Ventilation Defects in Asthma on Hyperpolarized Gas MRI Are Associated with Airway Mucus Plugs on CT

D. Mummy[1], E. Dunican[2], T. Lampkins[3], W. Zha[4], M. Evans[5], M. Schiebler[6], S. Nagle[6], R. Sorkness[7], N. Jarjour[8], J. Fahy[9], S.B. Fain[1,4,6]

[1]Biomedical Engineering, University of Wisconsin – Madison, [2]Medicine, University College Dublin, [3]Biology, [4]Medical Physics, [5]Biostatistics and Medical Informatics, [6]Radiology, [7]Pharmacy, University of Wisconsin – Madison, [9]Medicine, University of California – San Francisco

Introduction

MUCUS PLUGS IN ASTHMA have been evaluated using CT and associated with eosinophilia and airflow obstruction [1]. Ventilation defects on hyperpolarized helium-3 (HP ^{3}He) MRI in asthma have been associated with locally increased neutrophils [2], air trapping [2] and increased airway wall thickness [3] on CT, and a history of severe exacerbation [4].

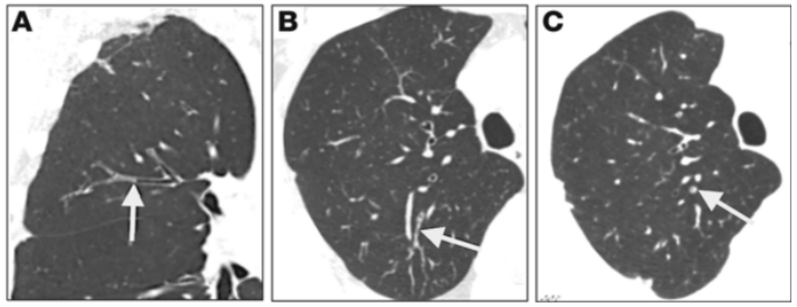

***Figure 1**. Examples of mucus plugs (arrows) visualized on CT (Figure from Dunican et al. [1]).*

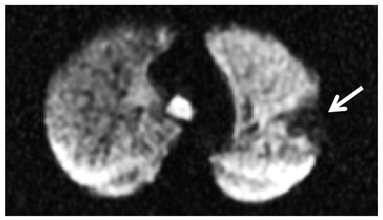

***Figure 2**. Example of ventilation defect (arrow) visualized on HP ^{3}He MRI.*

Despite the implication of mucus plugging in airflow obstruction, to our knowledge no investigation has yet been conducted to confirm correlations of mucus plugging at the segmental level with ventilation heterogeneity observed on HP ^{3}He MRI.

Our previous work has examined correlations between lobar mucus plug scores on CT and lobar ventilation defects on HP ^{3}He MRI [5]. This work extends this approach to encompass comparisons at the whole lung, lobar, and segmental levels.

Materials and Methods

Our study population was drawn from the National Heart, Lung, and Blood Institute (NHLBI) Severe Asthma Research Program III **(SARPIII)** population.

All subjects underwent spirometry to obtain forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. Percent predicted (PP) values were calculated using reference values from the Global Lung Function Initiative standard [6]. MRI and CT were acquired after bronchodilation using inhalation of albuterol. CT was acquired at TLC and MRI was acquired at FRC plus the volume of a gas bag (approximately one liter) normalized to the subject's TLC.

Study population characteristics

	Mild/Moderate	Severe	All
N	13	20	33
Sex	7F (53.8%)	12 F (60.0%)	19F (57.6%)
Age	42.7 ± 16.9 yrs	57.0 ± 10.1 yrs	51.4 ± 14.8 yrs
BMI	27.0 ± 5.6	31.8 ± 5.3	29.9 ± 5.8 yrs
FEV1 PP	85.5 [78.3 – 94.2]	66.9 [51.9 – 90.9]	78.3 [65.1 – 94.2]
FEV1/FVC PP	90.0 [84.6 – 95.9]	87.3 [77.8 – 96.6]	89.9 [81.3 – 96.4]
FVC PP	100.6 [88.7 – 104.5]	79.0 [67.9 – 92.8]	84.9 [76.6 – 102.5]
FeNO (ppb)	24.0 [16.0 – 33.0]	14.0 [10.2 – 22.8]	19 [11.5 – 31.0]
Mucus Score	0.0 [0.0 – 0.5]	0.3 [0.0 – 8.1]	0.0 [0.0 – 2.0]
VDP (%)	2.5 [1.1 – 4.6]	5.6 [3.4 – 12.3]	4.1 [2.5 – 10.4]

***Table 1**. Summary of population characteristics. Results given as mean ± standard deviation or median [1st quartile – 3rd quartile]. Spirometry is pre-bronchodilator. PP – percent predicted; ppb – parts per billion.*

Mucus plug scoring. Mucus plug scoring was performed on CT using the bronchopulmonary segment-based scoring system developed by Dunican et al. [1]. Mucus plugs were scored by lobe and aggregated into whole lung scores. In a subset of subjects, a dichotomous mucus plug score was generated by bronchopulmonary segment.

MRI-CT Registration. CT acquired was processed through VIDA Diagnostics software (VIDA Diagnostics, Coralville, IA) to generate lobar and segmental anatomical masks. The HP ^{3}He image boundary was segmented with reference to proton MRI using in-house software written in MATLAB (The MathWorks, Natick, MA). CT was registered to HP ^{3}He MRI using the ANTs software package (http://stnava.github.io/ANTs/).

Materials and Methods (cont.)

Ventilation Defect Quantification. Regions of **ventilation defect** were classified on HP ^{3}He MRI using a semi-automated algorithm developed by Zha et al. [6] to measure whole lung ventilation defect percent (VDP). Defect volume was located anatomically by lobe using the registered CT lobar and segmental masks to measure VDP by lobe and by sublobar segment.

Results

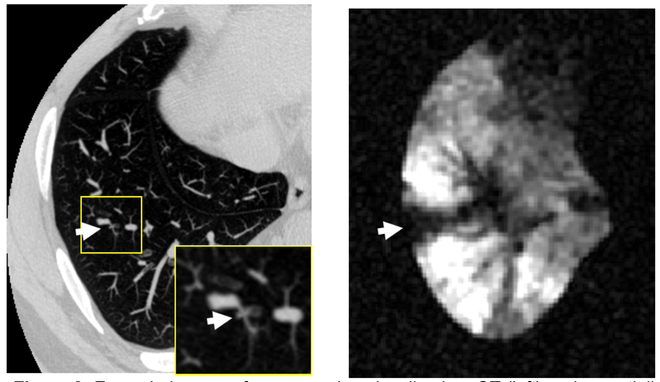

***Figure 3**. Example images of a mucus plug visualized on CT (left) and a spatially overlapping ventilation defect on HP ^{3}He MRI (right). Inset on left shows close-up of mucus plug. CT image is a maximum intensity projection through five axial slices to approximately match the slice thickness of the HP ^{3}He MRI .*

Whole Lung Comparison

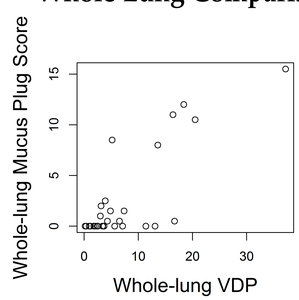

***Figure 4**. Whole-lung mucus score vs. whole-lung VDP. Spearman's correlation is 0.65 (p < 0.0001).*

Lobar Comparisons

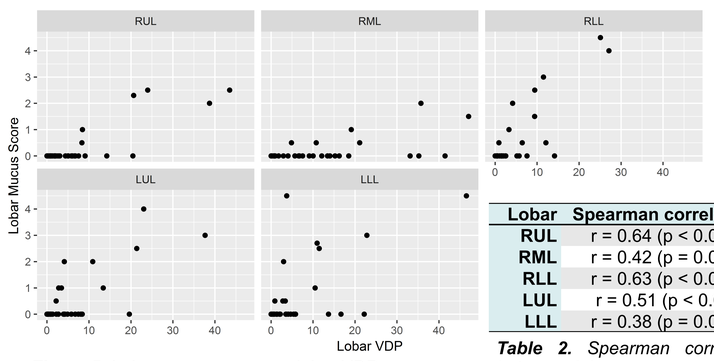

***Figure 5.** Lobar mucus score vs. lobar VDP.*

Lobar	Spearman correlation:
RUL	r = 0.64 (p < 0.001)
RML	r = 0.42 (p = 0.019)
RLL	r = 0.63 (p < 0.001)
LUL	r = 0.51 (p < 0.01)
LLL	r = 0.38 (p = 0.035)

***Table 2.** Spearman correlation between lobar mucus score and lobar VDP.*

Segmental Comparison

In a subset of eight subjects, a dichotomous measure of mucus plugging was assessed by bronchopulmonary segment, resulting in measurements for 8 ×19 = 152 total segments.

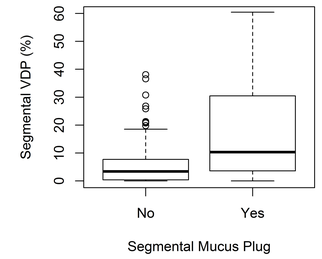

***Figure 6.** Segmental VDP vs. dichotomous measure of mucus plugging.*

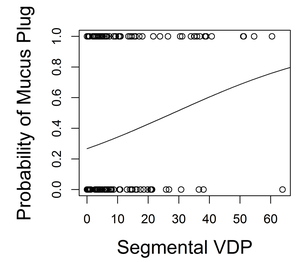

***Figure 7.** Logistic regression model of segmental mucus plugging is shown superposed on sample data from the subpopulation.*

In a **mixed effects logistic regression model** with subject as a random effect, segmental VDP was significantly associated with the presence of a mucus plug (p = 0.038). The model predicted a 26.7% chance of an associated mucus plug at VDP = 0% and a 75.8% chance of a mucus plug at VDP = 60%.

Mucus plugs on CT were correlated with ventilation defects on MRI at the whole lung, lobar, and segmental level.

Discussion and Conclusion

Mucus plugging is common in asthma and can be visualized on CT. Hyperpolarized helium-3 (HP ^{3}He) MRI provides a means of **directly visualizing ventilation heterogeneity** in obstructive lung disease.

In this population of 33 mild/moderate and severe asthmatics, **segmental mucus plugging on CT** is associated with **ventilation defects on HP ^{3}He MRI**, confirming previous observations in the whole lung and by lobe.

This multimodal approach enables assessment of the **functional significance of observed mucus plugs** and confirms that mucus plugs are associated with **regions of airflow limitation** in asthma.

Further work will explore the significance of mucus plugs on CT in the context of regional **bronchodilator reversibility** and **longitudinal changes in ventilation heterogeneity** observed on HP ^{3}He MRI.

References

[1] E.M. Dunican et al., *The Journal of Clinical Investigation*, 2018. **128**(3).

[2] S.B. Fain et al., *Academic Radiology, 2008*. **15**(6): p. 753-762

[3] S. Svenningsen et al., *Thorax*, 2013: p. thoraxjnl-2013-203711.

[4] D.G. Mummy et al., *Journal of Allergy and Clinical Immunology*, 2018. **141**(3): p. 1140-1141. e4.

[5] E.M. Dunican et al., *American Thoracic Society International Conference*, 2016.

[6] Zha, W., et al., *Regional Heterogeneity of Lobar Ventilation in Asthma Using Hyperpolarized Helium-3 MRI.* Academic radiology, 2017.

Electronic copy here:

Acknowledgements

- The Severe Asthma Research Program (SARP)
- NIH/NHLBI R01 HL080412
- NIH/NHLBI U10 HL109168
- Wisconsin Alumni Research Foundation (WARF) Technology Transfer Research Assistantship