK LOOK

Current knowledge

Elevated dead space to tidal volume ratio in patients with ARDS is associated with increased mortality. The use of steroids in ARDS remains controversial with respect to dose and timing.

What this paper contributes to our knowledge

Methylprednisolone administered to patients with intermediate and late ARDS is associated with improved oxygenation and reduced dead space to tidal volume ratio as early as 4 days following initiation.

Methods

Patients

This nonrandomized non-placebo-controlled observational study included 19 patients with ARDS treated with methylprednisolone, who were nonconsecutively admitted in the intensive care unit (ICU) of our tertiary university hospital (Hospital Universitari Son Dureta, Palma de Mallorca, Spain) from February 2005 through December 2008. The study protocol was approved by our institutional review board, and informed consent was obtained from each patient or relatives.

Patients older than 18 years, with endotracheal intubation, receiving invasive mechanical ventilation for acute hypoxemic respiratory failure, who met the American-European consensus definition of the ARDS[1] were eligible for the study if they presented:

- A persistent ARDS, defined by remaining bilateral opacities on the chest radiograph and ventilator-dependence due to persistent hypoxemia, a P_{aO_2}/F_{IO_2} of 200 mm Hg or less,[7] or persistent decrease in quasistatic respiratory compliance (lower than 20 mL/cm H_2O),[21] after 7 or more days of onset the ARDS, and
- No evidence of untreated infection
- The American-European consensus definition of the ARDS[1] included a P_{aO_2}/F_{IO_2} of 200 mm Hg 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, or pulmonary vascular disease, or patients who had a pleural drainage with air leak were excluded.

Management

Patients were mechanically ventilated with a lung-protective strategy during volume controlled mode, using a tidal volume (V_T) of 6–8 mL/kg of ideal body weight, maintaining plateau pressure less than 33 cm H_2O, and following the ventilation algorithm of combination of F_{IO_2} and PEEP described in the ARDS Network low-V_T trial.[7] Each patient's clinical management, consideration of persistent ARDS, and the decision to initiate corticosteroid therapy were based on the ICU attending physician's criteria.

A bronchoalveolar lavage or aspirate was performed in all cases prior to corticosteroid treatment initiation, to exclude occult ventilator-associated pneumonia. Patients with documented infection required appropriate antibiotic therapy for at least 3 days prior to corticosteroid treatment.

According to a Meduri et al study,[18] corticosteroid treatment was given with a methylprednisolone loading dose of 2 mg/kg, followed by 2 mg/kg per day from day 1 to day 14, 1 mg/kg per day from day 15 to 21, 0.5 mg/kg per day from day 22 to day 28, 0.25 mg/kg per day on days 29 and 30, and 0.125 mg/kg per day on days 31 and 32. Methylprednisolone was administered at 6-hour intervals (one fourth of daily dose) because the approximate half-life is 180 min. If the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to the schedule detailed above.[18]

Measurement of Dead-Space Fraction and Quasistatic Compliance

Dead-space fraction 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.[11] We measured the partial pressure of mixed expired carbon dioxide (P_{ECO_2}) by collecting expired gas in a Douglas bag for 5 min, during which we also drew an arterial blood sample to measure P_{aCO_2}. The Douglas bag was placed at the expiratory valve outlet of the ventilator (EVITA 4, Dräger, Lübeck, Germany). We measured P_{ECO_2} from the Douglas bag, and P_{aCO_2} from an arterial blood sample, with a blood gas analyzer (IL-1650, Instrument Laboratory, Izasa, Spain). Arterial blood samples were obtained from an indwelling arterial catheter at the mid-point of the 5-min interval. We used a previously described method to correct the P_{ECO_2} for ventilator circuit compressible volume.[22,23] The compressible volume value applied to correct P_{ECO_2} was 2 mL/cm H_2O (measured compressible volume was 1.9–2.1 mL/cm H_2O). Tidal volume was not adjusted for the measurement of dead-space fraction. We then calculated the dead-space fraction with the Enghoff modification[24] of the Bohr equation:

$$V_D/V_T = (P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$$

Quasistatic respiratory compliance was calculated with standard methods from measurements made during the collection of expired gas. Expired gas was measured with a Wright spirometer. Minute volume ($\dot{V}_E$) was calculated by dividing expired gas by collecting minutes, and tidal volume was calculated by dividing $\dot{V}_E$ by respiratory frequency. Quasistatic respiratory compliance was calculated as the value obtained by dividing the difference between the tidal volume (in mL) and the volume compressed in the ventilator circuit (in mL) by the difference between the plateau pressure (in cm H_2O), measured after a 0.5-second pause at the end of inspiration, and the PEEP (in cm H_2O) of the ventilator.[5] Patients on pressure support ventilation were changed to volume controlled ventilation for plateau pressure and quasistatic respiratory compliance measurements on the same day.

Corrected $\dot{V}_E$ for P_{aCO_2} was calculated from $\dot{V}_E$ measured, according to the protocol and methods used by the ARDS Network during the screening from the Late Steroid Rescue Study (LaSRS),[7] using the following formula:

$$\text{Corrected } \dot{V}_E = \dot{V}_E \times P_{aCO_2}/40$$

Data Collection and Definitions

The following data were recorded: age, sex, weight, height, comorbidities (eg, diabetes, chronic alcohol abuse, cirrhosis, and malignancy), and severity of illness evaluated by the Simplified Acute Physiology Score II (SAPS II) during the first day of ICU stay[25] and the Sequential Organ Failure Assessment (SOFA) score.[26] The etiology associated with ARDS and the different respiratory parameters of interest were also recorded. According to the pathway of lung injury the ARDS was categorized as direct (via airways), such as occurs in pneumonia, aspiration of gastric contents, or near-drowning, or as indirect (via bloodstream), such as occurs in sepsis, pancreatitis, or severe trauma.[2]

The dead-space fraction and other physiological pulmonary variables, such as the P_{aO_2}/F_{IO_2} ratio, the level of PEEP, the quasistatic compliance, and opacities on chest radiograph, needed to calculate the lung injury score,[27] were evaluated before methylprednisolone treatment initiation (day 0), and again on days 4 and 7 after corticosteroid therapy initiation in those patients who remained mechanically ventilated. Patients were followed up until they died or until hospital discharge.

Patients were divided in 2 groups according to the length between the diagnosis of ARDS and the initiation of methylprednisolone treatment: intermediate group, when methylprednisolone treatment was initiated between 8–14 days of ARDS onset, and late group, when methylprednisolone was initiated after 14 days of ARDS onset.[7]

Statistical Analysis

Data are expressed as mean ± standard deviation or median and interquartile ranges for continuous variables and number and percentages for categorical variables as appropriate. Comparisons between intermediate and late groups were made using the independent Student *t* test or the Mann-Whitney test for continuous data, and with the chi-square or the 2-sided Fisher exact test for categorical data. Comparisons between respiratory parameters in days 0, 4, and 7 after methylprednisolone treatment initiation were made using Friedman 2-way analysis of variance test. We performed the statistical analysis with statistics software (SPSS 15.0, SPSS, Chicago, Illinois).

Results

Nineteen patients were studied: 7 male and 12 female. Fifteen (79%) out of the 19 patients had pneumonia or aspiration (Table 1), and 16 patients (84%) had septic shock. The mechanism of the ARDS was direct lung injury in 18 (94.7%) of the cases. Bronchoalveolar lavage was performed in 9 patients, and bronchoalveolar aspirate in

Table 1. Clinical Characteristics of 19 Patients at ARDS Onset

Age, mean ± SD, y	51 ± 16
Male, no. (%)	7 (36.8)
Weight, mean ± SD, kg	71 ± 14
Ideal body weight, mean ± SD, kg	60 ± 10
Height, mean ± SD, cm	166 ± 10
SAPS II score, mean ± SD	36 ± 14
Comorbidities, no. (%)	
Diabetes	0 (0)
Chronic alcohol abuse	2 (10.5)
Cirrhosis	1 (5.3)
Malignancy	1 (5.3)
Cause of ARDS, no. (%)	
Pneumonia	13 (68.4)
Aspiration	2 (10.5)
Sepsis	1 (5.3)
Blunt chest trauma	2 (10.5)
Fat embolism	1 (5.3)
Direct lung injury	18 (94.7)
P_{aO_2}/F_{IO_2}, mean ± SD, mm Hg	110 ± 43

SAPS = Simplified Acute Physiology Score

Table 2. Clinical and Pulmonary Function the Day of Initiating Corticosteroid Therapy, Distributed by Time Elapsed After ARDS Onset*

	Days After ARDS Onset		
	≤ 14 d (no. = 10)	> 14 d (no. = 9)	*P*
Age, y	55 ± 17	46 ± 15	.25
SAPS II score	36 ± 15	36 ± 4	.90
SOFA score	5.4 ± 3.1	5.1 ± 3.2	.84
P_{aO_2}/F_{IO_2}, mm Hg	135 ± 43	156 ± 82	.80
pH	7.40 ± 0.10	7.41 ± 0.08	.86
P_{aCO_2}, mm Hg	52 ± 15	60 ± 32	.53
Lung injury score	2.5 ± 0.4	2.6 ± 0.7	.83
PEEP, cm H_2O	9.6 ± 5.9	6.8 ± 6.1	.32
Plateau pressure, cm H_2O	27.8 ± 6.0	32.1 ± 7.9	.19
Tidal volume, mL	351 ± 70	372 ± 130	.67
Tidal volume, mL/kg of IBW	6.1 ± 1.5	6.3 ± 1.9	.82
Minute ventilation, L/min	9.2 ± 1.8	10.9 ± 4.0	.22
Corrected minute ventilation, L/min	11.8 ± 3.5	16.9 ± 12.5	.27
Quasistatic compliance, mL/cm H_2O	20.7 ± 7.6	15.1 ± 6.1	.10
Dead-space fraction	0.63 ± 0.04	0.69 ± 0.14	.21

* Values are mean ± SD.
SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment
IBW = ideal body weight

10 patients. Positive cultures were found in 3 patients: 2 cases for *Klebsiella pneumoniae* and one for *Pseudomonas aeruginosa*.

Mean time from the diagnosis of ARDS to methylprednisolone treatment was 11 ± 2 days in the intermediate group (10 patients) and 21 ± 8 days in the late group (9 patients). At the day of initiating corticosteroid therapy, all patients had bilateral infiltrates, 14 had $P_{aO_2}/F_{IO_2} \leq 200$ mm Hg, and 13 had quasistatic respiratory compliance < 20 mL/cm H_2O. Two patients had $P_{aO_2}/F_{IO_2} > 200$ mm Hg and quasistatic respiratory compliance > 20 mL/cm H_2O. At the same time, 18 out of 19 patients (94.7%) had a dead-space fraction > 0.55, whereas in the remaining one the dead-space fraction was 0.52. All patients were on volume controlled ventilation except one patient who was receiving pressure support ventilation on days 4 and 7 with a pressure support of 20 cm H_2O and 5 cm H_2O of PEEP.

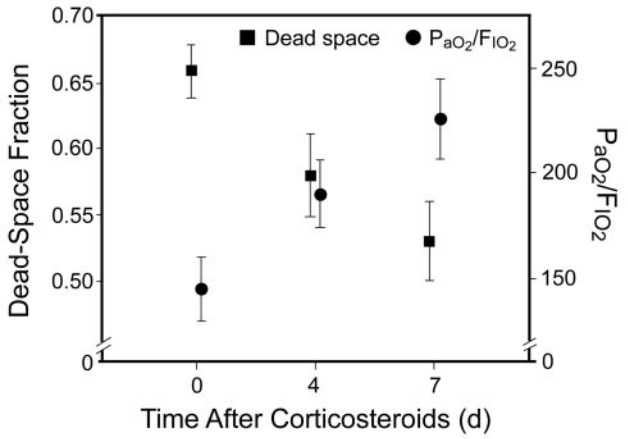

Fig. 1. Changes in dead-space fraction and P_{aO_2}/F_{IO_2} at days 4 and 7 after corticosteroids treatment initiation.

We found no statistically significant differences in age, SAPS II, SOFA, and respiratory parameters between the intermediate and late groups (Table 2). The late group showed a trend to having higher plateau pressure and lower compliance of the respiratory system than the intermediate group, without reaching significant statistical difference (see Table 2).

When comparing days 0, 4, and 7 after methylprednisolone treatment, we found an increase in the P_{aO_2}/F_{IO_2} (Fig. 1) and compliance of the respiratory system, and a decrease in the physiological dead space (see Fig. 1), the P_{aCO_2}, the corrected $\dot{V}_E$, and the lung injury score, without differences in measured $\dot{V}_E$ (Table 3).

There were no statistically significant differences in duration of mechanical ventilation, ICU or hospital stay, or in-hospital mortality between the intermediate and late groups (Table 4). Overall, 7 of 19 patients died (36.7%, 95% CI 15.8–57.9%). Three of the 10 patients in the intermediate group and 4 of the 11 patients in the late group died ($P = .65$).

Discussion

The main finding of our clinical study of patients with persistent ARDS was the improvement of pulmonary phys-

Table 3. Physiological Pulmonary Parameters Before Corticosteroid Treatment (Day 0), and Days 4 and 7 After Corticosteroids Treatment, Distributed by Time Elapsed After ARDS Onset*

	no.	Day 0	Day 4	Day 7	*P*
P_{aCO_2} (mm Hg)					
< 14 d after ARDS onset	10	52 ± 15	42 ± 7	34 ± 4	< .001
≥ 14 d after ARDS onset	9	60 ± 32	44 ± 17	38 ± 13	.02
All patients	19	56 ± 24	43 ± 13	36 ± 9	< .001
Minute ventilation (L/min)					
< 14 d after ARDS onset	10	9.2 ± 1.8	9.5 ± 1.5	9.6 ± 1.6	.58
≥ 14 d after ARDS onset	9	10.9 ± 4.0	10.7 ± 3.1	10.9 ± 2.6	.90
All patients	19	10.0 ± 3.1	10.1 ± 2.4	10.3 ± 2.2	.43
Corrected minute ventilation (L/min)					
< 14 d after ARDS onset	10	11.8 ± 3.5	9.8 ± 2.0	8.2 ± 1.0	< .001
≥ 14 d after ARDS onset	9	16.9 ± 12.5	12.5 ± 8.4	10.9 ± 6.5	.005
All patients	19	14.2 ± 9.1	11.1 ± 6.0	9.5 ± 4.6	< .001
P_{aO_2}/F_{IO_2} (mm Hg)					
< 14 d after ARDS onset	10	135 ± 43	178 ± 50	222 ± 65	.001
≥ 14 d after ARDS onset	9	156 ± 82	202 ± 86	231 ± 105	.06
All patients	19	145 ± 64	190 ± 68	226 ± 84	< .001
Physiological dead-space fraction					
< 14 d after ARDS onset	10	0.63 ± 0.04	0.57 ± 0.05	0.50 ± 0.06	.001
≥ 14 d after ARDS onset	9	0.69 ± 0.13	0.59 ± 0.17	0.57 ± 0.15	.001
All patients	19	0.66 ± 0.10	0.58 ± 0.12	0.53 ± 0.11	< .001
Quasistatic compliance (mL/cm H_2O)					
< 14 d after ARDS onset	10	20.7 ± 7.6	29.4 ± 14.0	29.7 ± 8.8	.06
≥ 14 d after ARDS onset	9	15.1 ± 6.1	17.4 ± 4.8	22.0 ± 7.9	.10
All patients	19	18.1 ± 7.3	23.8 ± 12.1	26.1 ± 9.1	.006
Lung injury score					
< 14 d after ARDS onset	10	2.6 ± 0.5	2.1 ± 0.5	1.8 ± 0.4	.001
≥ 14 d after ARDS onset	9	2.5 ± 0.7	2.2 ± 0.7	1.9 ± 0.5	.004
All patients	19	2.5 ± 0.6	2.1 ± 0.6	1.8 ± 0.5	< .001

* Values are mean ± SD.

Table 4. Outcome Measures Distributed by Time Elapsed After ARDS Onset

	Days After ARDS Onset		*P*
	≤ 14 d (no. = 10)	> 14 d (no. = 9)	
Duration of mechanical ventilation, median (IQR), d	40 (26–50)	37 (29–45)	.78
Intensive care unit stay, median (IQR), d	38 (30–50)	38 (32–46)	.81
In-hospital stay, median (IQR), d	47 (34–70)	50 (38–77)	.62
In-hospital mortality, no. (%)	3 (30)	4 (44)	.65

iology parameters within 4 to 7 days after the initiation of corticosteroids therapy. These changes on pulmonary physiology were observed in both the intermediate and the late groups. However, the lack of a control group limits the applicability of our findings.

The main result was the decrease in the dead-space fraction in ARDS patients treated with corticosteroids. One could speculate that underlying mechanisms involve the potential improvement in lung inflammatory injury induced by corticosteroid therapy, which leads to a better ventilation-perfusion matching. This finally results in decreased dead-space fraction and $\dot{V}_E$ requirements. This study shows results similar to those evaluating the effects of activated protein C therapy studies in ARDS patients.[19,20] It highlights the potential usefulness of measuring dead-space fraction in ARDS patients as a tool to identify the patients who may benefit most from a particular therapeutic intervention and to evaluate the benefit of a treatment in the most severely ill patients, as supported by Nuckton et al.[5] Other interesting results of our study were that an increased physiologic dead-space fraction was characteristic of persistent ARDS in all cases. The improvement in P_{aO_2}/F_{IO_2}, compliance of the respiratory system, and lung injury score observed after 4 to 7 days of corticosteroids were consistent with the studies of the ARDS Network[7]

and Meduri et al[18] that evaluated the efficacy of corticosteroids for persistent ARDS.

The patients were included in the study with a P_{aO_2}/F_{IO_2} value < 200 mm Hg, as in the ARDS Network study,[7] or with a quasistatic respiratory compliance < 20 mL/cm H_2O. This value is considered a very severe reduction and corresponds to a lung volume of 20% of the original healthy lung.[21] A dead-space fraction > 0.55 was defined as elevated, since this cutoff was associated with a significantly higher mortality during the acute and subacute phases of ARDS.[9] Of note, although in the subgroup of patients with late ARDS treated with corticosteroids, the dead-space fraction decreased in a similar magnitude to those with intermediate ARDS after corticosteroid treatment, the mean values were still > 0.55. The group with late ARDS presented a trend to having higher plateau pressure, corrected $\dot{V}_E$, and dead-space fraction, and lower quasistatic compliance than the intermediate group at day 0 (nonsignificant *P* value), probably due to a higher degree of pulmonary fibrosis.

The 37% mortality of our series of patients is somewhat higher than that observed in the ARDS Network study.[7] We found no statistical differences in terms of mortality between patients with corticosteroids therapy when initiated before or after 14 days of ARDS onset, in accordance with a recent meta-analysis that suggested that the reduction in mortality risk is not significantly affected by the timing of the treatment.[28] The effect on mortality of corticosteroids therapy in persistent ARDS remains controversial,[29] as shown by the results of 2 randomized studies.[7,17] Despite our finding improvements in pulmonary physiology parameters in intermediate and late ARDS groups treated with corticosteroids, we believe that randomized controlled studies showing improvements in oxygenation and dead-space fraction, as well as survival or ventilation free-days, are needed before recommending corticosteroid therapy in these patients. The last is more difficult to demonstrate,[17] as occurred in the study of Liu et al,[19] where the improvement in oxygenation and dead-space fraction after activated protein C did not translate into improved survival.

The limitations of our study have to be acknowledged: we evaluated a low number of patients, and we had no control group, which is a major problem in the analysis of our results. However, while survival is the ultimate benefit and the outcome measure most often considered for critically ill patients, our interest was focused on physiological parameters. The pulmonary physiologic improvement with corticosteroids therapy allowed us to diminish the oxygen concentration supplied and the $\dot{V}_E$, and as a consequence of that we began the weaning process of mechanical ventilation earlier, altering the course of persistent ARDS.

Conclusions

In summary, this clinical study showed that the increase in oxygenation was accompanied by a decrease in the dead-space fraction after a few days of corticosteroids treatment in the intermediate and late groups. Potential benefit of corticosteroid therapy on physiological parameters and mortality or ventilation-free days will require an appropriately powered randomized placebo controlled trial.

REFERENCES

1. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3 Pt 1):818-824.
2. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342(18):1334-1349.
3. Coffey RL, Albert RK, Robertson HT. Mechanisms of physiological dead space response to PEEP after acute oleic acid lung injury. J Appl Physiol 1983;55(5):1550-1557.
4. Greene R, Zapol WM, Snider MT, Reid L, Snow R, O'Connell RS, Novelline RA. Early bedside detection of pulmonary vascular occlusion during acute respiratory failure. Am Rev Respir Dis 1981; 124(5):593-601.
5. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;346(17):1281-1286.
6. Meduri GU, Belenchia JM, Estes RJ, Wunderink RG, el Torky M, Leeper KV Jr. Fibroproliferative phase of ARDS. Clinical findings and effects of corticosteroids. Chest 1991;100(4):943-952.
7. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome N Engl J Med 2006;354(16):1671-1684.
8. Cepkova M, Kapur V, Ren X, Quinn T, Zhuo H, Foster E, et al. Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. Chest 2007;132(3):836-842.
9. Kallet RH, Alonso JA, Pittet JF, Matthay MA. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. Respir Care 2004;49(9):1008-1014.
10. Gattinoni L, Carlesso E, Cressoni M. Assessing gas exchange in acute lung injury/acute respiratory distress syndrome: diagnostic techniques and prognostic relevance. Curr Opin Crit Care 2011;17(1): 18-23.
11. Raurich JM, Vilar M, Colomar A, Ibáñez J, Ayestarán I, Pérez-Bárcena J, Llompart-Pou JA. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir Care 2010;55(3):282-287.
12. Doyle RL, Szaflarski N, Modin GW, Wiener-Kronish JP, Matthay MA. Identification of patients with acute lung injury. Predictors of mortality. Am J Respir Crit Care Med 1995;152(6):1818-1824.
13. Ware LB. Prognostic determinants of acute respiratory distress syndrome in adults: impact on clinical trial design. Crit Care Med 2005; 33(3 Suppl):S217-S222.
14. Monchi M, Bellenfant F, Cariou A, Joly LM, Thebert D, Laurent I, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. Am J Respir Crit Care Med 1998;158(4):1076-1081.

15. Cooke CR, Kahn JM, Caldwell E, Okamoto VN, Heckbert SR, Hudson LD, Rubenfeld GD. Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. Crit Care Med 2008;36(5):1412-1420.
16. Seeley E, McAuley DF, Eisner M, Miletin M, Matthay MA, Kallet RH. Predictors of mortality in acute lung injury during the era of lung protective ventilation. Thorax 2008;63(11):994-998.
17. Spragg RG, Bernard GR, Checkley W, Curtis JR, Gajic O, Guyatt G, et al. Beyond mortality: future clinical research in acute lung injury. Am J Respir Crit Care Med 2010;181(10):1121-1127.
18. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998;280(2):159-165.
19. Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am J Respir Crit Care Med 2008;178(6):618-623.
20. Kallet RH, Jasmer RM, Pittet JF. Alveolar dead-space response to activated protein C in acute respiratory distress syndrome. Respir Care 2010;55(5):617-622.
21. Rossi A, Polese G, Milic-Emili J. Monitoring respiratory mechanics in ventilator-dependent patients. In: Tobin MJ, editor. Principles and practice of intensive care monitoring. New York: McGraw-Hill; 1998:553-596.
22. Crossman PF, Bushnell LS, Hedley-Whyte J. Dead space during artificial ventilation: gas compression and mechanical dead space. J Appl Physiol 1970;28(1):94-97.
23. Forbat AF, Her C. Correction for gas compression in mechanical ventilators. Anesth Analg 1980;59(7):488-493.
24. Enghoff H. Volumen inefficax: Bemerkungen zur Frage des schädlichen Raumes. Upsala Lakareforen Forh 1938;44:191-218. *Article in German.*
25. Le Gall Jr, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957-2963.
26. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707-710.
27. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138(3):720-723.
28. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care Med 2009;37(5):1594-1603.
29. Sessler CN, Gay PC. Are corticosteroids useful in late-stage acute respiratory distress syndrome? Respir Care 2010;55(1):43-55.