Helium-3 Magnetic Resonance Imaging of Treatment Response in Exercise Induced Bronchoconstriction

S. J. Kruger[1], D. Niles[1], G. Parraga[2], S. Fain[1], B. Dardzinski[3], M. Ruddy[3], A. Harman[3], S. Choy[2], S. Nagle[4], C. Francois[4], D. G. McCormack[2], and N. Jarjour[5]
[1]Medical Physics, University of Wisconsin, Madison, WI, United States, [2]Robarts Imaging Institution, University of Western Ontario, London, ON, Canada, [3]Merck Research Labs, West Point, PA, United States, [4]Radiology, University of Wisconsin, Madison, WI, United States, [5]Medicine and Public Health, University of Wisconsin, Madison, WI, United States

Introduction: Exercise-induced bronchoconstriction (EIB) describes the episodic airway constriction following exercise in asthmatic patients. This dynamic process is characterized by airway narrowing and closure in response to physical exercise that leads to significantly reduced forced expiratory volume in 1 second (FEV1) for up to 30 minutes after cessation of exercise that coincide with the evolution of ventilation defects on He-3 MRI [1]. Prophylactic drug therapies including use of bronchodilators and oral drug therapies prior to exercise have been proposed to reduce the severity of EIB, but their success depends on the duration of their bronchodilator effect. In this work a double blind drug therapy trial was performed using images of ventilation on hyperpolarized He-3 MRI acquired at two different sites. The ventilated volume as a percent of total lung volume and lung region is used as an exploratory end-point comparing to FEV1.

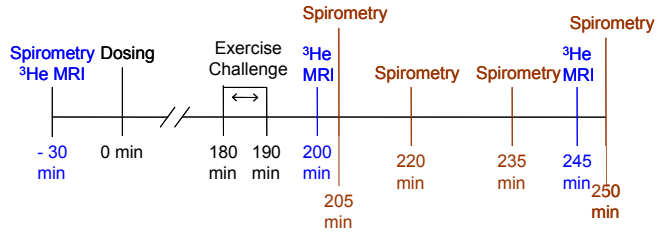

Figure 1: Timeline of study design for each visit.

Methods: A total of 13 subjects with EIB as determined by a 15% drop in FEV1 after exercise on 2 consecutive days were imaged with He-3 MRI at 3 separate visits (occurring within a 2 week time period) and at 3 different time points per visit – baseline, after 10 minutes of exercise challenge on a treadmill at 60% of VO_2 max, and 45 minutes after the end of exercise (**Fig. 1**). On 2 of the 3 visits an oral placebo was given after the baseline scan, which occurred 3 hours before exercise challenge. On one of the 3 visits an oral leukotriene inhibitor (Montelukast, Merck Pharmaceuticals, Whitehouse Station, New Jersey) was given. The subject and investigators were blinded to which visit involved active drug.

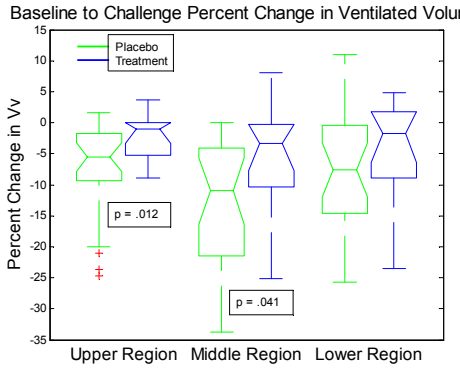

Figure 2: Box-Whisker plot demonstrating the overall improvement in Vv with treatment (green to blue) with preferential response in the apical/middle regions.

Hyperpolarized He-3 MRI was performed on 7 of the subjects at Site 1 on a 3T Signa HDx MRI (GE Healthcare, Milwaukee WI) using a rigid body single channel coil (Rapid Biomedical, Columbus, Ohio) and 6 subjects at Site 2 using a 1.5T Signa HDx MRI (GE Healthcare, Milwaukee WI) using a flexible wrap single channel coil (IGC-Medical Advances, Milwaukee, WI). Hyperpolarized gas was produced using a commercial spin exchange optical polarizer (Helispin – GE Healthcare, London, UK). Polarization ranged from 25-35% and dose was equilibrated to 4.5 mM of polarized nuclei in a 1L volume mixture of He-3 mixed with nitrogen. Safety monitoring included continuous pulse oximetry during MRI as well as supplementary oxygen between scans.

Data analysis consisted of defect segmentation using in-house software written in Matlab (The Mathworks, Natick MA) by imaging scientists at Site 2 who evaluated the Ventilated Volume (Vv) for each scan while blinded to the time point and therapy given. Lungs were then divided into an apical, middle, and basal region by volume. Vv was then compared between baseline and challenge time points for the entire lung and each individual region.

Results: The post challenge FEV1 dropped 19 (12) % after placebo compared to 3 (7) % after treatment ($p < 0.001$). Post challenge Vv dropped 9.3 (5.8) % after placebo compared to 3.6 (6.69) % after treatment ($p=0.016$). At placebo post challenge Vv dropped more in the middle region than in the upper or lower regions ($p = .027$ and .066 respectively; Fig. 2). In the apical and middle regions, treatment scans showed increased response in Vv (4.8 %, $p = .011$ and 6.74%, $p = .041$ respectively; **Fig. 2**) relative to placebo compared to the basal region ($p = .19$). The evolution of defects between baseline and exercise challenge included defects emerging at pre-existing and entirely new regions (**Fig. 3, arrows**).

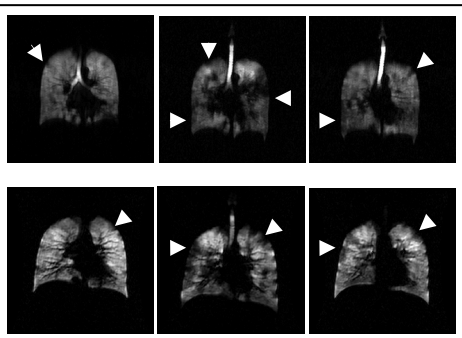

Figure 3: Sample images from subjects on 3T (top) and 1.5T (bottom) GE scanners with baseline (left), post challenge placebo (center), and post challenge treatment (right) time points showing an example of more prominent development of middle region by defects (arrows) and response to treatment.

Conclusion and Discussion: A challenge paradigm for testing regional response of lung ventilation to therapy in asthma revealed both a whole lung and regional response to oral drug therapy in exercise induced bronchoconstriction. The study and protocol were successfully performed at two different sites and field strengths in a blinded fashion. The preferential drop of post challenge Vv in the middle region with placebo suggests a model where bronchoconstriction may be more prevalent in the middle of the lungs in EIB. Decreased response to treatment in the lower relative to the upper and middle regions may reflect more persistent disease in the lower lung lobes. Imaging results support He-3 MRI as a robust tool for characterization of ventilation defects across multiple sites and field strengths.

References:

[1] Samee et al., J Allergy Clin Immunol. 2003 Jun;111(6):1205-11.