Respiratory Impedance in a Mouse Model of Asthma using Hyperpolarized ^{3}He MR Imaging

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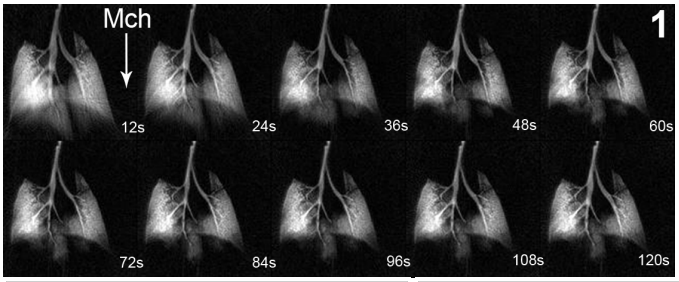
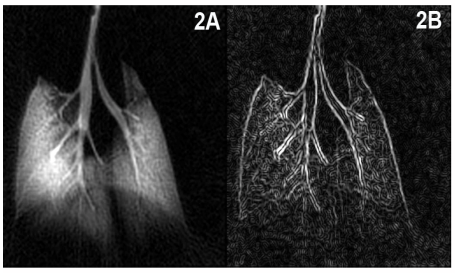
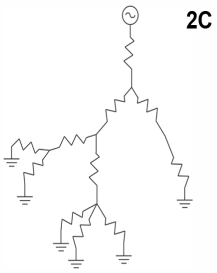
Introduction: Asthma is characterized by inflammation and constriction of the upper airways (airway hyper-responsiveness), when exposed to ambient irritants. There is currently substantial interest in understanding asthma pathophysiology through the use of animal models **[1]**. In these studies, animals are typically treated with the bronchoconstrictor Methacholine (MCh), and airway hyper-responsiveness is then monitored in vivo by respiratory impedance (Flexivent) **[2]**, which monitors increases in airway smooth muscles constriction of the airways. Although Flexivent provides reliable and robust estimates of the Newtonian resistance (R_n), elastance (G) and compliance (H) of the lung, it provides only a global measurement of impedance. We recently demonstrated that it is possible to visualize *in vivo* the time course of MCh induced broncho-constriction in mice using hyperpolarized (HP) ^{3}He gas MR imaging **[3]**. In this work, we observe dynamic changes in airway size using 2D HP ^{3}He MR images obtained at multiple time points after the MCh injection. From the measured diameters of the visible airways, we then calculate the airway contribution to the global impedance. Thus, HP ^{3}He MR imaging provides a novel method to precisely assess regional, time dependent estimates of Newtonian resistance in mouse models of asthma.

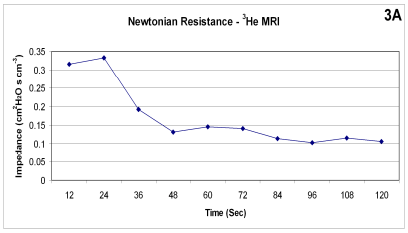
Methods: ^{3}He was polarized using optically pumped Rb vapor in a commercial polarizer (MITI, Durham NC). Male BalbC mice were mechanically ventilated **[4]** with a 0.25 ml tidal volume of HP ^{3}He and O_2 according to a Duke-approved IACUC protocol. Ten 2D, HP ^{3}He radial images were acquired every 12 s at peak inspiration (matrix=128x128, FOV=20mm, BW=32.5 kHz, number of projections=400, TR/TE=5.0/0.272 ms) by applying 20, variable flip angle RF pulses **[5]** per breath. MCh was administered after the first 2D image acquisition. Images were processed in Matlab™ using a Sobel edge detection filter to enhance the airways edges. Five points were picked along each edge of 9-11 airways (3 generations). A linear least squares fitting was performed for the points picked along the trachea and a third order polynomial non-linear least squares fit was performed for the points along the other airways. Distance between the resulting curves was used to obtain the airway diameters. The R_n for air was then calculated using $R_n = \frac{8}{\pi}\frac{\mu L}{r^4}$ [L= length of airway, μ=viscosity of gas mixture, r=width of airway] **[2]** for each airway. The individual R_n values were then used to construct a resistive network **(Fig 2C)** and determine the overall airway impedance at each time point.

Results and Discussion:









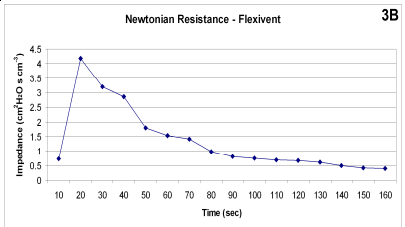


Fig 1: A 2D time course data set – House Dust Mite antigen model of asthma. MCh was injected after the first image was acquired. Airways immediately constrict but return to their original widths by the final two time points. **Fig 2: (A)** 2D image of the mouse lung; **(B)** Sobel Filtered version of (A); **(C)** Corresponding resistor network for the data set. **Fig 3: (A)** a respiratory impedance plot obtained through our method. The estimated airway impedance is ~10% of the global impedance reported by Flexivent (**Fig 3B**)

The impedance values estimated for the upper airways from ^{3}He MRI displays similar, time-dependent trends as impedance obtained using Flexivent (**Fig 3A** and **3B)**. However, the maximum calculated values from ^{3}He MRI account for only ~10% of the peak value reported by Flexivent, suggesting that the global lung impedance is dominated by the smaller airways.

Conclusions: We have shown that respiratory impedance of the upper airways can be assessed by ^{3}He MRI. Although the general trends for image-based impedance and Flexivent are the same, the peak respiratory impedance obtained from the images is only ~10% of the observed Flexivent value. This result suggests that the majority of the MCh response measured by Flexivent occurs in the smaller, more peripheral airways. Although the image-based impedance measurement is still in preliminary stages, and would benefit from higher spatial and temporal resolution, it could provide a method of quantifying regional MCh response in animal models of asthma, and fully translational to MRI imaging of humans. This quantification, in turn, may aid in the development of targeted site-specific drug delivery by distinguishing between central and peripheral airway diseases.

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References: [1] Bates et al, Am J Physiol Lung Cell Mol Physiol, 2009 **[2]** Wagers et al, JAP 2004 **[3]** Thomas et al, NMR in Biomedicine, 2008 **[4]** Chen et al, MRM, 2003 **[5]** Zhao et al, JMR, 1996