RESPIRATORY MECHANICS AND HISTOLOGY DURING SEVOFLURANE ANESTHESIA IN A MURINE MODEL OF CHRONIC ASTHMA

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ABSTRACT

Background: Sevoflurane is an anesthetic routinely used and there are no studies disclosing its effects on a chronically inflamed and remodeled airway as that found in asthma. The present study aimed to define the respiratory effects of sevoflurane in a model of chronic allergic asthma. Methods: Thirty-six BALB/c mice (20-25 g) were randomly divided into four groups. In OVA groups, mice were sensitized with ovalbumin and exposed to repeated ovalbumin challenges. In SAL groups, mice received saline using the same protocol. Twenty-four hours after the last challenge, the animals were anesthetized with pentobarbital sodium (PENTO, 20 mg/kg i.p.) or sevoflurane (SEVO, 1 MAC). Lung static elastance (Est), resistive (ΔP1) and viscoelastic/inhomogeneous (ΔP2) pressures were analyzed by end-inflation occlusion method. Lungs were fixed and stained for histopathological analysis. Results: OVASEVO group showed lower ΔP1 (38%), ΔP2 (24%), and Est (22%) than animals of OVAPENTO group ($p < 0.001$). Histopathology demonstrated greater airway dilation (16%) and a lower degree of alveolar collapse (25%) in OVASEVO compared to OVAPENTO group. ΔP1 was lower (35%) and airway diameters larger (12%) in SALSEVO compared to SALPENTO group. Conclusion: Sevoflurane anesthesia acted both at airway level and lung periphery reducing airway resistance, viscoelastic pressure and static elastance in chronic allergic asthma.

INTRODUCTION

- Sevoflurane is a inhalational anesthetic largely used since it provides faster induction and awakening, and causes less airway irritation than other inhaled agents. Despite that, there are no reports describing its effects on a chronically inflamed and remodeled airway as that found in asthma.
- Allergic asthma is the type experienced by approximately 80% of asthmatics presenting eosinophilic inflammation and structural changes of the airway wall.
- Inflammation in chronic asthma involves the activation of airway cells, including T-cells, eosinophils, mast cells, macrophages, epithelial cells, fibroblasts, and bronchial smooth muscle cells.
- Chronic inflammation is associated with injury and repair of the bronchial epithelium, which results in structural and functional changes known as remodeling. These structural changes include: smooth muscle hypertrophy, mucous gland hyperplasia, blood vessel proliferation, and sub-basement membrane collagen deposition.
- The underlying chronic inflammatory process compromises not only central airways but also distal airways and lung parenchyma.

AIMS

- The aim of this study was to determine the respiratory effects of sevoflurane in a murine model of chronic allergic asthma.
- Objective: To that end, lung mechanics and histology were analyzed.

METHODS

Animal Preparation

- Thirty-six BALB/c mice (20-25 g) were randomly divided into four groups (Figure 1).
- In OVA groups, mice were sensitized with ovalbumin and exposed to repeated ovalbumin challenges.
- In SAL groups, mice received saline using the same protocol.
- After the last challenge, nine mice of OVA group (OVASEVO group) and nine of SAL group (SALSEVO group) were anesthetized with sevoflurane 1 MAC.
- Similarly, nine animals of OVA group (OVAPENTO group) and nine of SAL group (SALPENTO group) were sedated and anesthetized with pentobarbital sodium (20 mg/kg i.p.).
- Animals were paralyzed with vecuronium bromide (5 μg/kg i.v.), and mechanically ventilated with a constant flow ventilator with a frequency of 100 breaths/min.
- Tidal volume (V_T = 0.2 mL) and airflow (V' = 1 mL/s) were kept constant.

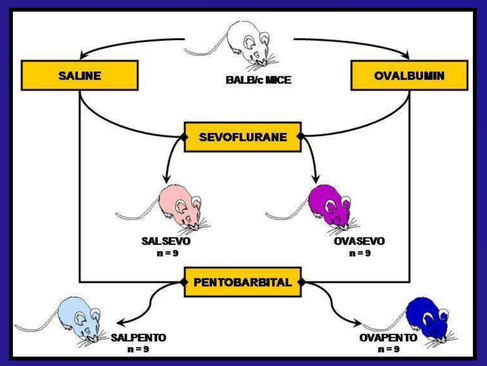

Figure 1. Experimental Groups

METHODS

Lung Mechanics

- Measurements were performed 10 times in each animal by the end-inflation occlusion method (Figure 2) and data were collected 15 to 20 min after tracheal intubation.
- Lung resistive (ΔP1), viscoelastic/inhomogeneous (ΔP2), and total pressures (ΔPtot), and static elastance (Est) were analyzed.

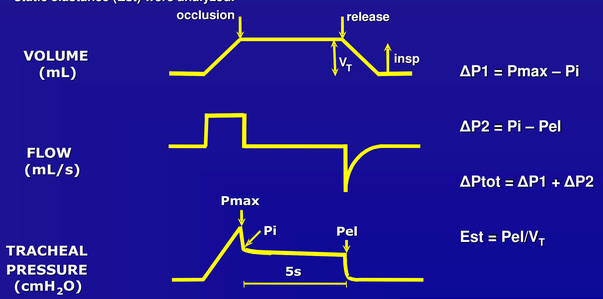

Figure 2. Airway occlusions were performed at end inflation (point indicated by the first arrow on volume tracing). After 5 s, occlusions were released (second arrow). Pmax = peak inspiratory pressure; Pi = inflexion point; Pel = elastic recoil pressure; V_T = tidal volume; insp = inspiration.

Lung Histology and Morphometry

- Lungs were removed *en bloc*, sliced (4-μm-thick), fixed, and stained with hematoxylin-eosin for histopathological analysis.
- The volume fractions of collapsed pulmonary areas and the magnitude of bronchoconstriction (Contraction Index), were computed by the point-counting technique across 10 random, non-coincident microscopic fields.

Statistical Analysis

- The normality of the data and the homogeneity of variances were tested. Differences among the groups were assessed by two-way ANOVA followed by Tukey test.
- Correlation between mechanical and histological data was determined by Spearman correlation test.
- A p value < 0.05 was considered significant.

RESULTS

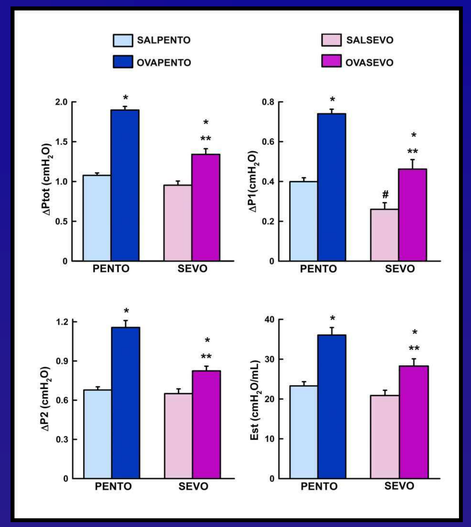

Figure 3. Lung Mechanics. Bars are means + SEM of 9 animals in each group. ΔPtot, ΔP1, ΔP2, and Est were higher in OVA than in SAL groups (*$p < 0.05$). OVASEVO mice presented lower values of ΔPtot (30%), ΔP1 (38%), ΔP2 (24%), and Est (22%) than OVAPENTO (**$p < 0.001$). SALSEVO group showed lower ΔP1 (35%) than SALPENTO group (#$p = 0.005$).

RESULTS

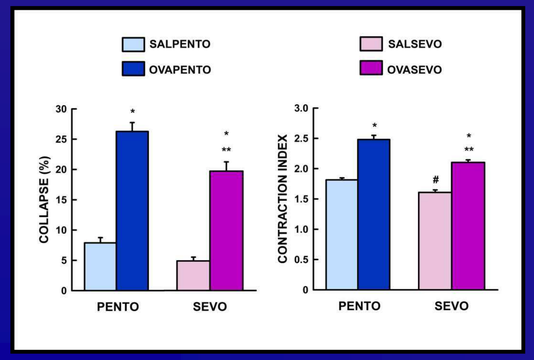

Figure 4. Morphometric Parameters. Results are means + SEM of 9 animals in each group. Data were gathered from ten random, non-coincident fields per mouse. The fraction of area of alveolar collapse was higher in OVA (260%) than in SAL groups (* $p < 0.001$). OVA groups showed smaller central and distal airway diameters (33%) than those found in the SAL groups (* $p < 0.001$). OVASEVO group presented wider central and distal airways (16%) and a smaller amount (25%) of alveolar collapse than OVAPENTO group (** $p < 0.001$). Furthermore, SALSEVO animals showed larger central airway diameters (12%) than SALPENTO group (# $p = 0.005$).

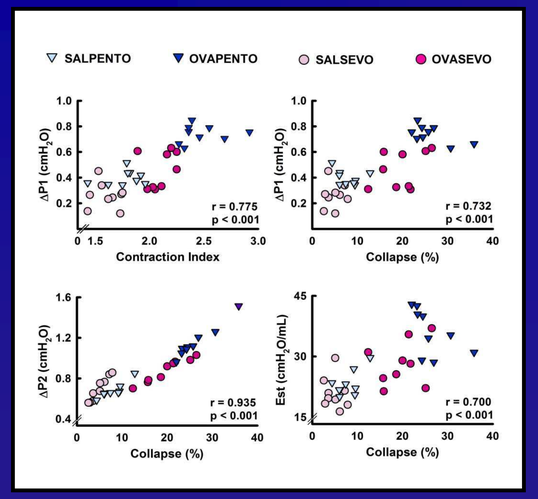

Figure 5. Spearman's Correlations between mechanical and morphological data showing that ΔP1, ΔP2 and Est values were well correlated with the fraction of area of alveolar collapse and contraction index.

RESULTS

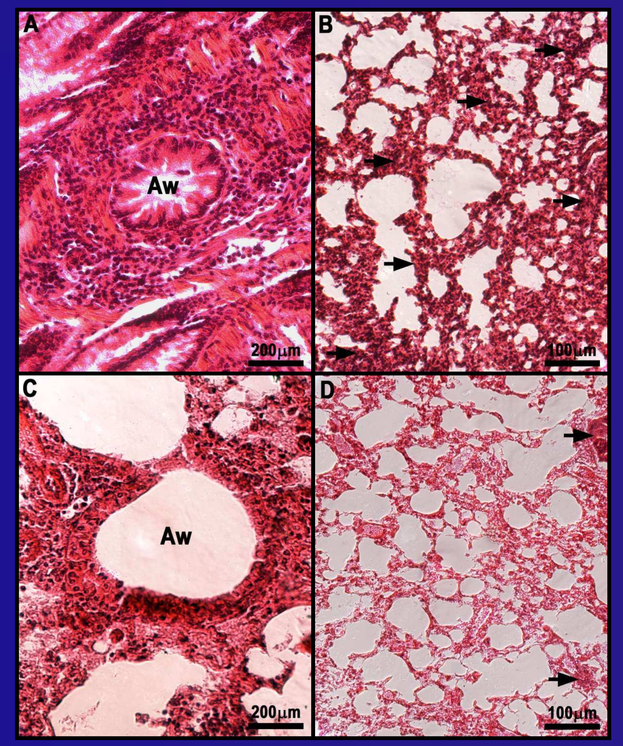

Figure 6. Photomicrographs. Airways (A and C), and distal lung parenchyma (B and D) from mice sensitized and exposed to repeated challenges with intratracheal instillation of ovalbumin (OVA). In A and B, animals were anesthetized with pentobarbital sodium (OVAPENTO, n = 9) and in C and D with sevoflurane (OVASEVO, n = 9) 1 MAC. The airway (Aw) was constricted and the amount of alveolar collapse (arrows) was higher in OVAPENTO than in OVASEVO group. Mice showed a peribronchial accumulation of inflammatory cells, including eosinophils and mononuclear cells. Hematoxylin-eosin staining. Original magnification: A and C = x400; B and D = x200.

CONCLUSION

The present experiment disclosed that sevoflurane anesthesia induced dilation in central and distal airways, yielding reduced airway resistance and viscoelastic/inhomogeneity pressure applied to the lung. The former finding was related to airway dilation, whereas the latter was supported by the histological demonstration of smaller areas of collapse of distal airspaces.

A thorough description of changes in lung mechanics caused by routinely used anesthetic agents, such as sevoflurane, can be beneficial to the management of asthmatic patients. Accordingly, our findings suggest that sevoflurane could be a suitable anesthetic agent for chronic asthma.

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