Lung (2018) 196:335–342
https://doi.org/10.1007/s00408-018-0096-8

RESPIRATORY MECHANICS

Alveolar Tidal recruitment/derecruitment and Overdistension During Four Levels of End-Expiratory Pressure with Protective Tidal Volume During Anesthesia in a Murine Lung-Healthy Model

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Received: 20 October 2017 / Accepted: 5 February 2018 / Published online: 12 February 2018

Abstract

Purpose We compared respiratory mechanics between the positive end-expiratory pressure of minimal respiratory system elastance ($\mathrm{PEEP}_{\mathrm{minErs}}$) and three levels of PEEP during low-tidal-volume (6 mL/kg) ventilation in rats.

Methods Twenty-four rats were anesthetized, paralyzed, and mechanically ventilated. Airway pressure (P_{aw}), flow (F), and volume (V) were fitted by a linear single compartment model (LSCM) $P_{\mathrm{aw}}(t) = E_{\mathrm{rs}} \times V(t) + R_{\mathrm{rs}} \times F(t) + \mathrm{PEEP}$ or a volume- and flow-dependent SCM (VFDSCM) $P_{\mathrm{aw}}(t) = (E_1 + E_2 \times V(t)) \times V(t) + (K_1 + K_2 \times |F(t)|) \times F(t) + \mathrm{PEEP}$, where E_{rs} and R_{rs} are respiratory system elastance and resistance, respectively; E_1 and $E_2 \times V$ are volume-independent and volume-dependent E_{rs}, respectively; and K_1 and $\mathrm{K}_2 \times F$ are flow-independent and flow-dependent R_{rs}, respectively. Animals were ventilated for 1 h at PEEP 0 $\mathrm{cmH_2O}$ (ZEEP); $\mathrm{PEEP}_{\mathrm{minErs}}$; 2 $\mathrm{cmH_2O}$ above $\mathrm{PEEP}_{\mathrm{minErs}}$ ($\mathrm{PEEP}_{\mathrm{minErs+2}}$); or 4 $\mathrm{cmH_2O}$ above $\mathrm{PEEP}_{\mathrm{minErs}}$ ($\mathrm{PEEP}_{\mathrm{minErs+4}}$). Alveolar tidal recruitment/derecruitment and overdistension were assessed by the index $\%E_2 = 100 \times [(E_2 \times V_{\mathrm{T}})/(E_1 + |E_2| \times V_{\mathrm{T}})]$, and alveolar stability by the slope of $E_{\mathrm{rs}}(t)$.

Results $\%E_2$ varied between 0 and 30% at $\mathrm{PEEP}_{\mathrm{minErs}}$ in most respiratory cycles. Alveolar Tidal recruitment/derecruitment ($\%E_2 < 0$) and overdistension ($\%E_2 > 30$) were predominant in the absence of PEEP and in PEEP levels higher than $\mathrm{PEEP}_{\mathrm{minErs}}$, respectively. The slope of E_{rs}(t) was different from zero in all groups besides $\mathrm{PEEP}_{\mathrm{minErs+4}}$.

Conclusions $\mathrm{PEEP}_{\mathrm{minErs}}$ presented the best compromise between alveolar tidal recruitment/derecruitment and overdistension, during 1 h of low-V_{T} mechanical ventilation.

Keywords Alveolar overdistention · Tidal recruitment/derecruitment · PEEP choice · Protective ventilation · Anesthesia

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Introduction

Atelectasis and intermittent airway closure may be common intraoperative findings [1] that can expose the lungs to high levels of shear stress generated during tidal recruitment/derecruitment [2]. This excessive stress in the lung tissue during anesthesia may increase the risk of ventilator induced lung injury (VILI), even in patients with healthy lungs [3–6]. Positive end-expiratory pressure (PEEP) has been successfully used to minimize atelectasis and tidal recruitment/derecruitment during anesthesia, especially after an alveolar recruitment maneuver (ARM) [7–9]. This effect of PEEP is one of the suggested mechanisms to explain the lower levels of pulmonary and systemic inflammation observed during anesthesia in patients without previous lung disease, when compared with those in the absence of PEEP [6]. Consequently, PEEP has been used in protocols of protective ventilation [10, 11]. However, higher levels of PEEP are associated with alveolar hyperinflation and overdistension [12, 13], which can also be a triggering condition for VILI [4, 14]. Consequently, an optimal level of PEEP would provide a balance between alveolar tidal recruitment/derecruitment and overdistension.

Different criteria have been used to define "optimal" PEEP to be used in protective ventilation, including the determination of PEEP of minimal respiratory system elastance ($\mathrm{PEEP_{minErs}}$) [12, 13, 15, 16]. Indeed, $\mathrm{PEEP_{minErs}}$ was associated with a better balance between alveolar overdistension and tidal recruitment/derecruitment during a descendent PEEP titration in healthy and injured lung [12, 13, 16]. Nevertheless, whether $\mathrm{PEEP_{minErs}}$ maintains this balance over time has yet to be determined.

The fraction of the volume-dependent respiratory system elastance ($\%E_2$) derived from a nonlinear model of respiratory mechanics has been used to quantify alveolar tidal recruitment/derecruitment and overdistension in healthy as well as in injured lungs [9, 12, 13, 16–18] and could potentially be used to guide strategies of protective ventilation in patients with healthy lungs. The hypothesis of this study was that $\mathrm{PEEP_{minErs}}$, when used as a criterion to select optimal PEEP, would maintain the best balance between alveolar tidal recruitment/derecruitment and overdistension during mechanical ventilation in a lung-healthy model. A secondary hypothesis was that $\%E_2$ is able to differentiate patterns of tidal recruitment/derecruitment and overdistension when different levels of end-expiratory pressure were used during ventilation with low tidal volume (V_T).

In the present study, we aimed at comparing the occurrence of indices of tidal recruitment/derecruitment and overdistension among $\mathrm{PEEP_{minErs}}$ and three other levels of end-expiratory pressure used during 1 h of low-V_T mechanical ventilation in lung-healthy anesthetized rats.

Methods

This study was approved by the Ethics Committee on the Animal Use of the Health Sciences Centre, Federal University of Rio de Janeiro (CEUA CCS, IBCCF-019).

Animal Preparation

Twenty-four rats were anesthetized with intraperitoneal ketamine (60 mg/kg) and midazolam (3 mg/kg), followed by IV administration of both agents at 60 mg/kg/h and 3 mg/kg/h, respectively. A tracheal cannula was placed and they were maintained in spontaneous ventilation with room air during instrumentation, comprising electrocardiogram, blood pressure, and rectal temperature. After instrumentation, the animals were placed in dorsal recumbency, paralyzed and ventilated (Inspira ASV, Harvard Apparatus Inc., Road Holliston, MA, USA) with room air in a volume-controlled mode with V_T of 6 mL/kg, no PEEP, inspiratory-to-expiratory time ratio (I:E) of 1:2, and respiratory rate (RR) of 90 breaths/min (initial settings).

Experimental Protocol

The experimental timeline is presented in Fig. 1. After a 5-min period under initial settings, an ARM of a plateau pressure (P_{plat}) of 20 $\mathrm{cmH_2O}$ maintained for 20 s was followed by a decremental PEEP trial from 6 to 0 $\mathrm{cmH_2O}$ in 1-min steps of 1 $\mathrm{cmH_2O}$. V_T was maintained at 6 mL/kg during the PEEP titration and $\mathrm{PEEP_{minErs}}$ was determined (see "Data Acquisition and Processing" section). Another ARM, identical to the first one, was performed after the PEEP trial and the animals were randomly assigned to one of following groups: (1) PEEP = 0 $\mathrm{cmH_2O}$ (ZEEP), $\mathrm{PEEP_{minErs}}$, $\mathrm{PEEP_{minErs}}$ + 2 $\mathrm{cmH_2O}$ ($\mathrm{PEEP_{minErs+2}}$), and $\mathrm{PEEP_{minErs}}$ + 4 $\mathrm{cmH_2O}$ ($\mathrm{PEEP_{minErs+4}}$). Each group had 6 rats ventilated for 1 h with room air and V_T of 6 mL/kg, RR of 90 breaths/min, and I:E of 1:2. At the end of the 1-h ventilation, the animals were euthanized during anesthesia by laparotomy and sectioning of abdominal aorta and caudal vena cava.

Data Acquisition and Processing

Airway pressure (P_{aw}) and airflow were recorded in a computer with a sampling rate of 1000 Hz and P_{aw} was fitted to one of the two models of respiratory mechanics: linear single compartment model (LSCM—Eq. 1), [19] or volume- and flow-dependent single compartmental model (VFDSCM—Eq. 2) [20]:

$$P_{\mathrm{aw}}(t) = E_{\mathrm{rs}} \times V(t) + R_{\mathrm{rs}} \times F(t) + \mathrm{PEEP} \tag{1}$$

$$P_{\mathrm{aw}}(t) = (E_1 + E_2 \times V(t)) \times V(t) + (K_1 + K_2 \times F(t)) \times F(t) + \mathrm{PEEP}, \tag{2}$$

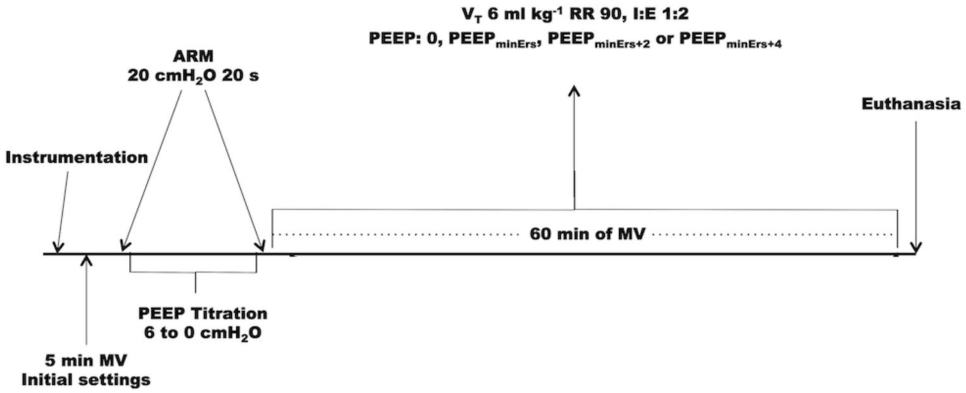

Fig. 1 Timeline of the chronological sequence of events performed during the experiments. *ARM* alveolar recruitment maneuver; *MV* mechanical ventilation; V_T tidal volume; and *RR* respiratory rate

where R_{rs} represents the linear resistance of the respiratory system; K_1 and K_2 are the flow-independent and flow-dependent components of R_{rs}, respectively; E_1 and E_2 are the volume-independent and volume-dependent components of E_{rs}, respectively; and PEEP represents the airway pressure when volume and flow are zero. From Eq. 2, the fraction of the volume-dependent elastance ($\%E_2$) was calculated as

$$\%E_2 = 100 \times [(E_2 \times V_T)/(E_1 + |E_2| \times V_T)]. \quad (3)$$

During the PEEP trial, the mechanical parameters of Eq. 1 were estimated on-line for the immediate identification of PEEP$_{minErs}$. An offline estimation encompassing the 60 min of ventilation was used for the parameters of Eq. 2 and $\%E_2$. The dynamics of E_{rs}(t) and $\%E_2$(t) were assessed by the slopes (*a* and *c*) of Eqs. 4 and 5, respectively, estimated as in Eq. 1:

$$E_{rs}(t) = a \times t + b \quad (4)$$

$$\%E_2(t) = c \times t + d. \quad (5)$$

The average of E_{rs} and $\%E_2$ from 50 respiratory cycles within the fifth (M5) and the sixtieth minute of ventilation (M60) were calculated for each group.

Statistics

Data normality was assessed by the Shapiro–Wilk test, and normally distributed data were expressed as mean (SD) and nonnormally distributed data as median (first and third quartiles).

Comparisons among groups were performed by one-way ANOVA or Kruskal–Wallis ANOVA, when appropriate, followed by the Student's *t*-test or the Mann–Whitney test, respectively, and the Bonferroni–Holm method [21] was used for the adjustment for multiple comparisons.

The null hypothesis was also tested for the slopes of $\%E_2$ and E_{rs} with the Student's t-test or Mann–Whitney with a $p < 0.05$ considered sufficient to reject the null hypothesis. Statistical analysis as well as figures and graphs were made in MATLAB (The Mathworks Inc., MA, USA).

Results

PEEP$_{minErs}$ achieved during each PEEP trial ranged from 3 to 6 cmH$_2$O in all groups and it was significantly higher in PEEP$_{minErs+4}$ (ranging from 4 to 6 cmH$_2$O) than in ZEEP and PEEP$_{minErs+2}$.

The dynamics of E_{rs} in all animals is presented in Fig. 2. At the beginning of the protocol, E_{rs}, estimated by the intercept of $E_{rs}(t)$, was higher in PEEP$_{minErs+4}$ and ZEEP groups than in PEEP$_{minErs}$. The slope of $E_{rs}(t)$ was positive in all but PEEP$_{minEsr+4}$ group, being larger in magnitude in ZEEP and smaller in PEEP$_{minErs+4}$ than in PEEP$_{minErs}$. By contrast, there was a significant temporal effect on $\%E_2$ [slope of $\%E_2(t)$] only in PEEP$_{minErs}$. $\%E_2$ at the beginning of the protocol [intercept of $\%E_2(t)$] was larger in PEEP$_{minErs+2}$ and PEEP$_{minErs+4}$ and smaller in ZEEP when compared to PEEP$_{minErs}$ (Fig. 3). The distribution of $\%E_2$ in all groups is shown in Fig. 4 and was characterized by tidal recruitment/derecruitment in 79% of the respiratory cycles with ZEEP, and an overdistension occurrence of 100%, 97%, and 28% of the respiratory cycles in PEEP$_{minErs+4}$, PEEP$_{minErs+2}$, and PEEP$_{minErs}$, respectively. In PEEP$_{minErs}$, 72% of the respiratory cycles had $\%E_2$ between 0 and 30%. E_{rs} and $\%E_2$ at M5 and M60 are presented in Table 1. $\%E_2$ was lower in M60 than in M5 only in PEEP$_{minErs}$, and was different from PEEP$_{minErs}$ in all groups and in M5 and M60. E_{rs} was higher at M60 than M5 in ZEEP, PEEP$_{minErs}$, and PEEP$_{minErs+2}$, and was higher in ZEEP and PEEP$_{minErs+4}$ than in PEEP$_{minErs}$.

Discussion

The main results of E_{rs} as well as tidal recruitment/derecruitment and overdistension assessed by $\%E_2$ in lung-healthy anesthetized rats mechanically ventilated with

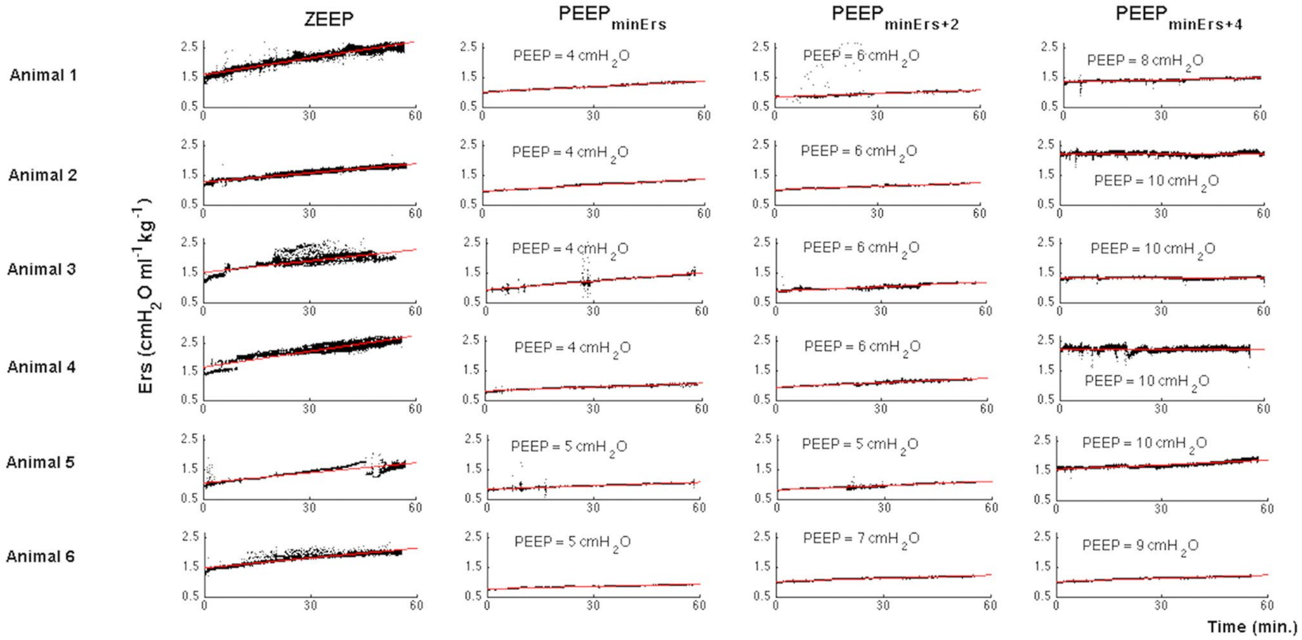

Fig. 2 Temporal dynamics of respiratory system elastance (E_{rs}) in all rats ventilated for 60 min with a tidal volume of 6 mL/kg and different levels of PEEP. PEEP presented for each animal in groups $\text{PEEP}_{\text{minErs}}$, $\text{PEEP}_{\text{minErs+2}}$, and $\text{PEEP}_{\text{minErs+4}}$ is the actual PEEP that each animal was ventilated during the 60 min of ventilation. ZEEP = no PEEP; $\text{PEEP}_{\text{minErs}}$ = PEEP of minimal E_{rs}; $\text{PEEP}_{\text{minErs+2}}$ = PEEP of minimal E_{rs} + 2 cmH_2O; and $\text{PEEP}_{\text{minErs+4}}$ = PEEP of minimal E_{rs} + 4 cmH_2O. Red lines represent the linear function estimated with the linear regression of E_{rs} as a function of time in each animal

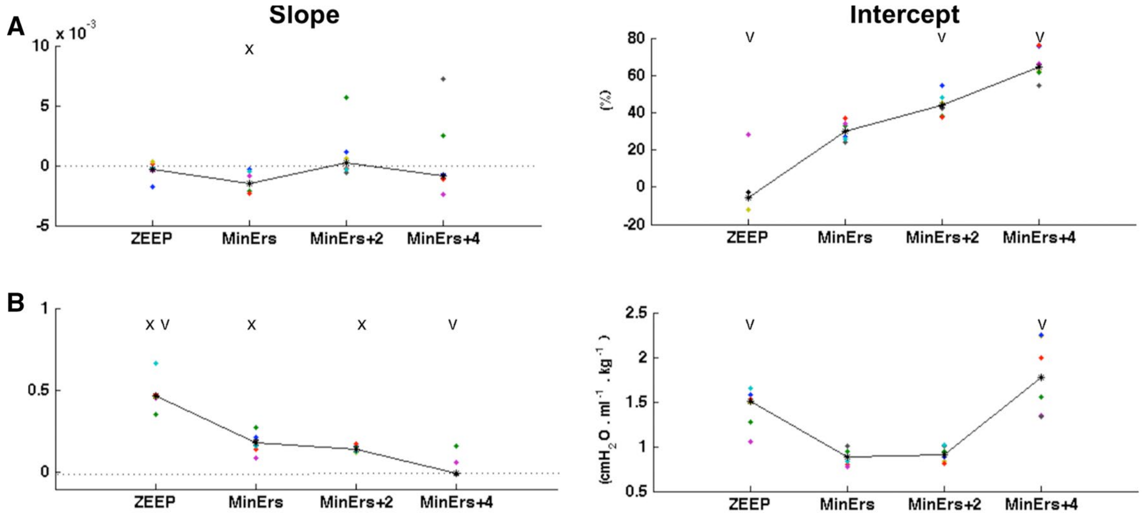

Fig. 3 Slope (left column) and intercept (right column) of the temporal linear function estimated to the fraction of volume-dependent respiratory system elastance (Panel A) and the respiratory system elastance (E_{rs}, Panel B) in all six rats ventilated for 60 min with tidal volume of 6 mL/kg at different levels of PEEP. ZEEP = no PEEP; MinErs = PEEP of minimal E_{rs}; MinErs + 2 = PEEP of minimal E_{rs} + 2 cmH_2O; and MinErs + 4 = PEEP of minimal E_{rs} + 4 cmH_2O. *v* significantly different from $\text{PEEP}_{\text{MinErs}}$; *x* significantly different from zero ($p < 0.05$). The values connecting all groups are the medians

protective V_T for 1 h were as follows: (1) $\text{PEEP}_{\text{minErs}}$ presented the best compromise between alveolar tidal recruitment/derecruitment; (2) ZEEP was associated with a positive temporal drift of E_{rs} and a predominance of tidal recruitment/derecruitment; (3) $\text{PEEP}_{\text{minErs+4}}$ was the only PEEP that provided temporal stability of E_{rs} but at the expense of overdistension; and (4) $\%E_2$ was able to

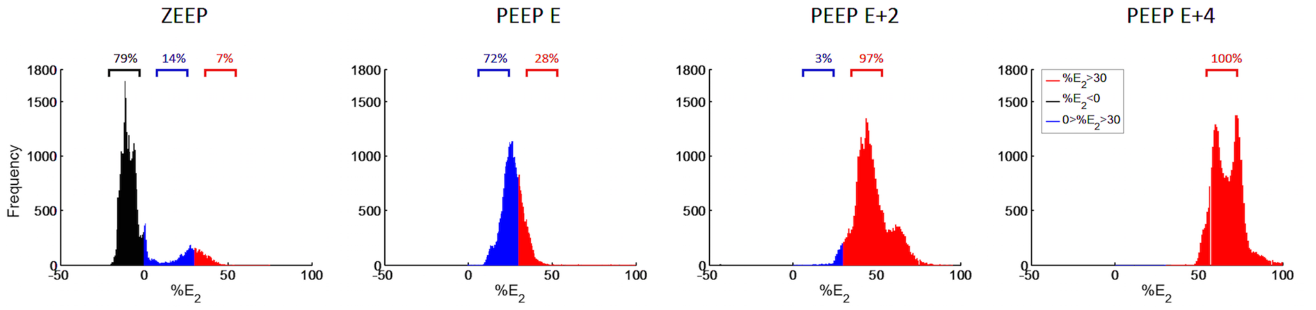

Fig. 4 Histogram of the fraction of volume-dependent respiratory system elastance ($\%E_2$) frequency distribution during 1 h of ventilation with 6 mL/kg and different levels of PEEP in rats. Red = $\%E_2 > 30\%$; Blue = $\%E_2$ between 0 and 30%; and Black = $\%E_2 < 0$. ZEEP = no PEEP; PEEP E = PEEP of minimal E_{rs}; PEEP E+2 = PEEP of minimal E_{rs} + 2 cmH_2O; and PEEP E+4 = PEEP of minimal E_{rs} + 4 cmH_2O

Table 1 Respiratory system elastance (E_{rs}) and $\%E_2$ within the fifth (M5) and sixtieth (M60) minutes of mechanical ventilation with protective tidal volume (6 mL/kg) and four different levels of end-expiratory pressure in lung-healthy anesthetized rats

	$\%E_2$ (%)		E_{rs} (cmH_2O/mL/kg)	
	M5	M60	M5	M60
ZEEP	$-3.5 \pm 11.6^{\dagger}$	$-3.8 \pm 11.8^{\dagger}$	$1.36 \pm 0.24^{\dagger}$	$2.00 \pm 0.38^{*\dagger}$
PEEP-$_{minErs}$	27.8 ± 6.6	$20.9 \pm 6.0^{*}$	0.86 ± 0.08	$1.13 \pm 0.20^{*}$
PEEP-$_{minErs+2}$	$40.4 \pm 7.4^{\dagger}$	$43.2 \pm 14.5^{\dagger}$	0.92 ± 0.06	$1.12 \pm 0.05^{*}$
PEEP-$_{minErs+4}$	$66.4 \pm 6.6^{\dagger}$	$63.9 \pm 7.7^{\dagger}$	$1.80 \pm 0.28^{\dagger}$	$1.75 \pm 0.17^{\dagger}$

ZEEP no positive end-expiratory pressure (PEEP); $PEEP_{minrErs}$ PEEP of minimum E_{rs}; $PEEP_{minErs+2}$ $PEEP_{minErs} + 2\,cmH_2O$; and $PEEP_{minErs+4} = PEEP_{minErs} + 4\,cmH_2O$

*Significant difference between M5 and M60 and †Significant difference from $PEEP_{minErs}$. $p < 0.05$

discriminate patterns of alveolar recruitment/derecruitment and overdistension among the different levels of PEEP.

$\%E_2$ increased with PEEP and was very similar to values previously reported in rats [22]. As a dynamic method to assess respiratory mechanics, it does not interfere with the current ventilation of the patient, and can be used noninvasively and at the bedside [23]. $\%E_2$ higher than 30% has been associated with alveolar overdistension and was predominantly observed with $PEEP_{minErs+2}$ and $PEEP_{minErs+4}$, while negative values were more frequent during ZEEP and were potentially related to tidal recruitment/derecruitment [17, 18]. $\%E_2$ was always positive and was lower than 30% in the vast majority of cycles with $PEEP_{minErs}$. Consequently, $PEEP_{minErs}$ seemed to yield a better balance between alveolar tidal recruitment/derecruitment and overdistension.

Atelectasis can develop promptly after the induction of anesthesia [24] contributing to intraoperative increases in venous admixture and decreases in PaO_2, particularly in the absence of PEEP [25]. Atelectasis can also be a substrate for elevated shear stress in the lungs generated by the tidal alveolar recruitment/derecruitment at the interface between normal and nonaerated areas of the lung [2]. The higher occurrence of negative $\%E_2$ in the rats ventilated with ZEEP suggested that more tidal recruitment/derecruitment ensued in these animals, likely due to significant atelectasis, as found in pigs [13]. Indeed, tidal recruitment/derecruitment was already expected in the rats ventilated with ZEEP and low V_T probably because of progressive atelectasis, as observed in an *ex vivo* rat model [26] and an in vivo model in mice [27]. However, ZEEP was included in the experimental design because it is still commonly used during anesthesia [28] and also to test whether $\%E_2$ would be able to identify alveolar tidal recruitment/derecruitment distinctly from the PEEP levels.

PEEP can reverse or prevent atelectasis as well as improve respiratory mechanics and oxygenation during anesthesia [8, 12, 29]. In a recent clinical trial with anesthetized patients with healthy lungs, PEEP of 12 cmH_2O was able to minimize tidal recruitment/derecruitment without increasing the levels of overdistension when compared to low levels of PEEP (≤ 2 cmH_2O) [9]. Different methods have been used to identify the best PEEP to be used during mechanical ventilation, including the $PEEP_{minErs}$ [12, 16, 30]. The concept of "optimal PEEP" was defined as the PEEP of minimal E_{rs} by Suter and colleagues [15] and resulted in the best oxygen delivery and the lowest dead-space fraction in ARDS patients. In the present study, $PEEP_{minErs}$ was considered the optimal PEEP because it was associated with the best balance between alveolar tidal recruitment/derecruitment and overdistension, similarly to the computerized tomography findings in a pig model of healthy and injured lung [12, 13, 16], as well as in a computational model of injured canine lungs [31]. Differently from studies that evaluated alveolar tidal recruitment/derecruitment and overdistension during PEEP titration [11–13], the evaluation during the whole period of ventilation, as presented here, provided a more meaningful information about the effectiveness of $\text{PEEP}_{\text{minErs}}$ as a method of PEEP choice for protective ventilation during anesthesia. In addition, to offer an objective assessment of tidal recruitment/derecruitment and overdistension in the lungs, $\%E_2$ detected dynamic changes in these patterns that could occur during ventilation, as observed in the rats ventilated with $\text{PEEP}_{\text{minErs}}$. If the period of ventilation used with $\text{PEEP}_{\text{minErs}}$ was longer, possibly $\%E_2$ would reach negative levels, indicating tidal recruitment/derecruitment due to progressive atelectasis. In this case, $\%E_2$ could be a parameter to identify the best moment for an ARM during protective ventilation using $\text{PEEP}_{\text{minErs}}$. This strategy of ARM seems more rational than performing an ARM every 30 min as previously described in a protective ventilation protocol [10].

The temporal increase in E_{rs} observed in ZEEP, $\text{PEEP}_{\text{minErs}}$, and $\text{PEEP}_{\text{minErs+2}}$ can be an additional indication of progressive alveolar derecruitment. This deterioration of E_{rs} during ventilation has been demonstrated before in models of healthy and injured lungs and seems to be related to alveolar derecruitment and progressive decrease in lung aeration [32–35]. However, the interpretation of the temporal increase in E_{rs} in the context of protective ventilation needs to be further investigated because its association with VILI seems to be variable in different experimental settings [33–35]. Probably, the combined evaluation of $\%E_2$ and $E_{\text{rs}}E_{\text{rs}}$ and their temporal progression can provide valuable information to guide ventilatory settings, as well as the timing for ARMs.

When similar criteria were used to select low PEEP levels in ARDS patients, a large clinical trial observed increased mortality at 28 days when $\text{PEEP}_{\text{minErs+2}}$ [36], while a smaller clinical trial reported less organ dysfunction and a trend toward decreased mortality when $\text{PEEP}_{\text{minErs}}$ was used [30]. This discrepancy between the results may be explained by the higher incidence of overdistension in the higher PEEP group, as observed when $\text{PEEP}_{\text{minErs+2}}$ and $\text{PEEP}_{\text{minErs+4}}$ were used in the present study. In fact, the PEEP difference between the low and high PEEP groups in the two previously mentioned studies was between 2 and 4 cmH_2O. Recent studies have shown that low driving pressure was the ventilatory variable most strongly correlated with improvements in clinical outcome in ARDS [37] and lung-healthy surgical patients [38]. These findings provide substantial support for the use of $\text{PEEP}_{\text{minErs}}$ as a method to choose the ideal PEEP, because it will always be associated with the lowest driving pressure given a fixed V_T. Consequently, $\text{PEEP}_{\text{minErs}}$ has the potential to improve the beneficial effects in outcome found with moderate PEEP (6 to 8 cmH_2O) and ARM in surgical patients at risk for postoperative pulmonary complications (PPC) [10]. Future clinical trials in patients with healthy lungs are warranted to shed some light on the clinical application of using $\text{PEEP}_{\text{minErs}}$ as a method of PEEP choice during anesthesia.

PEEP levels higher than $\text{PEEP}_{\text{minErs}}$ were used to explore the concept of "open-lung PEEP," since in lung-healthy rats it seemed to be associated with the mathematical inflection point of the PV curve—approximately 4 cmH_2O above $\text{PEEP}_{\text{minErs}}$ ($\text{PEEP}_{\text{minErs+4}}$) [22]. In fact, the only PEEP that maintained alveolar stability was $\text{PEEP}_{\text{minErs+4}}$, but at the expense of detrimental alveolar overdistension.

Despite the lack of lung computerized tomography (CT) scans or other standard methods to confirm the results achieved by the $\%E_2$, this method has been able to detect alveolar tidal recruitment/derecruitment and overdistension more consistently in healthy than injured lungs [13], which reinforce the reliability of our results. Moreover, the mathematical model used in this study included a nonlinear component of R_{rs}, which was shown to improve the estimation of $\%E_2$, especially when inspiratory waveforms other than constant flow are used or when nonlinearities associated with the endotracheal tube resistance are present [19, 39]. Future studies correlating $\%E_2$ with levels of inflammatory biomarkers in the lungs and/or plasma, lung histology, and more importantly patient outcome should be performed for a rational clinical use of this technique to evaluate protective ventilation in the lung-healthy patient.

This study presents some limitations such as the short duration of ventilation, ventilation with room air, and the respiratory mechanics differences between rats and humans. Webb and Tierney [40] reported that significant pulmonary edema developed after few minutes of using high P_{peak} in rats. However, the same degree of lung injury requires a much longer period of mechanical ventilation in larger species [41, 42]. Consequently, we believe that our model possibly represent the majority of anesthetic procedures, considering the differences in the time course of VILI within species [40–42]. Ventilation with room air does not necessarily represent the usual clinical anesthesia scenario, but was used to minimize reabsorption atelectasis, which is commonly seen with high $\text{F}_\text{i}\text{O}_2$ [43]. Probably, if higher $\text{F}_\text{i}\text{O}_2$ were used in the present study, a magnification of atelectasis and alveolar instability would be observed as previously reported in humans [43]. Finally, the respiratory mechanics of rats is somewhat different from humans [44, 45]. First, the temporal evolution of E_{rs} seen in rats would probably take longer in humans because of the much faster respiratory rate in the later. Second, the body weight-normalized chest wall elastance of rats is approximately a fourth of that in humans [44, 45]. This difference, associated with the smaller vertical gradient in the rat respiratory system and the lower pleural pressure at functional residual capacity, affects the transpulmonary pressure and the end-expiratory lung volume at a given PEEP in such way that the PEEP needed to provide less alveolar collapse as well as $\text{PEEP}_{\text{minErs}}$ should be higher in humans than in rats. However, $\text{PEEP}_{\text{minErs}}$ is determined in an individual basis and should represent the PEEP with the best compromise between alveolar overdistension and tidal recruitment/derecruitment independently of variations between subjects or species, as demonstrated in pigs with healthy and injured lungs [12, 13, 16], as well as in the rats of the present study.

In conclusion, $\text{PEEP}_{\text{minErs}}$ presented the best balance between alveolar tidal recruitment/derecruitment and overdistension, and is a promising clinical criterion to select the best PEEP during protective ventilation of the healthy lung. Future studies evaluating the outcomes of patients using $\text{PEEP}_{\text{minErs}}$ and $\%E_2$ to guide protective ventilation are warranted to define the clinical importance of this method to optimize protective ventilation in the anesthesia clinical scenario.

Funding This study was supported by grants from the Brazilian Council for Scientific and Technology Development (CNPq)—140047/2008-5.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study were in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guiding Principles in the Care and Use of Animals" approved by the Council of the American Physiological Society, USA. The present study was approved by the Institutional Animal Care and Use Committee (CEUA CCS, IBCCF-019).

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