



Protective mechanical ventilation in patients with risk factors for ARDS: prospective cohort study

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ABSTRACT

Objective: To evaluate the association that protective mechanical ventilation (MV), based on V_T and maximum distending pressure (MDP), has with mortality in patients at risk for ARDS. **Methods:** This was a prospective cohort study conducted in an ICU and including 116 patients on MV who had at least one risk factor for the development of ARDS. Ventilatory parameters were collected twice a day for seven days, and patients were divided into two groups (protective MV and nonprotective MV) based on the MDP (difference between maximum airway pressure and PEEP) or V_T . The outcome measures were 28-day mortality, ICU mortality, and in-hospital mortality. The risk factors associated with the adoption of nonprotective MV were also assessed. **Results:** Nonprotective MV based on V_T and MDP was applied in 49 (42.2%) and 38 (32.8%) of the patients, respectively. Multivariate Cox regression showed that protective MV based on MDP was associated with lower in-hospital mortality (hazard ratio = 0.37; 95% CI: 0.19-0.73) and lower ICU mortality (hazard ratio = 0.40; 95% CI: 0.19-0.85), after adjustment for age, Simplified Acute Physiology Score 3, and vasopressor use, as well as the baseline values for PaO_2/FiO_2 ratio, PEEP, pH, and $PaCO_2$. These associations were not observed when nonprotective MV was based on the V_T . **Conclusions:** The MDP seems to be a useful tool, better than V_T , for adjusting MV in patients at risk for ARDS.

Keywords: Respiration, artificial; Tidal volume; Respiratory distress syndrome, adult.

INTRODUCTION

Although mechanical ventilation (MV) is an essential supportive measure for patients with severe respiratory failure,^(1,2) it can cause lung injury characterized by inflammatory infiltrates and hyaline membranes, as well as alveolar and interstitial edema, being designated ventilator-induced lung injury (VILI).⁽³⁾

Previously injured lungs, as in ARDS, are more susceptible to VILI,⁽⁴⁾ and, in such cases, lung-protective ventilator settings, such as reducing V_T to ≤ 6 mL/kg of predicted body weight and plateau pressure to ≤ 30 cmH₂O, are associated with lower mortality.⁽⁵⁻⁷⁾ Amato et al.⁽⁸⁾ demonstrated that distending pressure (DP, i.e., plateau pressure minus PEEP) correlated better with mortality than did V_T , plateau pressure, or PEEP. This correlation was confirmed by Bellani et al.,⁽⁹⁾ and a DP of < 14 -15 cmH₂O has been recommended as a lung-protective ventilation strategy in ARDS.⁽¹⁰⁾

Although experimental studies have shown that VILI can occur in previously normal lungs,^(11,12) the impact of lung-protective MV on patients without ARDS is controversial. In a randomized clinical trial in patients without ARDS, Determann et al.⁽¹³⁾ showed that low V_T resulted in a lower occurrence of VILI. However, in

another randomized clinical trial in patients without ARDS, no differences were found between patients receiving ventilation with a low V_T and those receiving ventilation with a high V_T regarding mortality and duration of MV.⁽¹⁴⁾

Observational studies have evaluated the impact of DP on mortality in patients without ARDS; however, the results have been conflicting. Although Simonis et al. showed an association between an increased DP and ICU mortality,⁽¹⁵⁾ Schimidt et al. found no association between DP and in-hospital mortality in patients without ARDS.⁽¹⁶⁾ One limitation of these studies was that maximum airway pressure was assumed to be equivalent to plateau pressure in patients receiving pressure-controlled ventilation and was used in order to calculate DP. Maximum airway pressure is necessarily greater than plateau pressure, and we propose that the term maximum DP (MDP) be used in order to refer to the difference between maximum airway pressure and PEEP.

One possible explanation for these conflicting results is that mechanically ventilated patients without ARDS can present with a variety of clinical conditions requiring ventilatory support, all of which can differ in terms of the risk for VILI. Given that VILI ultimately results in an inflammatory lung injury that is similar to ARDS, it is to

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be expected that VILI is more likely to occur in patients without ARDS with one or more risk factors for ARDS than in those with no risk factors for ARDS.⁽¹⁷⁾ The primary objective of this prospective cohort study was to evaluate the association that protective MV (based on V_T and MDP) has with mortality in patients at risk for ARDS. A secondary objective was to identify factors associated with nonprotective MV in these patients.

METHODS

This was a prospective cohort study conducted between May of 2016 and March of 2018 in the ICU of the *Hospital Universitário da Universidade Federal de Juiz de Fora* (HU-UFJF, Federal University of Juiz de Fora University Hospital), located in the city of Juiz de Fora, Brazil. The HU-UFJF ICU is a 9-bed medical-surgical ICU for adult patients. The study followed the principles of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the HU-UFJF (Ruling no. 2,494,061). Close relatives of the patients gave written informed consent.

Study cohort

The inclusion criteria were being ≥ 18 years of age, having been admitted to the ICU, being on MV, and having at least one of the following risk factors for ARDS: pneumonia, sepsis, shock, aspiration of gastric contents, pancreatitis, blood component transfusion, trauma, pulmonary contusion, and lung injury caused by inhalation or near drowning. The exclusion criteria were as follows: having been diagnosed with ARDS in accordance with the Berlin Definition of ARDS⁽¹⁸⁾ within two days of endotracheal intubation; having been transferred from another hospital while on MV; having been on MV for less than 48 h; and having been started on palliative care by decision of the treatment team.

All patients were ventilated with a Servo-S ventilator (Maquet, Solna, Sweden), initially in pressure-controlled mode. Patients were switched to pressure support ventilation if they were awake and stable, as evaluated by the treatment team.

Variables

Data on baseline clinical and demographic characteristics were collected at ICU admission for the Simplified Acute Physiology Score 3 (SAPS 3) and SOFA, as were data on diagnosis at admission and comorbidities. The day of endotracheal intubation was designated day 0, the following data being recorded: reason for intubation, risk factors for ARDS, the SAPS 3, SOFA scores, predicted body weight—weight = $50.0 + 0.91 \times (\text{height in cm} - 152.4)$ for males and weight = $45.5 + 0.91 \times (\text{height in cm} - 152.4)$ for females—BMI, ventilatory parameters, and arterial blood gases.

From MV day 1 to MV day 7, ventilatory parameters were collected daily at 8:00 a.m. and 8:00 p.m., as were data on the use of vasopressors, corticosteroids,

and neuromuscular blocking agents while on MV. Data on 28-day mortality, ICU mortality, and in-hospital mortality were also collected.

The exposure variable was whether or not protective MV based on V_T was used within the first 7 days of MV. Protective MV based on V_T was considered to have been provided when the V_T was found to be lower than 8 mL/kg of predicted body weight in at least 80% of the 14 measurements performed within the first 7 days of MV. A second exposure variable was whether protective MV based on MDP (difference between maximum airway pressure and PEEP) was used within the first 7 days of MV. Protective MV based on MDP was considered to have been provided when the MDP was found to be lower than 15 cmH₂O in at least 80% of the 14 measurements performed within the first 7 days of MV. MV was also considered to be protective when it met the criteria for protective MV as defined by both the V_T and the MDP.

Outcome measures

The outcome measures were 28-day mortality, in-hospital mortality, and ICU mortality.

Statistical analysis

The results are presented as mean and standard deviation, median and interquartile range, or proportions, as appropriate. For continuous variables with normal distribution, the groups protective MV and nonprotective MV were compared by the Student's t-test; for continuous variables with non-normal distribution, they were compared by the Wilcoxon test, the Shapiro-Wilk test being used in order to determine the distribution of the variables. For categorical variables, the groups were compared by the chi-square test.

Multivariate Cox regression was used in order to estimate the hazard ratio (HR) for 28-day mortality, ICU mortality, and in-hospital mortality as a function of whether or not protective MV had been used. The HR was adjusted for age, SAPS 3, use of vasopressors, the PaO₂/FIO₂ ratio, PEEP, respiratory system compliance (C_{rs}), pH_i, and PaCO₂.

Multivariate logistic regression was performed to analyze factors independently associated with the use of nonprotective MV, all of the variables showing $p < 0.2$ in the univariate analysis being included in the multivariate analysis. The coefficients were estimated by the maximum likelihood method.

Values of $p < 0.05$ were considered statistically significant. All analyses were performed with the Stata statistical package, version 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

During the study period, 258 patients were admitted to the HU-UFJF ICU. Of those, 148 met the inclusion criteria. Of those, 32 were excluded, the study cohort therefore consisting of 116 patients. The main reason

for exclusion was having been started on palliative care by decision of the treatment team. As can be seen in Figure 1, nonprotective MV based on V_T was used in 49 patients (42.2%; 95% CI: 33.5-51.1%) and nonprotective MV based on MDP was used in 38 (32.8%; 95% CI: 24.7-41.9%).

The main baseline characteristics of the patients are summarized in Table 1. The mean age was 59.3 ± 17.7 years, and the SAPS 3 at ICU admission was 49.9 ± 15.8 . Major risk factors for ARDS included shock, in 71 patients (61.2%), sepsis, in 68 (58.6%), and pneumonia, in 27 (23.3%); a total of 66 patients (56.9%) had more than one risk factor for ARDS. Table 2 shows the outcomes of patients receiving protective or nonprotective MV based on V_T and MDP.

At baseline, patients receiving protective MV based on V_T had lower severity scores (SAPS 3), higher predicted body weight, higher pH values, and lower FiO_2 than did those receiving nonprotective MV (Table 1). Protective MV based on V_T was not associated with lower in-hospital mortality, ICU mortality, or 28-day mortality (Tables 3 and 4). Given that sample size was not initially calculated, the power of the study to detect an association between protective MV based on V_T and ICU mortality was calculated. On the basis of the number of patients included in the study ($N = 116$) and the results obtained ($HR = 0.72$), with $p < 0.05$ being considered significant, the power of the study to detect an association between protective MV based on V_T and ICU mortality was 39%. The following variables were independently associated with nonprotective MV based on the V_T : the SAPS 3 at admission, predicted body weight, and the PaO_2/FiO_2 ratio (Table 5).

Patients receiving protective MV based on MDP had higher C_{rs} , better gas exchange (higher PaO_2/FiO_2 and lower $PaCO_2$), and higher pH values, as well as requiring lower FiO_2 and PEEP (Table 1). After

adjustment for covariates, protective MV based on MDP was associated with lower in-hospital mortality, ICU mortality, and 28-day mortality (Tables 3 and 4). On the basis of the number of patients included in the study ($N = 116$) and the results obtained ($HR = 0.68$), with $p < 0.05$ being considered significant, the power of the study to detect an association of protective MV based on MDP with mortality was 43%. The following variables were independently associated with nonprotective MV based on the MDP: pneumonia as the reason for initiating MV, C_{rs} , the PaO_2/FiO_2 ratio, and pH (Table 5).

When protective MV was defined on the basis of both the V_T and the MDP, it was significantly associated with 28-day mortality, although not with in-hospital mortality or ICU mortality (Tables 3 and 4).

DISCUSSION

In the present study, no association was found between lower mortality and protective MV based on a V_T of < 8 mL/kg of predicted body weight in more than 80% of the measurements performed within the first 7 days of ventilatory support in patients at risk for ARDS. However, when protective MV was defined on the basis of an MDP of < 15 cmH₂O, it was associated with lower in-hospital mortality, ICU mortality, and 28-day mortality.

Although it is well established that protective MV reduces mortality in patients with ARDS,^(6,7) the benefits of protective MV in patients without ARDS remain controversial. In a meta-analysis of randomized clinical trials and observational studies conducted in ICUs or during major surgery, protective MV with low V_T was associated with better clinical outcomes in patients without ARDS, including lower mortality and lower occurrence of lung infection and injury.⁽¹⁹⁾ However, in a clinical trial of patients without ARDS, no differences in mortality (ICU mortality, in-hospital

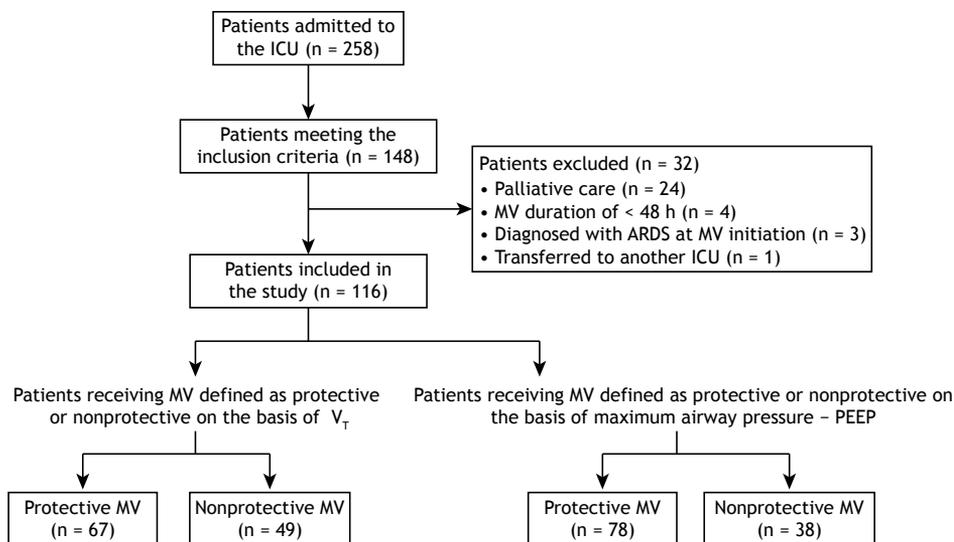


Figure 1. Cohort study flow chart. MV: mechanical ventilation.

Table 1. Baseline characteristics of patients receiving protective or nonprotective mechanical ventilation.^a

	Total sample (N = 116)	Group				p
		Protective MV (n = 67)	V _T Nonprotective MV (n = 49)	Protective MV (n = 78)	MDP Nonprotective MV (n = 38)	
Age, years	59.3 ± 17.7	57.0 ± 18.2	62.3 ± 16.7	57.6 ± 18.6	62.6 ± 15.2	0.152
Males	65 (56.0)	44 (65.7)	21 (42.9)	47 (60.3)	18 (47.4)	0.189
SAPS 3 at admission	49.9 ± 15.8	46.8 ± 15.2	54.3 ± 15.8	48.7 ± 15.8	52.4 ± 15.9	0.247
SOFA at admission	7.8 ± 3.7	7.7 ± 3.5	8.0 ± 3.9	7.7 ± 3.7	8.0 ± 3.6	0.684
SAPS 3 at intubation	51.2 ± 14.8	47.9 ± 14.3	55.7 ± 14.2	50.0 ± 14.8	53.6 ± 14.6	0.219
SOFA at intubation	8.3 ± 3.3	8.2 ± 3.2	8.5 ± 3.4	8.2 ± 3.3	8.5 ± 3.3	0.724
BMI, kg/m ²	22.5 [19.0-27.0]	22.3 [19.6-26.3]	23.3 [18.0-28.3]	22.2 [18.8-25.6]	23.6 [20.9-28.3]	0.171
Predicted body weight, kg	58.5 ± 10.3	61.7 ± 9.1	54.2 ± 10.5	58.9 ± 10.7	57.7 ± 9.8	0.549
Reason for ICU admission						0.715
Clinical						
Elective surgery	95 (81.9)	55 (82.1)	40 (81.6)	63 (80.8)	32 (84.2)	
Urgent surgery	13 (11.2)	8 (11.9)	5 (10.2)	10 (12.8)	3 (7.9)	
Urgent surgery	8 (6.9)	4 (6.0)	4 (8.2)	5 (6.4)	3 (7.9)	
Risk factor for ARDS						
Pneumonia	27 (23.3)	16 (23.9)	11 (22.5)	14 (17.9)	13 (34.2)	0.052
Sepsis	68 (58.6)	38 (56.7)	30 (61.2)	47 (60.3)	21 (55.3)	0.608
Shock	71 (61.2)	37 (55.2)	34 (69.4)	46 (59.0)	25 (65.8)	0.480
Aspiration	4 (3.5)	4 (5.9)	0 (0.0)	3 (3.9)	1 (2.6)	0.737
Blood product transfusion	21 (18.1)	10 (14.9)	11 (22.5)	14 (18.0)	7 (18.4)	0.951
Other	10 (8.6)	6 (8.9)	4 (8.2)	8 (10.3)	2 (5.3)	0.368
Number of risk factors						0.464
1	50 (43.1)	32 (47.8)	18 (36.7)	34 (44.0)	16 (42.1)	
2	47 (40.5)	26 (38.8)	21 (42.9)	33 (42.3)	14 (36.8)	
3	18 (15.5)	8 (11.9)	10 (20.4)	11 (14.1)	7 (18.4)	
4	1 (0.9)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.4)	
MV (day 0)						
FIO ₂	0.5 [0.4-0.6]	0.45 [0.4-0.6]	0.5 [0.4-0.7]	0.4 [0.4-0.5]	0.6 [0.5-0.7]	<0.001
FR, breaths/min	18 [16-22]	20 [16-22]	17 [16-20]	18 [16-21]	18 [16-22]	0.608
V _T /predicted body weight, mL/kg	7.5 ± 1.4	6.9 ± 1.1	8.3 ± 1.4	7.5 ± 1.5	7.4 ± 1.4	0.617
MDP, cmH ₂ O	14.5 ± 3.4	14.3 ± 3.4	14.8 ± 3.5	13.5 ± 3.0	16.6 ± 4.1	<0.001
Paw _{max} , cmH ₂ O	20.6 ± 4.5	20.5 ± 4.7	21.0 ± 4.4	19.3 ± 3.7	23.5 ± 5.0	<0.001
PEEP, cmH ₂ O	5 [5-7]	5 [5-6]	6 [5-7]	5 [5-6]	6 [5-7]	0.019
C _{rs} , mL/cmH ₂ O	31.8 ± 10.3	31.5 ± 9.8	32.2 ± 11.0	33.7 ± 10.1	27.7 ± 9.5	<0.001
Arterial blood gas analysis (day 0):						
pH	7.34 ± 0.11	7.36 ± 0.1	7.32 ± 0.1	7.36 ± 0.11	7.30 ± 0.10	0.005
PaCO ₂ , mmHg	289.0 ± 104.0	301.8 ± 96.0	272.5 ± 112.1	320.0 ± 98.0	224.0 ± 85.0	<0.001
PaCO ₂ , mmHg	38.5 ± 11.6	38.7 ± 10.6	38.2 ± 12.9	36.2 ± 9.1	43.3 ± 14.4	0.002

MDP: maximum distending pressure; SAPS 3: Simplified Acute Physiology Score 3; MV: mechanical ventilation; Paw_{max}: maximum airway pressure; and C_{rs}: respiratory system compliance. ^aValues expressed as n (%), mean ± SD, or median [IQR].

Table 2. Outcomes of patients receiving protective or nonprotective mechanical ventilation.^a

Variable	Total sample (n = 116)	Group					
		V _T		p	MDP		p
		Protective MV (n = 67)	Nonprotective MV (n = 49)		Protective MV (n = 78)	Nonprotective MV (n = 38)	
Use of vasopressors	100 (86.2)	56 (83.6)	44 (89.8)	0.338	65 (83.3)	35 (92.1)	0.198
Use of corticosteroids	90 (77.6)	49 (73.1)	41 (83.7)	0.179	57 (73.1)	33 (86.8)	0.095
Use of neuromuscular blocking agents	19 (16.4)	11 (16.4)	8 (16.3)	0.990	7 (9.0)	12 (31.6)	0.002
28-day mortality	35 (30.2)	14 (20.9)	21 (42.9)	0.011	19 (24.4)	16 (42.1)	0.051
ICU mortality	47 (40.5)	22 (32.9)	25 (51.0)	0.049	23 (29.5)	24 (63.2)	0.001
In-hospital mortality	59 (50.9)	28 (41.8)	31 (63.3)	0.22	30 (38.5)	29 (76.3)	< 0.001

MDP: maximum distending pressure; and MV: mechanical ventilation. ^aValues expressed as n (%).

Table 3. Univariate Cox regression for the association of mortality with protective mechanical ventilation based on V_T on maximum distending pressure, and on both.

Outcome	Protective MV based on					
	V _T ^a		MDP ^b		Both the V _T and the MDP	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
In-hospital mortality	0.63 (0.37-1.05)	0.079	0.60 (0.36-1.01)	0.053	0.46 (0.29-0.93)	0.03
ICU mortality	0.72 (0.40-1.28)	0.261	0.49 (0.27-0.88)	0.189	0.60 (0.30-1.21)	0.151
28-day mortality	0.44 (0.22-0.86)	0.017	0.56 (0.29-1.11)	0.096	0.38 (0.17-0.83)	0.016

MV: mechanical ventilation; MDP: maximum distending pressure; and HR: hazard ratio. ^aProtective MV based on V_T: a V_T of < 8 mL/kg of predicted body weight in at least 80% of the 14 measurements performed within the first seven days of MV. ^bProtective MV based on MDP: an MDP of < 15 cmH₂O in at least 80% of the 14 measurements performed within the first seven days of MV.

Table 4. Multivariate Cox regression for the association of mortality with protective mechanical ventilation based on V_T on maximum distending pressure, and on both.^a

Outcome	Protective MV based on					
	V _T ^b		MDP ^c		Both the V _T and the MDP	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
In-hospital mortality	0.75 (0.43-1.32)	0.320	0.48 (0.26-0.90)	0.022	0.53 (0.28-1.01)	0.055
ICU mortality	0.78 (0.42-1.47)	0.443	0.45 (0.24-0.90)	0.023	0.59 (0.28-1.25)	0.151
28-day mortality	0.53 (0.24-1.16)	0.113	0.41 (0.18-0.94)	0.036	0.40 (0.17-0.94)	0.036

MV: mechanical ventilation; MDP: maximum distending pressure; and HR: hazard ratio. ^aModel adjusted for age, Simplified Acute Physiology Score 3, use of vasopressors, PaO₂/FiO₂, PEEP, respiratory system compliance, pH, and PaCO₂. ^bProtective MV based on V_T: a V_T of < 8 mL/kg of predicted body weight in at least 80% of the 14 measurements performed within the first seven days of MV. ^cProtective MV based on MDP: an MDP of < 15 cmH₂O in at least 80% of the 14 measurements performed within the first seven days of MV.

mortality, 28-day mortality, or 90-day mortality), duration of MV, or ICU length of stay were found between patients randomized to MV with low V_T (4-6 mL/kg of predicted body weight) and those randomized to MV with high V_T (10 mL/kg of predicted body weight).⁽¹⁴⁾ In an observational study of a cohort of 935 patients without ARDS,⁽¹⁶⁾ no correlations were found between V_T and mortality. These results are consistent with ours and constitute evidence against the use of low V_T in mechanically ventilated patients without ARDS.

One possible explanation for the lack of association between lower V_T and better outcomes in patients without ARDS is that such patients have higher C_{res}, which can reduce the risk of injury even if they receive MV with high V_T. Therefore, DP (or MDP, as in our study) might be better than V_T to adjust MV for

lung-protective ventilation in patients without ARDS. DP is calculated by dividing V_T by static compliance of the respiratory system.⁽⁸⁾ Therefore, whenever compliance is reduced, translating to greater pulmonary involvement, V_T should be reduced for protective MV based on the DP. A randomized clinical trial⁽¹⁴⁾ corroborated this hypothesis, showing no differences between MV with low V_T and MV with intermediate V_T regarding the outcomes of patients without ARDS, with the levels of DP in both groups being protective against VILI (11 cmH₂O in the low V_T group and 13 cmH₂O in the intermediate V_T group).

In our study, protective MV based on the MDP correlated with lower mortality, suggesting that MDP is an important parameter to be considered for protective MV in patients without ARDS. The association between protective MV and mortality was found to be worse

Table 5. Factors associated with nonprotective mechanical ventilation based on both the V_T and the maximum distending pressure.

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
V_T				
Age	1.02 (1.00-1.04)	0.109		
Male sex	0.39 (0.18-0.84)	0.015		
SAPS 3	1.03 (1.01-1.06)	0.014	1.05 (1.02-1.08)	0.002
Predicted body weight	0.92 (0.89-0.96)	< 0.001	0.91 (0.86-0.95)	< 0.001
PaO ₂ /FiO ₂	1.00 (0.99-1.00)	0.135	0.99 (0.99-1.00)	0.020
pH	0.96 (0.93-0.99)	0.035		
Use of corticosteroids	1.88 (0.74-4.77)	0.183		
MDP				
Age	1.01 (0.99-1.04)	0.153		
Male sex	0.60 (0.27-1.30)	0.191		
BMI	1.05 (0.98-1.11)	0.162		
Pneumonia	2.38 (0.98-5.76)	0.055	3.23 (1.07-9.71)	0.037
PEEP	1.25 (0.10-1.56)	0.052		
C _{rs}	0.93 (0.88-0.98)	0.004	0.94 (0.89-0.99)	0.029
PaO ₂ /FiO ₂	0.99 (0.98-0.99)	< 0.001	0.99 (0.98-0.99)	< 0.001
pH	0.95 (0.91-0.99)	0.007	0.95 (0.90-0.99)	0.017
PaCO ₂	1.06 (1.02-1.10)	0.004		
Use of corticosteroids	2.43 (0.84-7.06)	0.102		
Use of neuromuscular blocking agents	4.68 (1.66-13.18)	0.003		
Use of vasopressors	2.33 (0.62-8.74)	0.209		

SAPS 3: Simplified Acute Physiology Score 3; MDP: maximum distending pressure; and C_{rs}: respiratory system compliance.

when MV was defined as protective on the basis of both the V_T and the MDP, the addition of V_T therefore being unnecessary. Our results are consistent with those of other studies^(16,20) showing correlations between MDP and the outcomes of patients without ARDS. In a study showing no correlation between V_T and mortality, a positive correlation was found between MDP and ICU mortality.⁽¹⁶⁾ In an observational study of a cohort of 986 patients receiving MV because of an acute neurological condition, Tejerina et al. demonstrated that increased mortality correlated with increased MDP but not with increased V_T .⁽²⁰⁾

We decided to use the term MDP in order to differentiate it from DP, which was initially correlated with better outcomes in ARDS in the study by Amato et al.⁽⁸⁾ DP is calculated as the difference between plateau pressure, which is measured at the end of an inspiratory pause, and PEEP. Some authors have used end-inspiratory airway pressure during pressure-controlled MV instead of plateau pressure for calculating DP.^(15,16,20) Although they are similar or even the same in some cases, especially when there is no significant increase in airway resistance, they are not necessarily always the same. However, MDP will always be equal to or greater than DP and is therefore a useful parameter for monitoring VILI.

To our knowledge, this is the first prospective study analyzing the risk factors associated with the adoption of nonprotective MV in patients at risk for ARDS. The factors associated with nonprotective MV based on the

V_T were those related to greater patient severity (the SAPS 3 and the PaO₂/FiO₂ ratio) and lower predicted body weight. The association between nonprotective MV and greater patient severity was likely due to priority being given to stabilizing arterial blood gas levels in these patients, possibly to the detriment of protective MV. The association between nonprotective MV and lower predicted body weight was likely due to an inadequate estimate of predicted body weight in shorter patients, given that it is calculated on the basis of patient height. It should be noted that an inappropriate V_T setting based on predicted body weight is more likely to occur in women, as indicated by the results of univariate analysis. The factors associated with nonprotective MV based on the MDP were those related to more severe lung disease (pneumonia, lower C_{rs}, and lower PaO₂/FiO₂) and greater ventilatory demand (lower pH values). These results suggest that not enough attention has been paid to MDP for protective MV, with the MDP increasing when lung mechanics are altered or when there is a need to compensate for acidosis.

Our study has several strengths. First, V_T and MDP were measured twice a day during the first 7 days of MV in order to define MV as protective or nonprotective. Previous observational studies of the correlations of V_T and DP with mortality in patients without ARDS have collected ventilator settings on a single day, usually the first day of MV.^(14,15,20) This single assessment, particularly in the case of DP,

may have been much more reflective of the severity of the initial lung disease and its impact on patient outcomes. We believe that our 7-day measurements of V_T and MDP more accurately reflect the correlation of the ventilatory strategy used with the occurrence of VILI and its impact on mortality. In addition, we evaluated the association between nonprotective MV and mortality in a specific group of patients without ARDS, i.e., those with one or more risk factors for developing ARDS. Such patients have worse outcomes (e.g., pulmonary complications and increased mortality) than do those without risk factors for ARDS.^(14,21) Therefore, among patients without ARDS, those with one or more risk factors for ARDS represent a subgroup of patients in whom a lung-protective ventilation strategy is most relevant.

Some limitations of our study should be noted. During the measurements of MDP, particularly in patients receiving pressure support ventilation, we did not consider the possibility of patient inspiratory effort increasing transpulmonary pressure, which is associated with VILI. This limitation is inevitable when esophageal pressure is not monitored in patients making inspiratory efforts. Given the observational nature of our study, it cannot be stated that the correlation between MDP and mortality indicates

causality; that is, it cannot be stated that nonprotective MV based on the MDP resulted in increased mortality. Despite multivariate analysis to adjust for potential confounders, a higher MDP may have represented greater patient severity of illness, thus explaining its association with mortality. The sample size may have been insufficient to detect associations between V_T and mortality, given that the power of the study to detect such associations was 39%. However, the fact that an association was found between MDP and mortality—the power of the study to detect such an association being 43%—suggests that MDP is better than V_T to adjust MV for lung-protective ventilation. Because this was a single-center study, our results should be extrapolated with caution.

In conclusion, an increased MDP during the first 7 days of MV was associated with increased mortality, although an increased V_T was not. Therefore, MDP is a parameter that should be considered in mechanically ventilated patients at risk for ARDS. Factors associated with nonprotective MV include lower $\text{PaO}_2/\text{FiO}_2$, lower C_{rs} , pneumonia as the reason for initiating MV, higher severity scores, acidosis, and lower predicted body weight. In the presence of one or more of these factors, MV settings should be adjusted to avoid harmful parameters.

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