Quantitative Analysis of MCh Induced Ventilation Changes in Mouse Lungs

N. N. Mistry[1,2], B. Driehuys[2], and G. A. Johnson[2]

[1]Dept. of Biomedical Engg., Duke University, Durham, NC, United States, [2]Center for In Vivo Microscopy, Duke University Medical Center, Durham, NC, United States

INTRODUCTION: Recently demonstrated high-resolution ^{3}He MRI in mouse models of asthma [1] provides an opportunity to understand airway biology by analyzing regional ventilation changes. Ovalbumin-sensitized mice [2] imaged before and after challenge with methacholine (MCh) showed significant regional airway closure [1]. However, images in mice challenged with lower MCh doses show no obvious airway closure, but may exhibit subtle ventilation changes that require better visualization methods. This work describes a post-processing scheme to demonstrate quantitative regional ventilation changes before and after MCh challenge, with a spatial resolution of 125x125x1000 μm^3. Using this method, regions of hypoventilation and hyperventilation after low-dose MCh challenge become readily apparent.

METHODS: Five BALB/c mice (2 control and 3 ovalbumin-sensitized) were imaged before and after MCh administration using a 3D radial acquisition sequence with 125×125×1000 μm^3 resolution requiring 5.8 min. and consuming 96 ml of hyperpolarized ^{3}He. A detailed description of the imaging sequence is available in [1]. All animal procedures were approved by the Duke Institutional Animal Care and Use Committee. Methacholine was administered at a dose of 80-160 µg/kg in 0.1 ml of saline in a rapid bolus (~1s). Post-MCh imaging acquisition was started as soon as a heart-rate drop was noted, usually just 1-2 seconds after injection. Low ^{3}He consumption permitted some animals to be imaged at baseline and after each of 3-4 escalating MCh doses.
Image Analysis: A critical component of the pre- and post-MCh challenge image analysis is to account for changes in signal intensity resulting from non-physiological factors—primarily loss of polarization. Therefore we converted the raw images into normalized ^{3}He volume images. First, the 3D volume was collapsed into a 2D coronal projection to allow a rectangular region of the trachea to be selected manually. The diameter and the height were measured and used to estimate the cylindrical volume containing fully concentrated ^{3}He. This volume was used to scale the image such that each voxel represented the volume of ^{3}He in µl. Normalizing the ^{3}He volume to the voxel volume created a percent gas distribution map. A difference map between the post- and pre-MCh challenge images was then generated to show the regions of hypoventilation (<0 on difference map) and hyperventilation (>0 on difference map).
3D Radial Advantage: Being able to visualize the trachea is extremely important for this analysis, as the normalization of signal density to ^{3}He volume is performed by calibrating the signal in a cylindrical tracheal region. Gases have high diffusion coefficients especially in the relatively freely diffusing regions of the trachea and the major airways. Diffusion-induced signal loss from the imaging gradients (slice-selective, phase-encoding and frequency-encoding) is significant in gas imaging [3], and is especially profound at high resolution required in small animals. 3D radial encoding has an advantage over conventional 2D slice-selective GRE sequences, as the center of *k*-space is not affected by diffusion as it is in Cartesian sampled schemes.

RESULTS AND DISCUSSION: Fig. 1a and b show images of an ovalbumin-sensitized mouse pre- and post-challenge with 80 µg/kg MCh. While visual inspection of the images reveals no striking differences, the ^{3}He volume distribution difference map clearly demonstrates altered ventilation. Fig 1c shows the difference map of regions of hyperventilation in the major airways and the upper left lobe. Regions of hypoventilation are more diffuse throughout the volume. Global quantitative measures of ventilation show hyperventilation in ~60% and ~40% hypoventilation of the lung. In Fig 2 one can readily visualize a more severe airway constriction elicited in the same mouse at 160 µg/kg dose. However, more quantitative analysis shows hypoventilation in most of the lung, but also shows regions of hyperventilation in the major airways caused possibly by the constriction of the more distal airways. Global quantitative measures of ventilation show ~28% hyperventilation and ~72% hypoventilation.

CONCLUSION: We have demonstrated a straightforward image analysis method to quantify regional changes in ventilation. This technique should allow pulmonary scientists to study asthma models on a global, as well regional scale, in a quantitative manner at a high spatial resolution.

REFERENCES:

1) B. Driehuys, *et al*, Proc. of ISMRM, p. 1347 2006, Seattle, USA.

2) Whitehead *et al*; Am J Physiol Lung Cell Mol Physiol 285:L32-L42, 2003.

3) Gao *et al*; MRM 37: 153-158, 1997.

Work was performed at the Duke Center for In Vivo Microscopy, an NCRR/NCI national resource (P41 RR005959/R24 CA092656), and GEMI Fund 2005.

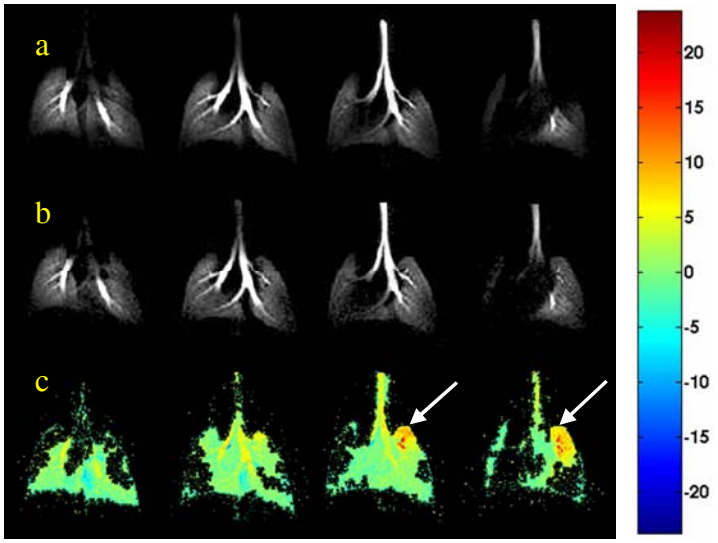

Fig. 1: a) pre-MCh challenge slices from a mouse. b) post challenge following 80 µg/kg c) ^{3}He volume difference map; Note the region of hyperventilation observed in the upper left lobe (arrow) whereas the remaining regions show subtle hypoventilation.

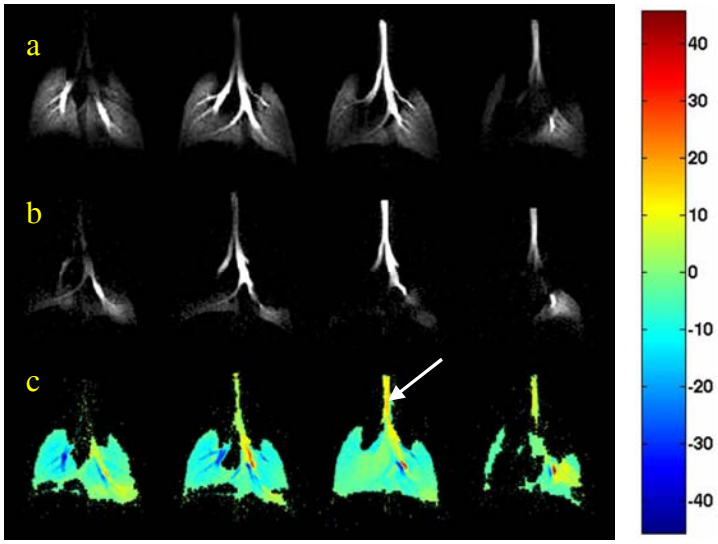

Fig. 2: a) pre-MCh challenge slices from a mouse. b) post- challenge following 160 µg/kg c) ^{3}He volume difference map; Most of the lung shows the hypoventilation readily visible from the raw images in 2nd row. However, increased gas density is observed in the trachea (arrow).