Available online at http://www.journalijdr.com

IJDR

ISSN: 2230-9926

International Journal of Development Research
Vol. 07, Issue, 11, pp.16938-16943, November, 2017

ORIGINAL RESEARCH ARTICLE **Open Access**

EFFECTS OF INCREASING TIDAL VOLUME ON THE MECHANICS OF THE RESPIRATORY SYSTEM OF HEALTHY RATS

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ARTICLE INFO

Article History:
Received 26th August 2017
Received in revised form
28th September, 2017
Accepted 13th October, 2017
Published online 29th November, 2017

Key Words:
Respiratory system;
Mechanical ventilation;
Tidal volume.

ABSTRACT

Mechanical ventilation is an advanced life support that has as one of its objectives to promote gas exchange. The use of protocols that vary the tidal volume is a practice that aims at maintaining the most stable minute volume, where this mode is cycled upon reaching the predetermined inspiratory tidal volume. In the midst of this context, the question is raised: What are the effects of increased tidal volume on parenchyma and pulmonary mechanics in healthy rats submitted to mechanical ventilation? Therefore, the present study aimed to analyze the effects of tidal volume increase on the mechanics of the respiratory system of healthy rats submitted to mechanical ventilation.18 Wistar rats were randomly divided into two groups:GCTRL, ventilated during the 4 hour with tidal volume of 10 mL/kg, and GTV, ventilated during the 4 hour with tidal volume of 20 mL/kg. Our results demonstrate significant differences between the GTV and GCTRL groups, for tissue resistance (G), tissue elastance (H), static compliance (C_{ST}), inspiratory capacity (IC) and PV loop area. Regarding the histological data, we observed alterations in the percentage of normal and hyperinflamed alveoli, in the mean alveolar diameter and number of polymorphonuclear cells in the GTV group in relation to the GCTRL group. In conclusion, the use of mechanical ventilation with high tidal volumes is associated with destruction of the alveolar wall, increased respiratory work and presence of inflammatory processes in the pulmonary parenchyma.

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Citation: Natalia Lima Barbosa, Gilvan Ribeiro dos Santos, Daniel Silveira Serra, Francisco Sales Ávila Cavalcante and Mirizana Alves de Almeida. 2017. "Effects of increasing tidal volume on the mechanics of the respiratory system of healthy rats", *International Journal of Development Research*, 7, (11), 16938-16943.

INTRODUCTION

Mechanical ventilation is an advanced life support that has as one of its objectives to promote gas exchange. For the mechanical ventilation settings, some parameters in addition to the ventilation mode, must be considered, highlighting the tidal volume, the positive end expiratory pressure (PEEP) and respiratory rate (West, 2010; Zin *et al*., 2008). According to the brazilian guidelines for mechanical ventilation (BGMV, 2013), the use of protocols that vary the tidal volume is a practice that aims at maintaining the most stable minute volume, where this mode is cycled upon reaching the predetermined inspiratory tidal volume.However, it is now known that the use of elevated tidal volume may be associated with the occurrence of high alveolar pressures, pulmonary hyperdistension and release of inflammatory mediators that determine important changes in pulmonary function and respiratory mechanics (Ricard *et al*., 2001; Gattinoni *et al.,* 2003; Choudhury *et al.,* 2004). In the mechanical process of breathing, the lung tissue presents complex characteristics that can be evaluated quantitatively. The techniques used to describe the function of respiratory system mechanics in terms

of relevant parameters, such as lung compliance and elastance, employ notions of physiology and physical principles combined in mathematical models, and can translate the behavior of a given structure given a particular circumstance (Duran, 2011). In clinical practice, some models of mechanical ventilators show curves related to ventilatory mechanics such as: airway pressure signals, gas flow and respiratory system volume change. In addition to this information, they use non-routine calculations of airway resistance, static complacency (C_{st}), peak pressure and pause, self-PEEP and distension pressure (BGMV, 2013. Machado, 2013). The values of tissue elastance (E), hysteresis (η), inspiratory capacity (IC) and area of the loop of the volume pressure curve were also evaluated, which were also evaluated in the present study.

Several studies (Rotta & Steinhorn, 2007; Neves *et al.,* 2009) address the use of different current volumes in the mechanical ventilation of patients with different pathologies. However, it is interesting to have knowledge about the effects of different tidal volume on pulmonary mechanics in healthy animals. In the midst of this context, the question is raised: What are the effects of increased tidal volume on parenchyma and pulmonary mechanics in healthy rats submitted to mechanical ventilation?

Therefore, the present study aimed to analyze the effects of tidal volume increase on the mechanics of the respiratory system of healthy rats submitted to mechanical ventilation.

MATERIALS AND METHODS

Animals: 18 male Wistar rats were used, with a body mass of 250 ± 30 g. Maintained with free access to water and feed, and controlled environmental conditions: temperature of 28ºC and cycle of 12 hours of light and dark. The animals were randomly divided into two groups: GCTRL group (n=9), ventilated during the 4 hour, respiratory rate of 90 breaths per minute (bpm), TV= 10 mL/kg and positive end-expiratory pressure (PEEP)= 3 cm/H_2O, and GTV group (n=9), ventilated during the 4 hour, with a respiratory rate of 90 bpm, TV= 20 mL/kg and PEEP= 3 cm/H_2O. This protocol is an adaptation of previous studies (Choi *et al.,* 2003; Fusco *et al*., 2005; Luque, 2008; Cavassani *et al.,* 2011) that evaluated the variation of ventilatory parameters in the mechanics of the respiratory system.

Respiratory system mechanics: Initially, the animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p., Hypnol® 3%, Syntect, Brazil) and tracheotomized. The animals were intubated with a 14-gauge cannula (Eastern Medikit, Delhi, India) that was then connected to a computer-controlled ventilator for small animals (Scirec© *-flexVent®*, Montreal, QC, Canada). The animals were ventilated at baseline settings: respiratory frequency of 90 breaths/min, tidal volume of 10 mL/kg, limiting pressure of 30 cmH_2O, and PEEP of 3 cmH_2O. Rats were then paralyzed with pancuronium bromide (0.5 mL/kg, i.p., Cristália, Lindoia, MG, Brazil).

Initially we standardized the mechanical history of the respiratory system with two deep inflations (DI, 6-s long, peak pressure: 30 cmH_2O), followed by 5 minutes of ventilation with baseline settings. The animals were ventilated for 4 hours according to the parameters mentioned above (GCTRL and GTV).Soon after, the impedance of the respiratory system (Z_{rs}) was measured with the forced oscillation technique (Hantos *et al*., 1992), 12 sequential 30-s sampling intervals, for a total of 6 minutes (Bates, 2009). The experimental Z_{rs} was fitted to the constant phase model as previously described (Hirai *et al.*, 1999):

$$Z_{rs} = R_N + I(2\pi f)i + \frac{G-Hi}{(2\pi f)^{\alpha}} \quad \text{.....(1)}$$

$$\alpha = \frac{2}{\pi}\tan^{-1}\left(\frac{H}{G}\right) \quad \text{.....(2)}$$

where R_N is the Newtonian resistance, which represents the central airways resistance, $i = \sqrt{-1}$, f is the frequency (Hz), I represents airway inertance, and G and H are respectively the dissipative and elastic properties of lung tissue (Hantos *et al*., 1992). Hysteresivity ($\eta = G/H$) was also calculated (Fredberg *et al*, 1989). Thereafter, starting at the functional residual capacity (FRC) defined by the PEEP, the flexiVent delivered 7 inspiratory pressure steps for a total pressure of 30 cmH_2O, followed by 7 expiratory steps, pausing at each step for 1 s. At each step plateau pressure (P) was recorded and related to the total volume (V) delivered to produce a quasi-static PV (pressure-volume) curve. Static compliance (C_{ST}) was calculated as the slope of the curve (Salazar and Knowles, 1964). Two quasi-static PV curves were obtained to measure C_{ST}, an estimate of inspiratory capacity (IC), and PV loop area.

Hyperresponsiveness of airway smooth muscle: Immediately after measurements of respiratory system mechanics, two DIs (Deep Inflation) were done, followed by 5 minutes of ventilation with baseline settings. Airway smooth muscle hyperresponsiveness was evaluated by inhalation of methacholine (MCh) (Sigma-Aldrich, St. Louis, MI, USA) delivered by aerosol produced by an ultrasonic nebulizer (Inalasonic, NS Indústria de Aparelhos Médicos, São Paulo, SP, Brazil) coupled to the inspiratory line of the ventilator. For such purpose, 4 mL of MCh solution (30 mg/mL) were added to the nebulizer container. The nebulization was carried out during 30 s under mechanical ventilation (Xue *et al*., 2008) and the average amount delivered to the animal was 1.2 mg/kg of MCh solution. After nebulization, the same previous analysis was repeated (forced oscillation, 30-s sequential intervals for 6 min).

Histological study: Immediately after the determination of respiratory system mechanics, the rib cage was opened and Heparin (1000 IU) was injected in right ventricle of the heart. The trachea was clamped at end-expiration, and the abdominal aorta and vena cava were sectioned, yielding a massive hemorrhage that quickly euthanized the animals. The lungs were perfused with saline and, then, removed en bloc. The right lung was isolated, frozen in liquid nitrogen, and stored for biochemistry analysis; the left lung was kept at functional residual capacity and fixed in Millonig's formaldehyde (100 mL HCHO, 900 mL H_2O, 18.6 g NaH_2PO_4, 4.2 g NaOH). Slides containing left lung sections were stained with hematoxylin and eosin (HE) and examined by optical microscopy according to their qualitative and quantitative aspects. An investigator, who was unaware of the origin of the coded material, examined the samples microscopically. Quantitative analysis was performed using an integrated eyepiece with a coherent system consisting of a 100-point and 50-line grid coupled to a conventional light microscope. The fraction area of collapsed alveoli or normal pulmonary areas,

and the amount of polymorphonuclear (PMN) cells, as well as pulmonary tissue were determined by the point-counting technique (Weibel *et al*., 1990). The air-space enlargement was quantified by the mean linear intercept length of the distal air spaces (L_m) in 30 randomly chosen fields of tissue sections per group (Knudsen *et al*., 2010). Cellularity was assessed at 1000× magnification across 10-15 random non-coincident microscopic fields in each animal. Morphometric analysis and determination of bronchoconstriction index were done at 400× magnification.

Statistical analysis

The pulmonary function data are presented as the mean ± standard deviation. The differences between the values of the groups were evaluated using the Student t-test. All statistical analyses were performed using SigmaPlot (Systat Software, Inc.). p<0.05 was considered statistically significant.

RESULTS

The results referring to the analysis of the respiratory system mechanics of the rats ventilated for 4 hours at a tidal volume of 10 mL/kg (GCTRL) or 20 mL/kg (GTV) is showed in Table 1. We did not observe changes in values regarding Newtonian resistance (R_N)and hysteresivity (η) between the GCTRL and GTV groups.

The Figure 1, shows the values of the variation of R_N, after administration of MCh (30 mg/mL) for 30 seconds, in the GCTRL and GTV groups. Values show a significant increase in the GTV group compared to the GCTRL group. The Figure 2 shows the photomicrographs of the pulmonary parenchyma and airway (inserts) in the GCTRL and GTV groups. Through the analysis, it can be observe the destruction of the alveolar wall in the GTV group.

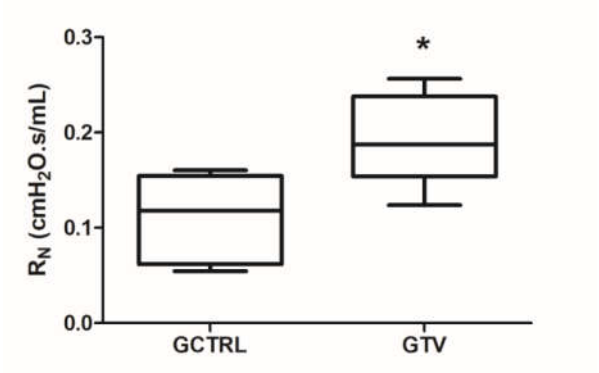

Figure 1. Methacoline challenge as a function of number of measurements after MCh nebulization (30 mg/mL for 30 s) in animals ventilated for 4 hours at a tidal volume of 10 mL/kg (GCTRL) or 20 mL/kg (GTV). 9 animals per group. *Represents statistically significant differences (p <0.05) in relation to the GCTRL group

Table 1. Mechanical data of animals ventilated for 4 hours at a tidal volume of 10 mL/kg (GCTRL) or 20 mL/kg (GTV).Values are mean ± SD. *p<0.05, statistically significant difference

Measure	Group	Value	p value (*t student)*
Newtonian Resistence ($\boldsymbol{R_N}$) (cmH$_2$O·s/mL)	GCTRL GTV	0.073±0.020 0.079±0.025	p = 0.56
Tissue Resistence ($\boldsymbol{G}$) (cmH$_2$O/mL)	GCTRL GTV	0.80±0.17 0.62±0.15	p = 0.03*
Tissue Elastance ($\boldsymbol{H}$) (cmH$_2$O/mL)	GCTRL GTV	3.34±0.35 2.43±0.58	p < 0.001*
Hysteresivity ($\boldsymbol{\eta}$)	GCTRL GTV	0.24±0.036 0.27±0.010	p = 0.33
Inspiratory Capacity ($\boldsymbol{IC}$) (mL)	GCTRL GTV	8.51±1.52 12.60±2.57	p = 0.007*
Static Compliance ($\boldsymbol{C_{ST}}$) (mL/cmH$_2$O)	GCTRL GTV	0.81±0.14 1.05±0.17	p = 0.007*
Loop Area (mL·mH$_2$O)	GCTRL GTV	55.44±6.30 66.61±14.18	p = 0.04*

Table 2. Morphometrical parameters. Normal, collapsed and hyperinsufflated alveolar pulmonary areas, mean linear intercept length of the distal air spaces (L_m) and the amount of polymorphonuclear (PMN) cells. The values correspond to mean ± standard deviation of 9 animals per group. Data were gathered from 10 random, noncoincident fields per rat. The animals were ventilated for 4 hours at a tidal volume of 10 mL/kg (GCTRL) or 20 mL/kg (GTV). Values are mean ± SD. *p<0.05, statistically significant difference

Groups	Normal Area (%)	Alveolar Collapse (%)	Alveolar hyperinsufflated (%)	$\boldsymbol{L_m}$(μm)	PMN Cells (x10^{-3}/μm^2)
GCTRL	84.93±4.46	9.08±5.64	5.99±1.58	33.64±3.35	17.95±3.82
GTV	64.52±6.89*	10.63±8.41	24.85±3.56*	49.42±8.80*	30.67±6.06*

However, we observed significant changes in the values of tissue resistance (G), tissue elastance (H), static compliance (C_{ST}), inspiratory capacity (IC) and PV Loop area. The Table 2 displays the analysis of pulmonary parenchymal morphometry, showing the fraction area of normal, collapsed and hyperrinsufflated alveolar pulmonary areas, the mean linear intercept length of the distal air spaces (L_m), and the amount of polymorphonuclear cells (PMN). In general, these rusults may suggest destruction of alveolar wall and pulmonary inflammation.

DISCUSSION

The tidal volume is the volume displaced in a respiratory cycle, inspiration and expiration. It is usually defined according to body weight and its normal value is around 7 mL/kg (Beardsell *et al*., 2009). Current volumes greater than 10 mL/kg were associated with increased risk of barotrauma and the use of high tidal volumes decreased venous return and cardiac output (Steven *et al.,* 2007). This parameter should be changed according to the pathology present in the patient.

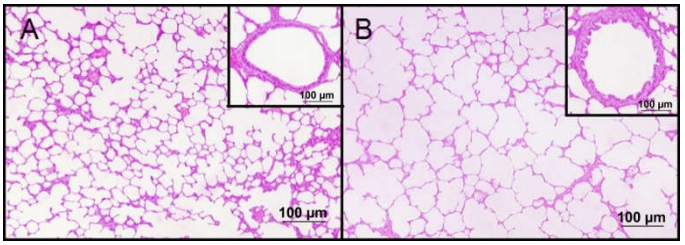

Figure 2. Photomicrographs of pulmonary parenchyma in rats. Photomicrographs of lung parenchyma stained with hematoxylin–eosin. Animals has ventilated for 4 hours at a tidal volume of 10 mL/kg (A-GCTRL) or 20 mL/kg (B-GTV)

For patients with neuromuscular diseases, the use of tidal volumes between 10 and 15 mL/kg of body weight (Mark *et al.,* 2013). Previous studies have shown a relationship between the use of a high tidal volume, with the presence of alveolar distension (Dreyfuss & Saumon, 1998)and pulmonary injury due to the stress generated by the opening and repeated closures of the pulmonary units (Bilek *et al.,* 2003). A relationship between ventilation in tidal volumes greater than 10 mL/kg and the presence of acute lung injury (ALI) (Gajic *et al.,* 2004). According to the network of acute respiratory distress syndrome (ARDS Network, 2000), the use of low tidal volumes, called protective ventilation, such as 6 mL/kg, is suggested for the ventilation of patients with ARDS. The use of tidal volumes between 4 and 6 mL/kg is used in the ventilation of neonates to avoid trauma due to high volume (Goldsmith*et al.,* 2016). Several studies are directed to the analysis of the effects of MV with different current volumes, and consequent acquisition of respiratory mechanics data in healthy patients (Verbrugge *et al.,* 2007; Cavassani *et al.,* 2011; Whitehead & Slutsky, 2015). Based on these studies, our work evaluated the effects of a ventilation strategy with a high tidal volume, through the analysis of respiratory system mechanics and histology of the pulmonary parenchyma.

We evaluated respiratory mechanics through the use of the forced oscillation technique using the constant phase model and curve volume pressure. The results showed changes in some variables of the GTV group when compared to the GCTRL group (Table 1). Newtonian resistance (R_N) is used as an estimate of the total resistance of the central airways (Bates, 2009). No changes were observed in the R_N between the groups. Suggesting that mechanical ventilation for 4 hours at a tidal volume of 20 mL/kg (GTV), does not cause significant changes in the smooth muscle of the airways. There was also no significant difference between groups for hysteresis (η). The proportion of the elastic dissipative component of the global energy is termed η and correlates with the degree of heterogeneity in lung ventilation (Fredberg *et al*, 1989; Bates, 2009). The η is closely related to the degree of contraction or closure of the airways and the absence of significant differences in the R_N, corroborates with the finding of η. For the variables of tissue resistance (G) and tissue elastance (H), significant differences were observed between groups (Table 1). G and H are related to the intrinsic properties of the pulmonary parenchyma. G reflects the energy dissipated by the viscoelastic forces in lung tissue and H reflects the elastic energy stored in the lung parenchyma.The decrease of these values in the GTV group suggests changes in the rheological properties of the tissue (Bates, 2009), as the highest number of hyperinflated alveoli (Table 2) caused by the destruction of the alveolar wall. Reflecting on the increase in mean alveolar diameter (Table 2-L_m).

Analysis of the quasi-static PV curve was based on the model proposed by Salazar and Knowles (1964).About theC_{ST}, an increase in the GTV group was observed in relation to the GTRL group, our result corroborates with previous studies that demonstrated the relation between the increase of the tidal volume offered during mechanical ventilation, with the increase of C_{ST} (Verbrugge *et al.,* 2007). This finding is consistent with the decrease in H and is related to the loss of elasticity of the lung tissue of the animals of this group. The increase in the inspiratory capacity (IC) estimate may be related to the destruction of the pulmonary parenchyma, resulting in an increase in lung volume. We can also relate the increase in $C_{ST}$and IC in the GTV group, the destruction of the alveolar septa, with consequent formation of alveolar sacs, a fact that can be corroborated in our histological and morphometric results (Figure 2- B; Table 2- Hypervolatile alveoli and L_m). However, the increase in the loop area of the PV curve may be associated with increased ventilatory work caused by hyperdistension of the alveoli (Table 2 - Alveoli hyperinflation), due to the high pulmonary volumes. Cannizzaro and collaborators (2010), used mechanical ventilation with different volumes in healthy and hemorrhaged mice and observed that mice with high tidal volumes had a significant increase in the loop area of the PV curve in $C_{ST}$and IC, corroborating our findings.

Also similar to our results, Bueno and collaborators (2002) ventilated rats with different tidal volumes and demonstrated that high volumes generate an increase in alveolar volume, providing an increase in the loop area of the PV curve. The pulmonary response to the challenge with MCh is shown in figure 1. An increase in the airway smooth muscle response to the use of MCh in animals of the GTV group was observed in comparison to the GCTRL, evidencing a hyperresponsiveness in the airway smooth muscle in the animals of this group. Hyperresponsiveness is generally associated with increased narrowing or contraction of the airways (Serra *et al.,* 2017), however, we did not observe increase R_N in animals of this group. Hyperresponsiveness is usually associated with an inflammatory process in the smooth muscle of the airways (Hizume *et al*., 2012). Our findings show an increase in the number of polymorphonuclear cells (Table 2), which represents the presence of an inflammatory process in the lung parenchyma. This inflammation can extrapolate the pulmonary parenchyma and lead to the onset of an inflammatory process in the smooth muscle of the airways, which can not yet be evidenced by the increase in R_N. However, with the use of MCh and exacerbation of the smooth muscle contraction response of the airways, this inflammatory process is evidenced and we observed a hyperresponsiveness in the smooth muscles of the airways of the animals of the GTV group.

Conclusion

In conclusion, the use of mechanical ventilation with high tidal volumes is associated with destruction of the alveolar wall, increased respiratory work and the presence of inflammatory processes in the pulmonary parenchyma. Our results alert us to the care taken in choosing the mechanical ventilation strategies of healthy patients. Studies aiming the study of mechanical ventilation in different volumes in healthy animals or with respiratory pathologies should be encouraged to increase the knowledge about the subject and to provide a greater safety in the choice of ventilatory strategies.

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