

Letter to the Editor

Ventilation defect percent in helium-3 magnetic resonance imaging as a biomarker of severe outcomes in asthma

To the Editor:

Imaging tools are of increasing interest in assessing patients with asthma for receipt of personalized therapy. Hyperpolarized (HP) ^3He magnetic resonance imaging (MRI) of the lungs is one example of a functional lung imaging method that provides reproducible regional detection of ventilation defects in asthma.¹ These ventilation defects are associated with areas of airway obstruction and air trapping.² The most common metric for measuring defect extent is the ventilation defect percent (VDP).²⁻⁴ Here, we measure VDP using HP ^3He MRI and compare VDP to asthma outcomes indicative of severe exacerbation, analogous to similar studies comparing VDP and exacerbation history in chronic obstructive pulmonary disease.^{5,6}

Our study population included healthy normal volunteers ($N = 11$ [10.8%]) and subjects with mild/moderate ($N = 75$ [73.5%]) or severe ($N = 16$ [15.7%]) asthma as defined by the Severe Asthma Research Program (SARP) criteria.⁷ Subjects with forced expiratory volume in 1 second (FEV_1) percent predicted (PP) value of less than 60% were excluded for safety reasons. Study population characteristics are summarized in Table E1 in this article's Online Repository at www.jacionline.org. HP ^3He MRI, proton MRI, and spirometry were obtained in all subjects. A subset of 88 (86.3%) subjects underwent plethysmography, which was obtained within 1 to 2 weeks of MRI. Sputum samples were available for 93 (91.2%) subjects and blood samples for 97 (95.1%) subjects.

Severe outcomes were determined from records of emergency department (ED) visits and hospitalizations due to trouble breathing as gathered from written questionnaires completed by each subject at enrollment. These binary outcomes were defined by the presence of 1 or more incidents of the corresponding visit type, as recalled by the subject, at any time before study enrollment. These records were present for 94 (92.2%) subjects.

Lung volume after inhalation of a gas dose was determined from proton MRI using a semi-automated region-growing algorithm. Ventilation defects on HP ^3He MRI were segmented manually using in-house software written in MATLAB (MathWorks, Natick, Mass) as previously described by Fain et al.² The resulting defect masks were used to calculate whole-lung VDP.

Spearman correlations between VDP and pulmonary function tests including FEV_1 PP, $\text{FEV}_1/\text{forced vital capacity (FVC)}$ PP, and residual volume/total lung capacity (RV/TLC) PP are presented in Table E2 of this article's Online Repository at www.jacionline.org. VDP was correlated with both FEV_1 PP and FEV_1/FVC PP in the full study population ($r = -0.32$, $P = .001$; $r = -0.54$, $P < .001$, respectively), as well as in the mild/moderate asthma subgroup ($r = -0.33$, $P < .01$; $r = -0.49$, $P < .001$). In the severe asthma group, VDP was correlated with FEV_1/FVC PP ($r = -0.52$, $P = .04$) only. In the normal subgroup, VDP was not correlated with either spirometry measurement. No statistically significant correlations were observed between VDP and RV/TLC PP. In addition, VDP

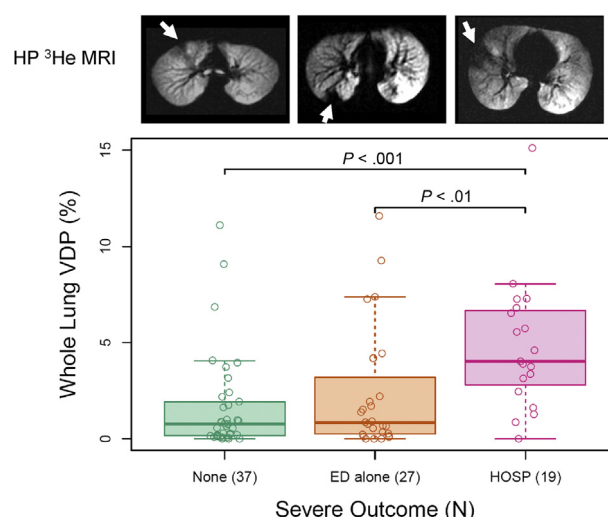


FIG 1. Whole lung VDP vs outcome group in subjects with asthma. VDP (median, interquartile range): No ED or hospitalization (HOSP), (0.78, 1.77); ED alone, (0.85, 2.95); HOSP, (4.0, 3.86). Shown above are typical images of hyperpolarized ^3He MRI for subjects in corresponding outcome groups. Arrows indicate apparent ventilation defects. VDP for example images: no ED or HOSP, 0.97%; ED alone, 1.93%; HOSP, 6.53%.

was associated with peripheral blood eosinophil counts ($r = 0.39$, $P < .001$) and sputum eosinophil differentials ($r = 0.36$, $P < .001$), but not with monocyte or neutrophil blood counts or macrophage or neutrophil sputum differentials.

Fig 1 illustrates the distribution of VDP values among patients with asthma stratified by outcomes (none, $N = 37$; ED alone, $N = 27$; hospitalization [HOSP], $N = 19$) together with typical HP ^3He MRI images from each outcome group. Subjects who were hospitalized had higher median VDP (4.0%) than those who visited the ED alone (0.9%; HOSP vs ED alone, $P < .01$) or did not require treatment (0.8%) (HOSP vs none, $P < .001$). VDP did not differ significantly between the ED-alone and no treatment groups.

Receiver-operating characteristic (ROC) curves, ROC area under the curve (AUC) values, and Wilcoxon rank-sum test results assessing VDP and other biomarkers as indicators of history of severe outcomes among patients with asthma are shown in Fig E1 and Table E3 in this article's Online Repository at www.jacionline.org. VDP was associated with ED visits (AUC = 0.69, $P < .01$) and hospitalizations (AUC = 0.78, $P < .001$). FEV_1/FVC PP was associated with ED visits (AUC = 0.64, $P = .04$), but not hospitalizations. None of the other conventional measures of lung function were associated with either outcome, although peripheral blood eosinophil counts were associated with hospitalizations (AUC = 0.66, $P = .035$). In a multivariate gradient boosting machine⁸ model fit using the gbm package⁹ and incorporating all biomarkers under consideration, the most informative indicator of severe outcomes was VDP, with over twice the relative influence compared with the number of blood eosinophils, the next most informative biomarker (Fig 2).

Importantly, because VDP was associated with hospitalizations irrespective of clinical severity designation, and because hospitalizations were reported in 12 of 68 (17.6%) subjects

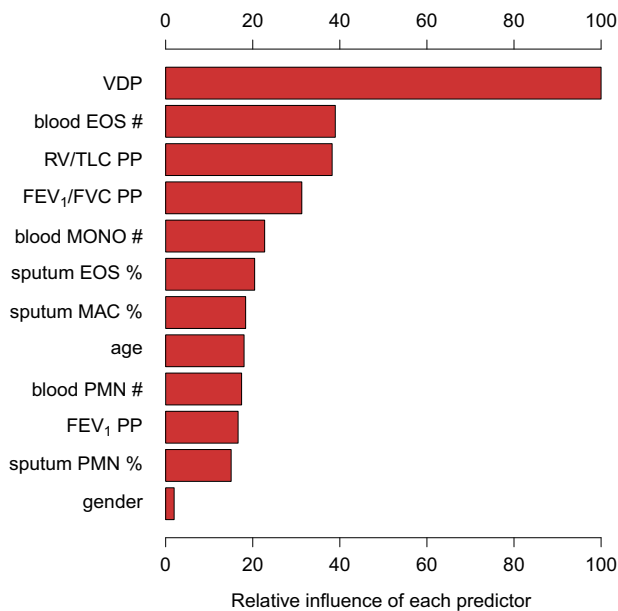


FIG 2. Gradient boosting machine results showing VDP with highest relative influence over other factors in predicting history of severe outcomes. EOS, Eosinophil; MAC, macrophage; PMN, neutrophil.

classified as mild/moderate under the SARP criteria, it is possible that improvements in prognostic techniques could indeed prove valuable in guiding disease surveillance and therapy in asthma. It is also interesting to note that associations between VDP and outcomes were observed despite the relatively uniform spirometry in this population, suggesting that the regional measurements involved in VDP may be providing additional insights into obstructive patterns and their relation to asthma instability.

This study was limited by the scope of the outcomes data set, which did not allow us to incorporate the number or chronology of severe outcomes. Instead, we simply tracked whether at least 1 instance of each outcome occurred at any time before study enrollment. Although additional outcomes data limited to the year before imaging were available, the incidence rate of severe outcomes during this time period was too low to allow for meaningful analysis. Furthermore, outcomes data were based on written questionnaires and depend on the ability of the subject to recall treatment history; incorporating medical records and including the frequency and timing of exacerbation events relative to imaging would likely allow us to make a more accurate description of clinical severity. Using the number of visits over a specific observation period would also strengthen the results, though this approach would require a sufficiently large subject population.

This study demonstrates that VDP measured on HP ³He MRI is associated with clinical outcomes indicative of severe asthma exacerbations. Future prospective studies with access to postimaging clinical outcomes will assess VDP as a predictor of future severe exacerbations. Although an HP MRI examination is more expensive than pulmonary function tests, a computed tomography scan, or a blood/sputum test, these results suggest that it may eventually prove to be justified for clinical use if test results could aid in the prediction or prevention of a severe

exacerbation leading to a hospital stay. Given these results, further study of VDP measured via HP gas MRI (³He or ¹²⁹Xe) as a tool for identifying patients with unstable asthma is warranted.

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REFERENCES

- Niles DJ, Kruger SJ, Dardzinski BJ, Harman A, Jarjour NN, Ruddy M, et al. Exercise-induced bronchoconstriction: reproducibility of hyperpolarized ³He MR imaging. *Radiology* 2013;266:618-25.
- Fain SB, Gonzalez-Fernandez G, Peterson ET, Evans MD, Sorkness RL, Jarjour NN, et al. Evaluation of structure-function relationships in asthma using multidetector CT and hyperpolarized He-3 MRI. *Acad Radiol* 2008;15:753-62.
- Woodhouse N, Wild JM, Paley MN, Fichelle S, Said Z, Swift AJ, et al. Combined helium-3/proton magnetic resonance imaging measurement of ventilated lung volumes in smokers compared to never-smokers. *J Magn Reson Imaging* 2005; 21:365-9.
- Kirby M, Svenningsen S, Ahmed H, Wheatley A, Etemad-Rezai R, Paterson NA, et al. Quantitative evaluation of hyperpolarized helium-3 magnetic resonance imaging of lung function variability in cystic fibrosis. *Acad Radiol* 2011;18: 1006-13.
- Kirby M, Pike D, Sin DD, Coxson HO, McCormack DG, Parraga G. COPD: do imaging measurements of emphysema and airway disease explain symptoms and exercise capacity? *Radiology* 2015;277:872-80.
- Kirby M, Pike D, Coxson HO, McCormack DG, Parraga G. Hyperpolarized (³)He ventilation defects used to predict pulmonary exacerbations in mild to moderate chronic obstructive pulmonary disease. *Radiology* 2014;273:887-96.
- Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the

- National Heart, Lung, and Blood Institute's severe asthma research program.
J Allergy Clin Immunol 2007;119:405-13.
8. Friedman JH. Greedy function approximation: a gradient boosting machine.
Ann Stat 2001;29:1189-232.
9. Ridgeway G. gbm: generalized boosted regression models. R package version 2.1.3
2017.
<https://doi.org/10.1016/j.jaci.2017.10.016>

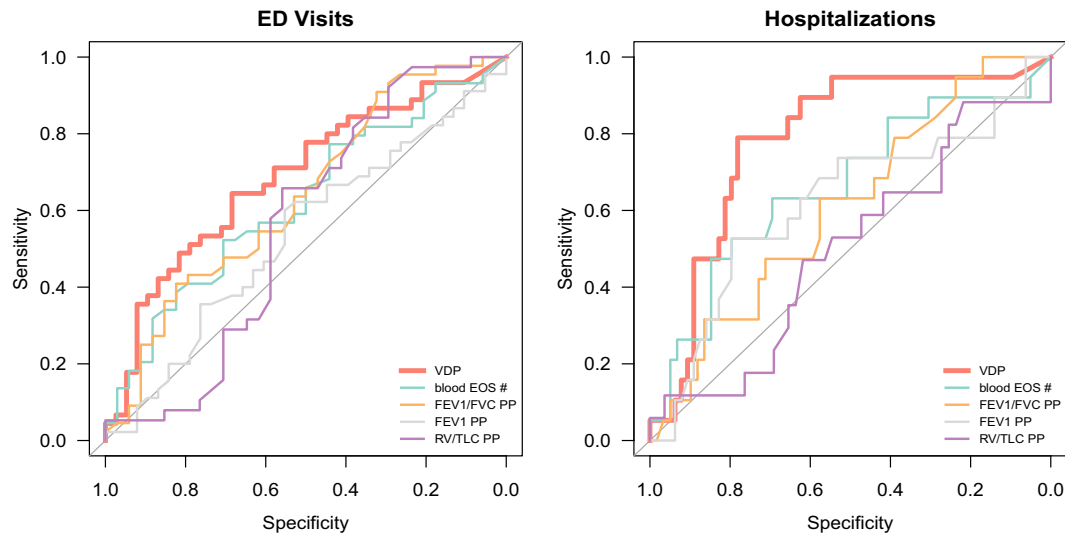


FIG E1. Receiver-operating characteristic (ROC) curves illustrating associations of selected biomarkers of obstruction with a history of ED visits and hospitalizations among subjects with asthma. *EOS #*, Eosinophil count.

TABLE E1. Summary demographic characteristics and lung function stratified by asthma severity

Characteristic	Normals	Mild/Moderate	Severe	Significant difference
N (row %)	11 (10.8%)	75 (73.5%)	16 (15.7%)	NA
Sex (column %)	7 F (63.6%)	46 F (61.3%)	11 F (68.8%)	(None)
Age (y)	22.7 ± 3.6	28.8 ± 11.3	35.8 ± 15.3	Severe vs normal ($P = .02$)
FEV ₁ PP	99.0 (83.6-121.0)	92.0 (61.2-129.0)	88.1 (73.0-115.7)	(None)
FEV ₁ /FVC PP	101.0 (82.7-111.0)	92.5 (62.2-113.8)	89.6 (73.0-105.0)	M/M vs normal ($P < .01$)
				Severe vs normal ($P = .01$)
Whole lung VDP (%)	0.2 (0.0-1.6)	0.9 (0-22.0)	2.8 (0-15.1)	M/M vs normal ($P = .01$)
				Severe vs normal ($P = .02$)
RV/TLC PP	117.3 (92.9-132.1)	109.4 (67.9-184.0)	105.7 (81.3-162.1)	(None)
ED visit, n (%)†	0 (0.0)	32 (47.1%)	13 (86.7%)	Severe vs M/M ($P < .01$)*
Hospitalization, n (%)†	0 (0.0)	12 (17.6%)	7 (46.7%)	Severe vs M/M ($P = .02$)*

Age is given as mean ± SD, all other measurements as median (min-max).

F, Female; NA, not applicable/available.

*Indicates P value of odds ratio. All other tests of significance are Wilcoxon rank-sum. Significance tests for ED and hospitalization outcomes do not include normal subjects.

†Percentage of subjects with outcomes data present.

TABLE E2. Correlation between VDP and pulmonary function tests

Asthma severity	FEV ₁ PP			FEV ₁ /FVC PP			RV/TLC PP		
	N	<i>r</i>	<i>P</i>	N	<i>r</i>	<i>P</i>	N	<i>r</i>	<i>P</i>
Normal	11	0.06	.86	11	−0.45	.17	8	−0.69	.07
M/M	75	−0.33	<.01	70	−0.49	<.001	67	0.17	.17
Severe	16	−0.22	.42	16	−0.52	.04	13	−0.06	.84
Total	102	−0.32	<.01	97	−0.54	<.001	88	0.08	.46

M/M, Mild to moderate; *P*, Spearman *P* value; *r*, Spearman rank correlation coefficient.

TABLE E3. Measures of inflammation and lung function as indicators of severe asthma outcomes

Source	Measurement	ED		Hospitalization	
		ROC AUC	<i>P</i> value	ROC AUC	<i>P</i> value
Blood	Eosinophil count	0.62	.07	0.66	.04
	Neutrophil count	0.49	.91	0.49	.90
	Monocyte count	0.53	.64	0.50	.97
Sputum	Eosinophil differential	0.61	.09	0.62	.10
	Neutrophil differential	0.56	.41	0.52	.80
	Macrophage differential	0.53	.70	0.55	.50
Spirometry	FEV ₁ PP	0.54	.59	0.62	.12
	FEV ₁ /FVC PP	0.64	.04	0.61	.16
Plethysmography	RV/TLC PP	0.56	.39	0.49	.99
MRI	VDP	0.69	<.01	0.78	<.001