Ventilation Defects in Hyperpolarized Helium-3 MRI are Predictive of 2-Year Exacerbation Frequency in Asthma

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Introduction

Ventilation defects on hyperpolarized helium-3 (HP ^{3}He) MRI in asthma have been associated with locally increased neutrophils [1], with air trapping [1], mucus plugging [2], and increased airway wall thickness [3] on CT, and with a history of severe exacerbation [4].

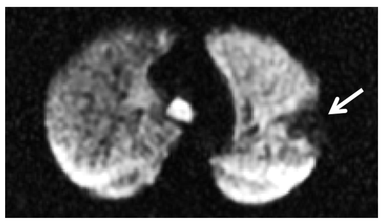


***Figure 1**. Example of ventilation defect (arrow) visualized on HP ^{3}He MRI.*

The purpose of our study was to evaluate the ventilation defect percent (VDP) on HP ^{3}He MRI as a prospective predictor of asthma **exacerbation frequency in a two-year period following baseline imaging** in a mixed population of moderate and severe asthmatics. Establishing VDP as a biomarker of propensity for asthma exacerbation is of interest in assessing disease severity, evaluating drug efficacy in clinical trials, selecting patients for targeted therapies, and timely evaluation of treatment response.

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

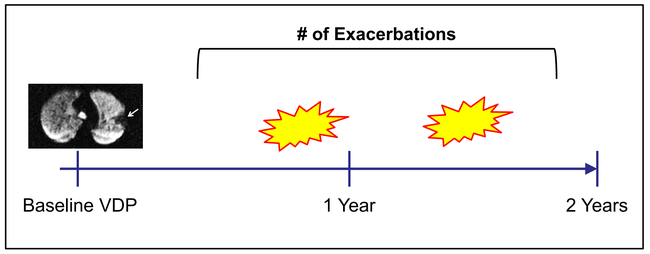


***Figure 2.** Study design. VDP is calculated from HP ^{3}He MRI acquired at baseline, and subjects were tracked for two years to determine number of exacerbations.*

Ventilation Defect Quantification. Regions of **ventilation defect** were classified on HP ^{3}He MRI using a semi-automated algorithm developed by Zha et al. [5] to measure whole lung ventilation defect percent (VDP).

Statistical Methods:

- Correlations between VDP and clinical measures of lung function (spirometry and FeNO) and serum measurements of cytokines and of blood and sputum eosinophils were assessed using the Spearman correlation.
- Poisson regression tree model to assess associations between VDP and exacerbation frequency and **estimate an optimal VDP threshold.**
- Negative binomial regression models of exacerbation counts to assess VDP in the context of other demographic and conventional clinical metrics gathered at baseline. These include estimates from univariate models for each predictor, a multivariate model with all predictors included, and a multivariate model with predictors chosen using stepwise model selection based on the Akaike Information Criterion (AIC).

Results

	Mild/Moderate	Severe	All	Difference
N	28	38	66	n/a
Sex	14F (50.0%)	25 F (65.8%)	39 F (59.1%)	n/a
Age (yrs)	31.1 ± 17.4	42.8 ± 21.2	37.9 ± 20.4	p = 0.028
BMI	24.5 [21.4 – 27.7]	28.5 [25.2 – 33.3]	27.3 [23.3 – 30.8]	p < 0.01
ACQ	0.6 [0.4 – 0.9]	1.4 [0.7 – 2.1]	0.93 [0.6 – 1.7]	p < 0.001
ACT	21.5 [20.8 – 23.0]	18.0 [14.3 – 20.8]	20.0 [18.0 – 22.0]	p < 0.0001
FEV1 %P	89.6 [81.2 – 101.9]	75.6 [55.8 – 95.0]	82.7 [66.9 – 96.3]	p < 0.01
FEV1/FVC %P	90.7 [85.9 – 94.0]	86.5 [78.6 – 93.7]	89.9 [81.5 – 93.7]	-
FVC %P	99.5 [88.6 – 104.8]	82.7 [71.0 – 97.8]	94.2 [78.8 – 103.5]	p < 0.01
FeNO	26.5 [16.0 – 41.5]	14.0 [9.5 – 25.5]	20.0 [11.5 – 34.0]	p = 0.041
Blood eosinophils (counts/µL)	198.5 [107.5 – 280.0]	309.5 [147.2 – 508.5]	229.5 [137.0 – 466.5]	-
Sputum eosinophils (%)	0.8 [0.0 – 1.1]	0.6 [0.1 – 3.2]	0.6 [0.0 – 2.0]	-
GERD (Y/N)	7 (25.0%)	22 (57.9%)	29 (43.9%)	p < 0.01
Sinusitis (Y/N)	6 (21.4%)	15 (39.5%)	21 (31.8%)	-
Max. Reversibility following BD (%)	10.4 [5.8 – 12.9]	11.8 [4.7 – 21.8]	10.5 [5.5 – 16.1]	-
VDP (%)	2.0 [0.6 – 3.2]	5.9 [3.4 – 14.4]	3.64 [1.2 – 7.4]	p < 0.0001
Exacerbations in 2 years post-baseline	0.0 [0.0 – 1.0]	1.0 [0.0 – 2.8]	1.0 [0.0 – 2.0]	p < 0.01

***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. ACT – asthma control test; ACQ – asthma control questionnaire; GERD – gastroesophageal reflux disease; FeNO – fraction inhaled nitric oxide.*

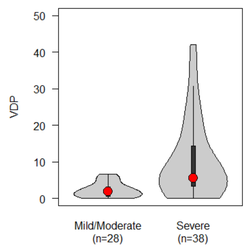
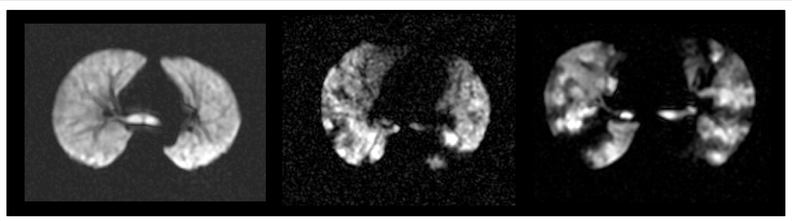


***Figure 3.** VDP in mild/moderate vs. severe subjects. Median [1Q – 3Q] VDP is 5.6% [2.6% – 13.6%] in severe subjects vs. 1.9% [0.55% – 3.0%] in mild/moderate (p < 0.0001).*

Clinical Measure	Correlation with VDP
FEV1 %P	r = -0.47, p < 0.0001
Sputum Eos	r = 0.31, p = 0.028
ACQ	r = 0.37 (p = 0.0019)

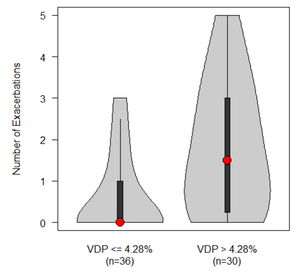
***Table 2.** Spearman's correlation between VDP and clinical measures of lung function and inflammatory response. VDP was similarly correlated with FEV1/FVC %P and FVC %P as with FEV1 %P. VDP was not correlated with FeNO, the Asthma Control Test (ACT), GERD, or sinusitis.*



	Subject A	Subject B	Subject C
Severity:	Mild/Moderate	Severe	Severe
Age:	38	56	61
Sex:	F	F	F
BMI:	32	43	26
FEV1 PP:	88%	47%	58%
FEV1/FVC PP:	92%	79%	76%
VDP:	0.3%	6.3%	25.8%
# Exacerbations:	0	2	4

***Figure 4.** Example images from subjects with a range of disease severity and exacerbations in the two years following baseline (left to right). Note that subject B and subject C have comparable spirometry but dramatically different VDP.*

Statistical Modeling Results



The Poisson regression tree-based optimal threshold for predicting exacerbation frequency was VDP = 4.28%. Subjects above the threshold had a median of 1.5 exacerbations, vs. zero exacerbations for subjects below the threshold (p = 0.0007), as shown in the violin plot in **Figure 5** (at left).

In each of the three negative binomial regression models, a VDP greater than the threshold value was associated with over a two-fold increase in exacerbation rate (**Table 5**, below).

		Univariate			Multivariate			Multivariate (Stepwise)		
	(Units)	**ERR**	**lower**	**upper**	**ERR**	**lower**	**upper**	**ERR**	**lower**	**upper**
VDP	Above 4.28% vs Below	2.82	1.59	5.12	2.29	1.10	4.85	2.6	1.39	4.96
Age	per 10 years	1.20	1.03	1.39	1.05	0.87	1.27			
Female Sex	Female vs Male	1.36	0.71	2.60	1.47	0.79	2.81			
BMI	per 10 points	1.13	0.70	1.86	0.62	0.36	1.07	0.67	0.42	1.04
ACT	per 1 point	0.98	0.90	1.05	1.04	0.94	1.16			
ACQ	per 1 point	1.41	0.98	2.06	1.23	0.67	2.27			
GERD	Yes vs No	1.89	1.04	3.49	1.42	0.78	2.60	1.65	0.96	2.84
Sinusitis	Yes vs No	1.52	0.80	2.91	1.61	0.89	2.91	1.53	0.88	2.65
Sputum Eos	per 2-fold	1.18	0.89	1.56	1.13	0.87	1.47			
FeNO	per 2-fold	0.97	0.72	1.31	0.98	0.71	1.36			
FVC	per 10%	0.78	0.66	0.92	0.86	0.67	1.09	0.83	0.7	0.98
Max Reversibility	per 10%	1.11	0.90	1.39	1.04	0.79	1.36			

***Table 5.** Exacerbation Rate Ratios (ERRs) with 95% CIs from negative binomial regression models of exacerbation counts for each participant (n = 66). ACT – asthma control test; ACQ – asthma control questionnaire; GERD – gastroesophageal reflux disease; FeNO – fraction inhaled nitric oxide; FVC – forced vital capacity.*

Ventilation defect percent (VDP) was significantly associated with asthma exacerbation rate in the two years following baseline.

However, in models where the number of exacerbations in past year recorded at baseline and history of severe exacerbation at baseline were included in the list of predictors, these were selected and VDP was not selected by the stepwise procedure.

Discussion and Conclusion

We found that VDP is predictive of increased exacerbation frequency in the two years following imaging, corroborating previously published results showing that VDP was associated with a history of severe exacerbation.

Although exacerbation history is still the best predictor of future exacerbation, VDP may provide a useful means of quantitively assessing change in exacerbation propensity in the absence of medical history or when disease instability worsens rapidly. In addition, monitoring VDP could provide a secondary endpoint in clinical trials for assessing therapy response in a timely manner, i.e. without the need for monitoring for exacerbations over an extended time window. Thus, a VDP-based approach could provide a valuable means of assessing and monitoring response to therapy as part of drug development, clinical trials, or clinical decision-making.

These results suggest that measurements of VDP may enable a quantitative approach to monitoring treatment response both in individual subjects and in clinical trials, and for selecting patients in need of intensive therapy intervention.

References

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