Driving Pressure Is a Risk Factor for ARDS in Mechanically Ventilated Subjects Without ARDS

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BACKGROUND: Driving pressure (ΔP) has been described as a risk factor for mortality in patients with ARDS. However, the role of ΔP in the outcome of patients without ARDS and on mechanical ventilation has received less attention. Our objective was to evaluate the association between ΔP on the first day of mechanical ventilation with the development of ARDS. METHODS: This was a post hoc analysis of a multicenter, prospective, observational, international study that included subjects who were on mechanical ventilation for > 12 h. Our objective was to evaluate the association between ΔP on the first day of mechanical ventilation with the development of ARDS. To assess the effect of ΔP, a logistic regression analysis was performed when adjusting for other potential risk factors. Validation of the results obtained was performed by using a bootstrap method and by repeating the same analyses at day 2. RESULTS: A total of 1,575 subjects were included, of whom 65 (4.1%) developed ARDS. The ΔP was independently associated with ARDS (odds ratio [OR] 1.12, 95% CI 1.07–1.18 for each cm H_2O of ΔP increase, $P < .001$). The same results were observed at day 2 (OR 1.14, 95% CI 1.07–1.21; $P < .001$) and after bootstrap validation (OR 1.13, 95% CI 1.04–1.22; $P < .001$). When taking the prevalence of ARDS in the lowest quartile of ΔP (≤9 cm H_2O) as a reference, the subjects with ΔP > 12–15 cm H_2O and those with ΔP > 15 cm H_2O presented a higher probability of ARDS (OR 3.65, 95% CI 1.32–10.04 [$P = .01$] and OR 7.31, 95% CI, 2.89–18.50 [$P < .001$], respectively). CONCLUSIONS: In the subjects without ARDS, a higher level of ΔP on the first day of mechanical ventilation was associated with later development of ARDS. (ClinicalTrials.gov registration NCT02731898.) *Key words: Driving pressure; mechanical ventilation; acute respiratory distress syndrome; ventilator-induced lung injury; mechanical power; compliance; mortality.* [Respir Care 2021;66(10):1505–1513. © 2021 Daedalus Enterprises]

Introduction

Mechanical ventilation is a supportive therapy that saves lives. However, it is associated with complications in the lungs as well as in distal organs.[1] As a consequence, the paradigm for setting the ventilator has moved from correcting gas-exchange abnormalities and providing mechanical support for respiratory muscle function to minimizing ventilator-induced lung injury.[2] Since the seminal studies published several decades ago, a lung-protective strategy has become the hallmark of ventilatory support of patients with ARDS.[3,4] A more controversial issue is the application of this ventilatory strategy in patients without ARDS who are on mechanical ventilation.[5-9] In fact, a recent randomized controlled trial that compared the setting of low tidal volumes (V_T) versus intermediate V_T in subjects without ARDS found no differences in ventilator-free days, length of stay, or mortality.[10]

One of the objectives of a lung-protective strategy is to maintain low plateau pressure (P_{plat}) to minimize ventilator-

induced lung injury.[11] However, the driving pressure (ΔP), calculated as P_{plat} minus PEEP, has emerged as a better predictor of outcomes in patients with ARDS.[12-16] The ΔP is calculated by the ratio between V_T and the compliance of the respiratory system (C_{RS}), and corresponds to the functional size of the lung. This ratio can be routinely estimated in patients who are not making inspiratory efforts. A few studies have assessed the relationship between ΔP and the occurrence of ARDS or other clinical outcomes in subjects without ARDS,[17-20] including subjects on mechanical ventilation for neurologic diseases[21] and surgical subjects.[22,23] In fact, the study by Futier et al[23] suggested that using a lung-protective strategy in subjects without ARDS was associated with better outcomes. In our study, we hypothesized that ΔP could be a risk factor for the development of ARDS and mortality in patients who are critically ill and who do not meet ARDS criteria. Therefore, our main objective was to analyze whether a higher ΔP could be a risk factor for the development of ARDS. Second, we analyzed the association of ΔP with mortality.

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QUICK LOOK

Current knowledge

The role of driving pressure (ΔP) in non-injured lungs has previously been assessed in some studies that presented important limitations. Some included a limited number of subjects or a selected population. Another study did not exclude patients with significant inspiratory effort. The largest of the studies was a post hoc analysis of a randomized controlled trial; this design may have led to a certain selection bias of the subjects included, due to the strict inclusion and exclusion criteria.

What this paper contributes to our knowledge

In a large international cohort of non-selected subjects without ARDS at the time of intubation, an association between higher ΔP and a later development of ARDS and of ICU and hospital mortality was demonstrated and validated. Indeed, when considering the prevalence of ARDS in the lowest quartile of ΔP as a reference, subjects with ΔP > 12 cm H_2O presented a higher probability of developing ARDS.

Methods

Study Design

We performed a post hoc analysis of a multicenter, prospective, observational, international study,[24] which included all adult patients admitted during 1 month in 2016 to 534 ICUs in 32 countries and who required invasive mechanical ventilation for >12 h. National coordinators recruited local investigators from eligible ICUs (see the full list of investigators in the supplementary materials at http://www.rcjournal.com). Only the research team members at each site were aware of the purpose and the precise timing of the study. The ethics committees at each participating institution approved the protocol, and waivers of informed consent were obtained in accordance with local regulations. This study followed the recommendations of the Strengthening the

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Reporting of Observational Studies in Epidemiology guidelines[25] for reporting observational studies.

Subjects

In this post hoc analysis, the inclusion criteria were the following: (a) mode of ventilation: volume-assisted controlled, pressure-assisted controlled, and pressure-regulated volume controlled; (b) total breathing frequency equal to the breathing frequency set in the ventilator. Exclusion criteria were the following: (1) patients in whom ARDS was the reason for mechanical ventilation or those who met ARDS criteria on the first day after inclusion, (2) patients who were spontaneously breathing, (3) patients who did not have ΔP measurement at day 1, and (4) patients with missing data on the measured and outcomes variables.

Variables Recorded

A rigorous, once-a-day clinical assessment of all the patients admitted to the participants' ICUs was performed by the investigators of each site. The ΔP was calculated as end-inspiratory P_{plat}, after an end-inspiratory occlusion, minus PEEP. The presence of ARDS was specifically addressed. ARDS was defined according to the Berlin definition,[26] and the subjects had to meet ARDS criteria for at least 1 day in the first 28 d of inclusion. The presence of ARDS was determined by the physician in charge of the subject. Moreover, static C_{RS} was calculated as $V_T/(P_{plat} - PEEP)$ and mechanical power was estimated by using the following equation: $(0.098 \times V_T \times$ breathing frequency $(P_{peak} - 1/2 \times \Delta P)$, expressed in J/min.[27]

We also collected baseline characteristics (age, sex, severity at admission estimated by the Simplified Acute Physiology Score,[28] which ranges from 0 [lower severity] to 163 [higher severity]), daily gas exchange, variables related to management ventilator settings, sedation, neuromuscular blockers, and complications (ARDS,[26] sepsis, ventilator-associated pneumonia,[29] organ function [cardiovascular, renal, hepatic, hematologic] evaluated according to the SOFA score[30] and organ failure defined as a SOFA subscore > 2 points for organ in question) while subjects were ventilated or until day 28. The subjects were followed up in the hospital to assess for mortality and stay outcomes.

Statistical Analysis

Quantitative variables are expressed as means ± SDs or medians (interquartile ranges) in non-normally distributed variables. Categorical variables are expressed as frequency (%). Continuous variables were compared by using the Student *t* test or the Mann-Whitney test, as appropriate. Differences in categorical variables were assessed with the chi-square test or the Fisher exact test, as appropriate. The main outcome was the development of ARDS within the first 28 d of mechanical ventilation. To assess whether ΔP measured at day 1 was an independent risk factor for ARDS, the Firth logistic regression analysis was performed with adjustment for potential confounding.[31,32] Confounder elections were defined as any third variable associated with the outcome or any other variable defined by using causal models.[33] However, because ΔP is defined as the difference between P_{plat} and PEEP, the multicollinearity among ΔP and PEEP and P_{plat} was studied. In the absence of multi-collinearity, the variable was also included in the logistic regression analysis. The P_{plat} was not included in the multivariate analysis because of its collinearity with ΔP.

We validated the results obtained with the ΔP measured at day 1 in 2 different ways. First, a bootstrap validation was performed. Random samples (1,000) of the dataset were taken; a statistical analysis was run on each random sample, and a bootstrap 95% CI for the primary finding was generated. Second, we repeated the same logistic regression analysis with the value of ΔP measured at day 2.[12] Moreover, additional sensitivity analyses were conducted. First, we considered only the occurrence of ARDS in the first 7 d as an outcome. Second, the same analysis was repeated when considering only the subjects with a higher risk of ARDS (pneumonia) and the subjects with a lower risk of ARDS (postoperative patients and patients with neurologic disease). Finally, ΔP was divided into quartiles, and the risk of each quartile for occurrence of ARDS and mortality was analyzed by adjusting for potential risk factors. The adjusted probability of ARDS for different quartiles of ΔP at different time points was assessed by Cox proportional hazard modelling when adjusting for covariates. All statistical analyses were performed by using Stata Statistical Software 14 (StataCorp, College Station, Texas). A 2-sided $P < .05$ was considered statistically significant.

Results

Baseline Characteristics and Respiratory Variables

From the 8,753 patients admitted to the participating units, 1,575 met the inclusion criteria for this analysis (supplemental Fig. 1, see the supplementary materials at http://www.

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Supplementary material related to this paper is available at http://www.rcjournal.com.

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Table 1. Differences in Baseline Characteristics (Within the First 24 h of Inclusion) Between the Subjects Who Developed ARDS in the First 28 d and the Subjects Who Did Not

Variable	All ($N = 1,575$)	ARDS in the first 28 d ($n = 65$)	No ARDS in the first 28 d ($n = 1,510$)	P
Age, mean ± SD y	60 ± 18	54 ± 16	61 ± 18	.006
Men, *n* (%)	1,020 (64.8)	40 (61.5)	980 (64.9)	.31
Reason for mechanical ventilation, *n* (%)				<.001
COPD	66 (4.2)	1 (1.5)	65 (4.3)	
Asthma	13 (0.8)	1 (1.5)	12 (.8)	
Other CRD	21 (1.3)	1 (1.5)	20 (1.3)	
Postoperative	314 (19.9)	5 (7.7)	309 (20.5)	
Chronic heart failure	76 (4.8)	1 (1.5)	75 (5.0)	
Aspiration	30 (1.9)	1 (1.5)	29 (1.9)	
Pneumonia	147 (9.3)	18 (24.6)	131 (8.7)	
Sepsis	174 (11.1)	7 (1.8)	167 (11.1)	
Trauma	81 (5.1)	10 (15.4)	71 (4.7)	
Cardiac arrest	109 (6.9)	2 (3.1)	107 (7.1)	
Other ARF	65 (4.1)	2 (3.1)	63 (4.2)	
Neurologic disease	460 (29.2)	17 (26.1)	443 (29.3)	
Neuromuscular disease	19 (1.2)	1 (1.4)	18 (1.2%)	
Body mass index, mean ± SD kg/m^2	26.5 ± 5.6	27.3 ± 6.0	26.5 ± 5.6	.30
SAPS II, mean ± SD	48.3 ± 19.4	48.7 ± 17.7	48.3 ± 19.5	.85
Fluid balance in the first 24 h, mean ± SD mL	922 ± 1,795	1218 ± 1,740	908 ± 1,796	.21
Creatinine, mean ± SD mg/dL	1.69 ± 2.15	1.58 ± 1.84	1.70 ± 2.16	.68
Bilirubin, mean ± SD mg/dL	1.36 ± 2.48	1.41 ± 2.17	1.36 ± 2.49	.89
Platelets, mean ± SD, $\times 10^9$/L	209 ± 119	215 ± 172	209 ± 116	.68
Cardiovascular dysfunction (SOFA score > 2), *n* (%)	809 (51.5)	34 (52.3)	777 (51.4)	.55
Respiratory variables, mean ± SD				
Arterial pH	7.33 ± 0.12	7.33 ± 0.11	7.34 ± 0.12	.49
P_{aCO_2}, mm Hg	40 ± 13	41 ± 11	40 ± 13	.56
P_{aO_2}/F_{IO_2}, mm Hg	237 ± 101	222 ± 97	238 ± 102	.25
Breathing frequency, breaths/min	17 ± 4	17 ± 4	17 ± 4	.49
Tidal volume, mL/kg/IBW	7.9 ± 1.4	7.8 ± 1.3	7.9 ± 1.4	.69
PEEP, cm H_2O	6.3 ± 2.2	6.7 ± 2.7	6.3 ± 2.2	.09
Plateau pressure, cm H_2O	18 ± 6	22 ± 5	18 ± 6	<.001
Driving pressure, cm H_2O	12 ± 5	15 ± 5	12 ± 5	<.001
Compliance, mL/cm H_2O	50 ± 36	36 ± 20	51 ± 37	.001
Mechanical power, J/min	15.7 ± 7.2	17.6 ± 6.5	15.6 ± 7.2	.032

CRD = chronic respiratory disease
SAPS = Simplified Acute Physiology Score
SOFA = sequential organ failure assessment
IBW = ideal body weight
ARF = acute respiratory failure

rcjournal.com). Sixty-five subjects (4.13%) developed ARDS during the period of mechanical ventilation. The differences in baseline characteristics between the subjects who developed ARDS and those without lung injury are shown in Table 1. The subjects with ARDS were younger, and the subjects with pneumonia or trauma as the reason for mechanical ventilation developed ARDS more frequently than those with postoperative acute respiratory failure or cardiac failure. The distribution of ARDS appearance is represented in supplemental Figure 2 (see the supplementary materials at http://www.rcjournal.com). Comparisons of respiratory variables at day 1 according to ARDS development are also displayed in Table 1. The subjects who developed ARDS had higher levels of P_{plat} and ΔP, and worse C_{RS} than the subjects who did not develop ARDS. Moreover, the subjects with ARDS presented higher mortality and higher length of stay compared with the subjects without ARDS (supplemental Table 1, see the supplementary materials at http://www.rcjournal.com).

Relationship Between ΔP and Outcomes: ARDS and Mortality

The ΔP at day 1 of mechanical ventilation was independently associated with a higher risk of ARDS (Table 2). In

Table 2. Multivariate Logistic Regression Analysis of the Effect of Driving Pressure

Variable	Univariate Analysis, OR (95% CI)*	*P*	Multivariate Analysis, OR (95% CI)*	*P*
ARDS				
Driving pressure	1.10 (1.06 – 1.14)	<.001	1.12 (1.07 – 1.17)	<.001
Age	0.98 (0.97 – 0.99)	.006	0.98 (0.97 – 1.00)	.052
COPD	0.51 (0.10 – 2.64)	.43	0.83 (0.14 – 4.71)	.83
Pneumonia	3.50 (1.95 – 6.28)	<.001	4.28 (1.92 – 9.55)	<.001
Sepsis	1.03 (0.47 – 2.24)	.94	2.18 (0.86 – 5.53)	.10
Neurologic disease	0.87 (0.50 – 1.52)	.62	1.64 (0.73 – 3.67)	.23
Trauma	3.81 (1.89 – 7.68)	<.001	4.49 (1.72 – 11.69)	.002
P_{aO_2}/F_{IO_2}	0.99 (0.99 – 1.00)	.26	0.99 (0.99 – 1.00)	.94
V_T	0.97 (0.81 – 1.16)	.72	1.04 (0.86 – 1.26)	.71
PEEP	1.09 (0.99 – 1.21)	.07	1.12 (0.99 – 1.25)	.054
ICU mortality				
Driving pressure	1.03 (1.01 – 1.05)	.006	1.03 (1.01 – 1.06)	.003
Age	1.03 (1.02 – 1.03)	<.001	1.03 (1.02 – 1.04)	<.001
COPD	0.80 (0.46 – 1.39)	.43	0.76 (0.42 – 1.43)	.42
Pneumonia	1.44 (1.02 – 2.04)	.041	1.44 (.96 – 2.18)	.08
Sepsis	1.91 (1.39 – 2.63)	<.001	2.29 (1.57 – 3.34)	<.001
Neurologic disease	1.15 (.91 – 1.46)	.24	1.64 (1.21 – 2.22)	.001
Trauma	0.44 (0.25 – 0.78)	.005	0.88 (0.45 – 1.71)	.70
P_{aO_2}/F_{IO_2}	0.99 (0.99 – 0.99)	.007	0.99 (0.99 – 1.00)	.056
V_T	0.96 (0.89 – 1.04)	.34	0.97 (0.94 – 1.05)	.47
PEEP	1.02 (0.97 – 1.07)	.43	0.99 (0.94 – 1.05)	.80
Hospital mortality				
Driving pressure	1.03 (1.01 – 1.05)	.003	1.04 (1.01 – 1.06)	.002
Age	1.03 (1.02 – 1.03)	<.001	1.03 (1.02 – 1.03)	<.001
COPD	0.76 (0.44 – 1.30)	.31	0.70 (0.38 – 1.30)	.26
Pneumonia	1.69 (1.18 – 2.42)	.004	1.69 (1.11 – 2.57)	.02
Sepsis	1.74 (1.23 – 2.46)	.002	2.02 (1.35 – 3.02)	.001
Neurologic disease	1.03 (0.81 – 1.30)	.84	1.39 (1.01 – 1.89)	.041
Trauma	0.38 (0.20 – 0.68)	.004	0.55 (0.24 – 1.26)	.16
P_{aO_2}/F_{IO_2}	0.99 (0.99 – 0.99)	.01	0.99 (0.99 – 1.00)	.14
V_T	0.98 (0.90 – 1.06)	.61	1.00 (0.91 – 1.10)	.99
PEEP	1.01 (9.97 – 1.07)	.56	0.98 (0.93 – 1.04)	.51

* OR and 95% CI are for each cm H_2O of driving pressure increase.
OR = odds ratio
V_T = tidal volume

Table 3. Validation of the Effect of the Driving Pressure on the Development of ARDS Within the First 28 d, ICU, and Hospital Mortality

Variable	Adjusted OR (95% CI) at Day 1*	*P*	Bootstrap OR (95% CI)	*P*	Adjusted OR (95% CI) at Day 2*	*P*
ARDS	1.12 (1.07–1.17)	<.001	1.11 (1.06–1.16)	<.001	1.11 (1.06–1.16)	<.001
ICU mortality	1.03 (1.02–1.04)	.003	1.03 (1.01–1.06)	.034	1.04 (1.01–1.06)	.003
Hospital mortality	1.04 (1.01–1.06)	.002	1.03 (1.01–1.06)	.032	1.04 (1.01–1.06)	.002

* Adjusted by age, COPD, pneumonia, sepsis, trauma, neurologic disease, P_{aO_2} / F_{IO_2}, tidal volume, and PEEP at day 1* and 2*, respectively. OR and 95% CI are for each cm H_2O of driving pressure increase.
OR = odds ratio

fact, each cm H_2O increase of ΔP increased the risk of ARDS by 10%, 95% CI 6–14. ICU and hospital mortality rates were 32.0% and 36.9%, respectively (for hospital mortality there were 192 missing values). In the multivariate analysis, ΔP was associated with ICU mortality (Table 2). Each 1 cm H_2O increase of ΔP raised the risk of ICU and hospital death by 3% (in both cases). The results for the effect of ΔP on ARDS occurrence and on ICU and

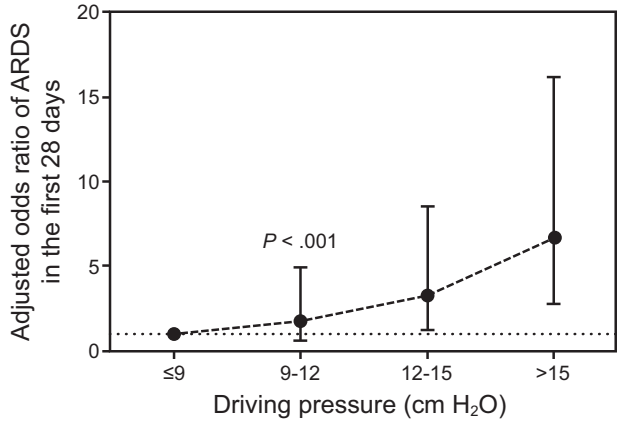
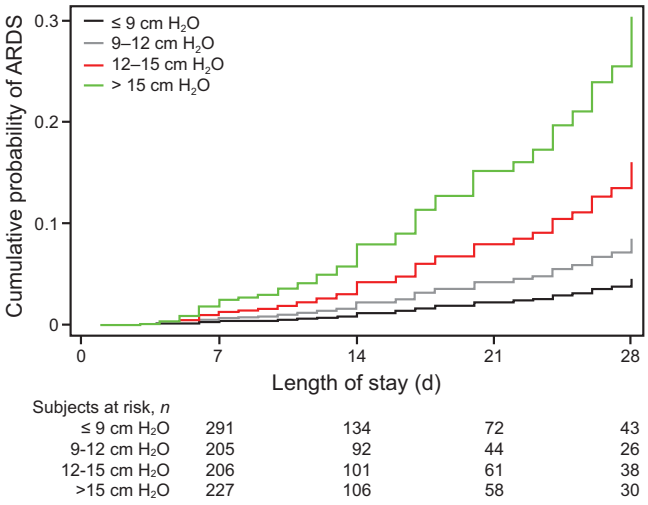


Fig. 1. Adjusted ARDS odds ratio in different quartiles of driving pressure. Adjusted by age, Simplified Acute Physiology Score (SAPS) II, COPD, postoperative, pneumonia, sepsis, CHF, trauma, neurologic disease, pH, P_{aO_2}/F_{IO_2} and P_{aCO_2}, tidal volume, and PEEP. Dotted line represents the trend of the adjusted odds ratio of ARDS at different time frames. CHF, chronic heart failure.



Subjects at risk, *n*

≤ 9 cm H_2O	291	134	72	43
9-12 cm H_2O	205	92	44	26
12-15 cm H_2O	206	101	61	38
>15 cm H_2O	227	106	58	30

Fig. 2. Adjusted probability of ARDS between different quartiles of driving pressure by using the Cox proportional hazard modelling.

hospital mortality were validated by using a bootstrap method and by using the values obtained at day 2 (Table 3). Only the effect of ΔP on hospital mortality was not significant at day 2. Because the occurrence of ARDS was greater in the first 7 d, we performed a sensitivity analysis about the effect of ΔP on ARDS development within the first week. Similar results were observed (supplemental Table 2, see the supplementary materials at http://www.rcjournal.com). Additional sensitivity analyses were performed. First, when considering only the subjects with pneumonia, and second when including only the postoperative subjects and those with neurologic disease. All sensitivity analyses showed consistent results (supplemental Table 3, see the supplementary materials at http://www.rcjournal.com).

Effect of Compliance and Mechanical Power on Outcomes

Because static compliance (C_{RS}) and mechanical power of the respiratory system were lower in the subjects who developed ARDS (Table 1) and had no collinearity with ΔP, the effect of C_{RS} and mechanical power was also assessed in the multivariate analysis. When adjusting for different covariates except ΔP, a higher C_{RS} was associated with a lower risk of ARDS (supplemental Table 4, see the supplementary materials at http://www.rcjournal.com) but not with a lower mortality rate. Moreover, when both ΔP and C_{RS} were included in the regression analysis, ΔP was associated with a higher incidence of ARDS and mortality, whereas C_{RS} was not (supplemental Table 5, see the supplementary materials at http://www.rcjournal.com). The same results were obtained when ΔP and mechanical power were included in the regression analysis (supplemental Table 6, see the supplementary materials at http://www.rcjournal.com).

Effects on Outcomes in Different Quartiles of ΔP

To investigate whether there is a dose-response association between ΔP and the outcome, we also analyzed the effect of ΔP on ARDS and mortality by splitting the overall cohort into different ΔP quartiles (supplemental Tables 7 and 8, see the supplementary materials at http://www.rcjournal.com). After adjusting for different covariates and when taking as a reference the prevalence of ARDS in the lowest quartile (ΔP ≤ 9 cm H_2O), a value of ΔP > 12 cm H_2O was associated with a higher probability of ARDS (supplemental Table 9 and Fig. 1, see the supplementary materials http://www.rcjournal.com). Equally, the subjects with ΔP > 15 cm H_2O had higher rates of ARDS development compared with the subjects with ΔP 12–15 cm H_2O at day 1. Cox survival plots that showed the difference in probability of ARDS between different ΔP quartiles are displayed in Figure 2. This effect of quartiles of ΔP was not observed on ICU or hospital mortality (supplemental Tables 10 and 11, respectively see the supplementary materials at http://www.rcjournal.com).

Discussion

To our knowledge, this was the first observational international multicenter study to analyze the effect of ΔP on the development of ARDS and mortality in a large cohort of non-selected subjects without ARDS. Our results showed that a higher ΔP was associated with an increased risk of ARDS. The ΔP at day 1 was also associated with higher ICU and hospital mortality. The effect of ΔP on mortality was first described in a post hoc analysis of several multi-center randomized trials of subjects with ARDS.[12] Interestingly, the

results of that study suggested that reductions in V_T or increases in PEEP were only beneficial if they were associated with decreases in ΔP. Since then, consistent results have been observed in other studies that included subjects with ARDS.[14,15,34] More recently, it has also been shown that the mortality benefit associated with the use of a lower V_T is greater in subjects with high elastance.[35] In fact, a lower ΔP has been described as one of the potentially modifiable factors that may be associated with better survival in patients with ARDS.[36] Similarly, high intraoperative ΔP has been associated with a higher incidence of postoperative pulmonary complications in a meta-analysis of individual subject data from 17 randomized controlled trials of protective ventilation during general anesthesia.[22]

The role of ΔP in subjects with non-injured lung and in the ICU has only been assessed in 6 studies.[21,17,18,19,38,20] First, Tejerina et al[21] showed that ΔP was associated with the development of ARDS in subjects with brain injury. Second, in a post hoc analysis of a prospective observational study that included 221 subjects, a higher ΔP was able to identify those subjects who were more likely to develop ARDS.[17] Third, in a secondary analysis of a before-after trial that assessed the effectiveness of early protective mechanical ventilation in subjects without ARDS while they were in the emergency department, ΔP was associated with mortality and ARDS development.[18] However, a recent study reported that ΔP was not associated with higher hospital mortality in subjects without ARDS and who were critically ill.[19] It should be noted that, in that study, 87% of the subjects without ARDS were spontaneously breathing,[19] whereas, in the present study, the presence of spontaneous breathing was considered as an exclusion criterion because ΔP might not be correctly measured in the presence of respiratory effort.[37] Moreover, the sample size included fewer than half of the subjects of the present study and so the study might have lacked the power to detect any association between ΔP and mortality.[37] Equally, no association between ΔP and mortality was observed in a secondary analysis of a study that included subjects at risk for ARDS.[38] However, in that study, ΔP was only available in 343 subjects (36% of the overall cohort), and so it is likely to be underpowered. In contrast, a more recently published observational study that included 822 subjects without ARDS, ΔP was independently associated with hospital mortality.[20]

The present study had several strengths in comparison with the previous studies. First, it was performed in the largest cohort of non-selected subjects who did not meet ARDS criteria at the time of inclusion, which thus avoided the possible bias related to the post hoc analysis of randomized trials, which excluded a significant number of patients due to the strict inclusion criteria and may also be affected by performance bias. Moreover, because of the large sample size, it is unlikely that the study was inadequately powered. Second, we provided 2 different validations of the results: using the bootstrap method, and repeating the same analysis at day 2.[12] Third, because the occurrence of ARDS was greater in the first 7 d and because the later occurrence of ARDS may have been due to factors other than ventilator settings on day 1 (eg, ventilator-associated pneumonia), we repeated the same analysis when considering the development of ARDS within the first week as an outcome and obtained consistent results. Fourth, we also assessed the effect of ΔP in different quartiles and demonstrated that the subjects without ARDS and with $\Delta P > 12$ cm H_2O presented a higher risk of ARDS. This analysis showed that the subjects with the highest ΔP had lower C_{RS}. However, when C_{RS} and ΔP were included in the same model, only ΔP was associated with ARDS development and mortality.

However, the study also had several limitations. First, this was an observational study; therefore, the results did not necessarily imply causality; nevertheless, there was a physiologic plausibility that linked a high ΔP to ARDS development, the association between ΔP and ARDS and mortality was validated in 2 different ways, and the effect of different ΔP quartiles on ARDS and mortality was also assessed. Moreover, the magnitude of the effect was consistent with previously reported data.[17,18] The effect on mortality was expected to be lower than on the development of ARDS because other factors, for example, the ARDS itself, may play an important role in the mortality of patients who are critically ill. Second, the percentage of ARDS detection may seem to be low (4.13%); however, this percentage is nearly 10% if we consider the ARDS prevalence in the excluded patients (607 cases in 6,672 patients). Third, the ΔP measurement was not performed in spontaneously breathing patients, and they were excluded, which led to a certain selection bias. Fourth, recorded variables may present some intra-daily variability. Fifth, although setting the V_T according to the ΔP may be an attractive physiologic approach, it is important to bear in mind that the question of whether different ventilator strategies designed to decrease ΔP are able to decrease ARDS development and improve survival in patients without ARDS remains unresolved.

Conclusions

We found that, in the subjects without ARDS, the level of ΔP on the first day of mechanical ventilation was associated with later development of ARDS and mortality. In fact, when taking the prevalence of ARDS in the lowest quartile of ΔP as a reference, the subjects with $\Delta P > 12$ cm H_2O presented a higher probability of developing ARDS. These results provide a rationale for assessing the effectiveness of reducing ΔP in patients without ARDS.

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