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Dynamic Effects of Incremental Positive End-Expiratory Pressure on Right Ventricular-Pulmonary Arterial Coupling in Mechanically Ventilated Patients: A Prospective Pilot Study

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Tables 1 to 4 are available in the Supplementary Files section.

Dynamic Effects of Incremental Positive End-Expiratory Pressure on Right Ventricular-Pulmonary Arterial Coupling in Mechanically Ventilated Patients: A Prospective Pilot Study

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Abstract

Objectives: The dynamic impact of incrementally elevated PEEP on RV-pulmonary arterial coupling (RVPAC) remains incompletely quantified. This study aimed to characterize the progressive changes in RVPAC during a stepwise PEEP challenge.

Measurements and Main Results: This study included 30 participants receiving invasive mechanical ventilation. Following baseline assessment at a PEEP of 5 cmH_2O, PEEP was sequentially increased to 8, 11, 13, and 15 cmH_2O. At each level, comprehensive transthoracic echocardiography was performed to assess RVPAC, quantified by the end-systolic to arterial elastance ratio (Ees/Ea). Tricuspid annular plane systolic excursion to pulmonary arterial systolic pressure ratio (TAPSE/PASP) and the TAPSE to isovolumic contraction time ratio (TAPSE/IVCT), were also evaluated.

Results: Incremental PEEP elevation significantly increased RV afterload, as evidenced by rising trends in PASP, IVCT, and Ea (*P* for trend *<0.001* for all). Conversely, TAPSE, systolic tissue velocity (S'), RV stroke volume (RVSV), and RV ejection fraction (RVEF) demonstrated significant declines (*P* for trend *<0.001* for all). Consequently, all RVPAC indices (Ees/Ea, TAPSE/PASP, and TAPSE/IVCT) deteriorated progressively (*P* for trend *<0.001*). Notably, a marked decline in Ees/Ea occurred when PEEP increased from 11 to 13 cmH_2O (1.38 ± 0.62 vs. 1.04 ± 0.43, *P<0.05*). Linear mixed-effects models revealed significant positive associations of both TAPSE/PASP (estimate=0.291 per 1-unit increase, p<0.001) and TAPSE/IVCT (estimate=0.035 per 1-unit increase, p<0.001) with the Ees/Ea ratio, although the strength of these associations varied with PEEP level.

Conclusion: Escalating PEEP progressively impairs RV systolic function and RVPAC, with a marked deterioration identified at 13 cmH_2O as an exploratory threshold. The TAPSE/PASP ratio reliably tracks these dynamic changes across PEEP levels and offers a practical bedside tool for individualized PEEP titration in mechanically ventilated patients.

Keywords: Positive End-Expiratory Pressure; Right Ventricular-Pulmonary Arterial Coupling; Ventilator-Induced Right Ventricular Dysfunction; Echocardiography; Ventilator Management

Introduction

Individualizing positive end-expiratory pressure (PEEP) titration to optimize lung recruitment while avoiding right ventricular (RV) compromise remains a critical challenge in managing acute respiratory failure[1,2]. PEEP, while essential for improving oxygenation, elevates intrathoracic pressure. This may impair right ventricular-pulmonary arterial coupling (RVPAC), a key metric of ventriculo-arterial matching efficiency, primarily by increasing RV afterload and reduced venous return. Its derangement is a precursor to acute cor pulmonale and is closely associated with adverse clinical outcomes[3]. This iatrogenic RV injury may offset the pulmonary benefits of PEEP, highlighting an urgent need for bedside-capable, dynamic assessment of RVPAC during ventilation management.

Precisely this need for dynamic assessment, however, is complicated by the variable hemodynamic impact of PEEP itself, which is not uniform but critically dependent on lung recruitability[4]. In patients with low recruitability, PEEP primarily induces lung overdistension, which increases pulmonary vascular resistance (PVR) and pulmonary artery pressure, thereby elevating RV afterload and impairing RVPAC[5]. In contrast, in highly recruitable lungs, PEEP may improve oxygenation without significant detrimental effects on RV function[4,5]. This heterogeneity underscores that a “one-size-fits-all” PEEP strategy is inadequate and highlights the necessity of integrating cardiopulmonary monitoring into titration protocols. A standardized, widely applicable bedside method for concurrently optimizing both lung recruitment and RV function is still lacking [6].

To assess RV function in this context,the ratio of end-systolic to arterial elastance (Ees/Ea), typically derived echocardiographically as the RV stroke volume to RV end-systolic volume ratio (SV/ESV) measureof RVPAC[3,7]. This index, normally maintained between 1.5 and 2.0, signifies optimal ventriculo-arterial matching. A decline below 1.0 indicates RV-pulmonary uncoupling and is associated with RV dysfunction and worse clinical outcomes[8,9]. However, its clinical application in real-time, bedside decision-making is limited due to the complexity of required volumetric assessments. This practical constraint has driven interest in simpler, echocardiographic surrogate indices. Among these, the ratio of tricuspid annular plane systolic excursion to pulmonary arterial systolic pressure (TAPSE/PASP) is one of the most studied and readily obtainable. Although preliminary studies suggest a correlation between TAPSE/PASP and Ees/Ea[10], but the evidence remains incomplete, especially in the dynamic context of changing ventilator settings.

Consequently, we conducted a prospective physiological study with the aims to quantifythe dynamic effects of incrementally increased PEEP (from 5 to 15 cmH_2O) on RVPAC (using Ees/Ea as the reference) and on comprehensive RV function parameters; and to validatethe effectiveness of surrogate echocardiographic indices (TAPSE/PASP and TAPSE/IVCT) in tracking PEEP-induced changes in RVPAC. This study aims to provide novel insights into cardiopulmonary interactions during mechanical ventilation and to evaluate a practical bedside tool for guiding an RV-protective strategy.

Methods

Study population

This study screened participants in the Intensive Care Unit of Peking University Shenzhen Hospital (PKUSZH) between March 2025 and January 2026. Written informed consent was obtained from all patients or their legal representatives. This study was conducted in accordance with the *Declaration of Helsinki* and approved by the Ethics Committee of Peking University Shenzhen Hospital (Approval No. 146/2024 and No. [2023]045) with Clinical Trial Number (ChiCTR2400092610||http://www.chictr.org.cn/) with the Clinical Trial Registry (20241120). Inclusion criteria: (1) age ≥18 years; (2) requiring invasive mechanical ventilation. Exclusion criteria were: (1) pneumothorax, pulmonary bullae, or significant lung injury; (2) baseline oxygenation index <200 mmHg; (3) baseline PEEP >8 cmH_2O or plateau pressure >30 cmH_2O; (4) pulmonary artery systolic pressure >50 mmHg; (5) advanced heart failure (Killip class ≥III) or mean arterial pressure (MAP) <65 mmHg or requirement for vasopressor support to maintain blood pressure; (6) congenital heart disease; (7) poor echocardiographic image quality; (8) declined participation. Baseline demographic, clinical, and laboratory data were collected, including comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and admission arterial blood gas analysis.

Study Protocol

All patients received volume-controlled mechanical ventilation with a target Richmond Agitation-Sedation Scale score of -4. Initial ventilator settings were: tidal volume (Vt) 6-8 mL/kg (predicted body weight), fraction of inspired oxygen 50%, respiratory rate 16 breaths/min, inspiratory-to-expiratory ratio 1:2, inspiratory flow 50 L/min, and PEEP 5 cmH_2O. The primary exposure factor is the incrementally increased level of Positive End-Expiratory Pressure (PEEP). PEEP was sequentially increased to 8, 11, 13, and 15 cmH_2O. Each PEEP level was maintained for 10 minutes for hemodynamic equilibration, after which transthoracic echocardiogram (TTE) and cardiorespiratory parameter recordings were repeated. A secondary aspect of the exposure analysis is the examination of PEEP as a continuous variable for trend analysis. The study used linear mixed-effects models to test for linear trends across the sequentially increased PEEP levels (5, 8, 11, 13, 15 cmH_2O).

Measurements

The primary outcome was RVPAC, which was calculated as Ees/Ea ratio, where Ees = PASP/ RVESV；Ea = PASP/RVSV；RVPAC = Ees/Ea =(PASP/RVESV) / (PASP/RVSV) = RVSV / RVESV(SV/ESV). Although Ees is traditionally derived from invasive pressure-volume loops, we used the simplified echocardiographic approach (Ees = PASP/RVESV) as a validated surrogate in critical care settings; this non-invasive method correlates well with invasive Ees but may be influenced by loading conditions[7]. The normal physiological range for Ees/Ea is 1.5-2.0, and a value <1.0 indicates right ventricular-pulmonary arterial uncoupling[3,7]. Alternative surrogate indices for RVPAC were also calculated, including TAPSE/PASP and TAPSE/IVCT[7,8]. All echocardiographic data were acquired by a single, trained investigator blinded to the study protocol. All echocardiographic data were acquired by a single, experienced sonographer. Measurements were taken over three consecutive cardiac cycles, and the average value was used for analysis to minimize variability. In the figure, the statistical

significance of each pairwise comparison is denoted by symbols.

Secondary outcome indicators were right ventricular function parameters, Such as right ventricular preload indicators, including right ventricular end-diastolic diameter (RVDD, cm), left ventricular end-diastolic diameter (LVDD, cm), diastolic systemic volume (DSV, ml), and end-systolic volume (ESV, ml). Right ventricular systolic function indicators, including TAPSE (mm), tricuspid annular peak systolic velocity (S', cm/s), Ees (mmHg/mL), RVSV (ml), and right ventricular ejection fraction (RVEF, %). Right ventricular afterload at different PEEP levels were compared by analyzing factors including PASP (mmHg), tricuspid regurgitation area (TRS, cm^2), IVCT (ms), and Ea(mmHg/mL). PASP was calculated as 4× (tricuspid regurgitation velocity) ^{2} + central venous pressure (CVP). CVP was measured via central venous catheter when available; otherwise, it was estimated from inferior vena cava diameter and collapsibility.

Hemodynamic parameters, including heart rate (HR, beats/min), MAP (mmHg), and peripheral oxygen saturation (SpO_2, %), Respiratory Mechanics parameters, including peak pressure (Ppeak, cmH_2O), plateau pressure (Pplat, cmH_2O), driving pressure (DP, cmH_2O), lung compliance (C, ml/cmH_2O), airway resistance (R, cmH_2O/L/s), and Vt (ml).

The following equipment was used patient monitors (iMEC-10/12, PM-9000; Mindray, China), blood gas analyzer (BGA-101; Wondfo, China), ventilator (EVita4 edition; Dräger Medical, Germany), and ultrasound system (M9; Mindray, China).

Statistical Analysis

R4.3.0 was used for data analysis. Descriptive statistics were first used to summarize the study variables. Continuous variables with a normal distribution are presented as mean±standard deviation, whereas non-normally distributed continuous variables are presented as median [interquartile range]. Categorical variables are reported as n (%).

The effects of different positive end-expiratory pressure (PEEP) levels on hemodynamic, respiratory mechanics, and right ventricular function were then analyzed to assess overall trends and differences. Repeated-measures ANOVA or the Friedman test was applied, as appropriate. Linear mixed-effects models were further employed to evaluate linear trends across increasing PEEP levels, with PEEP level included as a fixed effect and participant included as a random effect to account for within-participant correlations. For outcomes showing significant overall differences, post-hoc pairwise comparisons between PEEP levels were performed.

Associations between surrogate indices and the right ventricular–pulmonary arterial coupling were examined to assess the validity of the surrogate measures. Linear mixed-effects models were used, with each surrogate index (TAPSE/IVCT or TAPSE/PASP) included as a fixed effect and participant included as a random effect.

Results

Patient description

Among 84 screened patients, 54 were excluded based on the above criteria, Consequently, A total of 30 participants requiring invasive mechanical ventilation were included in this study. **(Figure 1)**

The demographic, clinical, and laboratory characteristics of the cohort are

summarized in **(Table 1).** The mean age was 62.47 ± 18.80 years, with a male predominance (60.0%). The median body mass index (BMI) was 23.00 kg/m² (IQR 20.00-27.00). Disease severity at admission was substantial, as indicated by a median Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 13.07 ± 6.77. Key baseline laboratory values, including arterial blood gas parameters and lactate levels, are presented in **(Table 1 and Figure 1)**.

Effects of Different PEEP Levels on Right Ventricular-Pulmonary Arterial Coupling Indicators

The fixed-effect analysis for a linear trend across PEEP levels revealed statistically significant decreases in all three indices of right ventricular-pulmonary arterial coupling (Ees/Ea, TAPSE/PASP, and TAPSE/IVCT; all $P < 0.001$), as detailed in **(Table 2)**. Post hoc pairwise comparisons of these indices between different PEEP levels are detailed in **(Figure 2)**. Specifically, for Ees/Ea, a marked and statistically significant reduction-suggesting an exploratory inflection point-was observed when PEEP increased from 11 to 13 cmH_2O (from 1.38±0.62 to 1.04±0.43, $P<0.05$). Post hoc comparisons confirmed that the Ees/Ea value at this level was significantly lower than those at all lower PEEP levels (5, 8, and 11 cmH_2O) **(Figure 2A)**.

Effects of Different PEEP Levels on Right Ventricular Function Indicators

Fixed-effects analysis revealed significant linear trends across increasing PEEP levels. Ventricular dimensions increased, as evidenced by rising right RVDD ($P < 0.001$), LVDD ($P = 0.001$), and ESV ($P = 0.003$). In contrast, systolic function parameters, including TAPSE, S' velocity, RVSV, and RVEF, exhibited significant declines (all $P < 0.001$), while Ees remained no significant trend ($P = 0.168$). Concurrently, indices of right ventricular afterload PASP, TRS, IVCT, and Ea all showed progressive increases (all $P < 0.001$) (**Table 2).**

Post hoc comparisons confirmed that the TAPSE, S' velocity and RVEF value was significantly lower when PEEP increased from 5 to 13 (**Figure 3),** while the PASP, TRS and IVCT value was significantly higher (**Figure 4)**.

Effects of Different PEEP Levels on Hemodynamics Parameters

The fixed-effect analysis for a linear trend across PEEP levels indicated no statistically significant changein HR, MAP, or SpO_2 (all $P > 0.05$) **(Table 3)**.

Effects of Different PEEP Levels on Respiratory Mechanics Parameters

(Table 3) demonstrated a linear trend increasement in Ppeak, Pplat and DP as PEEP levels increase ($P < 0.001$, $P < 0.001$, and $P =0.029$, respectively). In contrast, no significant linear trends were observed for C, R, or Vt (all $P > 0.05$).

Analysis of Linear Associations Between TAPSE/IVCT, TAPSE/PASP, and Ees/Ea (SV/ESV)

Linear mixed-effects model analysis revealed statistically significant positive associations of both TAPSE/IVCT (estimate = 0.035 per 1-unit increase, $P < 0.001$) and TAPSE/PASP (estimate = 0.291 per 1-unit increase, $P < 0.001$) with Ees/Ea (SV/ESV) **(Table 4)**. However, scatter plots stratified by PEEP levels demonstrated that the strength and significance of these linear relationships varied according to PEEP level (**Supplementary Figure S1 and Supplementary Figure S2**). Specifically, for

TAPSE/IVCT, a significant linear relationship with Ees/Ea was observed only at higher PEEP levels (13 and 15 cmH_2O; $P < 0.05$), whereas no significant association was found at lower PEEP levels (5, 8, 11 cmH_2O; $P > 0.05$). In contrast, TAPSE/PASP showed a statistically significant linear association with Ees/Ea at PEEP levels of 5 and 13 cmH_2O (both $P < 0.05$).

Discussion

Our study provides a dynamic, quantitative assessment of the cardiopulmonary interaction during incremental PEEP application. The principal finding is that escalating PEEP progressively impairs RVPAC, as quantified by Ees/Ea (i.e., SV/ESV) ratio, with a marked deterioration observed at 13 cmH_2O. This uncoupling is mechanistically driven by a progressive increase in RV afterload, as evidenced by rising PASP and Ea, concurrent with a decline in RV systolic performance indicated by decreasing TAPSE, S' velocity, and RVEF. Equally important, we identify and validate the readily obtainable echocardiographic index TAPSE/PASP serves as a clinically feasible surrogate, demonstrating a significant positive correlation with Ees/Ea across PEEP levels, thus bridging a critical gap between physiological insight and bedside application.

It is well-established that PEEP, while essential for lung recruitment and oxygenation, can precipitate hemodynamic compromise by reducing venous return (preload) and increasing pulmonary vascular resistance (afterload) [1, 11]. This trend underscores the need for cautious PEEP titration to mitigate potential adverse hemodynamic effects. Increased PEEP elevates RV afterload. RV contractility typically increases compensatory to maintain stable cardiac output; in cases of cardiac insufficiency, RV contractility may decompensate, leading to RV dilation, even leftward ventricular septal shift, and ultimately circulatory failure [12,13]. Crucially, as corroborated by our data, conventional parameters like mean arterial pressure and heart rate lack the sensitivity to detect this impending RV dysfunction prior to overt collapse[3]. This diagnostic inertia underscores the urgent need for integrative indices capable of preemptively signaling ventriculo-arterial mismatching to guide intervention.

Consistent with prior knowledge, we observed a general trend of increasing RV afterload with higher PEEP, reflected in rising PASP, isovolumic contraction time (IVCT), and tricuspid regurgitation severity. Interestingly, however, the composite afterload index Ea exhibited a nuanced response. Ea, as a comprehensive indicator of right ventricular afterload, an elevation in Ea signifies an increase in the impedance against which the right ventricle must eject, which can lead to a decrease in the Ees/Ea ratio—that is, right ventricular–pulmonary arterial uncoupling[8, 14]. This explains why, under high PEEP conditions, the right ventricle may be at risk of decompensation even before a decline in cardiac output becomes apparent[15]. Our research has revealed that, while Ea showing a significant progressive increase overall (P for trend <0.001), its trajectory was not strictly linear. Its initial attenuated rise (or transient dip) at moderate PEEP levels (e.g., 8 cmH_2O, though not statistically significant) may reflect the complex interplay between increased pulmonary vascular resistance and a potentially preserved or even slightly improved stroke volume due to optimized ventricular interdependence or transient preload reserve. This suggests that the relationship

between PEEP and RV afterload may not be linear but rather U-shaped or dependent on individual cardiopulmonary compliance, which merits exploration in larger cohorts. where moderate PEEP might optimize some aspects of ventricular-arterial interaction before deleterious effects dominate at higher levels[4,5]. This nuance explains why the RV may be at risk of decompensation from afterload mismatch even before a frank decline in cardiac output is apparent.

RV Ees, the gold standard for evaluating RV contractility, derived from the end-systolic pressure-volume relationship, is relatively impervious to alterations in preload and afterload[16, 17]. Our data further delineate the distinct facets of RV systolic performance under PEEP stress. While conventional longitudinal and volumetric function parameters—TAPSE, S' velocity, RVSV, and RVEF—demonstrated significant declines, the end-systolic elastance (Ees), a load-independent measure of intrinsic myocardial contractility, remained statistically unchanged across PEEP levels (P=0.168). Although Ees did not change significantly across PEEP levels, the decline in the Ees/Ea ratio was inevitable against the backdrop of significantly increased afterload and impaired contractility. This dissociation is physiologically instructive. The observed decline in TAPSE, S', and RVEF likely reflects the afterload-induced impairment of RV performance (i.e., afterload mismatch) rather than a primary depression of myocardial inotropy. This finding reinforces the concept that PEEP-induced RV dysfunction in this context is primarily a disorder of ventricular-arterial coupling rather than of intrinsic contractile failure, underscoring the unique value of Ees in isolating true contractile state from load-dependent functional changes[7, 18].

The cardiovascular system functions as an integrated unit, where optimal performance depends on the precise matching of ventricular contractility (Ees) to its arterial afterload (Ea). Isolated assessment of either systolic function or afterload provides an incomplete picture[8, 14]. RVPAC describes the relationship between the right ventricle and the pulmonary artery[15,19,20,21]. Research indicates that Ees/Ea is a sensitive indicator for assessing RV dysfunction, beginning to decline even before a reduction in ejection fraction or RV dilation, allowing for early evaluation of RV insufficiency[18]. Studies show that Ees/Ea can early identify occult RV dysfunction in patients with pulmonary arterial hypertension (PAH) who have normal RVEF, aiding in the early detection of right heart failure[22]. van de Veerdonk[23] followed 110 PAH patients for 12 months and found that in the deceased group, RVEF and SV/ESV decreased by 5% and 11% respectively; in the survivor group, they increased by 3% and 7% respectively, suggesting that dynamic changes in SV/ESV are more sensitive for predicting PAH prognosis.

Our study provides compelling evidence for the superior sensitivity of RVPAC. We observed a significant, progressive deterioration in all RVPAC indices (Ees/Ea, TAPSE/PASP, TAPSE/IVCT) with incremental PEEP. Most notably, a marked and statistically significant drop—representing an exploratory inflection point— in the Ees/Ea ratio occurred specifically when PEEP increased from 11 to 13 cmH_2O. At this pivotal threshold (13 cmH_2O), while SV showed no significant pairwise differences and RVEF was significantly lower only compared to the baseline (5 cmH_2O), the Ees/Ea ratio was significantly impaired compared to all lower PEEP levels (5, 8, and 11 cmH_2O)

(Figure 2A). This indicates that RVPAC uncoupling precedes substantial changes in volumetric output, serving as an earlier and more sensitive marker of RV-pulmonary circulatory dysfunction. This aligns with growing evidence positioning RVPAC as a prognostic marker that deteriorates early in the course of RV stress, often before overt echocardiographic signs of failure manifest[9,22,23]. Therefore, the application of RVPAC for evaluating RV function is receiving increasing attention. The early detection of this uncoupling provides a critical "therapeutic window" for clinicians to intervene, such as by adjusting PEEP, optimizing fluid status, or initiating inotropic support before the onset of overt RV failure and hemodynamic collapse, thereby potentially improving patient outcomes[3, 18].

Validating practical surrogates for Ees/Ea is crucial for clinical translation. TAPSE is a relatively common parameter for evaluating RV systolic function. Its advantage lies in not being confounded by the RV's complex anatomy or the clarity of the RV endocardial border, making it an ideal indicator of RV contractility[20]. Many experts recommend it for RV systolic function assessment[24,25,26]. TAPSE/PASP may be a practical, bedside-accessible ultrasound parameter highly sensitive to afterload changes. Compared to Ees/Ea, which requires complex volume calculations, TAPSE/PASP integrates TAPSE (reflecting RV longitudinal function) and PASP (reflecting afterload), offering a more comprehensive and convenient tool for dynamically assessing the RV-pulmonary circulation interaction under different PEEP levels, thus providing a powerful tool for real-time adjustment of ventilation parameters. Some studies[10,27,28] suggest TAPSE/PASP can serve as a surrogate for Ees/Ea. IVCT the brief phase between tricuspid valve closure and pulmonary valve opening, is a sensitive indicator of RV afterload with accurate and reproducible measurements [29]. Our linear mixed-effects models confirmed significant positive associations for both TAPSE/PASP and TAPSE/IVCT with Ees/Ea. However, stratified analysis revealed that TAPSE/PASP maintained a significant correlation across multiple PEEP levels, particularly at both low(5 cmH_2O) and critical high(13 cmH_2O) levels, whereas TAPSE/IVCT's correlation became significant only at higher PEEP levels(13 and 15 cmH_2O)(Supplementary Figures S1 & S2). This suggests that TAPSE/PASP, by integrating a direct measure of afterload (PASP) with a longitudinal function parameter (TAPSE), offers a more robust and comprehensive non-invasive assessment of the RV-PA unit's coupled state under varied loading conditions[10, 27, 30]. The correlation of TAPSE/IVCT with Ees/Ea predominantly at high PEEP may reflect a specific link between systolic timing parameters and ventricular-arterial matching under conditions of significantly elevated intrathoracic pressure, where preload reduction and afterload increase are pronounced. Its bedside feasibility makes it a promising tool for integrating "right heart-protective" principles into ventilation strategies, allowing clinicians to identify the PEEP level at which favorable lung recruitment is offset by detrimental RV-pulmonary uncoupling[2]. TAPSE/IVCT may provide specific insights at high PEEP levels，it could also serve as a surrogate for Ees/Ea (i.e., SV/ESV), warranting further clinical investigation in the future.

Traditional lung-protective ventilation focuses on preventing ventilator-associated lung injury, whereas right heart-protective ventilation emphasizes avoiding iatrogenic

harm to RV function during ventilation[2,8]. Our findings suggest that blind or formulaic application of high PEEP may pose a risk of RV injury. Therefore, in patients requiring higher PEEP, such as those with ARDS, incorporating dynamic monitoring of RVPAC or its surrogates (e.g., TAPSE/PASP, TAPSE/IVCT) via ultrasound may help achieve "individualized lung recruitment"—obtaining optimal oxygenation and recruitment while minimizing PEEP's adverse effects on the right heart.

However, this study has several limitations: 1) As a single-center, exploratory study, the sample size (n=30) is relatively small, with the primary aim of providing new insights for future clinical research. The identification of 13 cmH_2O as a threshold for RVPAC deterioration is based on post-hoc pairwise comparisons and should be considered an exploratory inflection point rather than a definitive clinical cutoff; external validation in larger, diverse cohorts is needed. 2) Patient population heterogeneity: Despite strict criteria, the underlying diseases (e.g., sepsis, pneumonia) introduce heterogeneity, potentially affecting RV function and pulmonary vascular reactivity differently. Subgroup analysis by etiology was not performed. 3) Measurement methods and limitations: Transthoracic echocardiography was used, whose accuracy is influenced by operator skill and patient acoustic windows. Although performed by a single operator to reduce bias, some patients may have been excluded due to poor image quality, introducing potential selection bias. Ees calculation used a simplified formula, which, although common, has limitations compared to the invasive pressure-volume loop method. 4) PEEP titration protocol: A fixed, incremental PEEP (5, 8, 11, 13, 15 cmH_2O) was used, maintained for 10 minutes at each level. This differs from individualized PEEP titration based on lung recruit ability or oxygenation response in clinical practice. The results more reflect the physiological effects of PEEP; their direct applicability for clinical settings needs to be considered in the context of individual patient conditions. 5) Generalizability to critically ill populations: Patients with severe hypoxemia (PaO_2/FiO_2 <200 mmHg), advanced heart failure, or significant pulmonary hypertension were excluded. Therefore, the observed physiological responses and RV–pulmonary arterial coupling thresholds may not be generalizable to these high-risk subgroups. Further studies with refined subgroup analyses are needed to confirm these findings across a broader range of critically ill patients.

Conclusion

In conclusion, in mechanically ventilated patients, incremental PEEP systematically impairs right ventricular-pulmonary arterial coupling, with a marked deterioration identified at 13 cmH_2O as an exploratory threshold. The echocardiographic ratio TAPSE/PASP correlates robustly with Ees/Ea and emerges as a practical, bedside-accessible surrogate for monitoring this interaction. However, these findings are limited to hemodynamically stable patients without severe hypoxemia or significant pulmonary hypertension, and should not be extrapolated to patients with advanced ARDS or shock. Further subgroup analyses are needed to confirm these findings across a broader range of critically ill patients.

List of abbreviations

PEEP: Positive end-expiratory pressure; RVPAC：right ventricular-pulmonary arterial coupling ；TAPSE: tricuspid annular plane systolic excursion; IVCT: Isovolumic contraction time; PASP: Pulmonary arterial systolic pressure; S`: tricuspid annular peak systolic velocity; Ees: end-systolic elastance；SV: stroke volume; EF: ejection fraction; DSV: diastolic systemic volume; ESV: end-systolic volume. TRS: Tricuspid regurgitation area; Ea: Arterial elastance; MI: body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; PaO2: Partial Pressure of Oxygen; PaCO2: Partial Pressure of Carbon Dioxide; BE: Base Excess; OI: Oxygenation Index; LAC: Lactate. RVDD: right ventricular end-diastolic diameter; LVDD: left ventricular end-diastolic diameter; HR: heart rate; MAP: Mean arterial pressure; SpO2: Pulse oxygen saturation; Ppeak: Peak pressure; Pplat: Plateau pressure; DP: Driving pressure; C: Lung compliance; R: Airway resistance; Vt: Tidal volume.

Ethics approval and consent to participate

This study was conducted in accordance with the *Declaration of Helsinki* and approved by the Ethics Committee of Peking University Shenzhen Hospital (Approval No. 146/2024 and No. [2023]045). Written informed consent was obtained from all participants prior to enrollment.

Consent for publication

Participants provided additional written consent for the publication of any potentially identifiable data included in this article.

Availability of data and material

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Competing interests

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

Qing Feng: This author contributed to data curation, investigation, methodology, and writing–review & editing.
Ruoyan Zhao: This author contributed to data curation, investigation, and writing–original draft.
Yifei Zhang: This author contributed to data curation, investigation.
Ying Shan: This author contributed to formal analysis, validation, methodology, review & editing.
Lei Huang: This author contributed to methodology, project administration, conceptualization, formal analysis, funding acquisition, investigation, review & editing.

Clinical Trial Number
Clinical Trial Number (ChiCTR2400092610||http://www.chictr.org.cn/) with the Clinical Trial Registry (20241120).

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Not applicable

Figure 1 Flow Diagram of Participant Inclusion and Exclusion.

Figure 2 Pairwise comparisons of Right Ventricular-Pulmonary Arterial Coupling Indicators across PEEP levels (where***, **, and * represent $P < 0.001$, $P < 0.01$, and $P < 0.05$, respectively, and "ns" indicates no significant difference).

Figure 3 Pairwise comparisons of systolic function parameters across PEEP levels (where***, **, and * represent $P < 0.001$, $P < 0.01$, and $P < 0.05$, respectively, and "ns" indicates no significant difference).

Figure 4 Pairwise comparisons of right ventricular afterload parameters across PEEP levels (where***, **, and * represent $P < 0.001$, $P < 0.01$, and $P < 0.05$, respectively, and "ns" indicates no significant difference).

Supplementary Material

Supplementary Figure S1 Correlation Between TAPSE/IVCT and Ees/Ea (i.e., SV/ESV) at Different PEEP Levels (Scatter plots of TAPSE/IVCT vs. Ees/Ea, stratified by PEEP level with P-value for each level).

Supplementary Figure S2 Correlation Between TAPSE/PASP and Ees/Ea (i.e., SV/ESV) at Different PEEP Levels (Scatter plots of TAPSE/PASP vs. Ees/Ea, stratified by PEEP level with P-value for each level).

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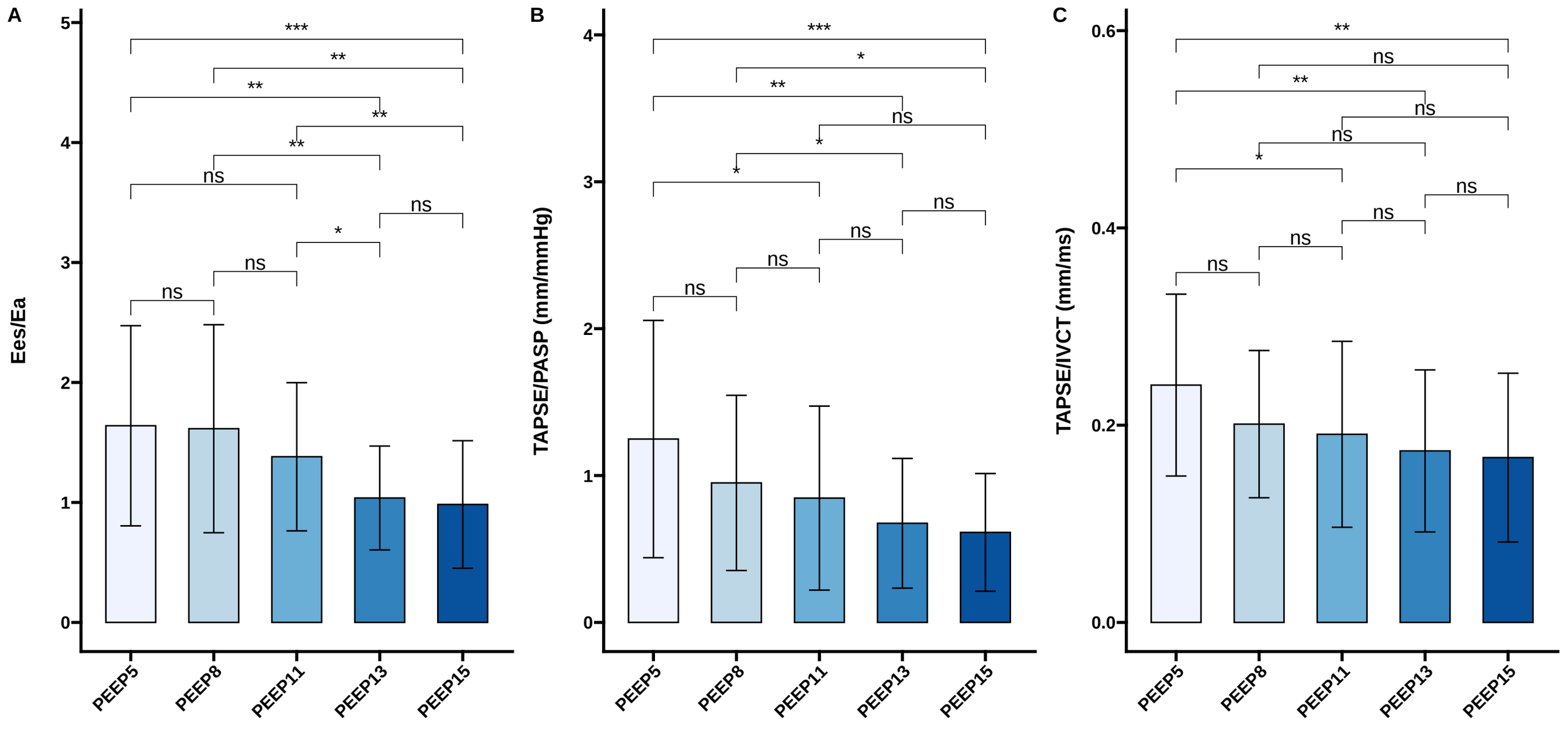
Met Inclusion Criteria
(n=84)

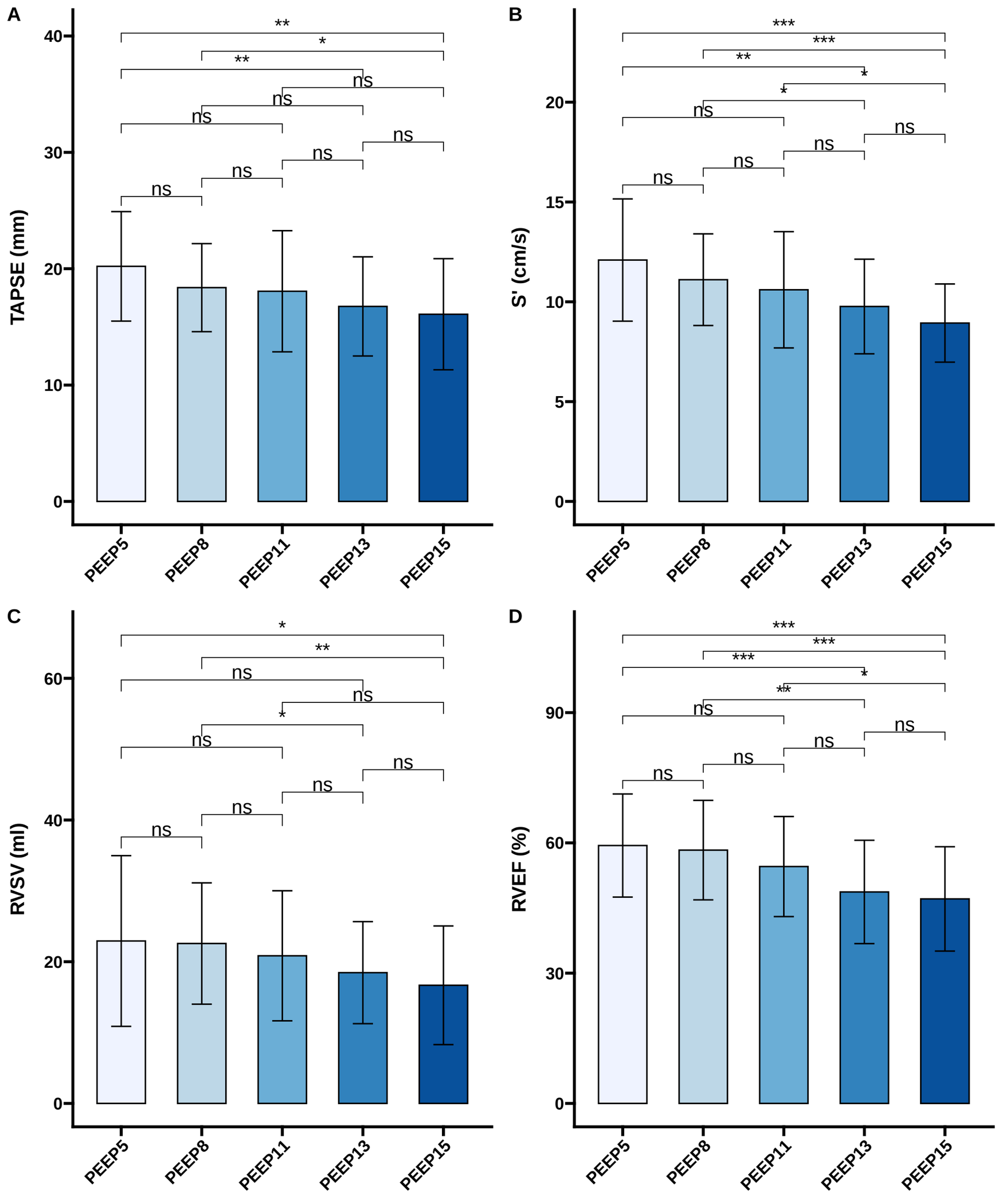
Excluded(n=54):
- Poor Echocardiographic Image Quality (n=7)
- Hemodynamic Instability (n=12)
- Low Baseline Oxygenation Index ($PaO_2/FiO_2 \leq 200$ mmHg) (n=16)
- High Baseline PEEP (>8 cm H_2O) (n=13)
- Pulmonary Bullae (n=4)
- High Pulmonary Arterial Pressure (≥50 mmHg) (n=2)

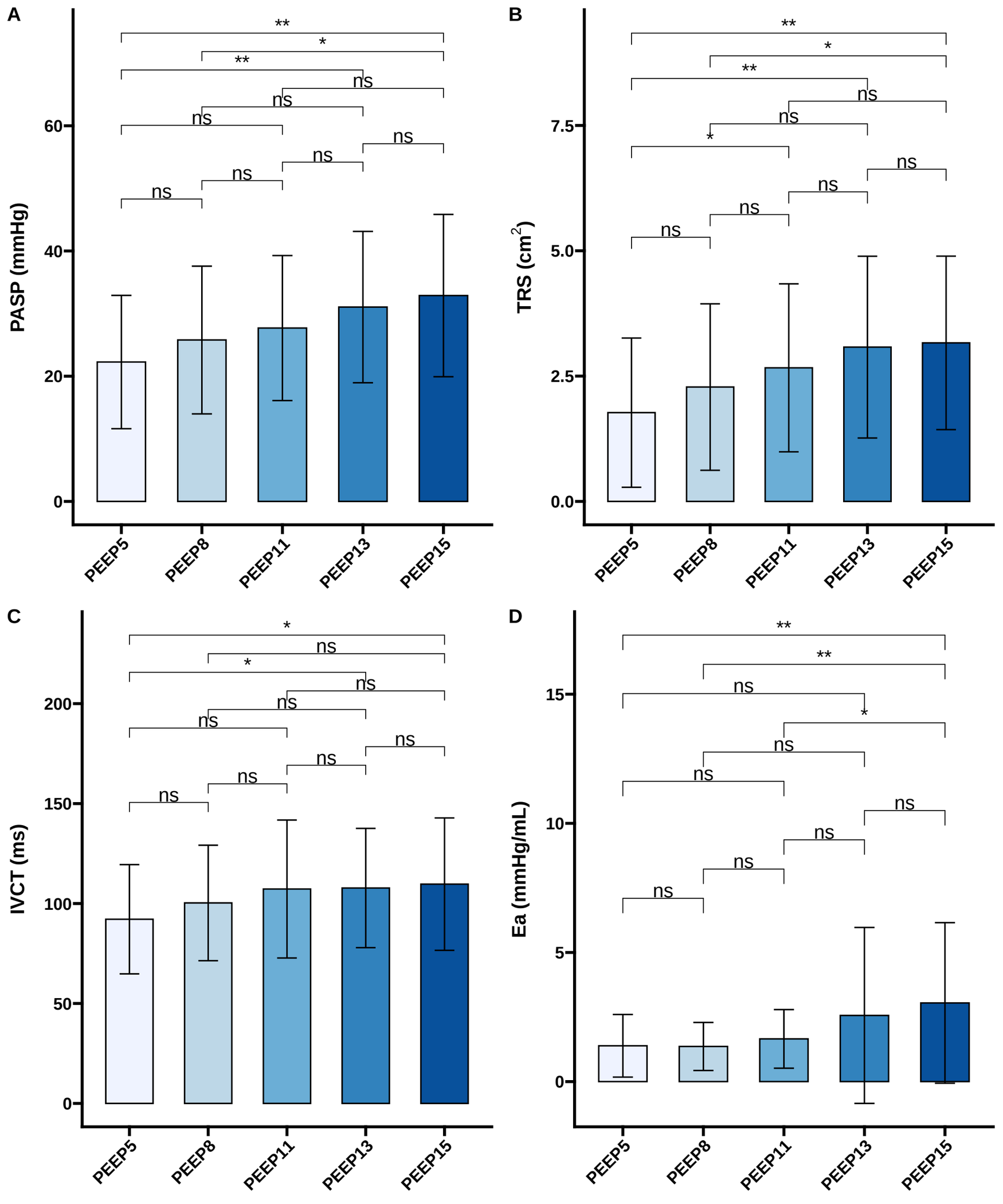
Enrolled
(n=30)

Step 1: Initial PEEP set at 5 cm H_2O
Step 2: Incremental PEEP Titration (8 → 11 → 13 → 15 cm H_2O; 10 min per level)
Step 3: Transthoracic Echocardiography at Each PEEP Level

Record Hemodynamic and Ventricular Function Data


A
Ees/Ea
5
4
3
2
1
0
***
**
**
**
**
ns
ns
ns
*
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
B
TAPSE/PASP (mm/mmHg)
4
3
2
1
0
***
*
**
ns
*
*
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
C
TAPSE/IVCT (mm/ms)
0.6
0.4
0.2
0.0
**
ns
**
ns
ns
*
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15


A
TAPSE (mm)
40
30
20
10
0
**
*
**
ns
ns
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
B
S' (cm/s)
20
15
10
5
0
***
***
**
*
*
ns
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
C
RVSV (ml)
60
40
20
0
*
**
ns
ns
*
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
D
RVEF (%)
90
60
30
0
***
***
***
*
**
ns
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15


A
PASP (mmHg)
0
20
40
60
**
*
**
ns
ns
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
B
TRS (cm2)
0.0
2.5
5.0
7.5
**
*
**
ns
ns
*
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
C
IVCT (ms)
0
50
100
150
200
*
ns
*
ns
ns
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15
D
Ea (mmHg/mL)
0
5
10
15
**
**
ns
*
ns
ns
ns
ns
ns
PEEP5
PEEP8
PEEP11
PEEP13
PEEP15

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