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TITLE PAGE:

Title: **INDIVIDUALIZED POSITIVE END-EXPIRATORY PRESSURE SETTING IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME. A RANDOMIZED CONTROLLED PILOT STUDY.**

Running title: **INDIVIDUALIZED PEEP IN ARDS.**

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ABSTRACT:

BACKGROUND: Low-volume ventilation may be associated with repetitive opening and closing of terminal airways. The use of possitive end-expiratory pressure (PEEP) is intended to keep the alveoli open. No method of adjusting the optimal PEEP level has shown to be superior and improve clinical outcomes.

We conducted a pilot study to evaluate the effect of setting an individualized level of PEEP at highest compliance on oxygenation, multiple organ disfunction (MOD) and survival in patients with the acute respiratory distress syndrome (ARDS).

METHODS: Patients with ARDS ventilated with low tidal volumes and limitation of airway pressure at 30 cmH_2O were randomized to a compliance-guided PEEP level or to an FiO_2-driven study group.

RESULTS: Out of 159 patients with ARDS admitted during the study period, 70 patients met inclusion criteria for the present study. Patients in the compliance-guided group showed non-significant improvements in PaO_2/FiO_2 ratio during the first 14 days and 28-day mortality (20.6% *vs*. 38.9%, p=0.12). MOD-free days (median 6 *vs.* 20, p=0.02), respiratory failure-free days (median 7 *vs.* 14, p=0.03) and hemodynamic failure-free days (median 16 *vs.* 22, p=0.04) at 28 days were significantly lower in patients with compliance-guided setting of PEEP level.

CONCLUSIONS: In ARDS patients, protective mechanical ventilation with PEEP application according to the highest compliance is associated with less organ dysfunction and a strong non-significant trend toward lower mortality.

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Key words: Acute Respiratory Distress Syndrome, Mechanical Ventilation, Positive-Pressure Ventilation, Tidal volume, Intensive Care Units, Humans

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TEXT OF THE MANUSCRIPT

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is characterized by the acute onset of hypoxemia and bilateral infiltrates that are consistent with pulmonary oedema without evidence of left heart failure[1]. The use of positive-pressure ventilation is potentially lifesaving in patients with ARDS, but may cause ventilator-associated lung injury (VILI). Lung-protective ventilation strategies seek to prevent VILI by using low tidal volume (V_T) to avoid overdistension and positive end-expiratory pressure (PEEP) to prevent repetitive alveolar collapse and reopening[2-4].

The application of PEEP improves gas exchange and lung function. The main effect of increasing PEEP is to maintain the recruitment of alveolar units that were previously collapsed. Thus, since tidal volume is distributed to more alveoli, peak airway pressure is reduced and compliance is increased[5]. However, the levels of pressure needed to open and recruit some alveoli may overdistend others. Overdistension in turn may directs blood perfusion away from these areas, thereby increasing dead space, pulmonary vascular resistance, mean hydrostatic pressures and thus extend lung damage[6]. The preferred method of adjusting for optimal PEEP levels is still controversial[7, 8]. The amount of potentially recruitable lung tissue has best been evaluated using computerized tomography[9], but this approach is usually not readily available in intensive care units (ICU) for routine assessment of ventilator settings.

Some suggests that lung mechanics is a better surrogate than gas exchange variations for the bedside assessment of lung recruitment[10], and that the PEEP level should be chosen individually[10-12]. In fact, several studies have shown improved survival when PEEP level is set above the lower inflection point on the pressure-volume curve, the steepest portion of the curve, a sign of increase of functional residual capacity[12-15]. Unfortunately, all these studies also compared low with high V_T ventilation, hindering an accurate evaluation of the effect directly attributable to PEEP. Recently, two studies comparing different methods of PEEP level setting one based on individual maximun alveolar recruitment, failed to demonstrate a reduction in mortality, although they observed significant improvements in oxygenation[16] and lung function[17].

We conducted an open, randomized control pilot study to test the hypothesis that an individualized level of PEEP, set at highest compliance, improves oxygenation when compared to a fixed PEEP level based on the fraction of inspired oxygen (FiO_2) applied[18].

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MATERIALS AND METHODS

This study was conducted in a 14-bed mixted medical-surgical intensive care unit (ICU) in Spain over a time period of sixty months. The study protocol was approved by the institucional Ethics and Clinical Trials Committee, and registered on clinicaltrials.gov with the number: NCT01119872. Written informed consent was required for inclusion and obtained from the nearest relatives. No commercial entities had a role in any aspect of this study.

We included all consecutive patients with ARDS according to the American-European Consensus Conference definition[1], who maintained ARDS criteria after 24 hours of mechanical ventilation, in order to confirm the ARDS criteria and exclude other causes of hypoxemia and pulmonary infiltrates, since mechanical ventilation parameters can modify oxygenation criteria of the ARDS definition[19]. We excluded patients who were younger than 18-years, pregnant, had neuromuscular disease, intracranial hypertension, head trauma, left ventricular dysfunction (on echocardiography), more than 72 hours of mechanical ventilation or barotrauma. Patients with end stage conditions with high expected mortality within 90 days were not included. We defined barotrauma as the presence of air outside the tracheobronchial tree resulting from presumptive alveolar rupture, and manifested as interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema[20]. A patient developping barotrauma during the first 24 hours of observation prior to randomization, was excluded from the study because of the unfeasibility to measure plateau pressure, and not included in final group assignment. In patients excluded after randomization, the respiratory protocol was not applied, although protective lung mechanical ventilation was maintaned, and they were kept in the assigned study group for outcome analysis.

Study design.

All patients with ARDS criteria were ventilated during 24 hours with low V_T (6-8 ml/kg predicted body weight (PBW)), an inspiratory plateau pressure below 30 cmH_2O, 30 breaths/min adjusted to maintain a pH between 7.30 and 7.45 and limited to a maximum of 35 breaths/min, FiO_2 ensuring arterial oxygen saturation (SaO_2) 88-95% or arterial partial oxygen pressure (PaO_2) of 55-80 mmHg, and a PEEP level adjusted to achieve the best oxygenation with the lowest FiO_2 without adverse hemodynamic effects. If the plateau pressure was greater than 30 cmH_2O with V_T of 6 ml/kilogram PBW, a stepwise reduction of V_T of 1 ml/kg PBW to 5 and 4 ml/kg/PBW was allowed. If this was the case, the plateau pressure limit was set at 35 cmH_2O.

After 24 hours, patients meeting all inclusion criteria were randomized to FiO_2-driven PEEP level (control group) or compliance-guided PEEP level. Randomization was performed in blocks of 10 using sealed envelopes.

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In the control group, PEEP level was set based on the patient´s FiO_2, as applied in the ARDSNet study[18]. In the compliance-guided group, PEEP level was set daily, according to the method described by Suter[12]. Static compliance (Cst) was measured at increasing levels of PEEP and at constant. Cst was calculated dividing V_T by the pressure difference at end of inflation hold (2 seconds) and PEEP was increased at steps of 2 cmH_2O beginning at 5 cmH_2O, without an upper PEEP titration limit. The highest Cst was considered to be the best PEEP. If at two different PEEP levels Cst was identical, we chose the one with the lower plateau pressure (the respiratory protocol is detailed in appendix 1). All patients received sedatives and opioids at the time of PEEP setting. Neuromuscular blocking agents were used as required for low V_T ventilation, although not for the measurement of intrinsic PEEP or plateau pressure.

PEEP level was adjusted once daily during the morning shift and according the study group during mechanical ventilation until the weaning phase started. Intrinsic PEEP was measured before and after every change of PEEP level and inspiratory to expiratory ratio was accordingly to prevent it.

All other ventilator parameters were set in the same way in both study groups, following the protocol applied for 24 hours before randomization[18].

The weaning protocol was identical for both groups. Weaning was begun if the cause of respiratory failure had resolved, PaO_2 was higher than 60 mmHg with an FiO_2 at 0.4 or less and PEEP level below 6 cmH_2O. In patients in the compliance-guided group, PEEP level was lowered stepwise by 2 cmH_2O. In the control group the protocol described in the ARDSNet study[18] was applied. (complete protocol is shown on appendix 2).

Patients were monitored with a pulmonary artery catheter (PAC) for at least the first 72 hours after randomization to study the hemodynamic effects of PEEP.

Therapy other than mechanical ventilation was prescribed at the discretion of the attending physicians not involved in the study. Local protocols are applied to guide the management of sedation, hemodynamic support and other standard interventions.

End-points were assesed at 28 days. The primary end-point of the study was PaO_2/FiO_2 ratio. Secondary end-points were mortality, ventilator-free days, ICU and hospital stay, multiple organ dysfunction (MOD) free days, respiratory and hemodynamic parameters.

Measurements.

Data collected from each patient included demographic characteristics, risk factors for ARDS; routine laboratory measurements, Acute Physiology and Chronic Health Evaluation II score (APACHE II[21]) at ICU admission, daily Lung Injury Score (LIS)[22], Sepsis-Related Organ Failure Assessment (SOFA)[23] and MOD

Score (MODS)[24], days on mechanical ventilation, ICU and hospital outcomes and length of stay, 28-day mortality, pulmonary physiologic and ventilatory measurements, cardiovascular parameters, adverse events, extrapulmonary organ failures, sedation and daily chest x-ray. All measurements and data were recorded at study inclusion, at 6 hours after inclusion and between 6 a.m. and 8 a.m. on days 1, 2, 3, 4, 7, 14, 21 and 28.

Organ failure is defined as a SOFA score[23] greater than 2 and MOD requires 2 or more organ failures. Organ dysfunction-free days were defined as days alive and free of any organ dysfunction[15, 17], and ventilator –free days as days of unassisted breathing, both calculated at 28 days (all deaths occuring prior to day 28 were considered as zero organ dysfunction-free or ventilator-free days)[18].

Patients were followed until hospital discharge or death.

Statistical analysis.

Normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Quantitative variables with normal distribution are expressed as means ± S.D. and compared using Student's t test. Non-normal distribution variables are shown as medians and interquartile ranges and compared using the Mann-Whitney test. Qualitative variables are shown as percentages and compared by the chi-square test.

Kaplan-Meier analysis with log-rank test was applied to compare survival at 28 days between groups.

Level of statistical significance was set to p values less than 0.05 and results are expressed with their 95% confidence intervals.

Statistical analysis was performed using SPSS 15.0 software (SPSS-Inc., Chicago, Illinois).

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RESULTS

A total of 159 patients met criteria for ARDS during the study period, 70 of whom were randomized to either compliance-guided (n=34) or FiO_2-driven PEEP level adjustement (n=36) (figure 1). No patient was excluded after randomization or discharged from hospital earlier than 28 days.

The main cause of ARDS was infection (n=50, 71,4%) (detailed causes of ARDS per study group are shown in appendix 3).

There were no significant differences in patients characteristics between study groups at randomization, except for the high incidence of MOD syndrome in the compliance-guided group (table 1).

Physiological measurements.

There was no difference in median PEEP level at study entry (figure 2).

Figure 3 shows ventilatory parameters over the 28-day study period. Regarding the primary end-point, we did not find significant differences in PaO_2/FiO_2 ratio. There as a trend toward improved oxygenation in the compliance-guided group over the first two weeks of study (figure 3, panel A) (data are shown in appendix 4).

In the compliance-guided group there was also a non-significantly higher pulmonary compliance and lower airway pressure (figure 3, panel B) (data are shown in appendix 4).

No differences were seen on pH, tidal volume, auto-PEEP or ventilator rates (data are shown in appendix 4).

In a post-hoc analysis we found that patients (80%) in the compliance-guided group would have had a different PEEP level if set according to their FiO_2 and the FiO_2/PEEP table. There were no limitations in daily PEEP changes, rather than the measurement frequency of PEEP.

Clinical outcomes.

Patients included in the compliance-guided group had significantly more MOD-free days at day 28 (table 2), in spite of a higher baseline incidence (table 1), as well as more ventilator-free days and hemodynamic failure-free days than patients of the control group (table 2).

Twelve patients developed barotrauma after randomization, six per study group (table 2). A total of 9 episodes of barotrauma occurred during the first week, 5 in the compliance-guided and 4 in the FiO_2- driven group, respectively. One patient in the compliance-guided group and 2 in FiO_2-driven group developed barotrauma in the second week of study.

Global 28-day mortality was 30% (21 patients), with a hospital mortality of 42.8% (30 patients). 28-day mortality was 20.6% (n=7) in the compliance-guided and 38.9% (n=14) in the FiO_2-driven PEEP group (p=0.12), respectively (figure 4). The main causes of death were multiorgan failure (n=50, 71.4%) and

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refractory hypoxemia (n=10, 14.3%). Patients who died had a higher SOFA score[23] at inclusion (11.4±0.7 *vs.* 8.1±0.5, p<0.01), as well as lower PaO_2/FiO_2 ratio (126.4±9.6 *vs.* 145.1±4.3 mmHg, p=0.04) and a higher lung injury score[22] (3.25 (2.50-3.50) *vs.* 3.00 (2.50-3.25), p=0.04).

No significant differences in hemodynamic variables or in the dosages of sedatives between both groups were observed (appendices 5 and 6). There were no complications associated with insertion of the pulmonay artery catheter.

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DISCUSSION

In the present pilot study we found that patients with ARDS, ventilated with low V_T and an airway pressure limited to 30 cmH_2O, individual patient pulmonary compliance-guided adjustement of PEEP level, compared to FiO_2-adjusted PEEP, had no significant effect on oxygenation, although it was associated with a significant reduction of the duration of MOD.

To our knowledge determination of best PEEP guided by the best Cst has not previously been studied in a large group of patients with lung protective ventilatory strategy[25]. Interestingly, there were no significant differences in mean PEEP levels applied to each group. In previous studies PEEP levels were higher if set according to "compliance"[13, 17, 26]. Although mean PEEP levels were similar, our post-hoc analysis showed that as many as 80% of patients allocated to compliance-guided adjustement would have been managed at different PEEP levels than in the control group. Hypothetically, patients with customized settings may have been on higher or lower PEEP levels than those prescribed according to the $PEEP/FiO_2$ table. Thus, similar mean PEEP values in our opinion do not exclude that, individual compliance-guided settings may be distributed over a wider range of values and be associated with less ventilator-induced lung injury.

We also found that patients on compliance-guided PEEP setting had non-significantly lower plateau pressures over the first 21 days of study (Figure 3, Panel D). This could be explained by improved alveolar recruitment, since other respiratory parameters were programmed according to the same protocol in both groups, but needs to be confirmed in a larger study. It should be pointed out that in previous studies lower plateau pressures have been associated with reductions in mortality[18] and, similar to our findings, shorter duration of MOD failure[17, 18].

There are only three randomized control clinical trials in which PEEP application according to the pressure-volume curve is compared with other methods of determining best PEEP level[13-15]. In those studies, the authors compared higher versus lower V_T showing a progressive improvement of oxygenation[14] over the first week[13, 15]. There are no comparative data about the course of oxygenation beyond the first week. These studies differ from ours in that PEEP levels are set slightly above the lower inflection point of the quasi static pressure-volume curve. This methods has been shown to have poor correlation with alveolar recruitment, and therefore with total alveolar compliance[27]. We also found a non-significant improvement in oxygenation in the compliance-guided group during the first two weeks of the protocol. This effect is not observed at later stages. Unlike in previous studies, improved oxygenation, if confirmed, may be attributed to the method of PEEP level

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determination, since this is the only difference between the two study groups. Comparisons of oxygenation data are methodologically very difficult because of important differences in clinical course and how death and weaning should statistically be accounted for. In addition, in later stages of ARDS, with increased lung fibrosis[28, 29], the use of the pressure-volume curve may be less effective in achieving alveolar recruitment and, consequently, in improving oxygenation.

We observed that customizing PEEP to the individual patient is associated with a reduction in the duration of MOD at 28 days. It is reasonable to assume that this effect is the cause for the strong trend toward lower mortality in this study group. Previous studies have been criticized for similar results because patients were ventilated with high V_T, which has been demonstrated to be associated with higher mortality[18]. A meta-analysis[30] performed with data from 3 studies[13-15] showed a statistically significant decrease in mortality if PEEP level is determined according to the pressure-volume curve.

This effect on duration of MOD may be related to a reduced release of inflamamtory cytokines. Several clinical studies have confirmed that an array of inflammatory cytokines is released into the systemic circulation as a consequence of high tidal volume or high PEEP, which corrrelates with higher morbidity and mortality[14, 18, 31, 32].

Other studies have compared methods of setting best PEEP level. The ExPress study[17] showed that, compared to a fixed and low PEEP an individualized PEEP set at the highest value allowing a plateau pressure of 28-30 cmH_2O, is associated with significant increase of MOD-free days at 28 days without improving survival. Talmor et al.[26] compared the application of fixed PEEP according to the ARDSnetwork standard-of-care recommendations[18], with an individualized method based on transpulmonary pressure at end expiration. They found improved oxygenation, as well as a trend toward lower mortality in the customized PEEP group. It is interesting to note that, as in our study, Talmor found that the respiratory system compliance appeared to be higher in the esophageal-pressure-guided group[26]. Unlike in our study, however, these authors determined PEEP level decrementally after a recruitment manoeuvres, which has been demonstrated to influence the evaluation of lung compliance according to the pressure-volume curve[27, 33].

Grasso et al.[34] found that, compared to the ARDSnet protocol[18], in patients with a focal pattern of loss of aeration PEEP level is lower if set according to stress index and that the application of the ARDSnet protocol[18] induces alveolar hyperinsuflation and increased cytokine plasma levels. The LOVs[16] study found a lower incidence of refractory hypoxemia and need for rescue therapies associated with the application of PEEP according to FiO_2 after a 40-second 40 cmH_2O airway pressure recruitment maneuver compared to the

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ARDSnet protocol[18] without previous recruitment maneuver, although without a statistically significant difference in rates of all-cause hospital mortality or barotrauma.

In our study 12 patients (17%) developed barotrauma. The incidence of barotrauma in ARDS has been reported to range between 0 and more than 76%[35], although recent studies show reduced incidences between 6 and 10%[16, 17, 36, 37]. Risk factors for barotrauma included high peak airway pressures, large tidal volumes and the level of acute lung injury[38]. The slightly incidence of barotrauma in our study may be explained by a high LIS[22] score, as large tidal volume and high peak airway pressures were avoided. The incidence of barotrauma was similar in both study groups. Previous studies have not found differences in the incidence of barotrauma according the different level or method of PEEP applied[16, 17, 36, 37].

Our study has several limitations. Being a pilot study with the aim to provide a basis for a future multicenter study, it has a only small sample size and its results require confirmation. The study was carried out in a single centre and only included 44% of patients who met inclusion criteria. Although randomized, the study was unblinded and bias can not be excluded. Some difficulties in setting PEEP at best compliance became apparent during the study. At times we several time-consuming attempts were required to find the best PEEP in the compliance group, including the need for muscle relaxants, or the study procedures had to be interrupted to allow for endotracheal suctioning. We also did not measured inflammatory cytokines to support the findings in MOD.

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CONCLUSIONS

In conclusion, this randomized, controlled pilot trial show that individualized PEEP selection based on the best Cst in patients with ARDS treated with low V_T and limited plateau pressure did not improve oxygenation, but was associated with a significant increase in organ dysfunction-free days and a strong trend towards lower mortality at day 28. Larger, randomized, multicenter trials are necessary to validate this approach as an integral part of lung protective strategy.

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Table 1. Baseline characteristics of patients at study inclusion.

	FiO_2-driven-PEEP group (n = 36)	Compliance-guided group (n = 34)
Gender, male, n (%)	29 (80.55)	20 (58.82)
Age, years, mean ± SD	54.1 ± 2.9	55.6 ± 3.1
APACHE II, mean ± SD	20.53 ± 1.33	18.71 ± 1.02
SOFA, mean ± SD	8.86 ± 0.61	9.38 ± 0.66
MODS, mean ± SD	8.36 ± 0.52	8.50 ± 0.57
LIS, median (P_{25}-P_{75})	3 (2.5 – 3.25)	3 (2.5 – 3.25)
Percentage of patients with multiple organ dysfunction syndrome$^{\Delta}$	77.8%	97.1%
PaO_2/FiO_2, mmHg, mean ± SD	133.15 ± 5.88	146.33 ± 6.19
PEEP pre-randomization, cmH_2O, median (P_{25}-P_{75})	10 (8-14)	10 (8-12)
Tidal volume, ml/kg of predicted body weight	6.61 ± 0.87	6.66 ± 1.01
Peak pressure, cmH_2O, mean ± SD	38.10 ± 1.11	38.22 ± 1.33
Plateau pressure, cmH_2O, mean ± SD	31.87 ± 1.56	28.24 ± 1.22
Total respiratory rate, breaths/min, mean ± SD	23 ± 1	25 ± 1
Minute ventilation, L/min, mean ± SD	12.1 ± 0.4	12.9 ± 0.4
pH, mean ± SD	7.34 ± 0.01	7.33 ± 0.01
$PaCO_2$, mmHg, mean ± SD	43.28 ± 1.27	42.11 ± 1.01

Table 1 shows baseline characteristics of patients at study inclusion. There were no significant differences in either group at study randomization, except the one marked with $^{\Delta}$ ($p = 0.02$).

Abbreviations: SD: standard deviation. APACHE II: Acute Physiology and Chronic Health Evaluation II. SOFA: Sepsis-Related Organ Failure Assessment. MODS: Multiple Organ Dysfunction Score. LIS: Lung Injury Score. PaO_2: partial pressure of arterial oxygen. FiO_2: fraction of inspired oxygen. PEEP: positive end-expiratory pressure. $PaCO_2$: partial pressure of arterial carbon dioxide.

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Table 2. Clinical outcomes

	FiO_2-driven-PEEP group (n = 36)	Compliance-guided group (n = 34)	P value
28-day mortality, no. (%)	14 (38.9)	7 (20.6)	0.12
No. of multiple organ dysfunction-free days at 28 days, days, mean ± SD	6 (0 – 23.75)	20.50 (0 – 26)	0.02
No. of respiratory failure-free days at 28 days, days, mean ± SD	7.5 (0 - 19)	14.5 (0 – 22.5)	0.03
No. of hemodynamic failure-free days at 28 days, days, mean ± SD	16 (0 – 23.75)	22 (0 - 25)	0.04
No. of renal failure-free days at 28 days, days, mean ± SD	28 (0 - 28)	28 (0 - 28)	0.39
No. of haematological failure-free days at 28 days, days, mean ± SD	25.5 (0 - 28)	28 (0 - 28)	0.52
No. of hepatic failure-free days at 28 days, days, mean ± SD	28 (0 - 28)	28 (0 - 28)	0.08
Length of ICU stay, days, median (P_{25}-P_{75})	20 (12 – 29)	21 (15 -46)	0.24
Length of hospital stay, days, mean ± SD	32 ± 3	55 ± 7	<0.01
No. of ICU-free days at 28 days, days, mean ± SD	0 (0 – 11)	0 (0 – 14)	0.84
No. of ventilator-free days at 28 days, days, mean ± SD	0 (0 – 15.75)	1 (0 – 18)	0.16
Barotrauma, No of patients (%)	6 (16.7)	6 (17.6)	0.99

Abbreviations: SD: standard deviation. SD: standard deviation. No: number. ICU: intensive care unit.
*For patients who died at day 28, a value of 0 days was assigned.

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Figure 1. SCREENING AND ENROLLMENT

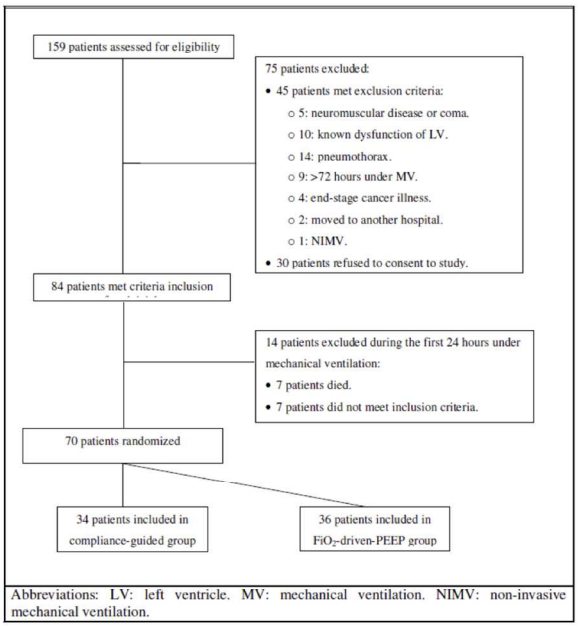

Figure 1. Flow diagram.of inclusion and exclusion of patients.
254x190mm (150 x 150 DPI)

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Figure 2. PEEP LEVELS.

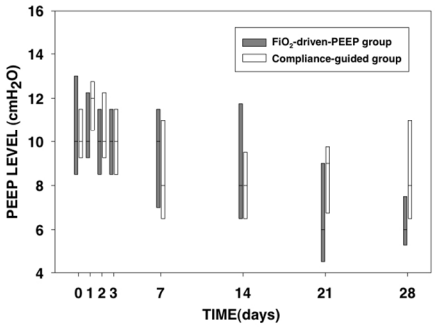

Figure 2. PEEP levels during the study.

Figure 2 shows the evolution of PEEP level during the study for both groups. No differences were found in the median value of PEEP level between both groups. Data are shown as median and percentile 25-75.
254x190mm (150 x 150 DPI)

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Figure 3. RESPIRATORY MEASUREMENTS DURING THE STUDY

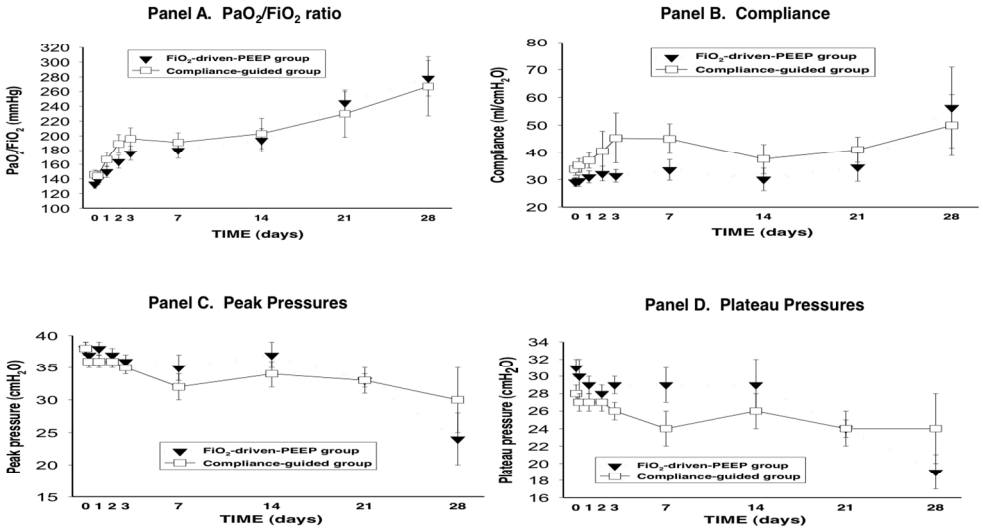

Figure 3. Respiratory determinations during the study.

The panels show the time course of PaO2/FiO2, compliance, peak and plateau airways pressures parameters in both groups of patients during the study. No differences were found between both groups in PaO2/FiO2, compliance, peak and plateau airways pressures. Data are expressed as the mean ± SD. N
Abbreviations: PaO2/FiO2: the ratio to the partial pressure of arterial oxygen to the fraction of inspired oxygen.
254x190mm (150 x 150 DPI)

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Figure 4. KAPLAN-MEIER 28-DAY PROBABILITY OF SURVIVAL CURVE.

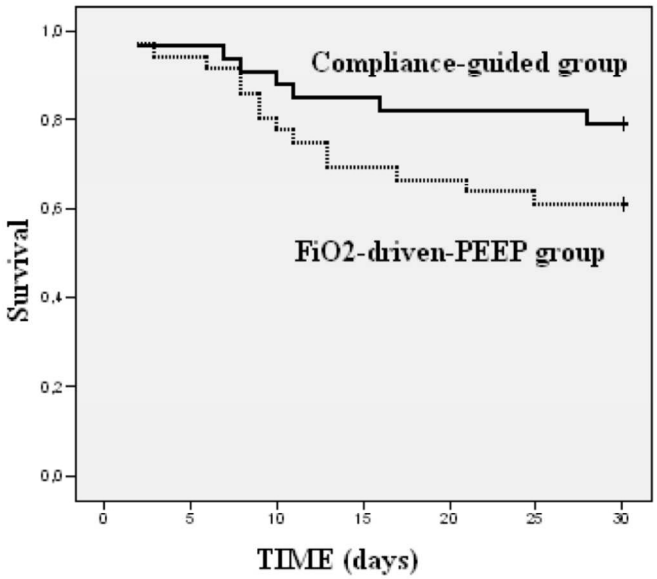

Figure 4. Kaplan-Meier 28-day probability of survival curve.

Figure 4 shows the Kaplan-Meier 28-day probability of survival curve for patients with ARDS ventilated with low tidal volumes (6-8 ml/kg) and plateau airway pressure limited at 30 cm H2O, after randomization to PEEP level according to FiO2 applied (FiO2-driven-PEEP group) or according to the best compliance (compliance-guided group).
Abbreviation: FiO2: fraction of inspired oxygen
190x254mm (150 x 150 DPI)

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APPENDIX 1

Appendix 1. Complete respiratory protocol.

First 24 hours: All patients with ARDS criteria were ventilated during 24 hours with low V_T (6-8 ml/kg predicted body weight (PBW)) (NEJM 2000; 342 (18): 1301-8 / Am rev Respir Dis 1981;123:659-64), inspiratory plateau pressure limited at 30 cmH_2O, initial ventilator rate of 30 breaths/min adjusted to maintain a pH goal of 7.30 to 7.45 to a maximum of 35 breaths/min, fraction of inspired oxygen (FiO_2) ensuring arterial oxygen saturation (SaO_2) 88-95% or arterial partial pressure of oxygen (PaO_2) of 55-80 mmHg, and PEEP level that permitted the best oxygenation with the lowest FiO_2 without adverse hemodynamic effects. In case of a plateau pressure greater of 30 cmH_2O with V_T of 6 ml/kilogram PBW, it was allow to reduce V_T 1 ml/kg PBW if necessary until 4 ml per kilogram PBW; in that case, plateau pressure limit was set at 35 cmH_2O.

After 24 hours: if they meet all inclusion criteria, they were randomized into two groups: FiO_2-driven-PEEP group or a compliance-guided group.

Randomization was performed in blocks of 10 using sealed envelopes.

In FiO_2-driven-PEEP group, PEEP was set based on the patient FiO_2 according to the PEEP strategy reported in the ARDSNet study (NEJM 2000; 342 (18): 1301-8). In FiO_2-driven-PEEP group, PEEP was set based on the patient FiO_2 according to the PEEP strategy reported in the ARDSNet study (NEJM 2000; 342 (18): 1301-8).

In compliance-guided group, PEEP level was set daily, according to the method described by Suter (Chest 1978; 73:158-62). Static compliance (Cst) was calculated at different levels of PEEP at a constant V_T of 6-8 ml/kg PBW. Cst was determined by dividing V_T by the difference between the pressure at the end of inflation hold (2 seconds) and the PEEP, at series of incrementally values for end-expiratory pressure, beginning at 5 cmH_2O and steps of 2 cmH_2O, without an upper PEEP titration limit. The maximum value of Cst in individual patients was considered as the best PEEP. If two PEEP level compliance was identical we choose the ones who gets the lower plateau pressure.

All the patients received sedatives and analgesics at the time of PEEP setting, and some patients were on treatment with muscle relaxants due to ARDS and mechanical ventilation, not specifically to measure autoPEEP or plateau pressure.

PEEP level was set once daily in the morning while the patient was under mechanical ventilation until weaning was started, according the study group. Intrinsic PEEP was measured before and after each change in PEEP; inspiratory time was adjusted to prevent its occurrence.

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Table A. Ventilation Protocol: respiratory parameters.

	Pre-randomization (first 24 hours)	Post-randomization	
		FiO_2-driven-PEEP group	Compliance-guided group
Tidal volume goal	6-8 ml/kg of predicted body weight$^{\Delta}$	6-8 ml/kg of predicted body weight$^{\Delta}$	6-8 ml/kg of predicted body weight$^{\Delta}$
Plateau pressure limit	$\leq$ 30 cmH_2O	$\leq$ 30 cmH_2O	$\leq$ 30 cmH_2O
Inspiration: expiration relation	1:2	1:2	1:2
Ventilator rate (breaths/min)	30 rpm initial, adjusted according pH	Adjusted according pH	Adjusted according pH
pH goal	7.30 – 7.45	7.30 – 7.45	7.30 – 7.45
Oxygenation goals - PaO_2 - SaO_2	 55 - 80 mmHg 88 - 95%	 55 – 80 mmHg 88 - 95%	 55 – 80 mmHg 88 - 95%
PEEP	The one that permits the best oxygenation without hemodynamic adverse effects*	Depending on the FiO_2 applied (see below)	Depending on the best compliance

Combinations of PEEP and FiO_2 (NEJM 2000; 342 (18): 1301-8)

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-20-22-24

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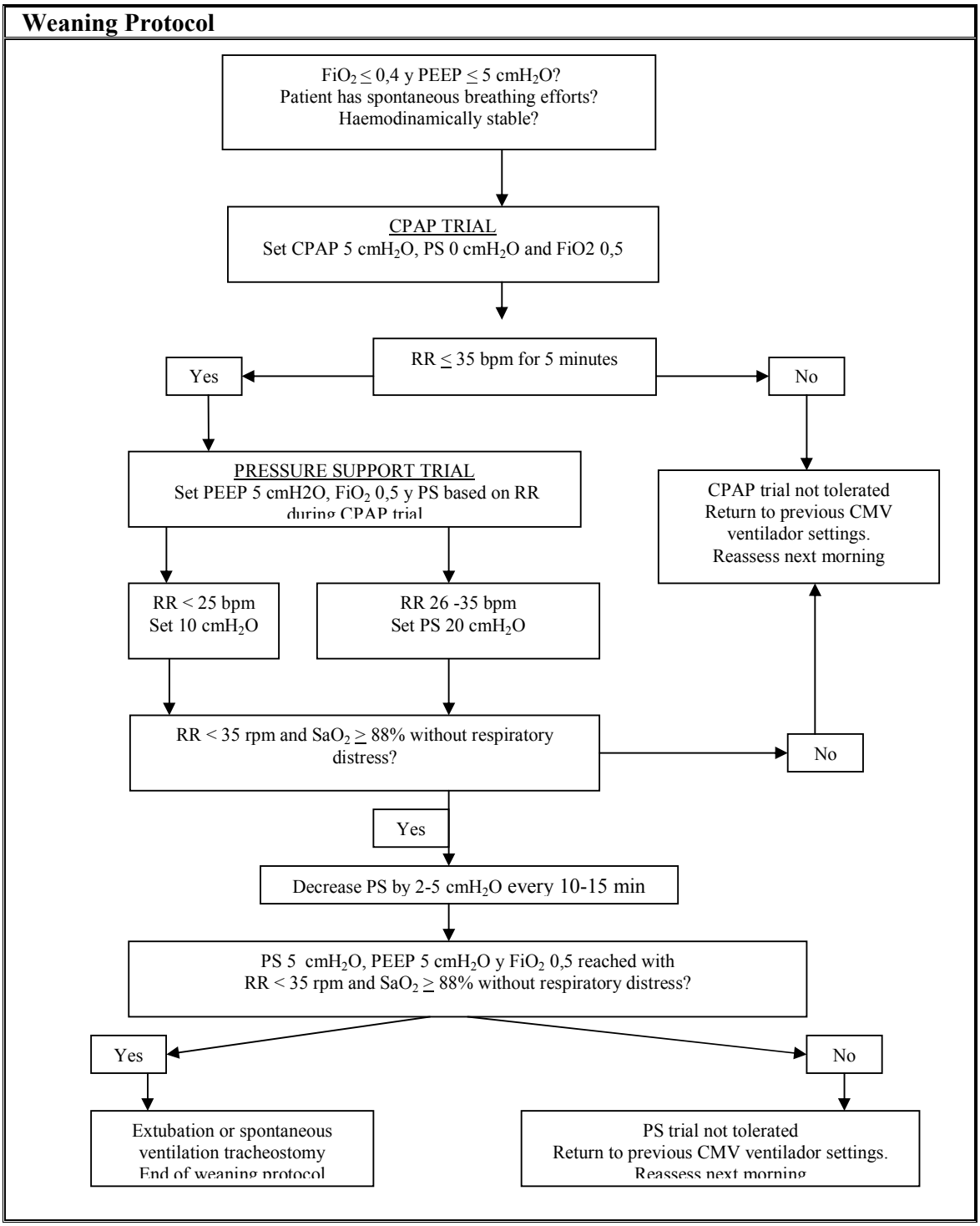
Appendix 2. Weaning protocol.



Abbreviations: CPAP: Continuous Positive Airway Pressure. PS:Pressure Support Ventilation. RR : Respiratory rate. BPM : breath per minute. CMV: Controlled Mechanical Ventilation.

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Appendix 3. ARDS etiology.

ARDS etiology.		
	FiO_2-driven-PEEP group (n = 36)	Compliance-guided group (n= 34)
Direct lung injury:	24 (66,7%)	15 (44,1%)
Pulmonary infection	18 (75%)	13 (86,6%)
Severe chest trauma	3 (12,4%)	1 (6,7%)
OP*	1 (4,2%)	
Aspiration of gastric contents	1 (4,2%)	
Diffuse alveolar hemorrhage	1 (4,2%)	1 (6,7%)
Indirect lung injury:	12 (33,3%)	19 (55,9%)
Sepsis	8 (66,7%)	11 (57,8%)
Acute pancreatitis	3 (25%)	3 (15,8%)
Multiple blood transfusions		3 (15,8%)
Drug overdose		1 (5,3%)
Others⌂		1 (5,3%)
Severe nonthoracic trauma	1 (8,3%)	

Results are shown as number of patients and porcentage.
* OP: crytogenetic organizing pneumonia.
⌂ Others: dermatomyositis.

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Appendix 4. Respiratory variables during the study.

Respiratory Variables during the study.									
	Basal			6 hours			24 hours		
	FiO_2-driven-PEEP group	Compliance-guided group	P value	FiO_2-driven-PEEP group	Compliance-guided group	P value	FiO_2-driven-PEEP group	Compliance-guided group	P value
Minute ventilation (l/min)	12.1 ±0.4	12.9 ±0.4	0.15	11.5 ±0.4	12.6 ±0.4	0.09	12.4 ±0.4	12.8 ±0.4	0.43
Respiratory rate (cicles/min)	23 ±1	25 ±1	0.30	25 ±1	26 ±1	0.26	25 ±1	26 ±1	0.52
Peak pressure (cmH_2O)	38.1 ±1.1	38.2 ±1.3	0.90	37.1 ±1.4	36.2 ±1.0	0.68	38.1 ±1.2	36.1 ±1.2	0.16
Plateau pressure (cmH_2O)	31.9 ±1.6	28.3 ±1.2	0.13	30.1 ±2.4	27.3 ±1.3	0.17	29.1 ±1.8	27.0 ±1.1	0.16
PEEP* (cmH_2O)	10 (8-14)	10 (10-12)	0.71	10 (10-14)	11 (10-13)	0.82	10 (10-13)	12 (10-13)	0.40
Compliance (ml/cmH_2O)	29.1 ±1.6	33.8 ±2.2	0.08	29.6 ±2.1	35.3 ±2.5	0.80	31.0 ±2.2	37.0 ±2.9	0.10
PaO_2/FiO_2 (mmHg)	133.3 ±6.5	146.3 ±6.7	0.12	139.5 ±7.3	144.2 ±7.5	0.56	150.1 ±8.2	167.7 ±11.0	0,17
pH	7.34 ±0.01	7.33 ±0.01	0.47	7.32 ±0.01	7.32 ±0.01	0.12	7.33 ±0.01	7.32 ±0.01	0.74
	48 hours			72 hours			7 days		
Minute ventilation (l/min)	12.6 ±0.1	13.6 ±0.1	0.36	12.5 ±0.5	12.9 ±0.5	0.57	13.9 ±0.6	13.1 ±0.6	0.30
Respiratory rate (cicles/min)	26 ±1	26 ±1	0.53	26 ±1	26 ± 1	0.70	26 ±1	24 ±1	0.11
Peak pressure (cmH_2O)	37.4 ±1.9	36.5 ±1.7	0.36	36.7 ±1.9	35.2 ±1.1	0.66	35.7 ±2.9	32.2 ±2.2	0.18
Plateau pressure (cmH_2O)	28.6 ±1.1	27.1 ±1.2	0.69	28.9 ±1.8	26.4 ±1.4	0.39	29.7 ±2.4	24.0 ±2.1	0.07
PEEP* (cmH_2O)	10 (8-12)	10 (9-13)	0.40	10 (8-12)	10 (8-12)	0.30	10 (6-12)	8 (6-12)	0.46
Compliance (ml/cmH_2O)	32.2 ±2.7	40.4 ±7.4	0.29	31.4 ±2.3	45.3 ±9.1	0.14	33.6 ±3.8	45.1 ±5.4	0.08
PaO_2/FiO_2 (mmHg)	164.0 ±9.0	189.0 ±13.0	0.11	176.3 ±10.3	196.0 ±15.1	0.25	180.1 ±11.0	191.1 ±13.0	0.56
pH	7.33 ±0.01	7.35 ±0.01	0.33	7.36 ±0.01	7.36 ±0.01	0.74	7.36 ±0.02	7.39 ±0.01	0.16
	14 days			21 days			28 days		
Minute ventilation (l/min)	12.9 ±1.1	13.3 ±1.1	0.80	13.3 ±1.1	13.9 ±0.8	0.68	11.3 ±1.2	11.2 ±1.5	0.94
Respiratory rate (cicles/min)	25 ±1	24 ±2	0.71	23 ±2	21 ±1	0.38	22 ±2	19 ±3	0.35
Peak pressure (cmH_2O)	37.8 ±2.4	34.2 ±2.1	0.29	33.5 ±2.3	33.5 ±1.3	0.74	24.5 ±4.4	30.0 ±5.7	0.30
Plateau pressure (cmH_2O)	29.4 ±3.8	26.3 ±2.1	0.27	24.2 ±2.3	24.7 ±1.3	0.88	19.5 ±2.7	24.5 ±4.3	0.30
PEEP* (cmH_2O)	8 (6-13)	8 (6-10)	0.46	6 (4-10)	9 (6-10)	0.23	6 (5-8)	8 (6-12)	0.24
Compliance (ml/cmH_2O)	30.1 ±4.1	37.6 ±5.5	0.28	34.6 ±5.2	41.0 ±4.7	0.39	56.4 ±14.6	49.9 ±11.0	0.75
PaO_2/FiO_2 (mmHg)	194.3 ±16.7	203.9 ±21.6	0.71	245.6 ±15.8	230.6 ±32.0	0.66	278.6 ±24.6	267.3 ±40.1	0.80
pH	7.37 ±0.02	7.41 ±0.02	0.13	7.43 ±0.02	7.39 ±0.03	0.29	7.39 ±0.02	7.36 ±0.02	0.25

Data are presented as mean ± standard deviation, except the marked ones with * that are presented as median (interquartile range).
Abbreviations: PEEP: Positive end-expiratory pressure. PaO_2/FiO_2: ratio to the partial pressure of arterial oxygen to the fraction of inspired oxygen.

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Appendix 5. Hemodynamic variables during the first 72 hours of study.

Hemodynamic variables during the first 72 hours of study													
		MAP (mmHg)		HR (beats/min)		RAP (mmHg)		CO (l/min)		PAWP (mmHg)		PVR (d/seg/cm-5)	
			p		p		p		p		p		p
Basal	FiO2-driven PEEP group	86.8 ±1.7	<0.01	97.1 ±3.8	0.21	15.6 ± 0.8	0.54	7.1 ±0.6	0.50	15.1 ±0.9	0.33	206.95 ±2.4	0.15
	Compliance-guided group	76.8 ±2.1		103.5 ± 3.4		14.2 ± 0.6		7.6 ±0.5		14.1 ±0.7		183.8 ±25.8	
6 h	FiO2-driven PEEP group	82.7 ±1.6	0.36	101.3±4.2	0.22	15.2 ±0.7	0.76	7.3 ±0.5	0.34	16.4 ±0.9	0.28	170.4 ±18.9	0.14
	Compliance-guided group	80.5 ±1.9		108.2 ±3.9		13.7 ±0.7		7.9 ±0.5		15.2 ±0.8		178.4 ±19.2	
24 h	FiO2-driven PEEP group	83.6 ±1.8	0.98	102.0±4.1	0.41	13.3 ±0.6	0.41	7.7 ±0.4	0.49	14.6 ±0.8	0.31	160.6 ±14.3	0.25
	Compliance-guided group	83.6 ±2.3		106.6 ±3.9		14.3 ±0.7		7.3 ±0.4		15.7 ± 0.7		182.1 ±20.1	
48 h	FiO2-driven PEEP group	88.3 ±1.9	0.30	96.9 ±3.6	0.45	13.2 ±0.6	0.64	7.3 ±0.3	0.32	15.5 ±0.8	0.75	177.0 ±21.9	0.46
	Compliance-guided group	80.4 ±3.0		100.8 ±3.7		13.9 ±0.8		6.7 ±0.5		15.1 ±1.1		162.8 ±21.1	
72 h	FiO2-driven PEEP group	87.2 ±1.9	0.75	96.4 ±3.9	0.90	13.9 ±0.8	0.72	7.3 ±0.5	0.79	18.1 ±1.6	0.83	151.9 ±23.7	0.45
	Compliance-guided group	86.2 ±2.4		96.9 ±3.5		14.9 ±0.9		7.5 ±6.7		17.6 ±1.3		166.8 ±35.6	

Data are presented as mean ± standard deviation.
Abbreviations: h: hours. MAP: mean arterial pressure. HR: heart rate. RAP: right atrium pressure. CO: cardiac output. PAWP: pulmonary artery wedge preseure. PVR: pulmonary vascular resistance.

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Appendix 6. Sedation.

Sedation: dosages of drugs administered by study day.

		Opioids (mg/h)		Midazolam (mg/h)		Propofol (mg/H)		Others*⌂ n (%)		Muscle relaxants*α n (%)	
			p		p		p		p		p
Basal	FiO_2-driven-PEEP group	3.3 ±0.3	0.78	9.9 ±0.9	0.48	44.9 ±21.1	0.30	9 (25%)	0.56	14 (39%)	0.80
	Compliance-guided group	3.2 ±0.4		8.9 ±1.1		86.4 ±33.7		6 (18%)		12 (35%)	
24 h	FiO_2-driven-PEEP group	3.2 ±0.4	0.45	9.1 ±0.7	0.33	38.4 ±15.1	0.25	7 (19%)	0.99	12 (33%)	0.80
	Compliance-guided group	2.8 ±0.3		7.9 ±0.9		71.1 ±24.3		7 (21%)		13 (38%)	
48 h	FiO_2-driven-PEEP group	3.6 ±0.5	0.17	9.3 ±0.9	0.08	58.1 ±26.9	0.32	5 (14%)	0.99	14 (40%)	0.31
	Compliance-guided group	2.8 ±0.3		6.9 ±1.1		96.3 ±24.9		4 (12%)		9 (27%)	
72 h	FiO_2-driven-PEEP group	3.6 ±0.6	0.56	8.1 ±0.9	0.84	56.7 ±21.8	0.28	6 (17%)	0.48	9 (26%)	0.9
	Compliance-guided group	3.2 ±0.5		7.8 ±1.1		100.1 ±25.9		3 (9%)		10 (30%)	
7 d	FiO_2-driven-PEEP group	2.9 ±0.4	0.39	7.8 ±1.3	0.71	67.9 ±19.7	0.18	4 (13%)	0.72	6 (19%)	0.36
	Compliance-guided group	3.8 ±0.9		8.5 ±1.7		128.5 ±36.9		5 (19%)		8 (31%)	
14 d	FiO_2-driven-PEEP group	3.6 ±0.5	0.09	10.9 ±1.5	0.03	123.1 ±0.1	0.53	1 (6%)	0.58	2 (12%)	0.64
	Compliance-guided group	2.1 ±0.7		5.5 ±1.8		57.9 ±44.2		2 (14%)		3 (21%)	
21 d	FiO_2-driven-PEEP group	3.2 ±1.3	0.40	11.2 ±2.9	0.22	15.8 ±0.2	0.41	3 (30%)	0.58	0 (0%)	
	Compliance-guided group	1.8 ±0.5		5.3 ±1.9		93.9 ±36.9		1 (12%)		0 (0%)	
28 d	FiO_2-driven-PEEP group	1.7 ±0.8	0.63	11.2 ±2.9	0.27	4.9 ±0.1	0.52	2 (40%)	0.60	0 (0%)	
	Compliance-guided group	2.2 ±0.4		4.5 ±1.5		125.2 ±75.1		3 (43%)		0 (0%)	

Figure shows the mean doses of opioids, midazolam and propofol used at each time of the study in milligrams per hour, and the number of patients requiring other sedatives and muscle relaxants .

Data are presented as mean ± standard deviation, except the marked ones with * that are presented as number of patients (percentage).

⌂ Others: Expresses the number of patients requiring other sedatives used in the sedation of these patients, fentanyl, tramadol, Thalamonal ® (fentanyl-droperidol), etomidate.

α Muscle relaxants: Expresses the number of patients requiring muscle relaxation by intravenous infusion.

Abbreviations: h: hours; d: days.