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Translational Research

Comparison of different degrees of variability in tidal volume to prevent deterioration of respiratory system elastance in experimental acute lung inflammation

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Abstract

Background: Variable ventilation improves respiratory function, but it is not known whether the amount of variability in tidal volume (V_T) can be reduced in recruited lungs without a deterioration of respiratory system elastance.

Methods: Acute lung inflammation was induced by intratracheal instillation of lipopolysaccharide in 35 Wistar rats. Twenty-eight animals were anaesthetized and ventilated in volume-controlled mode. Lungs were recruited by random variation of V_T (mean 6 ml kg^{-1}, coefficient of variation 30%, normal distribution) for 30 min. Animals were randomly assigned to different amounts of V_T variability (n=7 for 90 min per group): 30, 15, 7.5, or 0%. Lung function, diffuse alveolar damage, and gene expression of biological markers associated with cell mechanical stress, inflammation, and fibrogenesis were assessed. Seven animals were not ventilated and served as controls for post-mortem analyses.

Results: A V_T variability of 30%, but not 15, 7.5, or 0%, prevented deterioration of respiratory system elastance [Mean (SD) −7.5 (8.7%), P<0.05; 21.1 (9.6%), P<0.05; 43.3 (25.9), P<0.05; and 41.2 (16.4), P<0.05, respectively]. Diffuse alveolar damage was lower with a V_T variability of 30% than with 0% and without ventilation, because of reduced oedema and haemorrhage. A V_T variability of 30, 15, or 7.5% reduced the gene expression of amphiregulin, cytokine-induced neutrophil chemoattractant-1, and tumour necrosis factor α compared with a V_T variability of 0%.

Conclusions: In this model of acute lung inflammation, a V_T variability of 30%, compared with 15 and 7.5%, was necessary to avoid deterioration of respiratory system elastance and was not associated with lung histological damage.

Key words: Escherichia coli; inflammation; respiratory mechanics; inspiratory positive-pressure ventilation; mechanical ventilation

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Editor's key points

- Lung damage can be mitigated by varying tidal volumes during mechanical ventilation.
- The limits of such variation in tidal volume are unclear.
- In this study, using a rat model, tidal volumes were varied by up to 30%.
- Only 30% variability in tidal volume was able to prevent decreased respiratory function.
- This may have implications for clinical practice.

Controlled mechanical ventilation with variable tidal volumes (V_T) has been shown to improve respiratory mechanics and pulmonary gas exchange[1] and to reduce lung damage[2] in animal models of the acute respiratory distress syndrome (ARDS). Increased lung surface area for ventilation appears to be a major mechanism explaining these effects.[3 4]

Lung recruitment resulting from variable ventilation is superior to, and lasts longer than, conventional recruitment manoeuvres.[3] A previous investigation by our group showed that a coefficient of variation (amount of variability) in V_T of 30% is able to stabilize respiratory function after conventional lung recruitment in experimental ARDS.[2] In another study, a similar amount of variability optimized gas exchange and respiratory system mechanics during assisted mechanical ventilation, probably by promoting recruitment of the lungs.[5] The ARDS Network has shown that a V_T of 12 ml kg^{-1} is associated with lung inflammation and increased mortality in patients with ARDS compared with a V_T of 6 ml kg^{-1}.[6] During variable ventilation with a mean V_T of 6 ml kg^{-1}, 30% variability results in periodic V_T values higher than 12 ml kg^{-1}, which could lead to volutrauma. In contrast, periodic increases in V_T may recruit the lungs, contributing to reduced regional stress and strain. Thus, one could postulate that, once lungs are recruited and provided that recruitment is stable, the variability of the respiratory pattern could be reduced to avoid potentially harmful V_T values, thereby maximizing lung protection. To our knowledge, this issue has not been addressed previously.

In the present study, we investigated the effects of different amounts of V_T variability on respiratory function, lung histological damage, and markers of cell mechanical stress, inflammation, and fibrogenesis in a rat model of acute lung inflammation. We hypothesized that, after improvement of lung surface area with variable ventilation, a V_T variability of 30% would be necessary to avoid deterioration of respiratory system elastance (E_{RS}) and could be achieved without worsening lung damage.

The protocol and results of this study have been presented in parts at the American Thoracic Society (ATS) scientific meeting in Denver in 2015, and were previously published as an abstract.[7]

Methods

The study protocol was approved by the Animal Care Committee of the Health Sciences Centre, Federal University of Rio de Janeiro, Brazil. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the US National Academy of Sciences *Guide for the Care and Use of Laboratory Animals* and complied with relevant aspects of the ARRIVE guidelines. Animals were kept at a controlled temperature (23°C) and controlled light–dark cycle (12 h–12 h) with free access to water and food.

Animal preparation and experimental protocol

Figure 1 depicts the time course of interventions. Thirty-five specific-pathogen-free adult male Wistar rats [weighing 347 (24 g)] were anaesthetized by inhalation of sevoflurane 2% (Sevorane®; Cristália, Itapira, SP, Brazil), and acute lung inflammation was induced by intratracheal (i.t.) instillation of *Escherichia coli* lipopolysaccharide (LPS; O55:B5; Sigma Chemical Co., St Louis, MO, USA) 800 μg suspended in saline solution to a total volume of 200 μl. Animals were then allowed to recover from anaesthesia and observed for a period of 24 h. Thereafter, animals were premedicated intraperitoneally (i.p.) with diazepam 10 mg kg^{-1} (Compaz®; Cristália), ketamine 50 mg kg^{-1} (Ketamin-S+®, Cristália), and midazolam 2 mg kg^{-1} (Dormicum; União Química, São Paulo, SP, Brazil). An i.v. catheter (Jelco 24G; Becton Dickinson, Franklin Lakes, NJ, USA) was inserted into the tail vein for continuous infusion of midazolam 2 mg kg^{-1} h^{-1}, ketamine 50 mg kg^{-1} h^{-1}, and Ringer's lactate 7 ml kg^{-1} h^{-1} (B. Braun, Rio de Janeiro, Brazil). The adequacy of anaesthesia was assessed by the response to a nociceptive stimulus before surgery. Anaesthetized animals were kept in dorsal recumbency. Local anaesthetic (0.4 ml, lidocaine 2%) was infiltrated, and a tracheostomy was performed via a midline neck incision. Seven animals were not ventilated (NV). These were used as a control group for diffuse alveolar damage and molecular biology analysis. In the remaining 28 animals, a polyethylene catheter (PE-50) was introduced into the right internal carotid artery for blood sampling and mean arterial blood pressure (MAP) measurement. Heart rate (HR), MAP, and rectal temperature were continuously recorded (Networked Multiparameter Veterinary Monitor LifeWindow 6000 V; Digicare Animal Health, Boynton Beach, FL, USA). Body temperature was maintained at 37.5 (1°C) using a heating plate. To maintain MAP>60 mm Hg, Ringer's lactate solution (B. Braun) was given i.v. as 1 ml boluses to a maximal volume of 5 ml. If further volume loading was necessary, Gelafundin® (B. Braun) was administered in 0.5 ml increments.

Neuromuscular block was then induced with pancuronium bromide (Pancuron®; Cristália) given i.v. (0.4 mg), followed by 0.4 mg i.m. The lungs were mechanically ventilated (Inspira; Harvard Apparatus, Holliston, MA, USA) in volume-controlled mode (VCV), with V_T=6 ml kg^{-1}, respiratory rate (RR) adjusted to an arterial carbon dioxide partial pressure (Pa_{CO_2}) target of 35–45 mm Hg, inspiratory to expiratory ratio (I:E) ratio=1:2, fraction of inspired oxygen ($F_{I_{O_2}}$) = 0.4, and PEEP=4 cm H_2O. After a 5 min stabilization period, arterial blood gases were measured with a Radiometer ABL80 FLEX (Copenhagen NV, Denmark) and lung mechanics recorded (BASELINE). To recruit the lungs, the V_T variability was set at 30% and maintained for 30 min using an external controller for the mechanical ventilator, as described elsewhere.[8] During variable ventilation, V_T varied on a breath-to-breath basis using a self-looping sequence of randomly generated V_T values (n=600, mean V_T=6 ml kg^{-1}, normal distribution). During the 30 min recruitment period, lung mechanics variables were continuously recorded. Values for the whole recruitment period were averaged and thus contained a few non-recruited and a majority of recruited lung breathing cycles. After the recruitment period, arterial blood gases and respiratory system mechanics were measured (START).

Animals were then randomly assigned to mechanical ventilation with one of four values of V_T variability (n=7 per group), using closed sealed envelopes, as follows: (i) 30% (CV30); (ii) 15% (CV15); (ii) 7.5% (CV7.5); and (ii) 0% (CV0). Arterial blood gases and respiratory system mechanics were assessed every 30 min during a total