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RAPID REPORT

Evaluation of time constant, dead space and compliance to determine PEEP in COVID-19 ARDS: a prospective observational study

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Abstract

Multiple variables exist to identify optimal positive end-expiratory pressure (PEEP) to keep alveolar recruitment in acute respiratory distress syndrome (ARDS). These include increased respiratory system compliance (C_{RS}) and decreased dead space to tidal volume fraction (Vd/Vt). Increasing C_{RS} reflects improved lung volume, whereas decreasing Vd/Vt reflects improved ventilation/perfusion matching. An increasing expiratory time constant (RC_{EXP}) reflects both, changes in C_{RS} and alterations in tissue resistance. Whether RC_{EXP} might reflect corresponding changes in Vd/Vt better than C_{RS} during alveolar recruitment is unknown. This prospective observational study examined the correlation between these variables during ascending PEEP titration in patients with novel Coronavirus disease (COVID-19) related ARDS. PEEP titrations were performed in ten patients with COVID-19 ARDS under passive, pressure-controlled ventilation with a fixed driving pressure of 14 cmH_2O. PEEP was increased stepwise between 5 and 20 cmH_2O with 2 minutes allowed for Vd/Vt equilibration. RC_{EXP}, Vd/Vt and C_{RS} were recorded at each PEEP level and statistically assessed.The overall correlation between Vd/Vt and RC_{EXP} was −0.72 (95% CI: −0.57 to −0.82); $p < 0.0001$. C_{RS} had a weaker correlation with Vd/Vt (−0.47 (95% CI: −0.25 to −0.64); $p < 0.0001$). RC_{EXP} was the highest at 12 cmH_2O of PEEP whereas Vd/Vt was the lowest at 10 cmH_2O of PEEP and C_{RS} was the highest at PEEP of 15 cmH_2O. Both parameters of exhalation, Vd/Vt and RC_{EXP}, are strongly correlated which likely reflects corresponding mechanical and global ventilation/perfusion responses during ascending PEEP titration.

Keywords

Acute respiratory distress syndrome; COVID-19; Positive end-expiratory pressure; Expiratory time constant; Lung perfusion; Dead space ventilation

1. Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition, typically requiring mechanical ventilation due to insufficient gas exchange. Previous research has shown that the concepts of protective mechanical ventilation improve clinical outcomes in patients with ARDS [1]. There are multiple key components when delivering protective ventilation with sufficient positive end-expiratory pressure (PEEP) representing a cornerstone of strategies [2]. Although assessing lung recruitment using inspiratory variables (*i.e.*, respiratory system compliance (C_{RS}) or driving pressure (dP)) is well researched, assessing recruitment and PEEP levels using exhalation variables is less investigated.

Measured expiratory time constant (RC_{EXP}), has recently been proposed to be a potential novel method to determine PEEP levels in mechanically ventilated patients [3]. With this study, we aimed to compare optimal PEEP levels determined by three different methods (RC_{EXP}, Vd/Vt and C_{RS}) in mechanically ventilated patients with COVID-19 related ARDS. Of those, RC_{EXP} and Vd/Vt are both obtained during exhalation, with RC_{EXP} reflecting dynamics (speed) of exhalation and Vd/Vt being rather a global perfusion-sensitive variable [4].

2. Materials and methods

2.1 Study design and participants

This prospective, observational study was performed in February 2022 in a tertiary referral hospital at the East Slovak Institute for Cardiovascular Diseases, Slovakia and conforms to the relevant Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All patients fulfilled the following criteria: age >18 and <80

years; COVID-19 was confirmed with the polymerase chain reaction testing; all patients were on a passive, controlled mechanical ventilation and had moderate ARDS according to the Berlin definition [5].

As per local protocol care, all patients received sedation with continuous infusion of propofol and sufentanyl and continuous neuromuscular blockade with atracurium. Parameters were measured within the first 48 hours after intubation using the Aura V mechanical ventilator (Chirana Medical, Stara Tura, Slovakia). All patients were pre-oxygenated with 100% oxygen (O_2) prior and throughout the study. Ventilatory settings for all patients included: pressure-controlled ventilation mode (PCV), frequency of 18 breaths per minute and inspiratory to expiratory ratio of 1:2. PEEP levels were set in the escalating order of 5, 8, 10, 12, 15, 18 and 20 cmH_2O. Each PEEP lasted for 2 minutes and a fixed inspiratory pressure of 14 cmH_2O was applied on top of each PEEP. Data collected at each PEEP level included: tidal volume (Vt), RC_{EXP}, Vd/Vt and C_{RS}. All variables were recorded as an average of the last 10 breaths before the PEEP level changed to a higher level. After the measurements, PEEP was returned to pre-study level.

2.2 Outcomes and definitions

The primary outcome of this study was to compare optimal PEEP determined with RC_{EXP}, Vd/Vt and C_{RS} during ascending PEEP titration. The secondary outcomes were correlation of RC_{EXP} with Vd/Vt and C_{RS} at all PEEP levels.

The RC_{EXP} was automatically measured using the method of approximate iterations by the mechanical ventilator from the previous breath as in previous studies [1, 6]. Such RC_{EXP} represents the real measured time in seconds through which 63% of Vt was exhaled with respect to the artificial airways, breathing circuits, humidification devices and mechanical ventilator (Fig. 1).

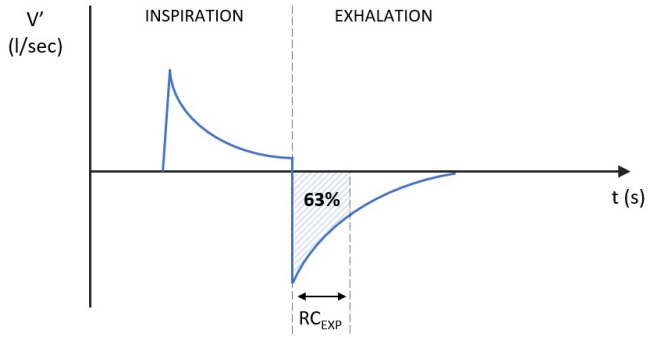

FIGURE 1. Flow versus time waveform illustrating the method how RC_{EXP} was measured. RC_{EXP} corresponds to 63% of exhaled tidal volume. V': flow; RC_{EXP}: expiratory time constant.

The Vd/Vt was also displayed on the ventilator using volumetric capnography, according to the Bohr equation: ($PaCO_2$–$PeCO_2$)/$PaCO_2$, where $PaCO_2$ is partial pressure of CO_2 in alveolar air and $PeCO_2$ is CO_2 in mixed expired air. $PaCO_2$ was determined from the slope of phase III of volumetric capnograph trace and corresponds to alveolar plateau [7]. The C_{RS} was calculated as Vt/(PIP-PEEP), where PIP is peak inspiratory pressure.

The optimal PEEP level was defined as the one obtained at the longest RC_{EXP}, the highest C_{RS} or the lowest Vd/Vt.

2.3 Statistical analysis

Categorical data are expressed as number (percentage) (n (%)), continuous data are expressed as the median with 95% confidence intervals (95% CI). Correlations were performed with Spearman correlation. The medians of expiratory tidal volume (Vte), C_{RS} and RC_{EXP} across PEEP levels were tested with Friedman's test; no further multiple comparisons were rational within the sample size. The $p < 0.05$ was used as the level of significance. Analyses were performed with GraphPad Prism v9 (GraphPad Software, San Diego, CA, USA).

3. Results

PEEP titrations were performed in ten patients (5 patients in supine position and 5 patients in prone position). Their age was 58 $\pm$ 9 years, BMI was 28 $\pm$ 5 kg/m^2, 7 of 10 patients were men and arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio for all patients was between 100–200 on mechanical ventilation with PEEP >5 cmH_2O.

Median values with 95% CI for Vt, C_{RS}, RC_{EXP} and Vd/Vt are presented in Table 1. The correlation of RC_{EXP} with Vd/Vt for all measurements was −0.72 (95% CI: −0.57 to −0.82; $p < 0.0001$) (Fig. 2A). The correlation of C_{RS} with Vd/Vt for all measurements was −0.47 (95% CI: −0.25 to −0.64; $p < 0.0001$) (Fig. 2C) and the correlation of C_{RS} with RC_{EXP} for all measurements was not statistically significant ($p < 0.302$).

The median values of RC_{EXP} were the highest at 12 cmH_2O of PEEP and the lowest Vd/Vt values were at PEEP of 10 cmH_2O (Fig. 2B), whereas median C_{RS} values were the highest at 15 cmH_2O of PEEP (Fig. 2D). Moreover, Vt where optimal PEEP was identified for RC_{EXP} and Vd/Vt was almost the same (600 *vs.* 609 mL), compared to significantly higher Vt where highest C_{RS} was identified (Vt 663 mL, $p < 0.01$).

4. Discussion

The main finding of this study is that the optimal PEEP determined by the highest RC_{EXP} was closer to optimal PEEP by the lowest Vd/Vt compared to optimal PEEP determined by the highest C_{RS}. Also, RC_{EXP} was more strongly correlated with Vd/Vt at all PEEP levels than C_{RS} which is considered the gold standard for lung recruitment during PEEP titration.

These results may be explained with pathophysiologic rationale. First, Vd/Vt and RC_{EXP} are both parameters assessing exhalation. Second, RC_{EXP} reflects time and all changes (regional and global) that occur in the lungs during the first 63% of Vt exhalation, including change in both, C_{RS} and R_{AW}, including small airways diameter change during positive pressure ventilation [8].

On the other hand, assessing recruitment with static parameters (parameters obtained from change in airway pressure and

TABLE 1. Median values with 95% CI for tidal volume (Vt), compliance of the respiratory system (CRS), expiratory time constant (RCexp) and dead space to tidal volume ratio (Vd/Vt) during ascending PEEP titration.

PEEP (cmH_2O)	Vt (mL) (n = 10)	C_{RS} (mL/cmH_2O) (n = 10)	RC_{EXP} (s) (n = 10)	Vd/Vt (n = 10)
5	540 (481–650)	35 (28–42)	0.63 (0.45–0.66)	0.35 (0.29–0.74)
8	537 (503–636)	35 (31–39)	0.65 (0.55–0.75)	0.35 (0.27–0.49)
10	600 (510–635)	34 (29–45)	0.67 (0.55–0.76)	0.31 (0.28–0.48)
12	609 (480–681)	38 (27–48)	0.70 (0.53–0.77)	0.36 (0.32–0.51)
15	663 (466–681)	40 (26–48)	0.67 (0.49–0.72)	0.38 (0.34–0.52)
18	641 (431–668)	38 (24–46)	0.65 (0.44–0.68)	0.43 (0.34–0.52)
20	623 (406–640)	35 (25–44)	0.62 (0.40–0.69)	0.46 (0.38–0.71)
p value	0.0630	0.1260	0.0020	<0.0001

The Friedman's nonparametric test was used to compare medians of Vt, C_{RS}, RC_{EXP} and Vd/Vt across different PEEP levels.

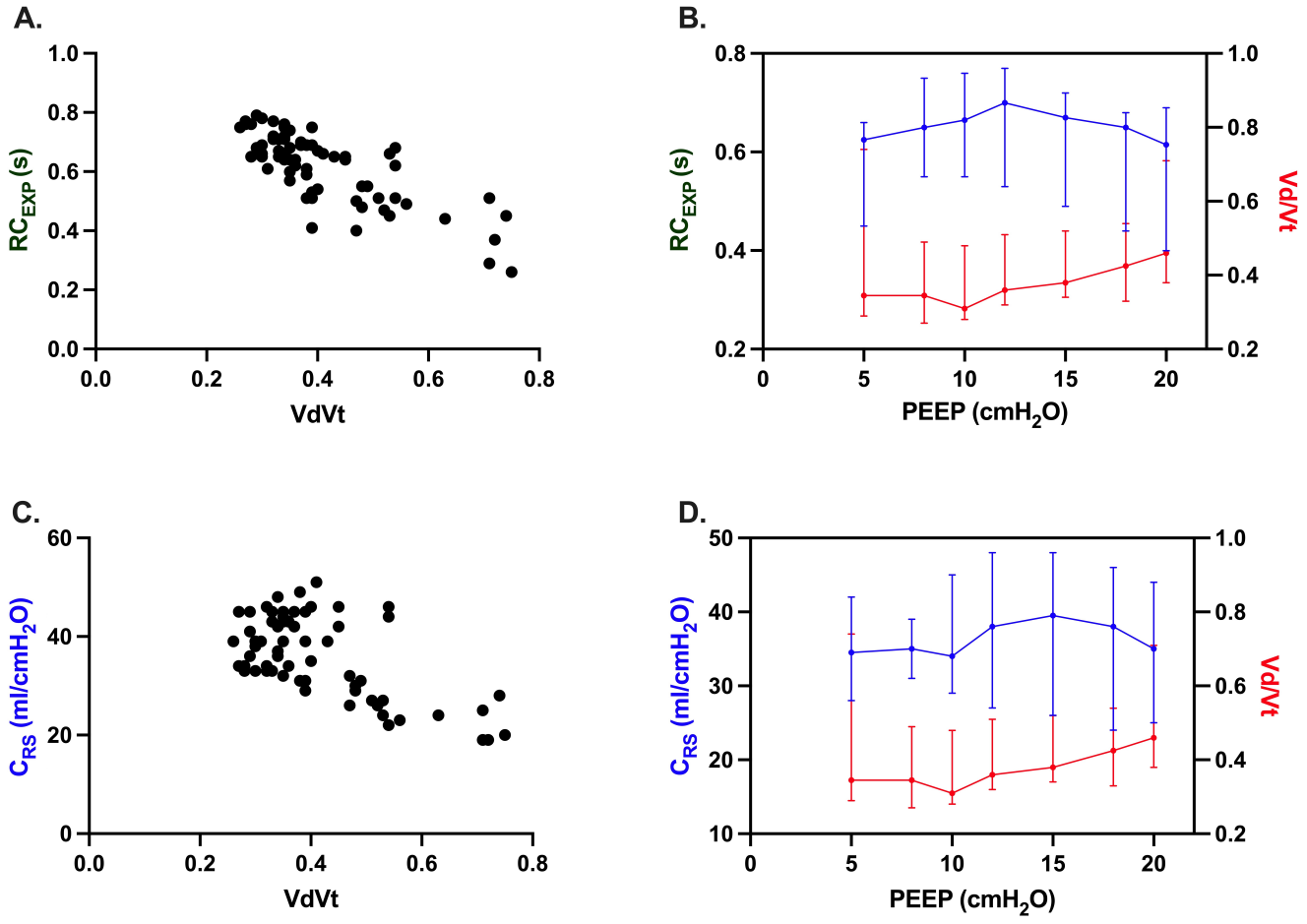

FIGURE 2. The correlation plots (A, C) and median values (B, C). A. Expiratory time constant (RC_{EXP}) versus dead space to tidal volume ratio (Vd/Vt) correlation plot. B. Median values with 95% CI for RC_{EXP} and Vd/Vt during 10 PEEP titrations (5 in supine and 5 in prone position) in 10 patients with ARDS. C. Respiratory system compliance (C_{RS}) versus Vd/Vt correlation plot. D. Median values with 95% CI for C_{RS} and Vd/Vt during 10 PEEP titrations (5 in supine and 5 in prone position) in 10 patients with ARDS. PEEP: positive end-expiratory pressure; ARDS: acute respiratory distress syndrome.

corresponding Vt) only reflects a specific time when measured. In this study, real measured RC_{EXP} derived from expiratory flow curve was used, rather than calculated RC_{EXP} (a product of C_{RS} and R_{AW}) that may be less accurate [9]. As a parameter reflecting exhalation dynamics, RC_{EXP} might be more sensitive to reflect global overdistention than static values of C_{RS} (*i.e.*, progressively shorter RC_{EXP} were recorded, while tidal volume was not significantly reduced at higher PEEP levels). As a result, the highest C_{RS} for all patients was recorded at higher PEEP levels, compared to the PEEP levels where RC_{EXP} was the longest.

Hemodynamic compromise, due to inappropriately high PEEP levels as the result of increased right ventricular afterload is well documented [10]. Under such circumstances, the distending pressure of the alveoli, rather than pulmonary venous pressure, serve as a backward pressure for the pulmonary flow [11]. Inappropriately high PEEP levels compromising the pulmonary circulation in our cohort, have likely caused reduction in perfusion (manifesting as increasing Vd/Vt) and the dynamics of measured RC_{EXP} reflected that phenomenon sooner than C_{RS}.

The positive correlation of RC_{EXP} with Vd/Vt may be clinically important as the Vd/Vt has been associated with mortality [12], effectiveness of prone positioning [13], and successful extubation [14]. Having RC_{EXP} as a measured variable may provide insight into adequacy of PEEP settings in terms of ventilation and indirectly also optimal global perfusion. Therefore, identifying ventilation variable (RC_{EXP}) that estimates PEEP levels causing recruitment close to the global lung perfusion may have some advantage in addition to Vd/Vt as it can be assessed on the breath-to-breath basis and is not complicated by the excessive humidity or secretions in the circuit associated with Vd/Vt measurement.

Our study is limited by short evaluation time for possibly manifesting full lung recruitment, the low sample size and its observational nature. Because PCV was used without an end-inspiratory pause, plateau pressure used to calculate static compliance was not obtained and therefore dynamic compliance was used instead as a gold standard. Dynamic compliance underestimates true (static) compliance due to the resistive pressure, although it was reported in previous studies that also used dynamic compliance during descending PEEP trial, that correlation between dynamic and static compliance was very high (r = 0.92) [15]. Stahl also suggested that application of dynamic respiratory mechanics as a diagnostic tool in ventilated patients should be more appropriate than using static pressure-volume curves [16].

Due to inability to obtain partial pressure of carbon dioxide ($PaCO_2$) during short intervals between changes in PEEP levels, we decided to use ventilator displayed values of calculated Vd/Vt using Bohr instead of Enghoff formula. Despite Enghoff method is preferred to estimate Vd/Vt, it also tends to overestimate true dead space [17]. What is more, measurement of Bohr dead space returns a more accurate reflection of ineffective ventilation and perfusion in the lungs and are not impacted by the shunt or low ventilation/perfusion inequalities that are common in ARDS patients [17].

Lastly, possible technical limitations could be obtaining all data from a single device. However, all mechanical ventilators were calibrated prior to measurements and operated according to the manufacturer's instructions.

5. Conclusions

In conclusion, the measured RC_{EXP} seems to better correlate with Vd/Vt than C_{RS} during ascending PEEP trial. Further controlled studies are needed to correlate RC_{EXP} with other methods of assessing lung perfusion and with optimal PEEP levels to achieve personalization of the protective mechanical ventilation.

ABBREVIATIONS

ARDS, acute respiratory distress syndrome; C_{RS}, compliance of the respiratory system; CO_2, carbon dioxide; $PaCO_2$, partial pressure of carbon dioxide in alveolar air; $PeCO_2$, partial pressure of carbon dioxide in mixed expired air; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RC_{EXP}, measured expiratory time constant; Vd/Vt, ratio of dead space ventilation to tidal volume; Vt, tidal volume; 95% CI, 95% confidence interval.

AVAILABILITY OF DATA AND MATERIALS

Data are accessible upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

FD—Conceptualization, Methodology, Writing—original draft; MAG—Writing—review & editing; RHK—Writing—review & editing; VD—Review & editing; MZ—Formal Analysis, Writing—review & editing. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the East Slovak Institute for Cardiovascular Diseases ethics committee (IEC No. N.A 201/2022) and confirms that all methods were performed in accordance with the relevant guidelines and regulations. IEC waived the need for informed consent due to a recognized and frequently used PEEP titration method to determine optimal PEEP levels in routine clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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