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Positive End-Expiratory Pressure Titration Based on Lung Mechanics May Improve Pulse Pressure Variation Interpretation in Acute Respiratory Distress Syndrome Patients

Vasiliki Tsolaki, MD, PhD[1]
George E. Zakynthinos, MD[2]
Nikitas Karavidas, MD[1]
Maria Eirini Papadonta, MD[1]
Ilias Dimeas, MD[3]
Kyriaki Parisi, MD[1]
Theofilos Amanatidis, MD[1]
Epaminondas Zakynthinos[1]

OBJECTIVES: To evaluate the effects of positive end-expiratory pressure (PEEP) on pulse pressure variation (PPV) in patients with moderate/severe acute respiratory distress syndrome (ARDS).

DESIGN: Prospective interventional self-controlled study.

SETTING: University Hospital of Larissa.

PATIENTS: ARDS patients admitted intubated in the ICU (from August 2020 to March 2022).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: PPV and inferior vena cava (IVC) respiratory variability were evaluated at two PEEP levels (first value mainly based on PEEP/FIO_2 and second value based on respiratory system compliance). Additionally, respiratory mechanics, hemodynamics, and echocardiographic indices assessing right ventricular (RV) size (RV end-diastolic area/left ventricular end-diastolic area [RVEDA/LVEDA]), RV systolic function, and RV afterload (pulmonary artery systolic pressure [PASP] and PASP/left ventricular outflow tract velocity time integral [PASP/VTI_{LVOT}]) were recorded. Ninety-five patients were evaluated. PPV decreased after PEEP reduction (11.7 ± 0.2 to 7.9% ± 0.2%), whereas IVC respiratory variability increased (9.1 ± 0.9 to 14.6% ± 0.1%) and central venous pressure decreased (all $p < 0.0001$). RV afterload indices decreased ($p < 0.0001$), simultaneously with RV size (< 0.0001) and systolic function indices' improvements (< 0.05); shock warranted less noradrenaline doses. The change in PPV correlated significantly to respiratory variability in IVC diameter distensibility ($p < 0.0001$) and moderately to changes in RV size and systolic function (change in RVEDA/change in LVEDA, change in tricuspid annular plane systolic excursion); RV afterload (change in PASP [ΔPASP], ΔPASP/VTI_{LVOT}); and change in $PaCO_2$ (all $p < 0.05$).

CONCLUSIONS: PPV alteration with PEEP decrease, associated with IVC distensibility increases, may indicate the presence of RV dysfunction and increased pulmonary vascular resistances. Whether the patients are in need for fluid loading, fluid responsiveness assessment may be further warranted.

KEYWORDS: acute respiratory distress syndrome; inferior vena cava distensibility; positive end-expiratory pressure; pulmonary vascular resistance; pulse pressure variation; right ventricular dysfunction

Fluid responsiveness is a commonly encountered question in everyday practice in the critically ill. Among indices used to predict fluid responsiveness, pulse pressure variation (PPV) is one of the most studied and applied. However, its validity is questioned during cardiac arrhythmias and

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KEY POINTS

Question: Is pulse pressure variation (PPV) affected by positive end-expiratory pressure (PEEP) titration based on respiratory system compliance (C_{RS}) in acute respiratory distress syndrome (ARDS) patients?

Findings: In ARDS patients, PEEP de-escalation from an initial value directed, although lower—by $PEEP/FIO_2$ to a C_{RS}-based value—led to a significant decrease in PPV and an increase in inferior vena cava (IVC) distensibility. The change in PPV correlated negatively to respiratory variability in IVC diameter distensibility and moderately to improvements in right ventricular (RV) size, systolic function, and RV afterload.

Meaning: PEEP may impact RV function and pulmonary vascular resistances leading to PPV and IVC distensibility increase in ARDS patients.

low tidal volume (VT) ventilation (≤ 6 mL/kg), when respiratory system compliance (C_{RS} < 30 mL/cm H_2O) is decreased and in cases of right ventricular (RV) dysfunction (1). Thus, PPV's reliability is questioned in patients with acute respiratory distress syndrome (ARDS), where all of the above may co-exist.

In ARDS patients, the pulmonary vasculature is affected by structural and functional pathophysiological changes that include pulmonary vasoconstriction induced by hypoxia and/or the release of vasoactive inflammatory mediators, microvascular thrombosis, reduction in functional lung volume, direct inflammatory endothelial damage, and vascular remodeling phenomena (2). The pulmonary vessels, the RV, and the lungs share the same cavity; thus, their operation and interaction are influenced by the surrounding pleural pressure (P_{pl}) and the cyclic changes in the lung distending pressure, the transpulmonary pressure. During normal breathing, pleural and transpulmonary pressure swings are of very low magnitude, but the balance is profoundly affected during positive pressure ventilation and especially in ARDS (3). Under pathologic conditions such as ARDS, where higher than normal pressures are applied in a heterogeneously diseased lung, this adaptation capacity is critically challenged. Positive end-expiratory pressure (PEEP) has a two-fold effect: on the one hand, it may increase the pulmonary vascular resistance (PVR) and the RV afterload by increasing the transpulmonary pressure; on the other hand, by increasing the intrathoracic pressure, it may decrease cardiac preload (4, 5).

Therefore, we hypothesized that PPV may be affected by the possible presence of RV systolic overload and dysfunction caused by the pathologic features of ARDS per se but also by mechanical ventilation (MV), which increases RV outflow impedance. Thus, manipulating PEEP, keeping the "mandatory" low VT constant, might result in PPV alterations through RV function and loading condition changes. The aim of the present study was to evaluate the effects of PEEP on PPV in patients with severe ARDS. We hypothesized that setting PEEP based on C_{RS} might result in a different PPV value, if RV dysfunction occurs.

MATERIALS AND METHODS

Study Population

The study was conducted from August 2020 to March 2022 and included patients admitted intubated in the ICU due to ARDS (6). Part of the included patients (56 patients) had been included in a previous study (7). Informed consent was waived by University Hospital of Larissa Institutional Review Board (IRB) on December 29, 2020 (17116/2020) under the title: PEEP effects on hemodynamics and respiratory mechanics in patients with ARDS. Procedures were followed in accordance with the ethical standards of the Einstein IRB on human experimentation and with the Helsinki Declaration of 1975.

Exclusion criteria were: 1) severe stenosis and/or regurgitation of the aortic or mitral valve, 2) known history of pulmonary arterial hypertension with or without RV impairment, 3) known history of RV dysfunction, 4) moderate/severe known respiratory disease, 5) presence of a pacemaker rhythm/implantable defibrillator, 6) presence of left bundle branch block, and 7) pulmonary embolism.

Study Protocol

All patients were evaluated during the first 48 hours of ICU admission. All patients were sedated, usually paralyzed, and ventilated on a volume assist/controlled mode. The initial PEEP was set according to the ARDS Network/Surviving Sepsis Campaign (SSC) guidelines

(8) and our initial observations (9). Thus, it was suggested to set the initial PEEP lower, approximately by 2 cm H_2O, than the proposed by the SSC guidelines, although the final choice was at the discretion of the attending physician. The PEEP decremental trial included a PEEP decrease (gradually by 1 cm H_2O) to the value that decreased arterial oxygen saturation or static respiratory system compliance (C_{RSst}).Then PEEP increased by 1 cm H_2O. The PEEP protocol was initially used in COVID-19-associated ARDS (CARDS) patients, where we observed PPV variation with PEEP manipulation. We systematically evaluated PPV changes in CARDS patients but also patients with non-CARDS admitted during the study period.

A full echocardiographic study, as well as respiratory values and hemodynamics were assessed at two PEEP levels. The initial PEEP value was maintained until the end of the first echocardiographic study. All measurements (echocardiography, respiratory, and hemodynamic indices' evaluation) were recorded just before and after the PEEP change, approximately 30 minutes later. No fluid administration or posture changes were allowed during the study period.

Measurements

Apart from demographics, we recorded before and after PEEP de-escalation, respiratory variables, respiratory mechanics, PPV (automatically measured from the arterial pressure curve displayed on the monitor (Carescape B850; General Electricre, GE Medical Systems; Information Technologies, Freiburg, Germany). Echocardiographic variables, assessing RV systolic function, afterload, and inferior vena cava (IVC) respiratory variability were also assessed. Mean arterial pressure, central venous pressure (CVP), superior vena cava oxygen saturation ($Scvo_2$), vasopressor type, and dosage were also recorded.

Comprehensive transthoracic echocardiographic examination (System Vivid E95; GE Medical Systems; GE Vingmed Ultrasound AS, Horten, Norway and Philips iE33; Philips Medical; Philips Ultrasound, Bothell, WA) was performed to assess RV ventricular dimensions and function (2D, 3D measurements) and the IVC according to the Recommendations of the American Society of Echocardiography (10–14). Apical long axis (four and two chamber) clips obtained with a frame rate greater than 50 Hz underwent off-line speckle tracking analyses on the semi-automated EchoPAC package; GE Vingmed Ultrasound AS (GEMS).

PVRs were indirectly estimated through quantification of the pulmonary artery systolic pressure (PASP) (via tricuspid regurgitation velocity plus the value of the CVP), evaluating the RV outflow tract (RVOT) flow velocity Doppler envelop to measure the acceleration time (AcT) and assess the presence of a systolic notch on the deceleration part (15). In addition, we calculated the ratio of PASP to the LVOT velocity time integral ($PASP/VTI_{LVOT}$). $PASP/VTI_{LVOT}$ can serve as a surrogate to roughly indicate PVRs, as the ratio integrates PASP and a cardiac output indicator and thus better expresses changes in PVRs (6, 15–17). We used VTI_{LVOT} instead of VTI_{RVOT} as the second is more difficult to be assessed in some patients. The coupling of RV contractility to the pulmonary circulation (right ventriculoarterial coupling) was also assessed; for this purpose, the tricuspid annular plane systolic excursion (TAPSE)/PASP ratio was used, previously shown to be a valid surrogate of the reversed ratio of end-systolic to arterial elastance (18, 19).

Furthermore, we performed a subgroup analysis dividing patients according to C_{RS} using the cut off value of 30 cm H_2O, as PPV has been reported to present a poor diagnostic performance in the subgroup of patients with C_{RS} less than 30 cm H_2O (20).

Statistical Analysis

Kolmogorov-Smirnov test was applied to test the variable distribution. Normally distributed variables were expressed as mean ± SEM; categorical variables were expressed as counts and percentages. Comparisons were performed using paired sample *t* test. The changes were expressed as percentage change ± SEM. Correlations, wherever performed, were done using Pearson correlation. Binary logistic regression analysis was performed to identify predictors of 20% change in both PPV and IVC distensibility. Variables concerning respiratory system mechanics, ventilatory variables, RV size, function, and afterload changed with a statistical significance less than 0.05 after PEEP de-escalation were entered in the regression model.

Statistical analyses were performed using SPSS, Version 26.0 (IBM Corp, Armonk, NY). A *p* value of less than 0.05 was considered statistically significant. All statistical tests were two sided.

RESULTS

Among152 patients with ARDS admitted, after intubation, in the ICU during the study period 95 patients (mean age 65.5 ± 1.3 yr) were analyzed (**Fig. 1**, flow chart). Acute Physiology and Chronic Health Evaluation II was 16.4 ± 0.7 and SOFA was 7.7 ± 1.8. Thirty-eight patients (40%) had moderate and 57 (60%) severe ARDS. The mean Pao_2/FIO_2 in the whole study was 119 ± 3.3 mm Hg. Baseline characteristics of patients with moderate and severe ARDS are presented in **Table 1**.

At the time of the echocardiographic evaluation, all patients were sedated and mechanically ventilated (volume assist/controlled mode) and no patient presented spontaneous respiratory efforts. All patients were on sinus rhythm. In 86.4% of the patients, a neuromuscular blocking agent was being administered. Mean VT was 7 ± 0.07 mL/kg and initial mean PEEP was 13.1 ± 0.3 cm H_2O, with a mean plateau pressure of 28.8 ± 0.5 cm H_2O (Table 1). PEEP was reduced by 28%. Oxygenation was not altered, but $Paco_2$ (53.7 ± 1.1 to 48.7 ± 0.8 mm Hg; $p < 0.0001$) values decreased with PEEP de-escalation. C_{RS} presented a significant increase as well (**Table 2**).

Interestingly, PPV decreased after PEEP titration (11.7 ± 0.2 to 7.9% ± 0.2%; $p < 0.0001$). IVC (which was found dilated measuring the minimum diameter in expiration) and CVP values rapidly decreased (2.2 ± 0.04 to 1.9 ± 0.04 cm; $p < 0.0001$ and 13.6 ± 0.3 to 10.3 ± 0.4 mm Hg; $p < 0.0001$, respectively). Furthermore, IVC respiratory variability increased (9.1 ± 0.9 to 14.6% ± 0.1%; $p < 0.0001$).

In addition, significant improvements were depicted in echocardiographic indices characterizing RV afterload ($PASP/VTI_{LVOT}$: 2.2 ± 0.1 to 1.37 ± 0.1 mm Hg/cm, PASP: 38.5 ± 1.4 to 32.6 ± 1.3 mm Hg, and pulmonary AcT: 61.6 ± 1.7 to 77.6 ± 1.9 ms; all $p < 0.0001$). Furthermore, RV size decreased (RV end-diastolic area/left ventricular end-diastolic area: 0.89 ± 0.03 to 0.72 ± 0.02; $p < 0.0001$), whereas RV systolic function improved (TAPSE: 18.8 ± 0.4 to 21.5 ± 0.5 mm, RV longitudinal strain: −11.4 ± 0.4 to −14.4% ± 0.5%, and RV EF: 33.6 ± 0.1 to 44.7% ± 0.1%; all $p < 0.0001$; RVFAC: 35.2 ± 1.0 to 39.1% ± 1.2%; $p = 0.004$). RV stroke volume (SV) significantly increased after PEEP titration (46.5 ± 1.7 to 52.4 ± 1.7 mL; $p < 0.0001$) (Table 2; and **Supplemental Table 1**, https://links.lww.com/CCX/B514).

Interestingly, along with the above, PEEP reduction led to a significant increase in VTI_{LVOT} (19.5 ± 0.4 to 21.1 ± 0.5; $p < 0.0001$), a decrease in noradrenaline dose (0.86 ± 0.1 to 0.65 ± 0.08 μg/kg/min; $p = 0.006$). In ten patients (out of 45 receiving double vasopressors), vasopressin was stopped. $Scvo_2$ increased from 69.4 ± 0.6 to 72% ± 0.5%; $p < 0.0001$ (Table 2). These changes indicate increased cardiac output. These improvements were complemented by a lower 12-hour fluid balance, after PEEP titration.

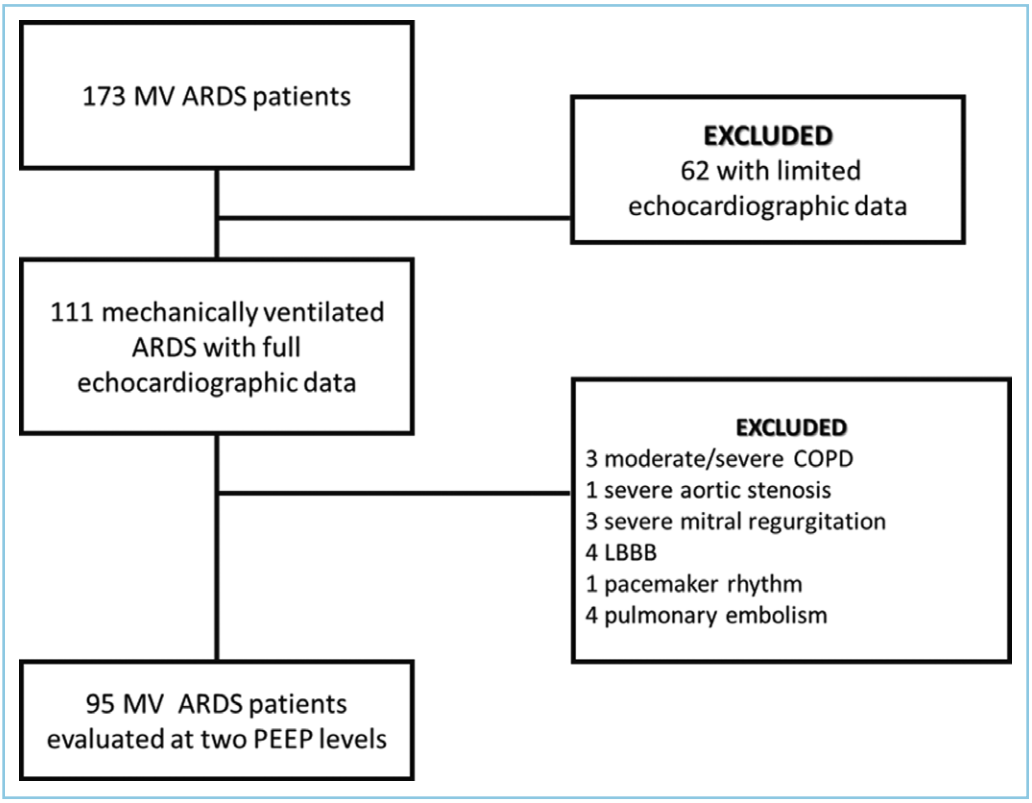

Figure 1. Flow chart. ARDS = acute respiratory distress syndrome, COPD = chronic obstructive pulmonary disease, LBBB = left bundle branch block, MV = mechanical ventilation, PEEP = positive end-expiratory pressure.

TABLE 1.
Baseline Characteristics of the Patients According to Acute Respiratory Distress Syndrome Severity

Variables	Moderate ARDS (*n* = 66)	Severe ARDS (*n* = 29)	*p*
Age	66.2 ± 1.5	66.4 ± 2.5	0.648
Sex	14.6 ± 0.1	14.6 ± 0.1	0.699
Body mass index	28.1 ± 0.6	28.4 ± 0.8	0.749
Tidal volume, mL/kg,	7 ± 0.9	7.1 ± 0.1	0.110
Positive end-expiratory pressure, cm H_2O	12.9 ± 0.7	13.4 ± 0.6	0.536
Respiratory system compliance, mL/cm H_2O	30.5 ± 1.2	28.3 ± 2	0.325
Plateau pressure, cm H_2O	28.1 ± 0.6	30.7 ± 1.1	0.022
Driving pressure	13.2 ± 0.5	14.8 ± 0.8	0.087
Pao_2/Fio_2, mm Hg	136.2 ± 2.8	81 ± 2.1	< 0.0001
$Paco_2$, mm Hg	52.5 ± 1.3	56.2 ± 1.6	0.108
Pulse pressure variation, %	11.6 ± 0.3	11.7 ± 0.4	0.854
Central venous pressure, mm Hg	13.7 ± 0.3	14.1 ± 0.6	0.573
Superior vena cava oxygen saturation, %	69.6 ± 0.7	69 ± 1	0.653
IVC (min diameter during expiration), cm[a]	2.2 ± 0.05	2.2 ± 0.07	0.685
Respiratory variability in IVC diameter ([IVCmaximum–IVCminimum]/IVCminimum), %	9.5 ± 1.1	8.01 ± 1	0.424
Mean arterial pressure, mm Hg	70 ± 0.7	69.7 ± 1	0.779
Heart rate	72.6 ± 2.6	81.7 ± 4.1	0.06
Noradrenaline, µg/kg/min[b]	0.8 ± 0.1	1 ± 0.2	0.354

ARDS = acute respiratory distress syndrome, IVC = inferior vena cava.
[a]Minimum diameter measured during expiration under mechanical ventilation.
[b]31 patients were receiving vasopressin at its maximal dose.

The change in PPV (ΔPPV) correlated strongly to respiratory variability in IVC diameter (ΔIVC) distensibility ($r = -0.758$; $p < 0.0001$) (**Fig. 2**). Furthermore, ΔPPV presented significant correlations with RV afterload (change in PASP [ΔPASP]: $r = 0.332$; $p = 0.002$ and $\Delta PASP/VTI_{LVOT}$: $r = 0.363$; $p = 0.001$) and change in $Paco_2$ ($r = 0.345$; $p = 0.001$).

Binary logistic regression analysis was performed to identify predictors of 20% change in both PPV and IVC distensibility. The change in C_{RS}, the change in PEEP, and the changes in RV size, systolic function and afterload were entered in the regression model. $\Delta PASP/VTI_{LVOT}$ was identified as the only significant variable to predict the combined change in IVC respiratory variability and PPV (Beta = 0.002 [0.000–0.119]; $p = 0.004$).

To find out whether the above differences were present when C_{RS} was low, we repeated the analyses dividing the patients in two C_{RS} subgroups. We used the cutoff 30 cm H_2O as this has been found to negatively affect the predictive value of PPV (18). Similarly, the subgroup of patients with C_{RS} less than 30 mL/cm H_2O presented significant decreases in PPV when PEEP was de-escalated (11.4 ± 0.3 to 8.5% ± 0.3%; $p < 0.0001$). Furthermore, CVP decreased (14.6 ± 0.4 to 11.7% ± 0.5%; $p < 0.0001$) and IVC respiratory variability increased (09.4 ± 1.5 to 12.1% ± 1.5%; $p = 0.048$), although the changes in the aforementioned values were somewhat lower than the ones observed in patients with C_{RS} greater than or equal to 30 cm H_2O (ΔPPV: 26.1 ± 2.4 vs. 35.4% ± 2.6%; $p = 0.01$; change in CVP: 18.6 ± 2 vs. 28.1% ± 2.7%; $p = 0.012$; and ΔIVC respiratory variability: 59 ± 19.5 vs. 106.6% ± 20.5%; $p = 0.099$).

DISCUSSION

Current guidelines do not prioritize titrating PEEP based on respiratory mechanics or the evaluation of

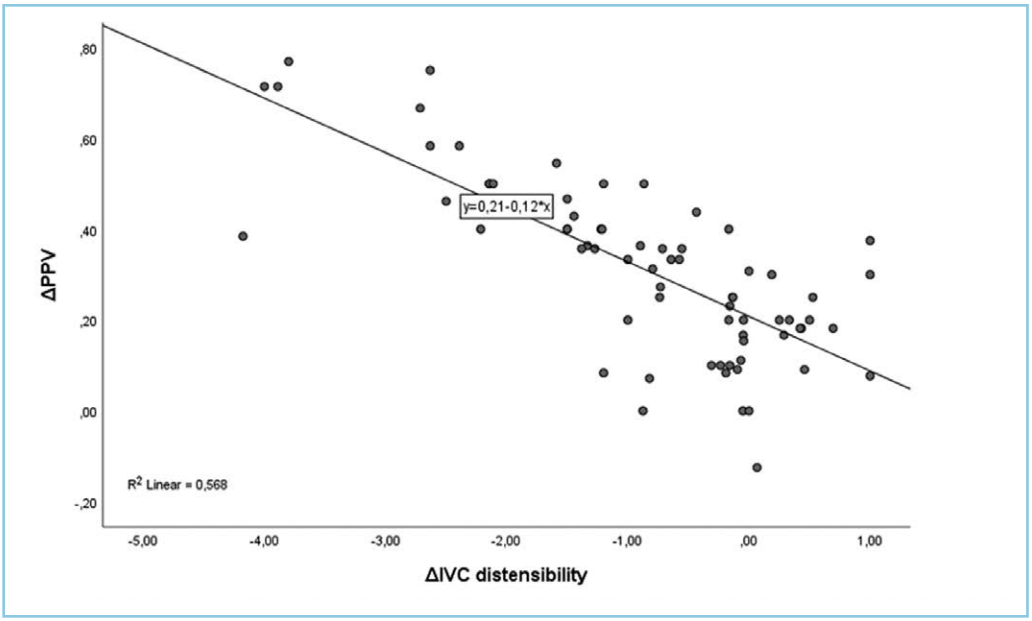

Figure 2. Correlation between change in PPV (ΔPPV) and respiratory variability in IVC diameter (ΔIVC) distensibility.

RV performance; yet, in clinical practice and certain patients, individualized PEEP optimization based upon dynamic compliance, oxygenation, and hemodynamics may be more appropriate (21). In the present study, we evaluated the PEEP effects in hemodynamics and especially PPV performance, in ARDS. We found two different PPV values when the two PEEP levels were applied. The changes were observed without altering the VT used. PEEP titration based on C_{RS}, led to a significant PPV decrease accompanied with increases in IVC respiratory variability and improvement in hemodynamic variables, caused by RV function and PVR improvements. IVC distensibility was increased despite the increase in cardiac output, indicating that RV function improved due to decreases in PVRs. If RV function was unaffected by PEEP changes, IVC distensibility would either decrease or not change. To our knowledge, this is one of the first studies to investigate the relationship between PEEP and PPV, exclusively in patients with moderate/severe ARDS.

Heart-lung interactions are used to indicate fluid responsiveness in MV patients. PPV is a valuable index yet, false positive values can occur in patients with RV dysfunction and ARDS (1, 22, 23). In our study, even a lower than the indicated for Pao_2/Fio_2 levels initial PEEP value, induced RV overload/dysfunction. By decreasing PEEP to an optimum for C_{RS} value, RV afterload improved and so did RV function, resulting in a lower PPV value and significant increase in IVC distensibility; variables that were negatively correlated. RV dysfunction induced by ventilator settings, PEEP in the present study, resulting from increased PVRs due to lung overdistension (decrease in dead space ventilation after PEEP de-escalation as depicted by lower $Paco_2$ values) might be a key element affecting PPV values. Recently, PEEP decrease has been shown to predict fluid responsiveness in mechanically ventilated patients (24). Decreasing PEEP leads to a decrease in CVP, which is the downstream pressure for venous return (25–27). Only 7% of the ARDS included patients in the study by Lai et al (24) had severe ARDS and PEEP effects on RV function were not quantified.

In accordance with the above, PEEP impedes RV outflow and affects RV systolic function, through increases in PVRs when it induced significant lung distension according to the recruitment-to-inflation ratio (28, 29). Furthermore, fluid restriction considering that a "dry lung" is aimed, increases the occurence rate of nonzone 3 formation, further increasing dead space (30). Indeed, PEEP titration in our study led to a decrease in PVRs, while all RV systolic function indices significantly improved; accordingly, Pco_2 decrease indicates a nonzone 3 condition improvement. Interestingly, the change in PVRs, measured by PASP/VTI_{LVOT} predicted the combined decrease in PPV and increase in IVC distensibility increase. Furthermore, the change in PPV after PEEP titration correlated to the change in RV systolic function and afterload. It must also be taken into account that in ARDS, from sepsis or COVID-19, RV dysfunction may be partly related to intrinsic depression of contractility. In this setting, a minor rise in airway pressure, as produced by MV–PEEP, may produce acute significant dysfunction or even acute RV failure when applied to a depressed right ventricle (2, 31).

TABLE 2.
Respiratory, Hemodynamic Variables, and Respiratory Mechanics Before and After Positive End-Expiratory Pressure De-Escalation

Variables	Before PEEP De-Escalation ($n = 95$)[a]	After PEEP De-Escalation ($n = 95$)[a]	Change (%)	*p*
Tidal volume, mL/kg, (*n*)	7 ± 0.07 (95)	7 ± 0.08	0.3 ± 0.8	0.977
PEEP, cm H_2O	13.1 ± 0.3 (95)	9.5 ± 0.3	−28 ± 1	< 0.0001
Pao_2/Fio_2, mm Hg	119 ± 3.3 (95)	123.5 ± 3	7.4 ± 2.7	0.144
$Paco_2$, mm Hg	53.7 ± 1.1 (95)	48.7 ± 0.8	−8.4 ± 1.1	< 0.0001
Respiratory system compliance, mL/cm H_2O	29.9 ± 1.04 (95)	37.4 ± 1.3	27.5± 3.2	< 0.0001
Plateau pressure, cm H_2O	28.8 ± 0.5 (95)	22.9 ± 0.5	−20.4 ± 8.4	< 0.0001
Pulse pressure variation, %	11.7± 0.2 (94)	7.9± 0.2	−31 ± 1.8	< 0.0001
Central venous pressure, mm Hg	13.6 ± 0.3 (84)	10.3 ± 0.4	−23 ± 1.9	< 0.0001
Superior vena cava oxygen saturation, %	69.4 ± 0.6 (84)	72 ± 0.5	3.9 ± 0.5	< 0.0001
IVC[e], cm	2.2 ± 0.04 (80)	1.9 ± 0.04	−13.3 ± 0.9	< 0.0001
Respiratory variability in IVC diameter, %	9.1±0.9 (80)	14.6±0.1	83± 14.3	< 0.0001
Mean arterial pressure, mm Hg	69.9 ± 0.6 (95)	75.4 ± 0.7	8 ± 8.3	< 0.0001
Heart rate	74.6 ± 2.2 (95)	74.8 ± 2.2	3.1 ± 1.9	0.902
Noradrenaline, µg/kg/min[c]	0.86 ± 0.1 (95)	0.65 ± 0.08	−20.6 ± 7.4	0.007
Lactate, mmol/L	2.05 ± 0.17 (95)	1.66 ± 0.17	−18.6 ± 2.2	< 0.0001
12-hr fluid balance[d]	1076.5 ± 71.8	405.1 ± 5.6	−45 ± 12.5	< 0.0001
Right ventricular end-diastolic area to left ventricular end-diastolic area	0.89 ± 0.03 (95)	0.72 ± 0.02	−17.2 ± 1.6	< 0.0001
Right ventricular fractional area change, %	35.2 ± 1.0 (95)	39.1 ± 1.2	20.6 ± 7	0.004
Tricuspid annular plane systolic excursion	18.8 ± 0.4 (89)	21.5 ± 0.5	14.9 ± 1.9	< 0.0001
Right ventricular longitudinal strain, %	−11.4 ± 0.4 (81)	−14.4 ± 0.5	38.1 ± 5.4	< 0.0001
Right ventricular ejection fraction, %	33.6 ± 0.1 (87)	44.7 ± 0.1	45.9 ± 7.3	< 0.0001
Right ventricular stroke volume[b], mL	46.5 ± 1.9 (74)	52.4 ± 1.7	32.6 ± 5.3	< 0.0001
PASP, mm Hg	39.5 ± 1.4 (84)	32.6 ± 1.3	−17.4 ± 2	< 0.0001
$PASP/VTI_{LVOT}$, mm Hg/cm	2.21 ± 0.1 (83)	1.73 ± 0.1	−21.1 ± 2.6	< 0.0001
Pulmonary acceleration time, ms	61.6 ± 1.7 (78)	77.6 ± 1.9	30.5 ± 3.7	< 0.0001
Right ventricular outflow tract velocity time integral	16 ± 0.5 (88)	18.6 ± 0.6	16.7 ± 2.1	< 0.0001
VTI_{LVOT}, cm	19.5 ± 0.4 (95)	21.1 ± 0.5	6.9 ± 1.2	< 0.0001

IVC = inferior vena cava, PASP = pulmonary artery systolic pressure, PEEP = positive end-expiratory pressure, VTI_{LVOT} = left ventricular outflow tract velocity time integral.

[a]Actual number of patients measured.

[b]3D measurements.

[c]Thirty-one patients were receiving vasopressin at its maximal dose.

[d]Refers to the fluid balance 12 hr before and 12 hr after PEEP titration.

[e]Minimum diameter measured during expiration under mechanical ventilation.

PPV's reliability lies on the use of relatively high Vts (> 8 mL/kg) in a fully sedated patient on sinus rhythm, with normal C_{RS} and absence of RV dysfunction. Two previous studies have identified high PPV values (> 12%) in patients with RV dysfunction, although the patients were not fluid responders (22, 23). In these

studies, PVRs were not measured. The significance of the present study lays to the fact that a small PEEP change might predict the presence of "some degree" of RV dysfunction that warrants further echocardiographic confirmation. Notably, an increased PPV value might have led to fluid administration, further worsening respiratory and cardiac function.

Furthermore, the Vts used (> 8 mL/kg) might have further affected the already increased PVRs and impaired RV (22, 23). On the contrary, in the present study, the interference of Vt as a variable affecting PPV was essentially limited. We kept a constant low Vt to facilitate lung protective ventilation and identified changes in PPV through PEEP value manipulation. Furthermore, a significant decrease was observed in increased IVC diameter and CVP and, more significantly, an increase in IVC distensibility with PEEP de-escalation, although the cardiac output increased. Apart from the increased RV afterload and RV dysfunction, venous return was probably affected by the higher PEEP level. Relatively high PEEP may significantly increase P_{pl} deteriorating venous return, as much of the airway pressures (and PEEP) are transmitted to the pleural space especially when C_{RS} is rather preserved (32). A transient increase in the Vt has been proposed to better predict fluid responsiveness, when a low Vt is used (33). However, the most challenging group of patients to assess fluid responsiveness are ARDS patients. As already mentioned, in ARDS patients an increase in Vt may disproportionally increase RV afterload and exaggerate RV dysfunction, leading to false PPV assessment (1, 33).

Decreased C_{RS} is another condition limiting PPV's reliability (20). In our study, the change in PEEP value resulted in significant changes in PPV and IVC respiratory variability in patients with C_{RS} less than 30 mL/cm H_2O, although the changes were smaller compared with patients with C_{RS} greater than 30 mL/cm H_2O.

In agreement with RV function and venous return improvement, circulatory failure (increased vasopressor need, tissue hypoperfusion) significantly improved after PEEP titration indicated by an increase in $Scvo_2$ and SV and a decrease in lactate, keeping all other respiratory variables constant, which is in agreement with our previous findings (9). The hemodynamic improvements resulted probably from both the increase in venous return and better-left ventricular performance resulting from a change in its geometry. The improvement in RV function led to significant hemodynamic improvements, resulting in part from the decreased stress imposed to the left ventricle by the paradoxical motion and deviation of the interventricular septum, decreasing effective contractility, relaxation, and filling (34). Furthermore, fluid balance was better controlled, indicating increased renal perfusion.

The study's monocentric character is a limitation. Yet, a large number of patients were prospectively evaluated with comprehensive echocardiography along with hemodynamic measurements at two PEEP levels. We did not confirm fluid responsiveness with a fluid challenge, so that loading conditions not to be altered before PEEP change and definitely not to unnecessarily load the already severe ARDS patients. However, PPV decreased, while IVC respiratory variability decreased without any fluid infusion or ventilatory setting change, other than PEEP titration. We did not perform a passive leg raising, as a continuous cardiac output monitoring device and suitable beds were not always available for our patients. Continuous cardiac monitoring would have enabled the detection of even minor changes in cardiac output in a timely and accurate manner. On the other hand, LVOT VTI has been measured, while the hemodynamic improvement has been documented for the majority of the patients. Finally, although the measured changes observed are positive, the effect of this approach on important clinical outcomes (i.e., mortality and duration of MV/hospital stay) are not known.

CONCLUSIONS

PPV and IVC respiratory distensibility values should be interpreted with caution in patients with ARDS. The absolute PPV values might result from a complex interplay between increased PVRs and fluid status. A PPV change with PEEP alterations in severe ARDS patients may indicate both the RV function improvement and cardiac output increase. If the patients are in need for fluid loading, fluid responsiveness assessment may be further warranted.

1 *Critical Care Department, University Hospital of Larissa, University of Thessaly, Faculty of Medicine, Larissa, Greece.*

2 *Third Cardiology Department, Sotiria Hospital, National and Kapodistrian University of Athens, Greece.*

3 *Department of Respiratory Medicine, General University Hospital of Larissa, University of Thessaly, Faculty of Medicine, Larissa, Greece.*

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Dr. Tsolaki was involved in conceptualization, data curation, formal analysis, investigation, methodology, and writing–original draft. Drs. G. E. Zakynthinos, Karavidas, Papadonta, Dimeas, Parisi, and Amanatidis were involved in data curation, formal analysis, investigation, and writing–review and editing. E. Zakynthinos was involved in the conceptualization, formal analysis, investigation, methodology, supervision, visualization, and writing–original draft. All authors approved the final version submitted for publication.

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For information regarding this article, E-mail: vasotsolaki@yahoo.com

All data and materials generated during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Teboul JL, Monnet X, Chemla D, et al: Arterial pulse pressure variation with mechanical ventilation. *Am J Respir Crit Care Med* 2019; 199:22–31
2. Price LC, McAuley DF, Marino PS, et al: Pathophysiology of pulmonary hypertension in acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2012; 302:L803–L815
3. Sipmann FS, Santos A, Tusman G: Heart-lung interactions in acute respiratory distress syndrome: Pathophysiology, detection and management strategies. *Ann Transl Med* 2018; 6:27
4. Mahmood SS, Pinsky MR: Heart-lung interactions during mechanical ventilation: The basics. *Ann Transl Med* 2018; 6:349
5. Jardin F, Brun-Ney D, Hardy A, et al: Combined thermodilution and two-dimensional echocardiographic evaluation of right ventricular function during respiratory support with PEEP. *Chest* 1991; 99:162–168
6. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
7. Tsolaki V, Zakynthinos GE, Papanikolaou J, et al: Positive end-expiratory pressure deescalation in COVID-19-induced acute respiratory distress syndrome unloads the right ventricle. Improving hemodynamics and oxygenation. *Am J Respir Crit Care Med* 2023; 208:205–208
8. Alhazzani W, Møller MH, Arabi YM, et al: Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020; 46:854–887
9. Tsolaki V, Siempos I, Magira E, et al: PEEP levels in COVID-19 pneumonia. *Crit Care* 2020; 24:303
10. Lang RM, Badano LP, Mor-Avi V, et al: Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16:233–270
11. Rudski LG, Lai WW, Afilalo J, et al: Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23:685–713; quiz 786–788
12. Sugimoto T, Dulgheru R, Bernard A, et al: Echocardiographic reference ranges for normal left ventricular 2D strain: Results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging* 2017; 18:833–840
13. Barbier C, Loubières Y, Schmit C, et al: Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med* 2004; 30:1740–1746
14. Takahama H, McCully RB, Frantz RP, et al: Unraveling the RV ejection Doppler envelope: Insight into pulmonary artery hemodynamics and disease severity. *JACC Cardiovasc Imaging* 2017; 10(10 Pt B):1268–1277
15. Opotowsky AR, Clair M, Afilalo J, et al: A simple echocardiographic method to estimate pulmonary vascular resistance. *Am J Cardiol* 2013; 112:873–882
16. Abbas AE, Fortuin FD, Schiller NB, et al: A simple method for noninvasive estimation of pulmonary vascular resistance. *J Am Coll Cardiol* 2003; 41:1021–1027
17. Roule V, Labombarda F, Pellissier A, et al: Echocardiographic assessment of pulmonary vascular resistance in pulmonary arterial hypertension. *Cardiovasc Ultrasound* 2010; 8:21
18. D'Alto M, Marra AM, Severino S, et al: Right ventricular-arterial uncoupling independently predicts survival in COVID-19 ARDS. *Crit Care* 2020; 24:670
19. Tello K, Wan J, Dalmer A, et al: Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. *Circ Cardiovasc Imaging* 2019; 12:e009047
20. Monnet X, Bleibtreu A, Ferré A, et al: Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med* 2012; 40:152–157
21. Grasselli G, Calfee CS, Camporota L, et al; European Society of Intensive Care Medicine Taskforce on ARDS: ESICM guidelines on acute respiratory distress syndrome: Definition, phenotyping and respiratory support strategies. *Intensive Care Med* 2023; 49:727–759
22. Mahjoub Y, Pila C, Friggeri A, et al: Assessing fluid responsiveness in critically ill patients: False-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med* 2009; 37:2570–2575

23. Wylervon Ballmoos M, Takala J, Roeck M, et al: Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: A clinical study. *Crit Care* 2010; 14:R111
24. Lai C, Shi R, Beurton A, et al: The increase in cardiac output induced by a decrease in positive end-expiratory pressure reliably detects volume responsiveness: The PEEP-test study. *Crit Care* 2023; 27:136
25. Pesenti A, Slobod D, Magder S: The forgotten relevance of central venous pressure monitoring. *Intensive Care Med* 2023; 49:868–870
26. Magder S: Right atrial pressure in the critically ill: How to measure, what is the value, what are the limitations? *Chest* 2017; 151:908–916
27. Madger S: Right atrial pressure and Guyton's approach to fluid management. *Ann. Intensive Care* 2024; 14:181
28. Schmitt JM, Vieillard-Baron A, Augarde R, et al: Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: Impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. *Crit Care Med* 2001; 29:1154–1158
29. Cappio Borlino S, Hagry J, Lai C, et al: The effect of PEEP on pulmonary vascular resistance depends on lung recruitability in ARDS patients. *Am J Respir Crit Care Med* 2024; 210:900–907
30. Grasselli G, Tonetti T, Protti A, et al; collaborators: Pathophysiology of COVID-19-associated acute respiratory distress syndrome: A multicentre prospective observational study. *Lancet Respir Med* 2020; 8:1201–1208
31. Jardin F, Vieillard-Baron A: Monitoring of right-sided heart function. *Curr Opin Crit Care* 2005; 11:271–279
32. Michard F: Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; 103:419–428; quiz 449–445
33. Myatra SN, Prabu NR, Divatia JV, et al: The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. *Crit Care Med* 2017; 45:415–421
34. Petit M, Vieillard-Baron A: Ventricular interdependence in critically ill patients: From physiology to bedside. *Front Physiol* 2023; 14:1232340