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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

An evaluation of end expiratory lung volume and pulmonary mechanics with different PEEP levels in ARDS patients

ARDS hastalarının mekanik ventilasyonunda farklı PEEP düzeyleri ile soluk sonu akciğer hacmi ve pulmoner mekaniklerin değerlendirilmesi

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ABSTRACT

Objective: The treatment of acute respiratory distress syndrome (ARDS) is highly complex, and its mortality rate remains significant. Positive end-expiratory pressure (PEEP) titration plays a crucial role in mechanical ventilation; however, the optimal approach for PEEP titration has yet to be established. This study evaluated the volume gain at different PEEP levels along the pressure-volume curve, changes in end-expiratory lung volume (EELV) measured via the modified multiple nitrogen wash-out/wash-in technique, and respiratory compliance.

Materials and Methods: Following approval from the ethics committee, 14 patients with ARDS receiving invasive mechanical ventilation in intensive care units were included in the study. According to the Berlin Criteria, there were 2 patients with mild ARDS, 7 with moderate ARDS, and 5 with severe ARDS. The repeated nitrogen wash-out/wash-in technique assessed functional residual capacity (FRC) and EELV at decreasing PEEP levels (±5 cm H_2O) were determined. Gain and compliance values were calculated based on the dynamic pressure-volume curves generated. Arterial blood gas analysis was conducted to measure oxygenation at each PEEP level.

Results: The highest compliance, gain, and EELV values, as well as the lowest driving pressure and strain values, were observed at a PEEP level of 10 cm H_2O. Conversely, the highest PaO_2 values, representing oxygenation indicators, were recorded at a PEEP level of 15 cm H_2O. Notably, the gain remained largely unaffected by changes in compliance, elastance, driving pressure, and static strain; it was not affected by lung distension.

Conclusions: In PEEP titration, alveolar distension was not detected by EELV or gain parameters. Sufficient evidence could not be obtained solely in clinical practice.

Keywords: functional residual capacity, gain, PEEP, EELV, pulmonary mechanics

ÖZ

Amaç: Akut respiratuvar distres sendromunun (ARDS) tedavi stratejileri oldukça karmaşık, mortalitesi yüksektir. Mekanik ventilasyonda soluk sonu pozitif basınç (PEEP) titrasyonunun önemi büyüktür. Ancak PEEP titrasyonuna optimal yaklaşım net olarak belirlenememiştir. Çalışmamızda basınç-volüm eğrisi üzerinden farklı PEEP seviyelerindeki volüm kazancı (gain), modifiye çoklu azot yıkama tekniği ile ölçülen soluk sonu akciğer hacmi (EELV) değişimi ve kompliyansın, solunum mekanikleri ile değerlendirilmesi amaçlanmıştır.

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Gereç ve Yöntem: Etik Kurul onayı alındıktan sonra yoğun bakım ünitelerinde invaziv mekanik ventilasyon uygulanan 14 ARDS hastası çalışmaya alındı. Berlin Kriterlerine göre; 2 hafif, 7 orta, 5 ağır ARDS hastasıydı. Azalan PEEP titrasyon prosedürü (±5 cm H_2O) ile fonksiyonel rezidüel kapasite (FRK) ve EELV, çoklu azot yıkama tekniği ile ölçüldü. İntratrakeal basınç sensörü ile oluşturulan dinamik basınç-volüm eğrileri üzerinden kazanç ve kompliyans ölçüldü. Her PEEP düzeyinde arteriyel kan gazı ile oksijenasyon değerlendirildi.

Bulgular: En yüksek kompliyans, kazanç, EELV değerine ve en düşük sürücü basınç değerine 10 cm H_2O PEEP düzeyinde ulaşıldı. Oksijenasyon göstergesi olan PaO_2'nin en yüksek değerleri 15 cm H_2O PEEP düzeyinde ölçüldü. Kazancın; kompliyans, elastans, sürücü basıncı, statik strain ile anlamlı olarak değişmediği ve akciğer distansiyonuna duyarlı olmadığı görüldü.

Sonuç: PEEP titrasyonunda alveol distansiyonunun, EELV veya kazanç parametreleri ile belirlenemediği görüldü. Klinik pratikte tek başına kullanılabilmesi için yeterli ve güçlü kanıtlar elde edilemedi. Bunun için daha fazla çalışmaya gerek vardır.

Anahtar kelimeler: fonksiyonel rezidüel kapasite, kazanç, PEEP, EELV, pulmoner mekanikler

Introduction

Acute respiratory distress syndrome (ARDS) was first described in the 1960s (1). Clinically, ARDS is characterized as a diffuse, acute inflammatory lung injury marked by rapid-onset hypoxic respiratory failure and alterations in pulmonary mechanics (2). In 2012, the Berlin criteria were established for diagnosing ARDS (3). It is estimated that ARDS affects more than 3 million people worldwide annually, necessitates mechanical ventilation, and carries a mortality rate of 35-46% (2,4). The primary objective of treatment is to improve gas exchange by reducing the respiratory workload (5). In the context of mechanical ventilation, positive end-expiratory pressure (PEEP) may enhance oxygenation and increase end-expiratory lung volume (EELV) (6). However, excessive PEEP may lead to lung overdistension, increased dead space ventilation, and hemodynamic instability due to reduced cardiac output (6-8).

Previous studies have indicated that measuring and monitoring of EELV can be beneficial in cases involving FRC or PEEP adjustments. An optimal PEEP value, defined by the intersection of maximum oxygen transport with the highest static compliance and FRC, has been identified (9). Additionally, it has been demonstrated that the ΔEELV/ΔPEEP ratio can be utilized alongside maximum respiratory system compliance, as both values typically reach their optimal levels at the same PEEP settings (10). One potential adverse effect of PEEP is lung overdistension, resulting from a PEEP-induced increase in EELV that excessively strains open alveoli. Concepts of lung stress and strain, derived from EELV measurements, can predict this phenomenon (11).

EELV can be measured using computed tomography (CT) (12). However, CT is unsuitable for routine bedside use. Traditional techniques for EELV measurement rely on tracer gas dilution methods, including sulfur hexafluoride wash-out, closed-circuit helium dilution, or open-circuit multiple nitrogen wash-out (13-15). These techniques, while accurate, require expensive and impractical equipment. A novel method for FRC measurement, based on a modified nitrogen multiple-breath wash-out (NMBW) technique, has been developed. This approach is simplified and integrated into mechanical ventilators, eliminating the need for additional tracer gases or specialized monitoring equipment. The method calculates FRC by analyzing changes in the fraction of inspired oxygen (FiO_2) (16).

Studies have shown that EELV measurements can be used to estimate recruitment volume, which is critical for distinguishing whether PEEP-induced volume increases result from the opening of collapsed alveoli or the overdistension of already open alveoli (17).

The present study aims to evaluate volume gains at different PEEP levels through pressure-volume curve analysis using a protocol of gradually decreasing PEEP values. It also seeks to assess the relationship between EELV and compliance changes measured by the modified nitrogen multiple-breath wash-out technique and respiratory mechanics. Oxygenation was evaluated through arterial blood gas analysis at each PEEP level. Furthermore, the measured volume gains were compared with estimated recruitment volumes calculated using EELV.

Materials and Methods

This study was conducted in the anaesthesiology and reanimation intensive care units of a tertiary hospital with the approval obtained from the 13th board meeting of the Pamukkale University Non-invasive Clinical Trials Ethics Committee (no: 60116787-020/83538, date:13.07.2021). Between August 2021 and August 2022, 14 patients over 18 years of age who met the Berlin criteria (18) and were diagnosed with ARDS were included in the study. These patients were sedated, intubated, and mechanically ventilated. Written informed consent was obtained from their relatives.

The patients were connected to a CARESCAPE R860 (GE Healthcare) mechanical ventilator. Rocuronium bromide was administered intravenously to suppress spontaneous respiratory effort, and opioids were used for sedation. Tidal volume was set at 6 mL/kg based on estimated body weight, respiratory rate was adjusted to ensure normocarbia in blood gas analysis, and FiO_2 was adjusted to maintain PaO_2 levels between 55 and 80 mmHg. The end-inspiratory pause was set at 20%, and the inspiratory/expiratory ratio was adjusted to 1:2.

Gas measurements were conducted using the ECOV-X (GE Healthcare) module, which was attached to the ventilator and allowed to warm up before use. A spirometer kit with heat and moisture retention properties was placed between the Y-piece in the ventilator circuit and the bacterial/viral filter. An intratracheal pressure sensor was inserted to measure pressure levels independent of circuit and tube resistance, and these measurements were analyzed using the SpiroDynamics (GE Healthcare) application. EELV was measured using the ECOV-X module with a modified NMBW technique based on changes in FiO_2. EELV was calculated using oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Once all connections were completed, VO_2 and VCO_2 values were measured. The PEEP titration procedure, Lung InViewTM (GE Healthcare), was initiated in patients whose values stabilized within 30 minutes. Before measurements, a recruitment maneuver was performed for 30-40 seconds at a PEEP level of 20 cm H_2O. Measurements were recorded during a descending PEEP trial conducted at four levels (15, 10, 5, and 0 cm H_2O).

For the same PEEP levels, the shunt fraction decreased when a descending PEEP maneuver was used instead of an ascending maneuver. This observation suggests that the relationship between optimal PEEP and maximum compliance is more accurately determined using descending PEEP trials, which is why the study protocol preferred descending PEEP trials (19).

The measurement time for each PEEP level was set at 10 minutes. At the end of each measurement, static compliance was determined by applying an end-inspiratory pause. Tidal volume, peak pressure, and driving pressure were recorded at each step. Respiratory system elastance was calculated using Henderson et al.'s (20) formula: respiratory system elastance = driving pressure/tidal volume. The static strain was calculated using Protti et al.'s (21) equation, which employs tidal volume at the relevant PEEP value: static strain = tidal volume at PEEP/FRC. The pressure-volume curve generated by the intratracheal pressure sensor at each PEEP level was evaluated using the SpiroDynamics application. Dynamic compliance curves were generated during analysis, and volume changes in these curves were determined for each PEEP level. The difference in EELV between two PEEP levels during a descending PEEP trial (ΔEELV) and the difference between ΔEELV and the volume derived from the pressure-volume curve were calculated as "volume gain" (gain = ΔEELV - volume derived from the curve). The estimated lung volume recovered was calculated using the formula ΔEELV - (ΔPEEP × Compliance at PEEPlow) and compared with the volume gain (17). The efficiency of the volume gains concept as an indicator of alveolar recruitment volume and its role in personalized PEEP titration was evaluated.

Statistical analysis

The effect size was calculated over the EELV at high and low PEEP levels in the referenced study. The effect size was reported as dz=0.974. Power analysis was conducted, assuming a strong effect size (F=0.4) could be achieved. Given that the study involved three distinct PEEP levels, it was determined that a sample size of at least 12 participants would provide 80% power at a 95% confidence level. To account for potential data loss, the study planned to include 14 participants, representing a 20% increase over the minimum required sample size.

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 25.0; IBM SPSS Statistics, Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk test. For dependent group comparisons, repeated measures analysis of variance (ANOVA) was applied when parametric test assumptions were met, whereas the Friedman test was used when these assumptions were violated. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. A p-value of <0.05 was considered statistically significant in all analyses.

Results

The mean age of the 14 patients included in our study is 64.50±15.14 years. The mean body weight, height, and body mass index (BMI) were 84.71±10.83 kg, 169.64±7.89 cm, and 29.29±5.59 kg/m^2, respectively. The cohort consisted of six females and eight males.

Regarding chronic comorbidities, eight patients (57.1%) had hypertension, six (42.9%) had diabetes mellitus, two (14.3%) had coronary artery disease, two (14.3%) had chronic kidney disease, and four (28.6%) had malignancy. Table 1 presents the distribution of diseases leading to ARDS and the severity of ARDS, as classified according to the Berlin Criteria.

Table 1. Risk factors and severity distrubution of patients for ARDS

	n	%
ARDS cause		
COVID-19 pneumonia	8	57.1
Femur fracture	1	7.1
Pneumonia	3	21.4
Pulmonary embolism	1	7.1
Fat embolism	1	7.1
ARDS severity distribution		
Mild	2	14.3
Moderate	7	50
Severe	5	35.7

ARDS: Acute respiratory distress syndrome.

Compliance measurements were significantly higher at 5 cm H_2O PEEP compared to 0 cm H_2O, and at 10 cm H_2O compared to both 0 and 15 cm H_2O PEEP. Driving pressure was significantly lower at the 10 cm H_2O PEEP level compared to 0 and 15 cm H_2O levels. Intragroup p values for elastance, EELV, and static strain were not significant (Table 2).

No statistically significant differences were observed in systolic blood pressure, diastolic blood pressure, and heart rate (HR) across different PEEP levels ($p>0.05$). Oxygen saturation (SpO_2) values at PEEP levels of 15 cm H_2O and 10 cm H_2O were significantly higher than those at 0 cmH_2O ($p<0.001$). Similarly, partial arterial oxygen pressure (PaO_2) values were significantly higher at a PEEP of 15 cmH_2O compared to 0 cm H_2O ($p<0.05$). Blood gas saturation (SaO_2) values were also significantly higher at PEEP levels of 15 cm H_2O and 10 cm H_2O compared to 0 cmH_2O ($p<0.05$; Table 3).

When assessing the changes in lung volume during reductions in PEEP by increments of 5 cm H_2O, the highest volume gain was observed when decreasing from a PEEP of 10 cm H_2O to 5 cm H_2O. This change was statistically significant but represented a net volume loss ($p<0.05$). The estimated lung volume and volume gain that were recovered were strongly and positively correlated with the gain observed during high PEEP trials (Table 4).

Table 2. Lung mechanics at different PEEP levels

	15 cm H_2O PEEP	10 cm H2O PEEP	5 cm H_2O PEEP	0 cm H_2O PEEP	in-group p
Static Compliance (mL/cm H_2O)	30.86±1.67	43.07±30.68	38.21±13.45	32.36±12.38	0.001*
Elastance (cm H_2O/L)	33.93±13.06	33.64±7.52	26.86±8.65	29.07±10.86	0.009
Driving pressure (cm H_2O)	15.36±3.00	12.21±3.31	13.07±4.23	15.29±5.44	0.003α
Static strain (cm H_2O)	0.67±0.66	0.64±0.32	0.36±0.23	0	0.257
EELV (mL)	2423.79±1828.44	2535.57±2350.27	1924.71±1442.33	1817.71±1403.36	0.433
Peak pressure (cm H_2O)	36.43±3.84	30.71±4.38	26.21±5.58	24.00±7.25	0.0001β

PEEP: Positive End Expiratory Pressure, EELV: End-Expiratory Lung Volume; *:p=0.002: Static compliance at 15-10 cm H_2O PEEP, p=0.011: Static compliance at 10-0 cm H_2O PEEP, p=0.001: Static compliance at 5-0 cm H_2O PEEP; α:p=0.002: Driving pressure at 15-10 cm H_2O PEEP, p=0.013: Driving pressure at 10-0 cm H_2O PEEP, p=0.007: Driving pressure at 5-0 cm H_2O PEEP; β:p=0.001 :Peak pressure at 15-10 cm H_2O PEEP, p=0.001: Peak pressure at 15-5 cm H_2O PEEP, p=0.001: Peak pressure at 10-5 cm H_2O PEEP, p=0.001: Peak pressure at 15-0 cm H_2O PEEP, p=0.001: Peak pressure at 10-0 cm H_2O PEEP, p=0.009: Peak pressure at 5-0 cm H_2O PEEP.

Table 3. SpO_2 (%), PaO_2 (mmHg), $PaCO_2$ (mmHg), and SaO_2 (%) at different PEEP levels

	15 cm H_2O PEEP	10 cm H_2O PEEP	5 cm H_2O PEEP	0 cm H_2O PEEP	p -value
Peripheral SpO_2 (%)	97.00±2.51	95.5±3.16	93.86±4.1	92.07±5.01	0.001*
pH	7.36±0.12	7.38±0.13	7.35±0.11	7.39±0.12	0.736
PaO_2 (mmHg)	92.56±42.77	86.84±31.10	77.34±28.71	73.61±34.15	0.008*
$PaCO_2$ (mmHg)	52.06±8.03	49.1±10.37	47.98±7.38	50.53±9.29	0.022*
SaO_2 (%)	92.58±4.28	92.80±4.62	90.84±5.61	86.02±10.15	0.036*

SpO_2: Peripheral oxygen saturation, PaO_2: Partial arterial oxygen pressure, $PaCO_2$: Partial arterial carbondioxide pressure, SaO_2: Arterial blood oxygen saturation.

Table 4. Correlation of volume gain and estimated recruintment volume

n=14	**RecEstimation**	**15-10 cm H_2O PEEP**	**10-5 cm H_2O PEEP**	**5-0 cm H_2O PEEP**
Gain	r	0.930**	0.999**	0.515
	P	0.000	0.000	0.6
Gain (mL)	0.223	-297.79±1418.52	815.07±1421.09	-94±622,95

r: correlation coefficient.

Discussion

The clinical manifestation of acute respiratory failure with bilateral infiltrates on lung imaging, that defies explanation by heart failure and fluid overload is known as ARDS (3). Predisposing risk factors for ARDS include multiple blood product transfusions, sepsis, pneumonia, gastric aspiration, trauma, pancreatitis, severe burns, and exposure to inhaled or systemic toxins (18). The mechanical ventilation strategies for ARDS are primarily based on the "ARMA" study (22). The fundamental recommendations include setting the tidal volume to 6 mL/kg of predicted body weight and maintaining the plateau pressure at or below 30 mmHg (22,23). It is possible to improve oxygenation with PEEP titration; however, the best strategy must be specified. We know that FRC decreases in patients with ARDS (24). Therefore, using PEEP-induced FRC, i.e., EELV, is of interest. Also, the volume gain, which can be measured simultaneously and shows the recovery of collapsed alveoli, suggests its use in PEEP titration.

TestChest®, a lung stimulator, was employed by Berger-Estilita et al. (25) to evaluate the accuracy of the InViewTM system. Their findings demonstrated that the volume differences between measurements obtained using the modified nitrogen flushing technique and the simulator were within an acceptable range and well correlated (25). Based on this evidence, the current study utilized InViewTM. For EELV measurement (25).

Dellamonica et al. (17) assessed EELV measurement alongside static compliance, $PaCO_2$, and pH levels at 5 and 15 cm H_2O different PEEP levels in 30 ARDS patients. No statistically significant differences were observed between the groups for these parameters. Similarly, the present study found no significant differences in these parameters. However, Dellamonica et al. (17) reported significant SaO_2, strain, and EELV values at higher PEEP levels. Consistently, the present study demonstrated that both EELV and SaO_2 increased with higher PEEP levels, reaching the highest static strain value at a PEEP of 15 cmH_2O. Dellamonica et al. (17) also estimated the recruitment alveolar volume using EELV, compared it with results from the pressure-volume curve technique, finding a strong correlation between the two methods. In the current study, during calculations of the Rec(estimate) and its correlation with volume gain, a very high correlated value was found when the pressure was moved from 15 to 10 and 10 to 5 cmH2O PEEP. (Table 4). These findings suggest that volume gain could serve as an indicator of alveolar recruitment at higher PEEP levels. However, this study's absence of correlation at lower PEEP levels and the lack of smaller PEEP transition intervals prevent strong recommendations for routine clinical application.

Chen et al. (26) demonstrated that using a nitrogen-washout approach integrated into the mechanical ventilator could predict recruitment and inflation in 45 patients with moderate to severe ARDS. The study showed significantly higher SpO_2 and EELV values at higher PEEP levels than lower ones. Similarly, in the present study, EELV values were significantly higher at a PEEP level of 10 cm H_2O compared to 0 cm H_2O. The highest compliance value was observed at a PEEP level of 10 cm H_2O, while the lowest was at 0 cm H_2O. This difference may be attributed to the recruitment maneuver performed prior to measurements in the current study and the greater number of PEEP trials conducted. Differences in patient populations, ARDS severity, and the inclusion of COVID-19-related ARDS may contribute to variations in results

Chiew et al. (27) used the patient-specific minimum elastance value as a criterion for PEEP titration in mechanically ventilated ARDS patients. Their study demonstrated that elastance was higher at 0 cm H_2O PEEP and decreased with increasing PEEP. A moderate correlation was identified among elastance, EELV, and work of breathing. The present study consistently observed a strong negative correlation between elastance and increased EELV at 15 and 0 cm H_2O PEEP, aligning with expectations for these extreme levels of PEEP.

Several studies suggest that the PaO_2/FiO_2 ratio is an unreliable marker for evaluating anatomical recruitment in ARDS patients (17,26,28). Instead, monitoring lung volume changes via FRC measurements may be more appropriate for assessing alveolar recruitment or collapse.

The present study achieved optimal EELV, compliance, driving pressure, and volume gain values at a PEEP level of 10 cm H_2O. This finding highlights the potential importance of this PEEP level but does not support its routine clinical use. Personalized PEEP adjustments remain the primary recommendation, as measurements were conducted at only three PEEP levels. The highest PaO_2 and SpO_2 values were observed at 15 cm H_2O PEEP. However, these values may lack clinical relevance regarding target oxygenation thresholds. Consequently, the primary aim of the mechanical ventilation strategy was to achieve a PaO_2 threshold of 60 mmHg while maintaining pulmonary mechanics as part of a balanced approach.

The amount of recruitable lung tissue varies in ARDS, and ARDS severity may be inferred by quantifying recruitable volume (29,30). Grieco et al. (31) used the recruitment-to-inflation (RI) ratio to titrate PEEP in their IPERPEEP trial by monitoring EELV at each step. Similarly, the current study sought to quantify recruited alveoli through EELV, ΔEELV, and volume gain measurements. The findings of the completed IPERPEEP trial will provide additional insights relevant to the context of this study.

The limitations of this study include the inability to thoroughly evaluate dynamic ventilation parameters due to the administration of neuromuscular blockers during measurements. Furthermore, the 10-minute intervals required between PEEP levels during the decremental PEEP trial, aimed at minimizing transmission risks during the COVID-19 pandemic, may have influenced oxygenation parameters in blood gas analyses.

Conclusion

Volume gain at high PEEP levels may guide individualized PEEP as it correlates with the estimated recruited lung volume. However, this correlation was not demonstrated at low PEEP levels. Also, there was no sufficient and robust evidence that volume gain or EELV correlates with compliance, strain, elastance, and driving pressure parameters that predict alveolar overdistension in PEEP titration.

Ethical approval

This study has been approved by the Pamukkale University Non-invasive Clinical Trials Ethics Committee (approval date: July 13, 2021, number: 60116787-020/83538). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: SYT, AK, HS; data collection: SYT, ÇT; analysis and interpretation of results: SYT, ÇT, HS; draft manuscript preparation: SYT, HS. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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