Original Article

Associations between changes in oxygenation, dead space and driving pressure induced by the first prone position session and mortality in patients with acute respiratory distress syndrome

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Background: Outcome prediction in acute respiratory distress syndrome (ARDS) is challenging, especially in patients with severe hypoxemia. The aim of the current study was to determine the prognostic capacity of changes in PaO_2/FiO_2, dead space fraction (V_D/V_T) and respiratory system driving pressure (ΔP_{RS}) induced by the first prone position (PP) session in patients with ARDS.

Methods: This was a post hoc analysis of the conveniently-sized 'Molecular Diagnosis and Risk Stratification of Sepsis' study (MARS). The current analysis included ARDS patients who were placed in the PP. The primary endpoint was the prognostic capacity of the PP-induced changes in PaO_2/FiO_2, V_D/V_T, and ΔP_{RS} for 28-day mortality. PaO_2/FiO_2, V_D/V_T, and ΔP_{RS} was calculated using variables obtained in the supine position before and after completion of the first PP session. Receiving operator characteristic curves (ROC) were constructed, and sensitivity, specificity positive and negative predictive value were calculated based on the best cutoffs.

Results: Ninety patients were included; 28-day mortality was 46%. PP-induced changes in PaO_2/FiO_2 and V_D/V_T were similar between survivors *vs.* non-survivors [+83 (+24 to +137) *vs.* +58 (+21 to +113) mmHg, and –0.06 (–0.17 to +0.05) *vs.* –0.08 (–0.16 to +0.08), respectively]. PP-induced changes in ΔP_{RS} were different between survivors *vs.* non-survivors [–3 (–7 to 2) *vs.* 0 (–3 to +3) cmH_2O; P=0.03]. The area under the ROC of PP-induced changes in ΔP_{RS} for mortality, however, was low [0.63 (95% confidence interval (CI), 0.50

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to 0.75]; PP-induced changes in ΔP_{RS} had a sensitivity and specificity of 76% and 56%, and a positive and negative predictive value of 60% and 73%.

Conclusions: Changes in PaO_2/FiO_2, V_D/V_T, and ΔP_{RS} induced by the first PP session have poor prognostic capacities for 28-day mortality in ARDS patients.

Keywords: Acute respiratory distress syndrome (ARDS); refractory hypoxemia; prone position (PP); prognostication; mortality; oxygenation; PaO_2/FiO_2; dead space; V_D/V_T; driving pressure; respiratory system driving pressure; ΔP; ΔP_{RS}

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Introduction

One randomized clinical trial in patients with moderate to severe acute respiratory distress syndrome (ARDS) convincingly showed mortality benefit from turning patients from the supine to the prone position (PP) (1). Two meta-analyses confirmed the benefit of the PP (2,3), though the PP remains underutilized (4,5). Different mechanisms have been proposed to explain survival benefit induced by repositioning to the PP, including homogenizing of transpleural pressures, decreasing lung stress and strain by increasing lung volumes, and decreasing overdistension by redistribution of lung ventilation.

Outcome prediction in ARDS patients is challenging (6,7), especially in patients with severe refractory hypoxemia in whom PP sessions are often needed. In ARDS patients, the ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) (8), dead space fraction (V_D/V_T) (9,10), and respiratory system driving pressure (ΔP_{RS}) (11,12) have an association with mortality. Turning a patient from supine to the PP affects PaO_2/FiO_2, V_D/V_T and ΔP_{RS} through various mechanisms, and changes induced by this repositioning could be helpful in outcome prediction (6,7,13). A recent post hoc analysis of the randomized clinical trial (RCT) mentioned above (1) did not confirm this, though (14). It must be mentioned, however, that that analysis only used changes in PaO_2/FiO_2 for outcome prediction, and also that changes were calculated from blood gas analysis results after positioning in the PP and before repositioning to the supine position.

The aim of the current analysis, therefore, was to determine the association between PP-induced changes in PaO_2/FiO_2, as well as V_D/V_T and ΔP_{RS}, using ventilation variables collected before placing patients in the PP and after repositioning to supine, and outcomes. For this purpose, the 'Molecular Diagnosis and Risk stratification of Sepsis' study (MARS), a large cohort study including patients with ARDS needing PP, was reanalyzed. The primary hypothesis tested was that changes in PaO_2/FiO_2, V_D/V_T and ΔP_{RS} induced by the first PP session have prognostic capacity for mortality.

Methods

Design and ethical approval

MARS was a conveniently-sized observational study capturing granular data of intensive care unit (ICU) patients in two Dutch hospitals (15,16). In MARS, detailed demographic and clinical data, including ventilator settings and ventilation variables, as well as outcome data were prospectively collected from ICU admission and start of invasive ventilation, until extubation and ICU discharge, and 1-year mortality. The Institutional Review Board approved the study protocol of the parent study and the use of an opt-out consent procedure (protocol no. 10-056C). MARS was registered at www.clinicaltrials.gov (identifier NCT01905033). The current report adheres to the STROBE guidelines (17).

Patients

Patients were eligible for participation in MARS if they had an expected length of stay in the ICU of more than 24 hours. MARS itself used no exclusion criteria.

For the purpose of this post hoc analysis, the following additional inclusion criteria were used: (I) admitted to the ICU of the Amsterdam University Medical Centers, location Academic Medical Center (AMC), Amsterdam, The Netherlands; (II) having ARDS; and (III) use of

the PP for refractory hypoxemia. The single reason for exclusion was impossibility to capture complete sets of variables, necessary for calculating PaO_2/FiO_2, V_D/V_T or ΔP_{RS} before and after the first PP session. Thus, patients who died during the first PP session and patients who were transferred to another hospital while in the PP, were excluded.

ARDS diagnosis

The MARS team existed of extensively trained clinical researchers who scored all patients prospectively for presence of acute lung injury (ALI) or ARDS according to the American–European Consensus Conference criteria for ARDS (18). Patients were later re-classified using the Berlin Definition for ARDS that was introduced after initiation of the MARS (8). All patients initially diagnosed with ARDS also fulfilled the Berlin definition and could thus be re-classified as having mild, moderate or severe ARDS based on the lowest PaO_2/FiO_2 within the first 24 hours after the initial diagnosis of ARDS (8).

Calculation of PaO_2/FiO_2, V_D/V_T and ΔP_{RS}

PaO_2 was measured using a point-of-care blood gas analyzer (Rapidlab 1265, Siemens Healthcare GmbH, Kemnath, Germany). Continuous end-tidal CO_2 ($EtCO_2$) monitoring was performed using main-stream capnography (Philips, Best, The Netherlands). FiO_2, positive end-expiratory pressure (PEEP) and maximum airway pressure (P_{max}) were recorded from the ventilator at the moment of blood sampling for blood gas analyses.

PaO_2/FiO_2, V_D/V_T, and ΔP_{RS} were calculated using variables obtained in the supine position before and after completion of the first PP session. For these calculations, data 1 hour before start, and 1 hour after repositioning to the supine position were used. If these data were missing, we used data closest to the 1-hour time point but never more than 3 hours before start and 3 hours after ending the first PP session. PaO_2/FiO_2 was calculated by dividing PaO_2 by FiO_2. V_D/V_T was calculated using the modified Bohr formula in which $V_D/V_T = (PaCO_2–PetCO_2)/PaCO_2$ (7). ΔP_{RS} was calculated by subtracting PEEP from P_{max}, measured at zero flow.

Primary and secondary endpoints

The primary endpoint was the prognostic capacity of PaO_2/FiO_2, V_D/V_T and ΔP_{RS}, expressed in the area under the Receiver Operating Characteristic (ROC) for all–cause mortality at day 28. Secondary outcomes were the prognostic capacities of PaO_2/FiO_2, V_D/V_T and ΔP_{RS} for ICU and 1-year mortality. These outcomes should be seen as explorative, and therefore no correction for multiple testing was performed.

The local guideline for ventilatory support

The local guideline for ventilatory support advised on main ventilator settings in patients with ARDS, and indications for the PP (19). Briefly, ARDS patients were to receive invasive ventilation using a pressure-controlled ventilation mode, or pressure support ventilation mode, with tidal volume targeting 6 ml per kilogram of predicted body weight and PEEP following a 'lower $PEEP/FiO_2$ table', where every increase in PEEP was to be preceded by a recruitment maneuver. Nurses and physicians adjusted the inspiratory pressure to maintain the correct tidal volume.

Patients were assessed at least three times daily to determine whether weaning could start, consisting of switches to a pressure support mode of ventilation, if not yet spontaneously breathing. If pressure support ventilation was accepted, the level of support was gradually decreased to a minimum of 5 cmH_2O at least three times per day. Tracheal extubation was performed at the discretion of attending physicians, based on general extubation criteria (20).

The local guideline for prone positioning

The local guideline dictated that PP sessions were indicated in patients in whom the PaO_2/FiO_2 remained <125 mmHg despite increases in PEEP level ≥10 cmH_2O at a minimum FiO_2 ≥0.6. Sessions were repeated if PaO_2/FiO_2 remained or dropped to <125 mmHg at a PEEP of ≥10 cmH_2O at a minimum FiO_2 ≥0.6 when back in the supine position. Of note, the local guidelines for ventilation do not allow changes in PEEP, neither when a patient is in the PP nor before the results of blood gas analyses become available when a patient is returned to supine.

Power calculation

A formal power calculation was not performed, but instead this analysis used all patients who had received at least one PP session during the 3 years MARS enrolled patients.

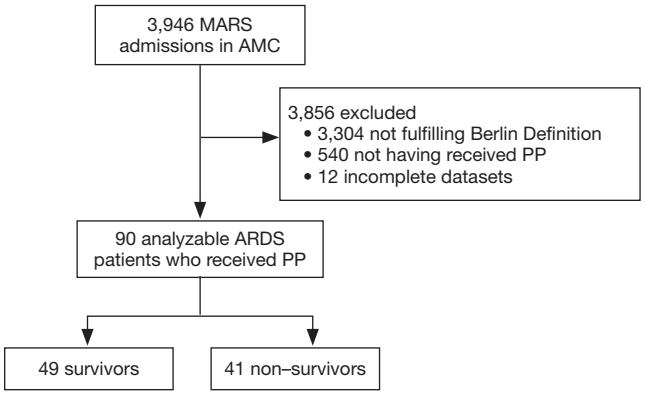

Figure 1 Patient flowchart. AMC, Amsterdam University Medical Centers, location Academic Medical Center.

Analysis plan

Variables and parameters were expressed as medians [25th to 75th interquartile range (IQR) for continuous variables, or percentages for categorical variables. Continuous variables and parameters were analyzed using a Mann-Whitney U-test or a Welch two-ample *t*-test, and proportions were compared using a Fisher exact test.

First, absolute and relative changes between PaO_2/FiO_2, V_D/V_T and ΔP_{RS} before to after the first PP session were calculated and compared between 28-day survivors and non-survivors using the Mann-Whitney U-test. The association between PP-induced changes in PaO_2/FiO_2, V_D/V_T, and ΔP_{RS}, and mortality was determined using a univariate and multivariable logistic regression. A propensity score was entered into the multivariate model as a covariate to correct for disease severity and other baseline factors that could have influenced patient outcome (21), using the following predefined baseline variables: disease severity [age, an age-corrected Acute Physiology and Chronic Health Evaluation (APACHE) IV score], and baseline PaO_2/FiO_2, V_D/V_T, ΔP_{RS}, V_T, and respiratory rate (RR). These variables were selected because they are all suggested to have an association with mortality. As there were 41 events of the outcome of interest, i.e., 28-day mortality, and the general rule of thumb is that 10 events of the outcome of interest are required for each variable entered in the model (22), the multivariable analysis using only 2 variables can be seen as sufficiently powered. An etiological model was chosen because of the restricted sample size.

Second, area under the ROC curve for 28-day mortality was calculated for PP-induced changes in PaO_2/FiO_2, V_D/V_T and ΔP_{RS}. The optimal cutoff was determined using the Youden index (23), and sensitivity, specificity, and positive and negative predictive values were calculated. A priori, an area under the curve (AUC) of ≤0.6 was considered 'poor', 0.6–0.7 'fair', 0.7–0.8 'good', 0.8–0.9 'very good' and ≥0.9 'excellent' (24).

Statistical analyses were performed using R and the R-studio interface (R version 3.0, www.r-project.org). A P value <0.05 was considered as statistically significant.

Results

Patients

Of 3,946 patients enrolled in MARS in the participating center, 642 (16%) patients were diagnosed with ARDS (*Figure 1*). Of these, 102 (16%) patients were repositioned in the PP for at least one session. After exclusion of patients with incomplete datasets, 90 patients remained in the analysis. Baseline demographics, ventilation variables, and ventilations parameters before and after the first PP session are presented in *Tables 1,2*. All cause 28-day mortality rate was 46%. Patients who died were sicker according to the APACHE IV scores. Patients who died had higher V_D/V_T at baseline, while baseline PaO_2/FiO_2 and ΔP_{RS} were not different between survivors and non-survivors. Patients with ARDS in MARS study who did not meet the criteria for and thus were not placed in the PP had similar baseline characteristics but were less sick according to the median APACHE IV score (*Table S1*). Time between start of invasive ventilation and the first PP session, total duration of the first PP session, and the total number of PP sessions during the entire ICU stay were not different between survivors and non-survivors (*Table S2*). In 90% and 96% of cases, data to calculate the parameters of interest were available within the last hour before the first PP session, and the first hour after repositioning to supine, respectively.

PP-induced changes in PaO_2/FiO_2, V_D/V_T, and ΔP_{RS}

The first PP session resulted in a rise in PaO_2/FiO_2 that persisted after the patient was repositioned back in the supine position in 90% of the cases, and a decrease in V_D/V_T and ΔP_{RS} in 66% and 56%, respectively (*Figure 2* and *Table 2*).

Survivors versus non-survivors

PP-induced changes in PaO_2/FiO_2 and V_D/V_T were not

Table 1 Baseline characteristics

Characteristics	Survivors (N=49)	Non-survivors (N=41)	P
Gender, male, n [%]	31 [63]	29 [71]	0.15
Age, median [IQR], years	55 [44 to 65]	58 [50 to 66]	0.59
Weight, median [IQR], kg	80 [73 to 90]	75 [62 to 89]	0.16
PBW, median [IQR]	66 [63 to 72]	71 [56 to 80]	0.65
BMI, median [IQR]	26 [24 to 29]	24 [22 to 28]	0.05
APACHE IV, median [IQR]	61 [50 to 86]	91 [75 to 110]	<0.001
Reasons for ICU admission, n [%]			
Surgical	13 [27]	12 [29]	0.77
Pneumonia	17 [35]	11 [27]	0.42
Sepsis	5 [10]	1 [2]	0.14
Cardiac arrest	1 [2]	4 [10]	0.11
Other	13 [27]	13 [32]	0.59
Causes of ARDS, n [%]			
Sepsis	9 [18]	10 [24]	0.48
Pneumonia	31 [63]	19 [46]	0.17
Trauma	6 [12]	6 [15]	0.74
Aspiration	1 [2]	5 [12]	0.05
Cardiac arrest	1 [2]	1 [2]	0.89
Transfusion	1 [2]	0 [0]	0.71

Baseline characteristics for all patients, survivors and non-survivors. Values are expressed in percentages (%) of total patients in the group or median with interquartile ranges [IQR], where applicable. kg, kilogram; PBW, predicted body weight; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

different between survivors and non-survivors. PP-induced changes in ΔP_{RS}, though, were different between survivors and non-survivors (*Figure 2* and *Table S3*). In the univariate logistic regression, only the absolute PP-induced change in ΔP_{RS}, and the absolute and relative change in arterial pH induced by the first PP session showed an association with 28-day mortality (*Table S4*). These associations did not sustain in the multivariate analysis when corrected for the propensity score.

After repositioning back in the supine position, differences were also noted in arterial pH between survivors and non-survivors (*Table S3*).

Prognostic value of PP-induced changes in PaO_2/FiO_2, V_D/V_T and ΔP_{RS}

Prognostic characteristics of absolute and relative changes in induced by the first PP session are shown in *Table 3*. Only the absolute PP-induced change in ΔP_{RS} had prognostic capacity, all other PP-induced changes performed poorly. The prognostic capacity for ICU-mortality and 1-year mortality of PP-induced changes were also poor (*Table S5*,*S6*).

Discussion

The findings of this post hoc analysis of MARS can best be summarized as follows: (I) PP-induced changes in PaO_2/FiO_2 and V_D/V_T are not different between survivors and non-survivors; (II) PP-induced changes in ΔP_{RS} are different between survivors and non-survivors, but the association with outcome is not independent; and (III) prognostic capacity for mortality of PP-induced changes in oxygenation and lung mechanics is insufficient for use in

Table 2 Ventilation variables and parameters

Variables and parameters	Before the first PP session			After the first PP session		
	Survivors (N=49)	Non-survivors (N=41)	P	Survivors (N=49)	Non-survivors (N=41)	P
V_T, mL/kg PBW	6.5 [5.8 to 6.9]	6.2 [5.1 to 6.5]	0.18	6.4 [6.0 to 7.0]	6.5 [5.5 to 8.0]	0.97
PEEP, cmH_2O	15 [10 to 16]	15 [11 to 16]	0.77	15 [12 to 16]	15 [14 to 18]	0.05
P_{max}, cmH_2O	32 [26 to 39]	35 [29 to 40]	0.22	31 [29 to 36]	36 [33 to 38]	0.04
FiO_2, %	70 [60 to 80]	70 [60 to 89]	0.72	53 [44 to 62]	50 [40 to 60]	0.10
PaO_2, mmHg	66 [59 to 80]	65 [60 to 77]	0.64	92 [72 to 122]	85 [69 to 110]	0.29
$PaCO_2$, mmHg	50 [39 to 58]	47 [42 to 62]	0.52	44 [38 to 50]	47 [35 to 56]	0.77
HCO_3^-, mmol/L	24 [21 to 27]	22 [19 to 26]	0.07	24 [21 to 28]	22 [18 to 26]	0.02
pH	7.32 [7.26 to 7.39]	7.25 [7.17 to 7.33]	0.02	7.39 [7.33 to 7.42]	7.31 [7.20 to 7.40]	0.01
PaO_2/FiO_2	99 [79 to 130]	101 [69 to 117]	0.60	188 [117 to 226]	166 [127 to 225]	0.99
V_D/V_T	0.27 [0.22 to 0.36]	0.43 [0.34 to 0.51]	<0.001	0.25 [0.17 to 0.35]	0.32 [0.23 to 0.52]	0.01
ΔP_{RS}, cmH_2O	18 [14 to 24]	20 [15 to 24]	0.44	17 [12 to 21]	19 [16 to 24]	0.03

Variables and parameters before and after the first PP session. Data are expressed as median with IQR. VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{max}, maximum airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; HCO_3^-, arterial bicarbonate; PaO_2/FiO_2, ratio of arterial oxygen tension to fraction of inspired oxygen; VD/VT, dead space fraction; ΔP_{RS}, respiratory system driving pressure.

clinical practice.

This is the first study that investigated the prognostic capacities of PP-induced changes in oxygenation, dead space and respiratory system mechanics for outcome prediction in ARDS patients. One strength of this study is that trained researchers collected data used for the calculation of PaO_2/FiO_2, V_D/V_T and ΔP_{RS}. In addition, these researchers were also extensively trained in using the diagnostic criteria for ARDS. MARS ran in a tertiary hospital, recruiting a broad selection of ARDS patients, increasing its external validity. Also, different from a recent post hoc analysis of the PROSEVA trial (1), in the current analysis we prevented 'contamination' of the early effects of repositioning a patient in the PP by using data from before the first PP session. We also focused on sustained effects of the first PP session, and therefore only used data after repositioning to supine. We consider this is a fairer interpretation of PP-induced changes in gas exchange and lung mechanics.

Though the PP has many benefits, it is still uncertain how ventilation mechanics are exactly altered during repositioning patients from the supine position to the PP, and whether they remain altered after repositioning back to the supine position. Recruitment of lung tissue, changes in intra-abdominal pressures, and chest wall and lung compliances have not been studied well in ARDS patients in the PP, and the exact physiological mechanisms remained uncertain so far. Factors such as weight and pressure relocation, compliance changes, changes in chest wall shape, perfusion and ventilation redistribution have been thought to be contributing factors (25). Even though lung compliance is known to improve in general during a PP session, this does not always happen (25).

While PaO_2/FiO_2 is used for risk classification in the Berlin Definition, the results of this current study did not find a difference between survivors and non-survivors. This may not be too surprising as the study included patients with more severe ARDS, in which mortality is highest. However, there was also no association between PP-induced changes in PaO_2/FiO_2 and outcome. This is in line with a previous study investigating the predictive value of PP-induced changes in PaO_2/FiO_2 (14,26). In that study, mortality rates were similar for 'responders' and 'non-responders', based on changes in PaO_2/FiO_2.

In line with a previous investigation (27), V_D/V_T before the first PP session was lower in survivors compared to non-survivors. Indeed, in that previous study it was shown that higher V_D/V_T is associated with worse outcome in ARDS patients.

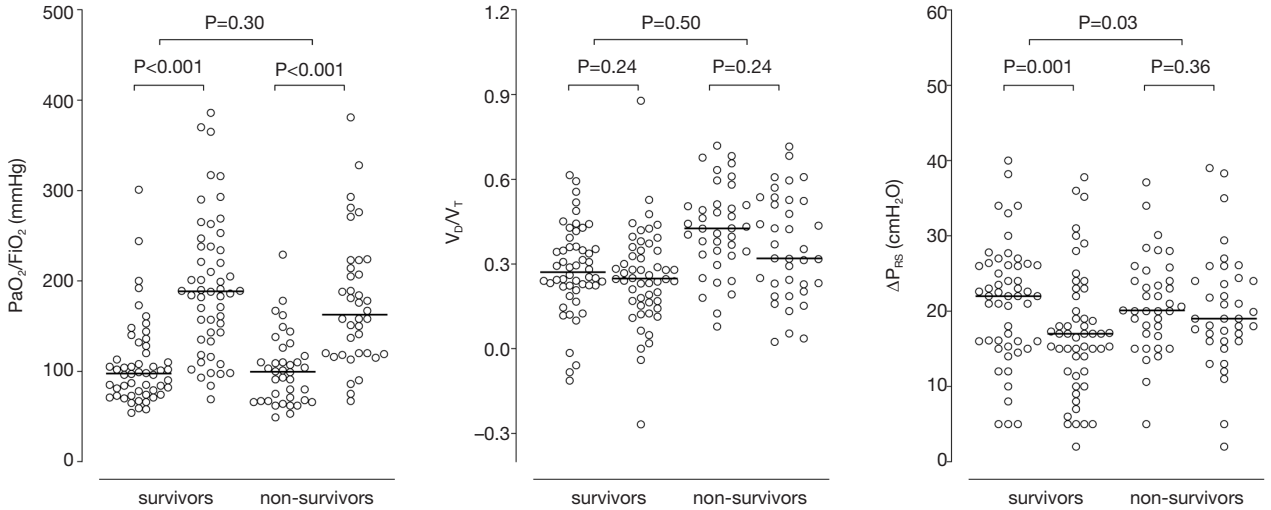

Figure 2 PP-induced changes in PaO_2/FiO_2, V_D/V_T and ΔP_{RS}. Dots represent individual PaO_2/FiO_2, V_D/V_T and ΔP_{RS} calculated using data collected closest to start, and as early as possible after the first PP session. Horizontal lines are medians. PaO_2/FiO_2, ratio between arterial oxygen tension and fraction of inspired oxygen; V_D/V_T, dead space fraction; ΔP_{RS}, respiratory system driving pressure.

Table 3 Prognostic capacities of changes induced by the first PP session

Parameters	AUROC (95% CI)	Best cutoff	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (%)	NPV (%)
Absolute change						
PaO_2/FiO_2	0.55 (0.43 to 0.67)	+68 mmHg	59 (42 to 74)	60 (45 to 74)	56	63
V_D/V_T	0.51 (0.39 to 0.63)	–0.10	46 (31 to 63)	65 (50 to 78)	53	58
ΔP_{RS}	0.63 (0.51 to 0.75)	–3 cmH_2O	76 (60 to 88)	56 (41 to 71)	60	73
Relative change						
PaO_2/FiO_2	0.55 (0.43 to 0.67)	+78%	63 (47 to 78)	54 (39 to 69)	54	63
V_D/V_T	0.51 (0.39 to 0.63)	–46%	88 (74 to 96)	31 (19 to 46)	52	75
ΔP_{RS}	0.62 (0.50 to 0.73)	–14%	76 (60 to 88)	50 (35 to 65)	56	71

AUROC, area under the receiver operator characteristics curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; PaO_2/FiO_2, ratio between arterial oxygen tension and fraction of inspired oxygen; V_D/V_T, dead space fraction; ΔP_{RS}, respiratory system driving pressure.

Several recent reports showed an association between ΔP_{RS} and outcome of ARDS patients (11,12,28). The ΔP_{RS} has even been suggested as one of the most important ventilation parameters predicting outcome (4,11,29,30). The results of this current study add to this understanding with the finding that PP-induced changes in ΔP_{RS} were significantly different between survivors and non-survivors. Changes in ΔP_{RS} induced by the first PP session, however, remain to have a disappointing low prognostic capacity. Of note, in all patients PP-induced changes in ΔP_{RS} resulted from a change in P_{plat}. This can be explained by the fact that the local guidelines for ventilation do not allow changes in PEEP during PP.

In some patients PaO_2/FiO_2 could have improved beyond the value that triggered the decision to start a PP session. This explains why the PaO_2/FiO_2 in the last hour before the first PP session was higher than the PaO_2/FiO_2 that triggered the team to initiate the first PP session, in line with the local guideline for invasive ventilation. Indeed, in between these two-time points changes, and even

improvements in PaO_2/FiO_2 are likely to occur, e.g., due to PEEP titrations or recruitment maneuvers. This finding is in line with what was found in the latest randomized clinical trial of the PP (1).

There are several reasons why we had to reject the hypothesis, apart from the realistic possibility that changes in oxygenation and lung mechanics induced by the first PP session may not be associated with outcome. The sample size of this study was relatively small, and hereby possibly not able to detect the prognostic capacity. It is also possible that changes in PEEP during the first PP session affected the PP–induced changes in the parameters of interest. The findings of the present study may also be seen in light of finding of other studies in which 'improvements' in physiologic parameters did not translate in better outcomes, or vice versa. For instance, the seminal RCT comparing low *vs.* high tidal volumes showed ventilation with a low tidal volume to improve survival, but to worsen oxygenation (31). More recently, a randomized clinical trial of high PEEP and recruitment maneuvers showed the intervention to improve oxygenation and even driving pressure, but to worsen outcome (32). We cannot exclude a similar difference between changes in physiologic parameters and outcomes for positioning in the PP.

This study has several limitations. First, the results must be seen as those from a post hoc analysis. The relative low sample size could limit the generalizability of this analysis. However, the values included in the 95% CI of our primary endpoint (i.e., the AUROC) do not suggest a type II error. It was not possible to determine whether or not patients had received additional recruitment maneuvers during the first PP session, as this was not routinely captured in the database of MARS. Also, esophageal pressure measurements were not performed routinely, and therefore the pulmonary ΔP could not be calculated. Because patients were exclusively under pressure-controlled ventilation, P_{max} instead of P_{plat} was used, as suggested previously (33-35). Furthermore, severity of illness scores like APACHE scores and SAPS have robust prognostic capacities, and thus should be held in consideration when investigating the prognostic capacities of the parameters of interest in this study. However, the multivariate analysis adjusted for a propensity score calculated from age, an age-corrected APACHE IV, and baseline PaO_2/FiO_2, V_D/V_T, ΔP_{RS}, V_T, and the respiratory rate, also failed to find an association between changes in the parameters and outcomes. Finally, the study focused on the first PP session and not successive sessions.

Conclusions

In conclusion, in this cohort of ARDS patients the first PP session induced changes in PaO_2/FiO_2, V_D/V_T, and ΔP_{RS}. Only changes in ΔP_{RS} were different between survivors and non-survivors. Neither the change in PaO_2/FiO_2 and V_D/V_T, nor in ΔP_{RS} induced by the first PP session had sufficient prognostic capacities for outcome.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Institutional Review Board approved the study protocol of the parent study and the use of an opt-out consent procedure (protocol no. 10-056C).

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Supplementary

Table S1 Baseline characteristics of ARDS who did not meet the criteria for the PP

Characteristics	Survivors (N=378)	Non-survivors (N=162)	P
Gender, male, n [%]	292 [65]	110 [68]	0.67
Age, median [IQR], years	61 [52 to 71]	63 [53 to 72]	0.43
Weight, median [IQR], kg	80 [70 to 90]	73 [65 to 87]	0.02
PBW, median [IQR]	65 [62 to 72]	72 [58 to 80]	0.06
BMI, median [IQR]	26 [23 to 29]	24 [22 to 28]	0.007
APACHE IV, median [IQR]	57 [49 to 84]	80 [63 to 109]	<0.001
Reasons for ICU admission, n [%]			
Surgical	126 [33]	37 [23]	0.01
Pneumonia	128 [34]	55 [34]	0.98
Sepsis	34 [9]	11 [7]	0.40
Cardiac arrest	11 [3]	12 [7]	0.02
Other	79 [21]	47 [29]	0.04
Causes of ARDS, n [%]			
Sepsis	73 [19]	36 [22]	0.44
Pneumonia	236 [62]	83 [51]	<0.001
Trauma	28 [7]	31 [19]	0.37
Aspiration	35 [9]	8 [5]	0.09
Cardiac arrest	5 [1]	4 [2]	0.34
Transfusion	1 [0]	0 [0]	0.27

Baseline characteristics for ARDS patients who did not receive the PP, survivors and non-survivors. Values are expressed in percentages (%) of total patients in the group or median with interquartile ranges [IQR], where applicable. kg, kilograms; PBW, predicted body weight; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

Table S2 PP characteristics in survivors and non-survivors

Characteristics	Survivors (N=49)	Non-survivors (N=41)	P
Time to first session, hours	15 [5 to 50]	12 [6 to 31]	0.46
Duration of first session, hours	8 [6 to 11]	9 [1 to 27]	0.28
Number of sessions	2 [1 to 2]	2 [1 to 2]	0.90

Characteristics of the PP sessions.

Table S3 Change in ventilation variables and parameters in survivors and non–survivors

Variables and parameters	All	Survivors (N=49)	Non-survivors (N=41)	P
V_T, mL/kg PBW	+0.3 [–0.3 to +1.2]	+0.5 [–0.4 to +1.0]	+0.4 [–0.9 to +1.4]	0.84
PEEP, cmH_2O	0 [–1 to +3]	0 [–1 to +1]	+1 [–1 to +5]	0.12
P_{max}, cmH_2O	–1 [–5 to +6]	–4 [–7 to +3]	+1 [–2 to +7]	0.10
FiO_2, %	–20 [–30 to –5]	–20 [–30 to –5]	–15 [–30 to –5]	0.75
PaO_2, mmHg	+18 [+2 to +44]	+22 [+3 to +47]	+14 [+2 to +40]	0.61
$PaCO_2$, mmHg	–4 [–11 to +2]	–4 [–11 to +1]	–5 [–11 to +6]	0.76
HCO_3^-, mmol/L	–1 [–2 to +2]	+1 [–2 to +3]	–0.7 [–3.7 to +2.6]	0.66
pH	+0.05 [–0.02 to +0.11]	+0.08 [+0.03 to +0.11]	+0.01 [–0.05 to +0.09]	0.02
PaO_2/FiO_2	+68 [+21 to +120]	+83 [+24 to +137]	+58 [+21 to +113]	0.30
V_D/V_T	–0.07 [–0.16 to +0.06]	–0.06 [–0.17 to +0.05]	–0.08 [–0.16 to +0.08]	0.50
ΔP_{RS}, cmH_2O	–1 [–6 to +3]	–3 [–7 to +2]	0 [–3 to +3]	0.03

Change in variables and parameters before and after the first PP session. Data are expressed as median with IQR. VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Pmax, maximum airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; HCO_3^-, arterial bicarbonate; PaO_2/FiO_2, ratio of arterial oxygen tension to fraction of inspired oxygen; V_D/V_T, dead space fraction; ΔP_{RS}, respiratory system driving pressure.

Table S4 Univariate logistic regression

Variables and parameters	Absolute change, OR [95% CI]	P	Relative change, OR [95% CI]	P
V_T, mL/kg PBW	1.00 [1.00 to 1.00]	0.85	1.01 [1.00 to 1.02]	0.37
PEEP, cmH_2O	1.09 [0.98 to 1.21]	0.12	1.00 [1.00 to 1.00]	0.96
P_{max}, cmH_2O	1.06 [0.99 to 1.13]	0.10	1.01 [0.99 to 1.02]	0.42
FiO_2, %	1.00 [0.97 to 1.02]	0.75	1.00 [0.98 to 1.01]	0.71
PaO_2, mmHg	0.98 [0.91 to 1.05]	0.62	1.00 [0.99 to 1.00]	0.65
$PaCO_2$, mmHg	1.04 [0.83 to 1.31]	0.74	1.01 [0.99 to 1.02]	0.51
HCO_3^-, mmol/L	1.01 [0.96 to 1.07]	0.68	1.00 [0.98 to 1.01]	0.66
pH	0.00 [0.00 to 0.58]	0.03	0.69 [0.49 to 0.95]	0.03
PaO_2/FiO_2	1.00 [0.99 to 1.00]	0.30	1.00 [0.99 to 1.00]	0.31
V_D/V_T	0.47 [0.05 to 3.76]	0.48	1.00 [1.00 to 1.01]	0.30
ΔP_{RS}, cmH_2O	1.06 [1.01 to 1.13]	0.03	1.08 [1.00 to 1.17]	0.09

Univariate logistic regression. Odds ratios are displayed for an increment of 1. OR, odds ratio; CI, confidence interval; VT, tidal volume; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Pmax, maximum airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; HCO_3^-, arterial bicarbonate; PaO_2/FiO_2, ratio of arterial oxygen tension to fraction of inspired oxygen; V_D/V_T, dead space fraction; ΔP_{RS}, respiratory system driving pressure.

Table S5 Prognostic capacity of changes induced by the first PP session for ICU-mortality

Parameters	AUROC (95% CI)	Best cutoff	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (%)	NPV (%)
Absolute change						
PaO_2/FiO_2	0.55 (0.43 to 0.67)	+68 mmHg	56 (34 to 70)	58 (38 to 74)	51	63
V_D/V_T	0.51 (0.39 to 0.64)	–0.10	46 (27 to 55)	64 (51 to 78)	50	60
ΔP_{RS}	0.61 (0.50 to 0.73)	–3 cmH_2O	54 (33 to 72)	63 (47 to 79)	56	73
Relative change						
PaO_2/FiO_2	0.54 (0.41 to 0.66)	+190%	90 (71 to 99)	24 (11 to 36)	48	75
V_D/V_T	0.56 (0.44 to 0.68)	–44%	85 (67 to 95)	32 (19 to 46)	49	73
ΔP_{RS}	0.59 (0.47 to 0.71)	–14%	74 (54 to 87)	48 (29 to 65)	53	71

AUROC, area under the receiver operator characteristics curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; PaO_2/FiO_2, ratio between arterial oxygen tension and fraction of inspired oxygen; V_D/V_T, dead space fraction; ΔP_{RS}, respiratory system driving pressure.

Table S6 Prognostic capacities of changes induced by the first PP session for 1-year mortality

Parameters	AUROC (95% CI)	Best cutoff	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (%)	NPV (%)
Absolute change						
PaO_2/FiO_2	0.60 (0.45 to 0.75)	+68 mmHg	67 (46 to 82)	68 (46 to 84)	64	70
V_D/V_T	0.54 (0.39 to 0.69)	–0.11	70 (51 to 79)	48 (34 to 61)	54	65
ΔP_{RS}	0.66 (0.52 to 0.81)	–3 cmH_2O	63 (43 to 81)	77 (59 to 90)	71	71
Relative change						
PaO_2/FiO_2	0.59 (0.44 to 0.74)	+75%	63 (42 to 81)	65 (45 to 81)	61	67
V_D/V_T	0.54 (0.38 to 0.69)	–28%	53 (36 to 73)	63 (47 to 71)	54	62
ΔP_{RS}	0.60 (0.48 to 0.73)	–13%	55 (35 to 68)	71 (52 to 88)	61	66

AUROC, area under the receiver operator characteristics curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; PaO_2/FiO_2, ratio between arterial oxygen tension and fraction of inspired oxygen; V_D/V_T, dead space fraction; ΔP_{RS}, respiratory system driving pressure.