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Original Article

Effects of inhalational anaesthetics in experimental allergic asthma*

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Summary

We evaluated whether isoflurane, halothane and sevoflurane attenuate the inflammatory response and improve lung morphofunction in experimental asthma. Fifty-six BALB/c mice were sensitised and challenged with ovalbumin and anaesthetised with isoflurane, halothane, sevoflurane or pentobarbital sodium for one hour. Lung mechanics and histology were evaluated. Gene expression of pro-inflammatory (tumour necrosis factor-α), pro-fibrogenic (transforming growth factor-β) and pro-angiogenic (vascular endothelial growth factor) mediators, as well as oxidative process modulators, were analysed. These modulators included nuclear factor erythroid-2 related factor 2, sirtuin, catalase and glutathione peroxidase. Isoflurane, halothane and sevoflurane reduced airway resistance, static lung elastance and atelectasis when compared with pentobarbital sodium. Sevoflurane minimised bronchoconstriction and cell infiltration, and decreased tumour necrosis factor-α, transforming growth factor-β, vascular endothelial growth factor, sirtuin, catalase and glutathione peroxidase, while increasing nuclear factor erythroid-2-related factor 2 expression. Sevoflurane down-regulated inflammatory, fibrogenic and angiogenic mediators, and modulated oxidant–antioxidant imbalance, improving lung function in this model of asthma.

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Introduction

Allergic asthma is a major public health issue, affecting 80% of asthmatics [1]. Chronic inflammation is a hallmark of asthma, and the cytokines released by inflammatory and airway cells lead to injury and repair of the bronchial epithelium, which results in structural and functional changes known as remodelling [1, 2].

Evidence suggests that tumour necrosis factor (TNF)-α, a pro-inflammatory cytokine present in increased concentrations in asthmatic patients, contributes to the pathogenesis of asthma by boosting inflammation and airway hyperreactivity [3]. Furthermore, in asthma, elevated levels of transforming growth factor (TGF)-β lead to subepithelial fibrosis. This is because TGF-β induces fibroblast proliferation

and proliferation of airway smooth muscle cells (ASMC), resulting in increased respiratory system resistance, and overproduction and release of vascular endothelial growth factor (VEGF) [4]. The latter is an angiogenic factor that enhances blood vessel formation and vascular permeability [5], contributing to airway vascular remodelling and TGF-β overexpression [6].

Recently, the role of oxidative stress in the pathogenesis and progression of asthma has received increased attention [7–9]. The airways of patients with asthma show increased levels of reactive oxygen species (ROS), and decreased antioxidant activity [8, 9]. Oxidative stress triggers inflammation, and may also occur as a result of inflammation [9]. Sirtuin (sirt)-1 induces Th2 pro-inflammatory responses and upregulates VEGF [5] in experimental allergen-induced airway inflammation [5, 10]. In addition, recent investigations have identified nuclear factor erythroid-2-related factor 2 (Nrf2) pathway activation as a therapeutic target in asthma [7]. This factor is a transcription factor that inhibits TGF-β [7, 11] and activates anti-inflammatory, antioxidant and detoxification enzymes [11]. Endogenous antioxidants include catalase and glutathione peroxidase (GPx), which are the most important H_2O_2-scavenging enzymes in the lung, with the ability to buffer ROS and prevent deterioration in lung morphofunction [8]. Reactive oxygen species mediate ASMC contraction, proliferation and inflammatory mediator release [7, 9].

Halothane, isoflurane and sevoflurane are routinely used inhalational anaesthetics that induce bronchodilation and attenuate airway responsiveness. Some case reports have described a beneficial action of anaesthetics in refractory asthma [12–14], and studies have demonstrated their anti-inflammatory effects in experimental [15–19] and clinical [20, 21] acute respiratory distress syndrome (ARDS) protocols. We have previously reported that sevoflurane promoted bronchodilation and reduced atelectasis in experimental allergic asthma [22]. To our knowledge, no studies have examined the immunomodulatory effects of volatile anaesthetics in a chronically inflamed and remodelled airway, such as that found in asthma. To investigate whether the improvement in lung mechanical and histological parameters induced by inhalational anaesthetics may be associated with a reduction in lung inflammation and remodelling, we measured mRNA expression of TNF-α, TGF-β and VEGF. In addition, given that oxidant–antioxidant imbalance plays a pivotal role in the pathogenesis of asthma, we studied the gene expression of Nrf2, sirt-1, catalase and GPx in a long-term exposure murine model of allergen-induced asthma with characteristics of the human disease, including airway remodelling [23].

Methods

This study was approved by the Ethics Committee of the Federal University of Rio de Janeiro. All animals received humane care in accordance with the 'Principles of Laboratory Animal Care' formulated by the National Society for Medical Research and the 'Guide for the Care and Use of Laboratory Animals' prepared by the US National Academy of Sciences.

Fifty-six BALB/c mice (weight 15–20 g, aged six weeks) were randomly assigned to two groups. In the experimental asthma (ASTHMA) group, mice were sensitised by the intraperitoneal (i.p.) injection of ovalbumin (10 μg in 0.1 ml saline) on each of seven alternate days [22, 23]. Forty days after the beginning of the sensitisation protocol, 20 μg ovalbumin in 20 μl sterile saline was instilled into the trachea [22, 23]. This procedure was performed three times at 3-day intervals. The other group (SALINE) received saline using the same protocol.

Twenty-four hours after the last challenge, animals were anaesthetised with isoflurane (ISO), halothane (HALO) or sevoflurane (SEVO) administered by mask with airflow through a calibrated vaporiser (HB, Rio de Janeiro, Brazil), or sedated with diazepam (1 mg i.p.) and anaesthetised with the control drug pentobarbital sodium, 70 $mg.kg^{-1}$ i.p. (CTRL). During spontaneous breathing, the level of anaesthesia was assessed by evaluating the size and position of the pupil, its response to light, the position of the nictitating membrane, and movement in response to stimulation of the mice's tails. When an appropriate plane of anaesthesia was reached, tracheotomy was performed, neuromuscular blockade was achieved with intravenous vecuronium bromide (0.05 $mg.kg^{-1}$), and a constant flow ventilator (Samay VR15; Universidad de la Republica, Montevideo, Uruguay) was used to ventilate the lungs with the following parameters: frequency = 100 $breaths.min^{-1}$;

tidal volume (V_T) = 0.2 ml; airflow (V') = 1 ml.s^{-1}; and fraction of inspired oxygen (F_IO_2) = 0.21. After neuromuscular blockade, adequate depth of anaesthesia was assessed by pupil size and reactivity to light [24]. Additional boluses of pentobarbital (20 mg.kg^{-1} i.p.) were administered every 20 min, whereas volatile anaesthetic concentration was increased, as needed, according to animal response. A positive end-expiratory pressure (PEEP) of 2 cmH_2O was applied and the chest wall was removed.

After a 60-min ventilation period, we measured airway resistance (Raw) and static lung elastance (Est, L) by the end-inflation occlusion method [22, 25]. We analysed data with ANADAT software (RHT-InfoData, Inc., Montreal, QC, Canada).

We performed morphometric analysis as previously described [22], and fractional areas of alveolar collapse, total cells (total cellularity), polymorphonuclear (PMN) and mononuclear (MN) cells were assessed.

We performed quantitative real-time reverse-transcription polymerase chain reaction (RT-PCR) in lung tissue. Total RNA was extracted using the SV total RNA Isolation System (Promega Corporation, Fitchburg, WI, USA) and RNA concentration was measured by spectrophotometry in a Nanodrop ND-1000 system. First-strand cDNA was synthesised from total RNA using the GoTaq® 2-STEP RT qPCR System (Promega Corporation). All samples were measured in triplicate and the expression of each gene was normalised to housekeeping gene 36B4. The results were normalised by fold changes relative to the corresponding control group.

We used the SigmaStat 3.1 statistical software package (Jandel Corporation, San Rafael, CA, USA) for data analysis. Between-group differences were assessed using ANOVA followed by Tukey test. The significance level was set at 5%.

Results

Asthmatic controls (ASTHMA-CTRL) exhibited significantly higher airway resistance (+91%) and static lung elastance (+38%) than non-asthmatic controls (SALINE-CTRL) (Fig. 1). In ASTHMA-CTRL groups, we observed an enhanced remodelling process and increased degree of atelectasis (+227%), bronchoconstriction (+35%), total cells (+39%) and polymorphonuclear (+147%) and mononuclear cells (+29%) compared with SALINE-CTRL groups (Fig. 2 and Table 1). ASTHMA-CTRL groups also showed higher expression of the mediators TNF-α (+425%), TGF-β (+554%), VEGF (+308%), sirt-1 (+787%), catalase

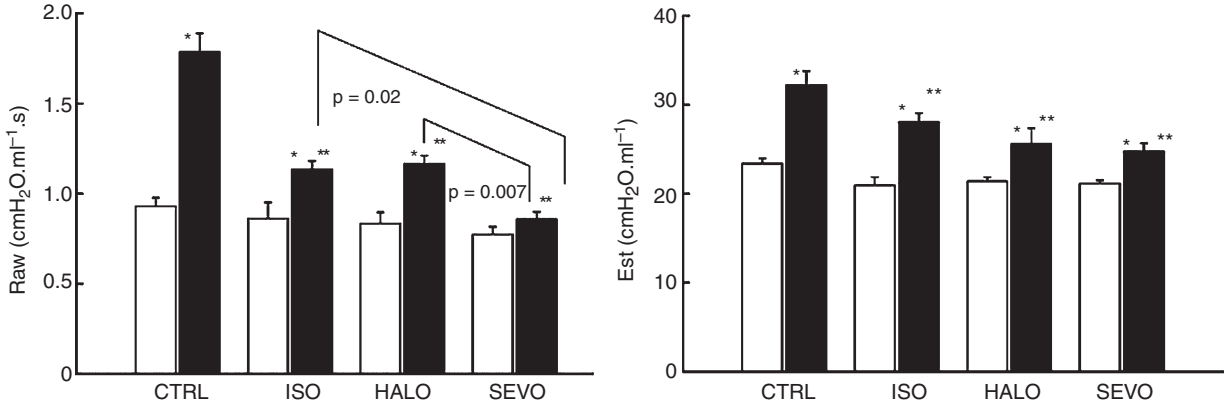

Figure 1 Lung mechanics in animals exposed to pentobarbital sodium (CTRL), isoflurane (ISO), halothane (HAL) or sevoflurane (SEVO). Columns are mean; error bars are SEM. Raw, airway resistance; Est, pulmonary static elastance. *Significantly different from the corresponding saline group: Raw – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$; ASTHMA-ISO vs SALINE-ISO, $p = 0.004$; ASTHMA-HALO vs SALINE-HALO, $p < 0.001$. Est – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$; ASTHMA-ISO vs SALINE-ISO, $p < 0.001$; ASTHMA-HALO vs SALINE-HALO, $p = 0.007$; ASTHMA-SEVO vs SALINE-SEVO, $p = 0.019$. **Significantly different from ASTHMA-CTRL group: Raw – ASTHMA-ISO vs ASTHMA-CTRL, $p < 0.001$; ASTHMA-HALO vs ASTHMA-CTRL, $p < 0.001$; ASTHMA-SEVO vs ASTHMA-CTRL, $p < 0.001$. Est – ASTHMA-ISO vs ASTHMA-CTRL, $p = 0.008$; ASTHMA-HALO vs ASTHMA-CTRL, $p < 0.001$; ASTHMA-SEVO vs ASTHMA-CTRL, $p < 0.001$.

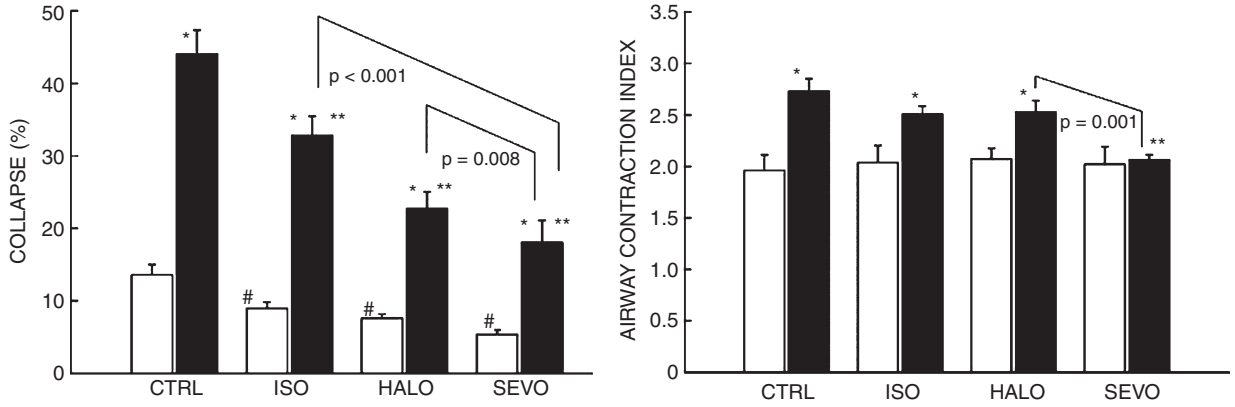

Figure 2 Amount of bronchoconstriction (AIRWAY CONTRACTION INDEX) and fraction area of collapsed alveoli (COLLAPSE) in animals exposed to pentobarbital sodium (CTRL), isoflurane (ISO), halothane (HAL) or sevoflurane (SEVO). Columns are mean; error bars are SEM. *Significantly different from the corresponding saline group: Collapse – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$; ASTHMA-ISO vs SALINE-ISO, $p < 0.001$; ASTHMA-HALO vs SALINE-HALO, $p < 0.001$; ASTHMA-SEVO vs SALINE-SEVO, $p < 0.001$. Airway Contraction Index – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$; ASTHMA-ISO vs SALINE-ISO, $p < 0.001$; ASTHMA-HALO vs SALINE-HALO, $p = 0.007$; ASTHMA-SEVO vs SALINE-SEVO, $p = 0.019$. **Significantly different from ASTHMA-CTRL group: Collapse – ASTHMA-ISO vs ASTHMA-CTRL, $p < 0.001$; ASTHMA-HALO vs ASTHMA-CTRL, $p < 0.001$; ASTHMA-SEVO vs ASTHMA-CTRL, $p < 0.001$. Airway Contraction Index – ASTHMA-ISO vs ASTHMA-CTRL, $p = 0.008$; ASTHMA-HALO vs ASTHMA-CTRL, $p < 0.001$; ASTHMA-SEVO vs ASTHMA-CTRL, $p < 0.001$. #Significantly different from SALINE-CTRL group: SALINE-ISO vs SALINE-CTRL, $p = 0.002$; SALINE-HALO vs SALINE-CTRL, $p < 0.001$; SALINE-SEVO vs SALINE-CTRL, $p < 0.001$.

(+631%) and GPx (+235%). Nrf2 expression was reduced (−64%) compared with the SALINE-CTRL group (Fig. 4).

The ISO, HALO and SEVO groups showed reduced airway resistance (−37%, −35% and −52%) and static lung elastance (−16%, −19% and −22%) compared with CTRL. Sevoflurane dampened airway resistance more than isoflurane and halothane (Fig. 1). A lesser degree of alveolar collapse was seen in the ISO, HALO and SEVO groups (−25%, −48% and −57%) compared with CTRL, and the HALO and SEVO groups exhibited reduced atelectasis compared with ISO. There was less bronchoconstriction in SEVO animals (−22%) than in the ISO, HALO and CTRL groups (Figs 2 and 3). SEVO also reduced PMN cell infiltration (−39%) compared with CTRL and ISO groups (Table 1 and Fig. 3).

Among non-asthmatic mice (SALINE), the ISO, HALO and SEVO groups showed significantly reduced atelectasis (−34%, −44% and −60%, respectively) compared with CTRL (Fig. 2). Furthermore, the SEVO group had lower PMN cell counts in lung tissue compared with the CTRL, ISO and HALO groups (−58%, −61% and −47%) (Table 1).

The SEVO animals exhibited reduced expression of TNF-α (−71%), TGF-β (−63%), VEGF (−50%), sirt-1 (−80%), catalase (−76%) and GPx (−69%), and significantly increased Nrf2 expression (+579%), when compared with CTRL. The SEVO group also had higher expression of Nrf2 than the ISO and HALO groups (Figs 4 and 5).

Discussion

This study provides evidence that sevoflurane anaesthesia minimised inflammatory processes and improved lung mechanics and histology in experimental allergic asthma. Although isoflurane and halothane also improved lung mechanics and lessened atelectasis, sevoflurane was more effective at reducing bronchoconstriction. These beneficial effects of sevoflurane may be related to modulation of the expression of mediators associated with inflammation (TNF-α), fibrogenesis (TGF-β), angiogenesis (VEGF) and oxidative stress (Nrf2, sirt-1, catalase and GPx).

Table 1 Lung morphometry. Values are mean (SEM) of seven animals per group.

Groups	Total cells (%)	PMN (%)	MN (%)
SALINE			
CTRL	41.8 (1.25)	3.6 (0.76)	38.2 (0.79)
ISO	43.7 (2.23)	3.8 (0.59)	39.9 (2.14)
HALO	44.1 (2.63)	3.2 (0.42)	40.9 (2.69)
SEVO	40.2 (1.87)	1.5 (0.30)‡,¶	38.6 (1.93)
ASTHMA			
CTRL	58.3 (1.83)*	8.9 (0.74)*	49.4 (1.76)*
ISO	54.2 (2.79)*	9.0 (1.19)*	45.2 (2.79)
HALO	56.6 (1.65)*	8.1 (1.24)*	48.4 (2.58)
SEVO	50.1 (2.29)*	5.4 (1.05)*,†,§	44.7 (2.51)

Fraction of polymorphonuclear (PMN) and mononuclear (MN) cells gathered from 10 random, non-coincident fields per mouse after exposure to pentobarbital sodium (CTRL), isoflurane (ISO), halothane (HAL) or sevoflurane (SEVO).
*Significantly different from the corresponding SALINE group: Total cells – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$; ASTHMA-ISO vs SALINE-ISO, $p = 0.001$; ASTHMA-HALO vs SALINE-HALO, $p < 0.001$; ASTHMA-SEVO vs SALINE-SEVO, $p = 0.002$. PMN – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$; ASTHMA-ISO vs SALINE-ISO, $p < 0.001$; ASTHMA-HALO vs SALINE-HALO, $p < 0.001$; ASTHMA-SEVO vs SALINE-SEVO, $p = 0.003$. MN – ASTHMA-CTRL vs SALINE-CTRL, $p < 0.001$.
†Significantly different from ASTHMA-CTRL group. ASTHMA-SEVO vs ASTHMA-CTRL, $p = 0.005$.
‡Significantly different from SALINE-CTRL group. SALINE-SEVO vs SALINE-CTRL, $p = 0.026$.
§Significantly different from ASTHMA-ISO group. ASTHMA-SEVO vs ASTHMA-ISO, $p = 0.044$.
¶Significantly different from SALINE-ISO and SALINE-HALO groups. SALINE-SEVO vs SALINE-ISO, $p = 0.007$; SALINE-SEVO vs SALINE-HALO, $p = 0.007$.

In the current study, we used an experimental chronic allergen-induced asthma model with characteristics of human asthma, such as chronic inflammation, airway hyper-reactivity and remodelling [22, 23]. As expected in this protocol, asthmatic controls (ASTHMA-CTRL) had impaired lung mechanics and morphometry, with increased airway resistance, lung elastance, bronchoconstriction, alveolar collapse and inflammatory cell infiltration (Figs 1–3 and Table 1). In experimental models, pentobarbital sodium has been considered a control drug, as it has no effect on airway baseline tone [26] and causes no modification of either respiratory mechanics or morphometry [24, 26].

We observed that TNF-α, TGF-β, VEGF, sirt-1, catalase and GPx expressions were markedly increased in asthmatic mouse controls, while Nrf2 expression was decreased (Figs 4 and 5). Mechanistically, oxidative stress activates pro-inflammatory genes and induces pathophysiological changes in the respiratory tract, perpetuating and amplifying the inflammatory response [9]. In asthma, increased TGF-β reduces Nrf2 activity, leading to: (1) increased expression of nuclear factor-κB (NF-κB) and cytokines [27]; (2) severe mucus cell hyperplasia and eosinophil infiltration in lung tissue [27]; (3) enhanced airway resistance [27]; and (4) defective antioxidant response, boosting susceptibility to severe airway inflammation and asthma [27, 28].

In the present study, catalase and GPx expression was increased in the lung tissue of ASTHMA animals (Fig. 5). Comhair et al. similarly reported higher expression of extracellular GPx mRNA and GPx protein levels in asthmatic bronchial epithelial cells in response to ROS [29]. In contrast, other studies have shown that GPx protein levels were unchanged in the bronchoalveolar lavage fluid (BALF) [30] or decreased in the blood [31] of asthmatic patients.

In our asthma model, anaesthesia with isoflurane, halothane and sevoflurane reduced airway resistance and static lung elastance, whereas sevoflurane lessened bronchoconstriction (Figs 1–3). Furthermore, we observed that isoflurane, halothane and sevoflurane induced dilatation of distal airways and alveolar units (Figs 2 and 3), suggesting that these anaesthetic agents may play a valuable role in lessening lung atelectasis.

These results support a previous study from our group [22], which demonstrated that sevoflurane led to morphofunctional improvement by acting at the airway level and lung periphery in the same model of asthma employed in the present study [22]. Similarly, Wiklund et al. showed that halothane and sevoflurane attenuated bronchoconstriction via inhibition of cholinergic and non-adrenergic/non-cholinergic neurotransmission, and reported that sevoflurane reduced bronchoconstriction induced by leukotrienes, while halothane did not [32]. Rooke et al. reported that sevoflurane decreased respiratory system resistance to a greater extent than halothane and isoflurane after tracheal intubation in healthy patients [33], whereas, in asthmatic children, Habre et al. found that tracheal intubation under sevoflurane was followed by a small increase in respiratory system resistance, which was

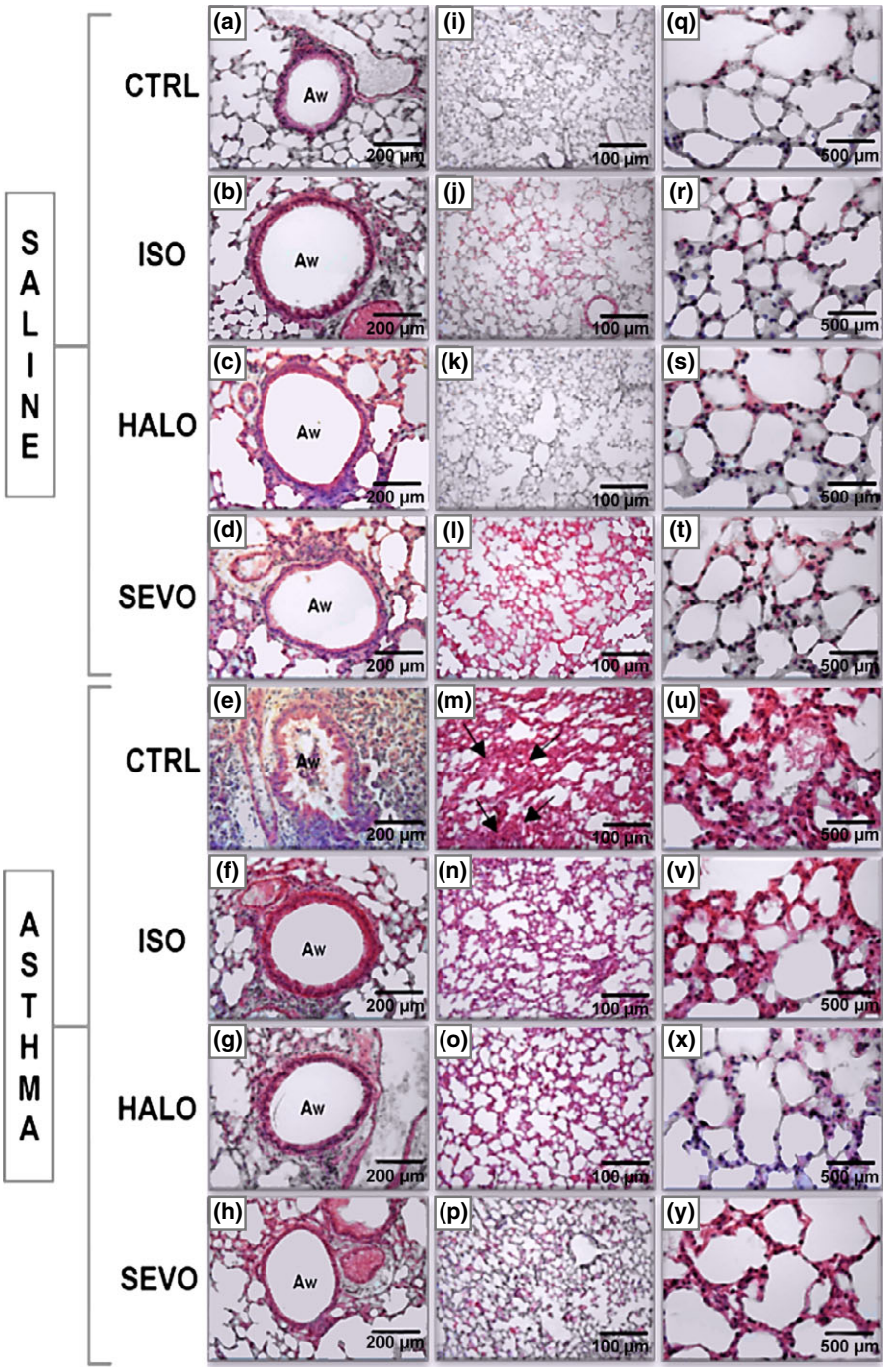

Figure 3 Representative photomicrographs of airways (A, B, C, D, E, F, G and H) and lung parenchyma (I, J, K, L, M, N, O, P, Q, R, S, T, U, V, X and Y) in animals exposed to pentobarbital sodium (CTRL), isoflurane (ISO), halothane (HAL) or sevoflurane (SEVO). Note the greater airway constriction (Aw) and the presence of alveolar collapse (arrows) in ASTHMA-CTRL group. Anaesthesia with sevoflurane promoted dilation of central and distal airways and lessened peribronchial accumulation of inflammatory cells. Haematoxylin and eosin staining. Original magnification: A, B, C, D, E, F, G and H = 400×; I, J, K, L, M, N, O and P = 200×; Q, R, S, T, U, V, X and Y = 1000×. Bars: A, B, C, D, E, F, G and H = 200 µm; I, J, K, L, M, N, O and P = 100 µm; Q, R, S, T, U, V, X and Y = 500 µm.

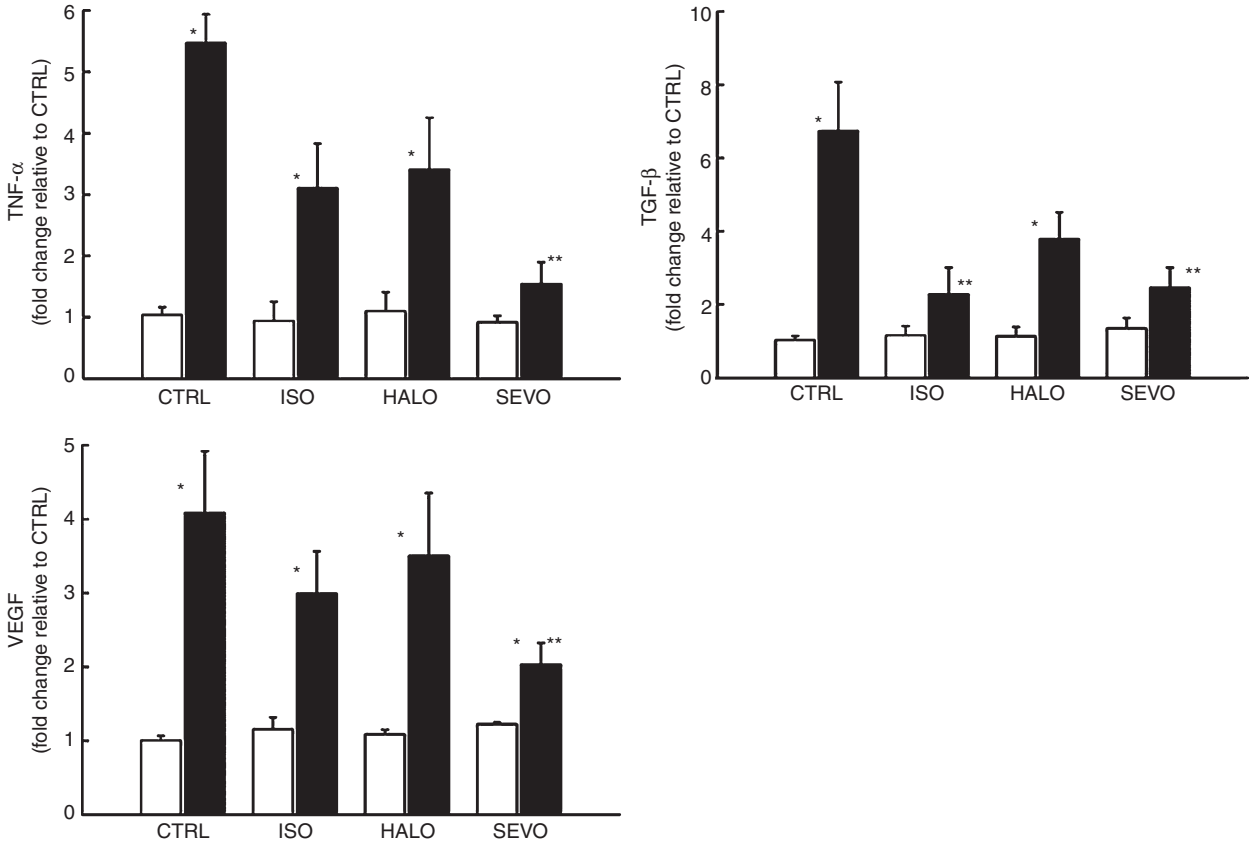

Figure 4 Real-time reverse-transcription polymerase chain reaction analysis for tumour necrosis factor (TNF)-α, transforming growth factor (TGF)-β and vascular endothelial growth factor (VEGF). Values are mean + SEM of 5 animals in each group. *Significantly different from the corresponding saline group: TNF-α – ASTHMA-CTRL vs SALINE-CTRL, p = 0.002; ASTHMA-ISO vs SALINE-ISO, p = 0.032; ASTHMA-HALO vs SALINE-HALO, p = 0.034. TGF-β – ASTHMA-CTRL vs SALINE-CTRL, p = 0.002; ASTHMA-HALO vs SALINE-HALO, p = 0.009. VEGF – ASTHMA-CTRL vs SALINE-CTRL, p = 0.029; ASTHMA-ISO vs SALINE-ISO, p = 0.021; ASTHMA-HALO vs SALINE-HALO, p = 0.029; ASTHMA-SEVO vs SALINE-SEVO, p = 0.029. **Significantly different from ASTHMA-CTRL group: TNF-α – ASTHMA-SEVO vs ASTHMA-CTRL, p = 0.002. TGF-β – ASTHMA-ISO vs ASTHMA-CTRL, p = 0.017; ASTHMA-SEVO vs ASTHMA-CTRL, p = 0.022. VEGF – ASTHMA-SEVO vs ASTHMA-CTRL, p = 0.044.

reversed once a deeper plane of anaesthesia was reached [34].

High levels of activated eosinophils in the lungs of asthmatic children have been associated with increased respiratory resistance and enhanced bronchial hyperreactivity [35]. In our study, sevoflurane reduced PMN infiltration in asthmatic mice (Table 1 and Fig. 3), which is consistent with prior experimental studies showing that sevoflurane can suppress cell recruitment [36, 37], decrease chemotaxis [36, 37] and reduce hyperpermeability [36] in ARDS protocols.

Anaesthesia with isoflurane, halothane and sevoflurane reduced alveolar collapse (Figs 2 and 3) in healthy mice (Table 1 and Fig 3). Atelectasis in non-asthmatics can be explained by the fact that even uneventful anaesthesia may induce lung collapse, caused by the loss of muscle tone and reduction in functional residual capacity [38], including absorption atelectasis behind closed airways, compression of lung tissue and surfactant loss or dysfunction [38]. Additionally, sevoflurane reduced PMN infiltration in non-asthmatic mice (Table 1 and Fig. 3), possibly due to inhibition of PMN activation and adhesion [39].

In this study, sevoflurane anaesthesia down-regulated TNF-α, TGF-β and VEGF expression

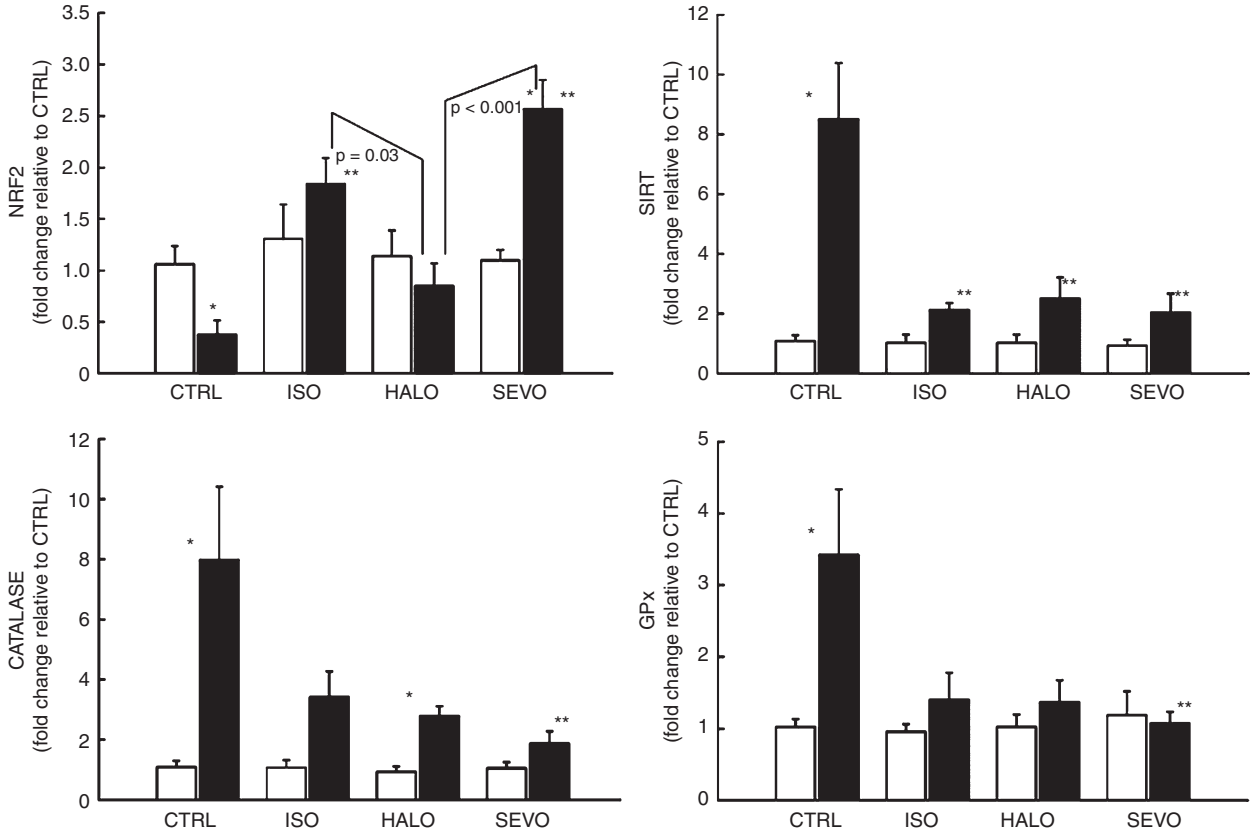

Figure 5 Real-time reverse-transcription polymerase chain reaction analysis for nuclear factor erythroid-2 related factor 2 (Nrf2), sirtuin (sirt)-1, catalase and glutathione peroxidase (GPx). Columns are mean; error bars are SEM, of five animals in each group. *Significantly different from the corresponding saline group: Nrf2 – ASTHMA-CTRL vs SALINE-CTRL, p = 0.026; ASTHMA-SEVO vs SALINE-SEVO, p = 0.001. Sirt-1 – ASTHMA-CTRL vs SALINE-CTRL, p = 0.002. Catalase – ASTHMA-CTRL vs SALINE-CTRL, p = 0.002; ASTHMA-HALO vs SALINE-HALO, p = 0.001. GPx – ASTHMA-CTRL vs SALINE-CTRL, p = 0.004. **Significantly different from ASTHMA-CTRL group: Nrf2 – ASTHMA-ISO vs ASTHMA-CTRL, p = 0.001; ASTHMA-SEVO vs ASTHMA-CTRL, p < 0.001. Sirt-1 – ASTHMA-ISO vs ASTHMA-CTRL, p = 0.006; ASTHMA-HALO vs ASTHMA-CTRL, p = 0.009; ASTHMA-SEVO vs ASTHMA-CTRL, p = 0.003. Catalase – ASTHMA-SEVO vs ASTHMA-CTRL, p = 0.030. GPx – ASTHMA-SEVO vs ASTHMA-CTRL, p = 0.047.

(Fig. 4), which are pro-inflammatory, pro-fibrogenic and pro-angiogenic mediators. These findings are consistent with previous studies in which volatile anaesthetics reduced TNF-α [15–21], exerting anti-inflammatory and organ-protective effects in ARDS models, even after a brief exposure [19]. The immunomodulatory effects of sevoflurane may be attributable to several mechanisms: (1) inhibition of synaptic transmission by activation of type-A gamma-aminobutyric acid ($GABA_A$) receptors in neurons [40], lung airways and alveolar cells [41], thus improving oxygenation and attenuating lung inflammation [15]; (2) reduction in TNF-α-induced endothelial permeability [42]; and (3) inhibition of TNF-α expression and inflammatory cytokine production through intracellular pathways [43]. However, some studies have reported that volatile anaesthetics modulate pro-inflammatory gene expression in the opposite direction [44, 45]. Kotani et al. reported enhanced expression of inflammatory cytokines in alveolar macrophages exposed to volatile anaesthetics [44], whereas Takala et al. found that sevoflurane anaesthesia increased leukotriene production in the BALF of pigs [45]. These contrasting results could be attributed to dissimilar experimental setups or differences in species, as well as to bronchoalveolar lavage itself triggering an inflammatory response.

We also found that sevoflurane increased the Nrf2 protective antioxidant response while dampening the expression of sirt-1, catalase and GPx (Fig. 5). Likewise, very recently, Casanova et al. reported that sevoflurane preconditioning inhibited oxidative stress and pro-inflammatory responses in pigs subjected to an ischaemia-reperfusion lung injury protocol [16].

Some limitations of this study warrant mention: (1) as a specific protocol of allergic asthma was used, results may not be extended to other experimental models; (2) asthmatic models mimic, but are unable to completely replicate, asthma as it occurs in humans; (3) gene expression of inflammatory mediators was measured in lung tissue, not in blood or BALF; (4) mRNA expression was measured using RT-PCR after one hour of anaesthesia, which is enough time to elicit a change in gene expression, but not to change protein levels; and (5) we focused on specific inflammatory and oxidative stress mediators involved in asthma, but further studies investigating non-adrenergic/non-cholinergic mechanisms and nitric oxide metabolism are warranted.

In this study, sevoflurane anaesthesia improved lung mechanics and histology, reduced oxidative stress and down-regulated the inflammatory process in a mouse model of experimental asthma. An understanding of the morphofunctional and immunomodulatory changes induced by commonly used anaesthetics can be beneficial to the management of asthmatic patients. Accordingly, our findings suggest that sevoflurane may be a suitable anaesthetic agent for asthmatics, although further clinical studies are required to clarify this issue.

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Competing interest

No competing interests declared.

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