Local fSAD Features Derived from CT Topological Parametric Response Maps are Associated with Ventilation Defects on Hyperpolarized Gas MRI in Asthma

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Introduction

Obstruction of the small airways (< 2mm in diameter) is a clinically relevant aspect of asthma that may not always be reflected by conventional clinical tests such as spirometry [1]. The presence of disease in peripheral regions of the lung is also of concern in designing and assessing suitability for inhaled therapies that may not reach affected regions due to particle size [1]. Imaging-based techniques may provide a means of characterizing regional small airways disease in asthma.

Localized measures of small airways disease features derived from CT topological parametric response maps (tPRM) have been associated with disease progression in COPD [2] and are thought to reflect obstruction due to small airways disease. Ventilation defects on hyperpolarized helium-3 magnetic resonance imaging (HP ^{3}He MRI) in asthma have been associated with air trapping [3], mucus plugging [4], and severe outcomes in asthma [5]. While PRM response maps have been associated with ventilation defects in HP ^{3}He MRI in COPD [6], these measures have not yet been compared in asthma.

The purpose of this study is to characterize tPRM-derived measurements of functional small airways disease (fSAD) in asthma and assess associations with VDP from HP ^{3}He MRI.

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 both TLC and FRC, and MRI was acquired at FRC plus the volume of a gas bag (approximately one liter) normalized to the subject's TLC.

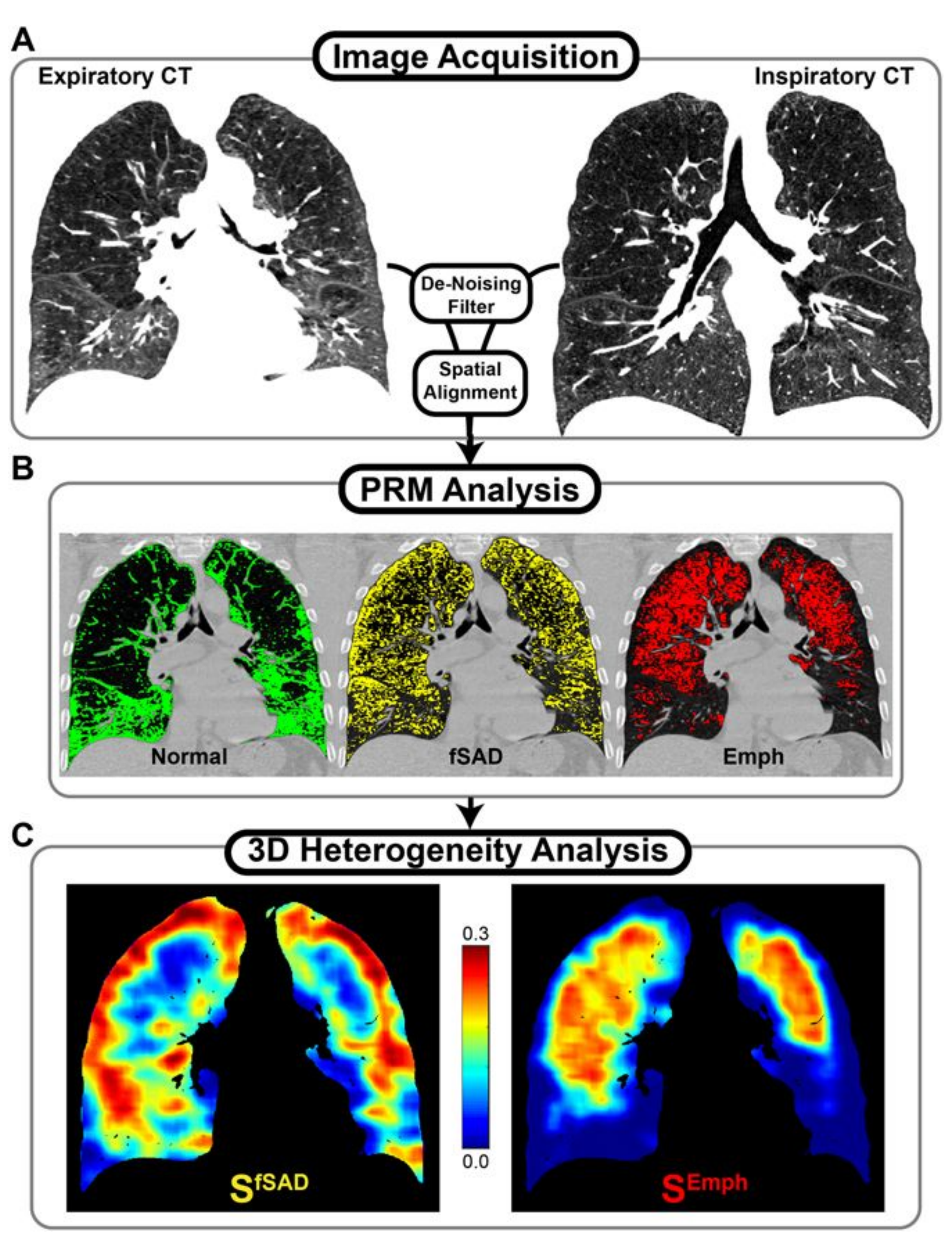

Figure 1. Workflow as presented in Hoff et al. [1] for deriving topological PRM. CT images at FRC and TLC (A) are processed to generate standard PRM (B) from which 3D topological maps (C) are derived.

Parametric response maps were derived from TLC and FRC using the method established by Galbán et al. [7] and further characterized using localized topological measures of fSAD volume and surface area [2]. This process yields conventional PRM fSAD as well as tPRM measures of fSAD volume and surface area.

Here, we also introduce the fSAD Volume to Surface Area Ratio (V/S) metric to provide a means of quantitatively evaluating the overall characteristic patterns of fSAD.

Ventilation Defect Quantification. Regions of **ventilation defect** were classified on HP ^{3}He MRI using a semi-automated algorithm developed by Zha et al. [8] to measure whole lung ventilation defect percent (VDP).

Results

	Healthy	Mild/Moderate	Severe
N	6	14	21
Sex	5F (83.3%)	9F (64.3%)	12F (57.1%)
Age (yrs)	35.5 ± 14.7	44.2 ± 15.1	55.3 ± 12.0%
BMI	25.1 ± 3.1	27.2 ± 5.2	31.5 ± 5.2
FEV1 PP	107.22 ± 15.5	95.2 ± 17.0	80.8 ± 19.6
FEV1/FVC PP	101.1 ± 4.1	93.9 ± 10.1	90.5 ± 10.7
FVC PP	105.5 ± 16.2	101.8 ± 15.6	88.6 ± 14.3
%PRM fSAD	0.98 ± 2.2	1.7 ± 2.0	6.6 ± 12.8
fSAD Surface Area (%/mm)	2.0 ± 4.4	3.4 ± 3.4	7.0 ± 9.0
fSAD Volume (%)	0.9 ± 2.0	1.7 ± 1.8	5.8 ± 11.3
VDP (%)	0.3 ± 0.4	4.4 ± 6.2	9.3 ± 9.0

***Table 1.** Summary of population characteristics. Results given as mean ± standard deviation. Spirometry and VDP are post-bronchodilator. PP – percent predicted*

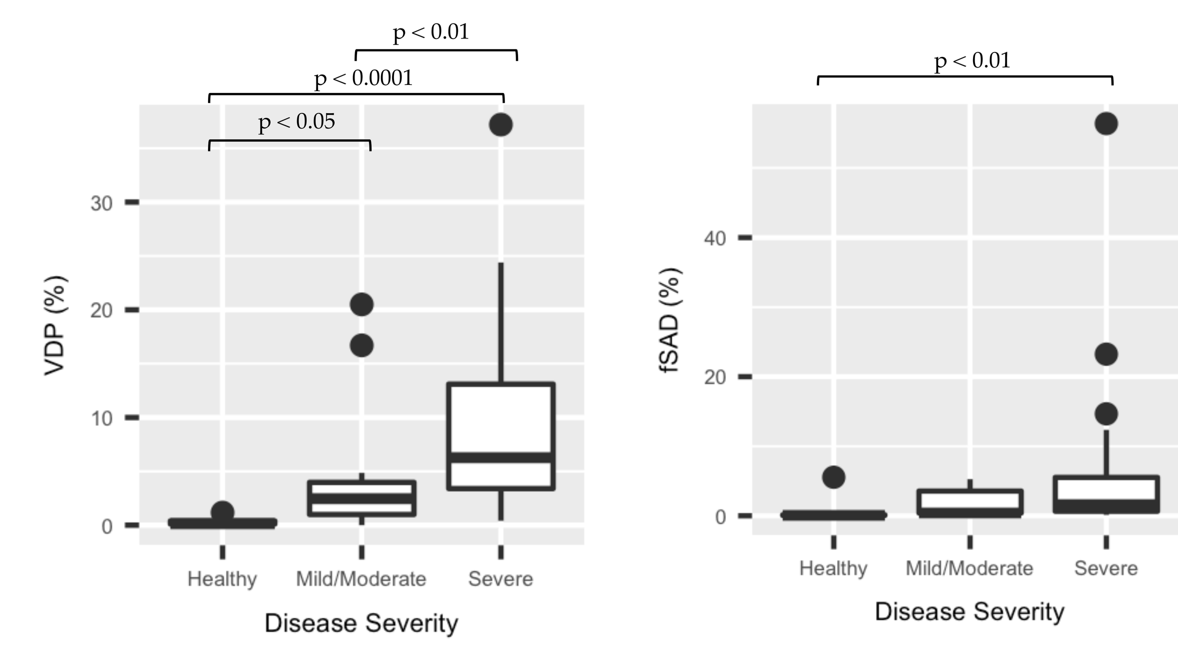

***Figure 2.** VDP (left) and whole-lung fSAD (right) stratified by asthma disease severity. All groups exhibited significantly different levels of VDP, and severe asthmatics exhibited increased fSAD vs. healthy subjects.*

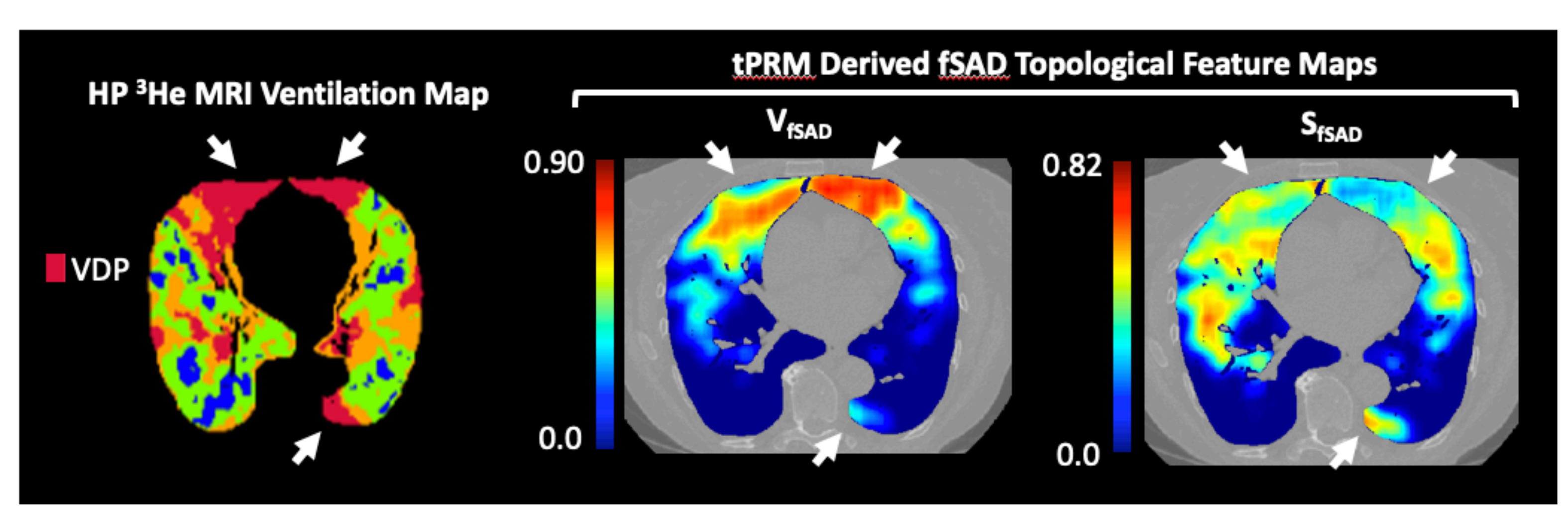

***Figure 3.** A subject with severe asthma with HP ^{3}He MRI ventilation map at left and tPRM-derived maps of V_{fSAD} and S_{fSAD} at middle and right respectively. Subject had VDP of 24.4%, mean V_{fSAD} of 10.9%, and mean S_{fSAD} of 14.9%/mm.*

VDP vs. (t)PRM fSAD

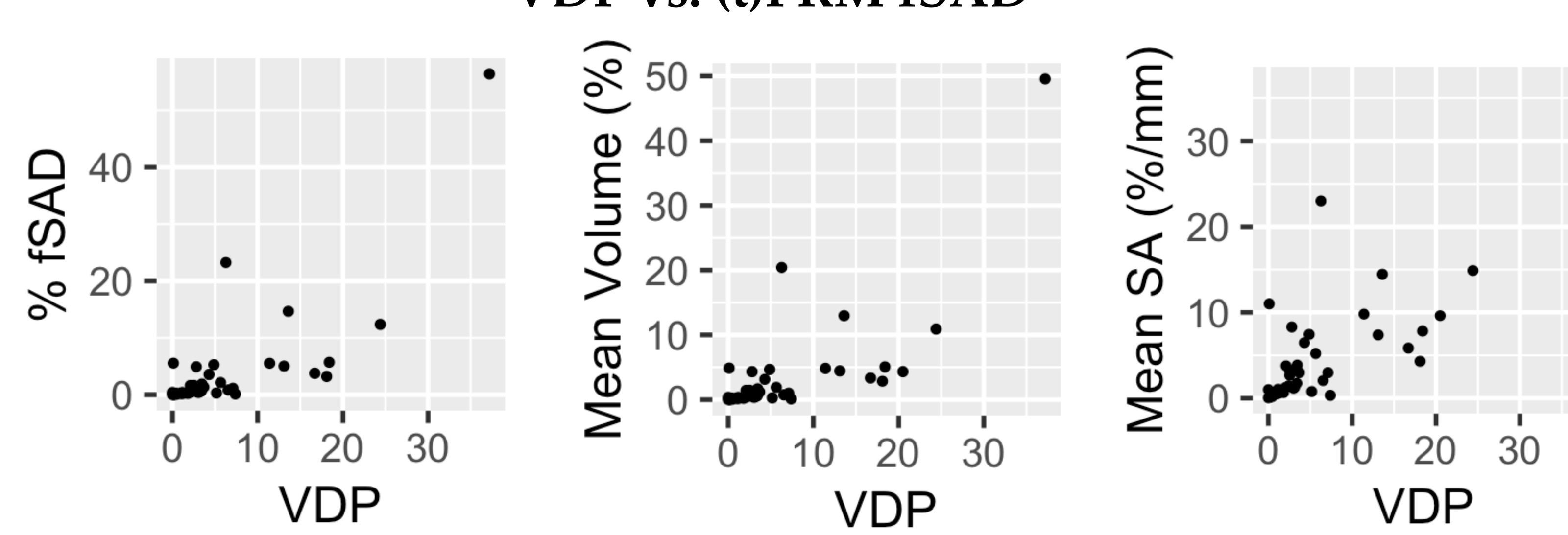

***Figure 4.** Whole-lung fSAD (%), Mean Surface Area (%/mm), and Mean Volume (%) vs. whole-lung VDP. Spearman's correlations are 0.73 (p < 0.00001), 0.74 (p < 0.00001), and 0.74 (p < 0.00001) respectively.*

fSAD Volume to Surface Area Ratio (V/S)

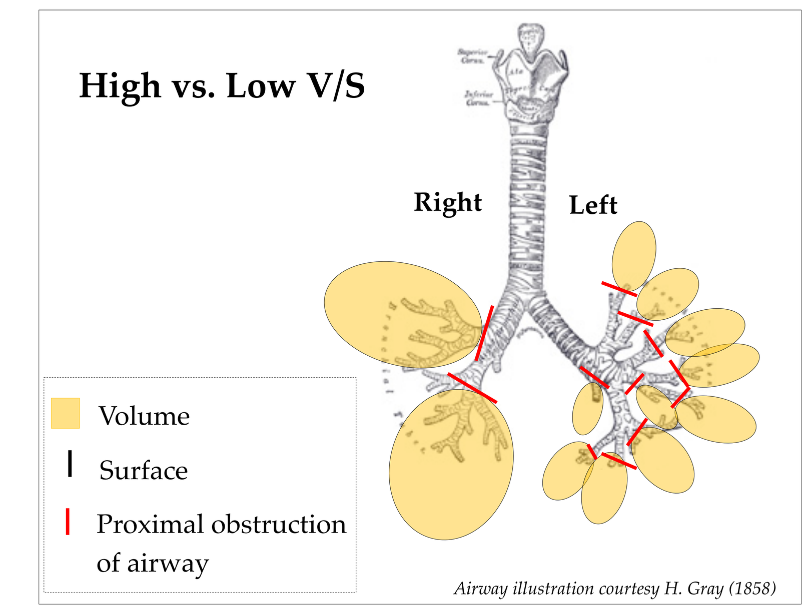

***Figure 5.** Illustration of high volume to surface area (V/S) of obstructed regions in right lung vs. low V/S in left lung, despite a relatively similar degree of overall obstruction volume in both lungs.*

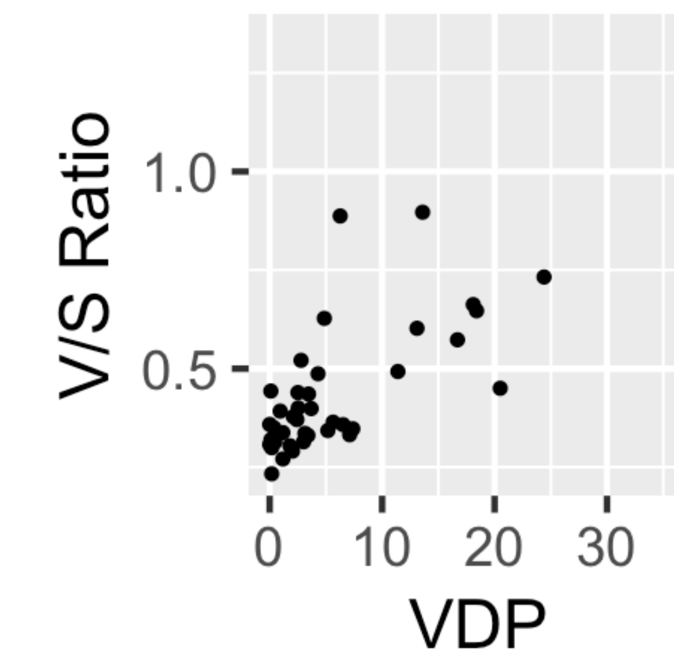

***Figure 6.** V/S fSAD ratio vs. VDP. The V/S ratio is positively correlated with VDP (r = 0.66, p < 0.0001).*

Measures of fSAD volume and surface area were positively correlated with VDP on HP ^{3}He MRI in asthma.

Moreover, the ratio of fSAD volume to surface area was positively correlated with VDP, suggesting that increased ventilation defect volume tended to be associated with contiguous (rather than diffuse) patterns of small airways disease.

Discussion and Conclusion

Advancing understanding of the role of small airways disease in functional ventilation deficits in particular with developing disease phenotypes and assessing suitability for targeted therapies.

These results suggest that obstruction of the small airways plays a significant role in the ventilation defects observed on HP ^{3}He MRI, and that increased ventilation defects are associated with the presence of larger, contiguous regions of small airways disease.

These preliminary results are consistent with the hypothesis that increased levels of ventilation defect are associated with tendency towards an increase in proximal, rather than distal, airway obstruction.

Ongoing work will assess correlations between on fSAD and fSAD V/S ration on a regional (e.g. lobar and segmental) basis to better understand the relationship between small airways disease and the evolution of functional ventilation deficits observed on HP gas MRI.

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