Measurement of Regional Ventilation in a Model of Airway Hyper-Responsiveness Using Polarized Gas MRI

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Introduction

Asthma is a common pulmonary disability that afflicts approximately one in 20 Americans. Inflammation of the small airways is a characteristic feature of asthma that causes decreases in airway diameter by various mechanisms and results in a corresponding decrease in regional ventilation. Unfortunately, few studies have characterized regional ventilation in asthmatics at baseline and during acute exacerbation. Although few models completely mimic the asthma phenotype, murine models of airway hyper-responsiveness have been developed, and they are important in furthering our understanding of fundamental mechanisms that promote bronchoconstriction and airway inflammation. In this study, we characterize and quantify regional ventilation in a murine model of airway hyper-responsiveness (AHR), and we test the hypothesis that the early stage of asthma can be quantitatively measured by the measurement of regional ventilation.

Methods

A murine model of ovalbumin (OA)-induced sensitization was used in BALB/c mice. In comparison with naive controls, mice sensitized intraperitoneally and challenged intranasally with 1% OA showed markedly increased total IgE and OA-specific IgE and IgG1, peribronchial/perivascular tissue inflammation, airway eosinophilia and secretion of IL-4 and IL-5 into the bronchoalveolar lavage fluid together with significant AHR to acetylcholine. The mice were placed on a surface coil in a supine position. They were anesthetized by intraperitoneal (IP) ketamine/xylazine, tracheostomized and paralyzed with IP pancuronium. Mice were then attached to a prototype mechanical ventilator (Amersham Health, Durham, North Carolina) and ventilated through the tracheal canula with air at 140 BPM and 0.25 ml tidal volume. Imaging was performed in a 4.7T small bore animal imager (Varian Systems) with ^3He during a breath hold of 3 s. The hyperpolarized ^3He was generated via the spin-exchange optical pumping method using a commercial polarizer (Amersham Health, Durham, NC). MRI images of the lung were obtained using a 2D fast gradient-echo pulse sequence with the following imaging parameters: $T_E = 3.4$ ms, $T_R = 6.8$ ms, FOV of 3x3 cm^2 and matrix size of 128x128 pixels. The small-animal ventilator was programmed to carry out imaging ventilation with ^3He breaths delivered as per Deninger [1]. During the experiment, heart rate was monitored with a pulse oximeter, and body temperature was maintained using a steady flow of warm air (37º C) through the bore of the magnet. Image analysis for regional ventilation was performed using a computer program designed at our institution.

Results and Discussion

Ventilation sequence was performed for an asthmatic mouse under study with images acquired after 1, 2, 3, 5, 8, 13 & 20 ^3He breaths of polarized helium respectively. A typical value of 2 minutes for the polarization decay time of the ^3He reservoir was computed from reference images that were taken at the beginning and at the end of the ventilation measurement. Figure 1.A shows the coronal projection image of the lung under study. The positioning of the animal on the RF surface coil caused the right lobe to be closer to the surface of coil and hence generates a higher signal intensity. Figure 1.B shows the regional ventilation map *r* in this mouse. The image displays a relatively non-uniform signal intensity throughout the lung. Also large regions of lower-than-normal ventilation can be seen, surrounded by areas of slightly higher ventilation. Naturally, a fraction of air replacement in the lung parenchyma depends on the diameter of the small airways. Figure 2 shows a typical histogram of the distribution of regional ventilation in the lung of an asthmatic mouse in comparison to that of a normal mouse. These histograms indicate that asthmatic mice are markedly less efficient in ventilating their lungs.

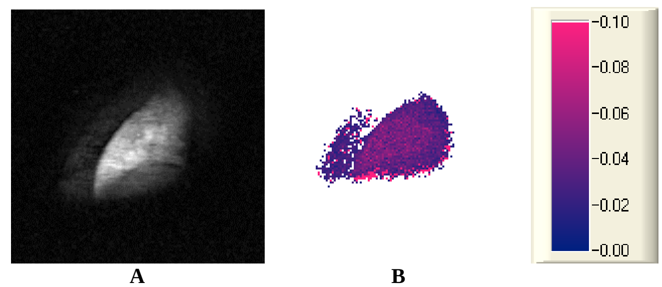

Figure 1. (A) Coronal projection of the asthmatic mouse lung under study (B) Regional ventilation map for an asthmatic mouse; FOV = 3x3 cm^2

Conclusion

The chronic inflammatory nature of asthma combined with a reversible obstruction of the airways may induce profound changes in local airway patency. Such alterations play an important role in the development of reduced lung function as seen in patients with asthma. The underlying mechanisms of the asthmatic airway obstruction are still unclear. Therefore, measurements of regional ventilation may significantly contribute to our understanding of the asthmatic airway physiology and it could be used as an early diagnostic marker to assist in the treatment and prevention of the disease.

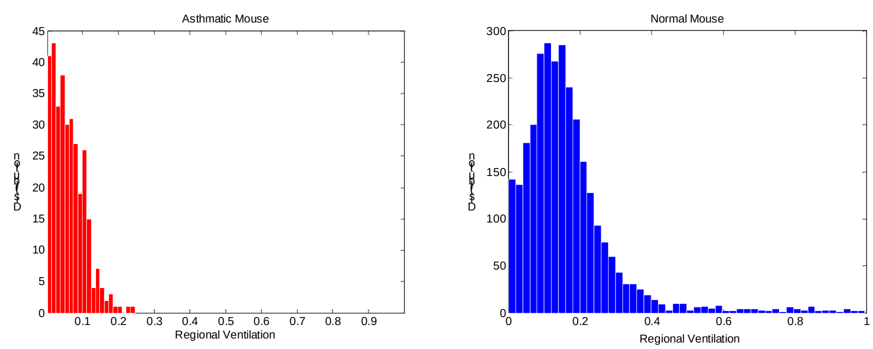

Figure 2. Histogram of the distribution of regional ventilation in an asthmatic mouse (red) in comparison to that of a normal mouse (blue)

Acknowledgement

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1. Deninger AJ, Mansson S, Petersson JS, Pettersson G, Magnusson P, Svensson J, Fridlund B, Hansson G, Erjefeldt I, Wollmer P, Golman K. Quantitative measurement of regional lung ventilation using ^3He MRI. Magn Reson Med 2002;48(2):223-232