Feasibility of hyperpolarized helium-3 MRI-guided bronchoscopic assessment of emergent ventilation defect regions in asthma

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Target Audience: Researchers and clinicians interested in pulmonary MRI and those interested in the use of targeted, longitudinal image-guided bronchoscopic sampling of regions of ventilation defect in pulmonary diseases.

Purpose: Bronchoscopic sampling in obstructive lung diseases such as asthma is of interest in characterizing regional changes in lung parenchyma and inflammatory response associated with ventilation defects.[1] The behavior of many such phenomena associated with ventilation defect progression over time remains unknown. It is possible that newly emergent ventilation defects in severe asthma may be a precursor of permanent local changes in that region of the lung. Thus, targeted sampling of regions of emergent defect may be valuable in elucidating the biological mechanisms underlying the spread and severity of asthma. Previous longitudinal studies have used hyperpolarized ^{3}He MRI (HP He MRI) in asthma subjects to determine changes in overall segmental defect percentage (SDP) as a result of therapy.[2] This work employs a longitudinal analysis of HP He MRI to determine SDP due to emergent ventilation defects with the aim of identifying high yield target sites for bronchoscopic sampling.

Methods: Proton MRI, HP He MRI, and CT were performed on five subjects enrolled in a HIPAA compliant, IRB-approved prospective severe asthma research study. MRI was acquired at baseline and at a follow-up visit approximately six weeks following asthma exacerbation, while CT was acquired at baseline only. All MRI images were co-registered to baseline CT using an automated, mutual information-based process implemented in ANTs.[3] Ventilation defects found on HP He MRI were manually segmented at both time points using a custom tool written in *MATLAB* (The MathWorks, Natick MA). A voxelwise comparison was performed to identify regions that were identified as ventilation defects after the exacerbation but not at baseline, thereby creating an emergent defect mask. In addition, a sub-lobar mask partitioning the lung into bronchus-supplied anatomic regions was generated automatically from CT using *Apollo Software* (VIDA Diagnostics, Coralville, IA). The percentage of each anatomic region comprised of emergent defect ("emergent SDP") was then determined.

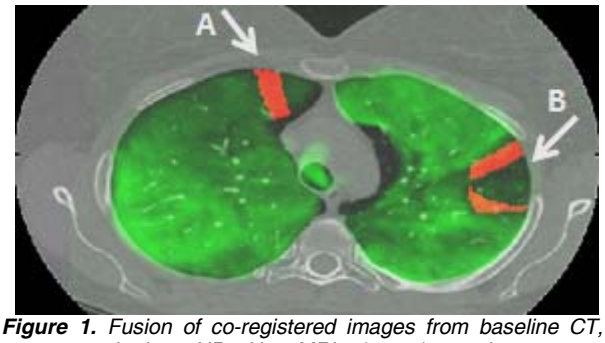

Figure 1. *Fusion of co-registered images from baseline CT, post-exacerbation HP He MRI (green), and emergent ventilation defect mask (red).Ventilation defect A (RUL) is supplied by RB3; defect B (LUL) is supplied by LB2 and LB3. Note that defect B is emergent only on its periphery, indicating enlargement relative to baseline. HP He MRI acquired using gradient echo (GRE), 28 slices at 10mm thickness. Acquired in-plane axial resolution was 3.12mm x 3.12mm for HP He MRI (reconstructed at 1.56mm x 1.56mm).*

Results: Data from all five subjects are shown in **Table 1.** Mean emergent SDP across all segments ranged from 0.09% (subject 1) to 30.11% (subject 2). Levels of emergent SDP across all five subjects varied widely, both between subjects and across segments. **Figure 1** depicts the image fusion of the co-registered CT and HP He MRI, with the emergent defect mask color-coded as red, from subject 5. Preliminary results show the highest emergent SDP in the left lower lobe in four of the five subjects. Results for segments in the right lower lobe (RB6-10) are omitted in the present analysis: these airways were inconsistently segmented and require a more supervised identification process, which is currently under development.

Emergent SDP by Bronchopulmonary Segment					
Subject	#1	#2	#3	#4	#5
LB1	0.04%	0.37%	0.00%	0.00%	0.64%
LB2	0.00%	5.98%	0.00%	0.55%	5.56%
LB3	0.23%	2.42%	8.44%	0.00%	7.27%
LB4	0.00%	N/A	N/A	0.00%	0.00%
LB5	0.00%	N/A	N/A	0.00%	0.72%
LB4+5	N/A	36.67%	12.60%	N/A	N/A
LB6	0.51%	38.30%	0.45%	11.92%	4.85%
LB8	0.00%	85.31%	4.92%	2.92%	0.27%
LB9	0.00%	77.50%	6.58%	23.09%	0.96%
LB10	0.00%	80.08%	9.24%	16.43%	1.18%
RB1	0.50%	6.28%	0.00%	0.01%	0.00%
RB2	0.00%	0.00%	0.00%	0.14%	0.00%
RB3	0.00%	7.55%	1.61%	0.00%	1.50%
RB4	0.00%	29.52%	0.00%	0.76%	0.00%
RB5	0.00%	21.42%	7.98%	0.02%	0.75%

Table 1. *Emergent segmental defect percentage (SDP) by bronchopulmonary segment in five asthma subjects. Note high degree of heterogeneity between segments and asthma subjects as has been well described previously in Ref. 4.*

Discussion: The variation of emergent SDP across subjects and segments reflects the well-known heterogeneity of the underlying asthma severity across subjects as well as spatial defect distribution within a subject.[4] Segments with high levels of emergent SDP may be used as targets for bronchoscopic sampling of emergent ventilation defect regions. Furthermore, the method presented here can be used to measure other types of longitudinally-based SDP simply by changing the method of defect mask comparison. For example, SDP due to persistent ventilation defects may be determined by identifying HP He MRI voxels that are found to have defects at both baseline and follow-up.

Conclusion: Longitudinally acquired HP He and proton MRI in conjunction with baseline CT provide a means of informing bronchoscopic sampling of regions of emergent ventilation defect in asthma, with potential target segments evaluated by their emergent SDP. This method can be easily modified to identify target sites exhibiting persistent or reversed defects instead of emergent defects, and may also be used as a means of identifying defect-free control sites. Further work is needed to allow for a fully automated identification of all bronchopulmonary segments. Image-guided bronchoscopic sampling of emergent defects may prove valuable in characterizing the physiological and cellular response associated with the development of ventilation defects in asthma during disease progression and in response to therapy.

References: [1] Fain et al. *Academic Radiology* 2008. [2] Thomen et al. *Radiology* 2014. [3] Avants et al. Advanced Normalization Tools (ANTs). http://stnava.github.io/ANTs/ [4] Samee et al. *J Allergy Clin Immunol.* 2003.