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A M E R I C A N C O L L E G E O F  
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## A Multivariate Analysis of Risk Factors for the Air-Trapping Asthmatic Phenotype as Measured by Quantitative CT Analysis\*

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**Background:** Patients with severe asthma have increased physiologically measured air trapping; however, a study using CT measures of air trapping has not been performed. This study was designed to address two hypotheses: (1) air trapping measured by multidetector CT (MDCT) quantitative methodology would be a predictor of a more severe asthma phenotype; and (2) historical, clinical, allergic, or inflammatory risk factors could be identified via multivariate analysis.

**Methods:** MDCT scanning of a subset of Severe Asthma Research Program subjects was performed at functional residual capacity. Air trapping was defined as  $\geq 9.66\%$  of the lung tissue  $< -850$  Hounsfield units (HU). Subjects classified as having air trapping were then compared to subjects without air trapping on clinical and demographic factors using both univariate and multivariate statistical analyses.

**Results:** Subjects with air trapping were significantly more likely to have a history of asthma-related hospitalizations, ICU visits, and/or mechanical ventilation. Duration of asthma (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.08 to 1.87), history of pneumonia (OR, 8.55; 95% CI, 2.07 to 35.26), high levels of airway neutrophils (OR, 8.67; 95% CI, 2.05 to 36.57), airflow obstruction (FEV<sub>1</sub>/FVC) [OR, 1.61; 95% CI, 1.21 to 2.14], and atopy (OR, 11.54; 95% CI, 1.97 to 67.70) were identified as independent risk factors associated with the air-trapping phenotype.

**Conclusions:** Quantitative CT-determined air trapping in asthmatic subjects identifies a group of individuals at high risk for severe disease. Several independent risk factors for the presence of this phenotype were identified: perhaps most interestingly, history of pneumonia, neutrophilic inflammation, and atopy. (*CHEST* 2009; 135:48–56)

**Key words:** air trapping; asthma; atopy; neutrophils; quantitative CT

**Abbreviations:** CI = confidence interval; FeNO = fractional exhaled nitric oxide; FRC = functional reserve capacity; HU = Hounsfield units; ICS = inhaled corticosteroids; %LAA = percentage of lung attenuating area; MDCT = multidetector CT; mSv = millisievert; OR = odds ratio; RV = residual volume; SARP = Severe Asthma Research Program; TLC = total lung capacity

Physiologically defined air trapping has long been considered a risk factor for severe forms of obstructive airways disease.<sup>1,2</sup> Air trapping is defined physiologically as an increase in residual volume (RV) or by the relationship of RV to total lung capacity (TLC). It can now also be defined and objectively quantified using multidetector CT (MDCT) imaging and quantitative software analysis. Software programs that identify the lung field within

a stack of CT images quantify the amount of lung tissue that falls within a range of Hounsfield units (HU), producing a histogram curve of lung voxels. Lower (negative) values represent the least dense (more air-like) areas, while higher numbers represent voxels containing not only air but parenchyma, blood, fibrotic tissue, and inflamed parenchyma.<sup>3–19</sup> In emphysema, previous studies<sup>3,4,16,19</sup> have suggested that CT images obtained with the lungs held

at near TLC with density thresholds of  $-970$  to  $-910$  HU are representative of severe-to-mild emphysematous regions that were respectively identified on pathologic specimens. The normal specific volume of the lung at TLC is  $6.0$  mL/g, corresponding to a CT density of  $-856$  HU.<sup>3,13</sup> The notion that at functional residual capacity (FRC) the normal specific volume and hence CT density should be less than the TLC value suggests that  $-850$  HU may also be a reasonable threshold for air trapping measured at FRC. The  $-856$  HU cut-off MDCT density has been previously used to quantify air trapping in asthmatic children.<sup>5</sup> If pulmonary airways within the lung boarders are included within the voxel count, it is clear that a certain percentage of the lung will always fall below these cut-off values.

Although severe asthma has been associated with air trapping measured plethysmographically, little is understood regarding factors predisposing to this condition. In asthma, there is a strong relationship between FEV<sub>1</sub> values and RV,<sup>20–22</sup> suggesting airway obstruction is inversely related to air trapping. However, no previous studies have integrated a range of risk factors, including those related to allergy, past medical events, comorbid conditions, and inflammatory processes.

The current study addresses two hypotheses: (1) air trapping measured by MDCT quantitative methodology would be a predictor of a more severe asthma phenotype; and (2) independent historical, clinical, allergic, or inflammatory risk factors could be identified in a multivariate analysis as a means of identifying risk factors for this phenotype. One hun-

dred twenty well-characterized asthmatic and normal subjects from the National Institutes of Health Severe Asthma Research Program (SARP) underwent MDCT scans at FRC and TLC (data not included in this analysis) between October of 2002 and June of 2006. CT images were compared across subject groups for air trapping calculated within the FRC data sets. After identifying the air-trapping phenotype, a multivariate analysis identified risk factors associated with this phenotype.

## MATERIALS AND METHODS

### *Study Design*

As part of SARP, subjects underwent a history, physical examination, allergy skin testing, laboratory tests (including sputum analysis and IgE levels), pulmonary function tests, and fractional exhaled nitric oxide (FeNO) testing; completed questionnaires on demographic factors, medication use, and medical history; and underwent chest MDCT prior to fiberoptic bronchoscopy (bronchoscopy methods are described in the online supplement). All procedures were performed following the SARP protocol. Details and descriptions of the SARP cohort have been previously described.<sup>23</sup> The study was approved by the Institutional Review Board at each site and were monitored by an independent Data and Safety Monitoring Board.

### *Human Subjects*

SARP subjects who underwent MDCT imaging studies were included in this study. The number is much lower than the total number of SARP subjects because not all SARP sites were performing MDCT. Subjects were 13 to 60 years old and nonsmokers (smoking history  $< 5$  pack-years and no smoking within the past year). Normal subjects were in good health with normal lung function and a negative methacholine bronchoprovocation (provocative concentration of methacholine causing a 20% decline in FEV<sub>1</sub>  $> 16$  mg/mL). All asthma subjects had physician-diagnosed asthma, no concurrent lung disease, and a positive methacholine bronchoprovocation result (provocative concentration of methacholine causing a 20% decline in FEV<sub>1</sub>  $\leq 8$  mg/mL) or  $\geq 15\%$  improvement in FEV<sub>1</sub> after bronchodilator. Asthma was defined as severe or nonsevere as previously described.<sup>23</sup> Subjects with severe asthma met American Thoracic Society workshop refractory asthma criteria.<sup>24</sup> All asthmatics who did not meet criteria for severe asthma were classified as having nonsevere asthma.

### *CT Technique*

Subjects underwent MDCT spiral scans of the chest with 4, 16, or 64 detector rows (GE Light Speed Ultra, GE Lightspeed 16, Siemens Volume Zoom, Siemens Sensation 16, Siemens Sensation 64 multidetector CT scanners; Siemens; Forchheim, Germany). Suspended expiratory measurements at FRC were obtained at the following settings: GE device: 1.675 to 1.75 pitch, 0.6-s rotation time, 120 kilovolts, 50 to 100 mA, detector collimation 0.625 and 1.25 mm, 0.625- to 1.25-mm reconstructed slice thickness, medium smooth "standard" reconstruction algorithm; Siemens device: 1.5 pitch, 0.5-s rotation time, 120 kilovolts, 50 mA, detector collimation of 0.75 mm, 1-mm recon-

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structured slice thickness, slice interval = field of view in millimeters/512, and a medium smooth reconstruction algorithm (Siemens B31f) – effective mA = 33 (low radiation dose). The radiation dose from the low-dose CT scans (one at TLC and at FRC) ranged from 1.55-millisievert (mSv) effective dose to 1.70-mSv effective dose. The radiation dose from the higher-dose CT scans ranged from 4.0- to 7.6-mSv effective dose. The higher effective doses occurred in larger female subjects. The total radiation dose (TLC and FRC combined) from the low-dose CT scans ranged from 1.55-mSv effective dose to 1.70-mSv effective dose, while the total radiation dose from the higher dose CT scans ranged from 4.0- to 7.6-mSv effective dose. The higher effective doses occurred in larger female subjects. The average dose per person from all sources of natural radiation is approximately 300 millirem or 3 mSv per year.<sup>25</sup> Thus a low-dose-volume MDCT scan (suitable for the measure of air trapping) as used in these analyses is equivalent to approximately 30% of the radiation an individual is naturally exposed to in a year, while the high dose is equivalent to 1.5 to 2 years of natural radiation exposure.

#### MDCT Evaluation Software

MDCT scans were obtained and analyzed using automated, lung parenchymal evaluation software. This software, using an

approach built on the density mask technique, segments the lung from the rest of the thoracic anatomy and generates histogram curves of the lung voxels to analyze the percentage of lung tissue between different MDCT voxel numbers, expressed in HUs (Pulmonary Profiler; VIDA Diagnostics; Coralville, IA).<sup>26</sup> A review of the software capabilities and a validation has been published elsewhere.<sup>27</sup> The specific MDCT measurements used in the data analysis included percentage of low attenuating area (%LAA) < - 850 HU, %LAA - 900 HU, and %LAA - 950 HU. The measurements were performed by a trained technician at the University of Iowa, Carver College of Medicine in a blinded manner. Figure 1 is a CT-derived image of the lung and airways for subjects with severe and nonsevere asthma. Trapped air, defined as voxels within the lung field falling < - 850 HU, is highlighted. By clicking on the airway path, the software labels the bronchial segments along the path of interest. There is a marked increase in air trapping in the patient with severe asthma.

#### Subject Classification

The lung percentage < - 850 HU was dichotomized using a median split of the full cohort (n = 120, median = 9.66%). Because airways within the lung boundaries are included in the VIDA software version of the density mask,<sup>5,14,28-30</sup> it is expected

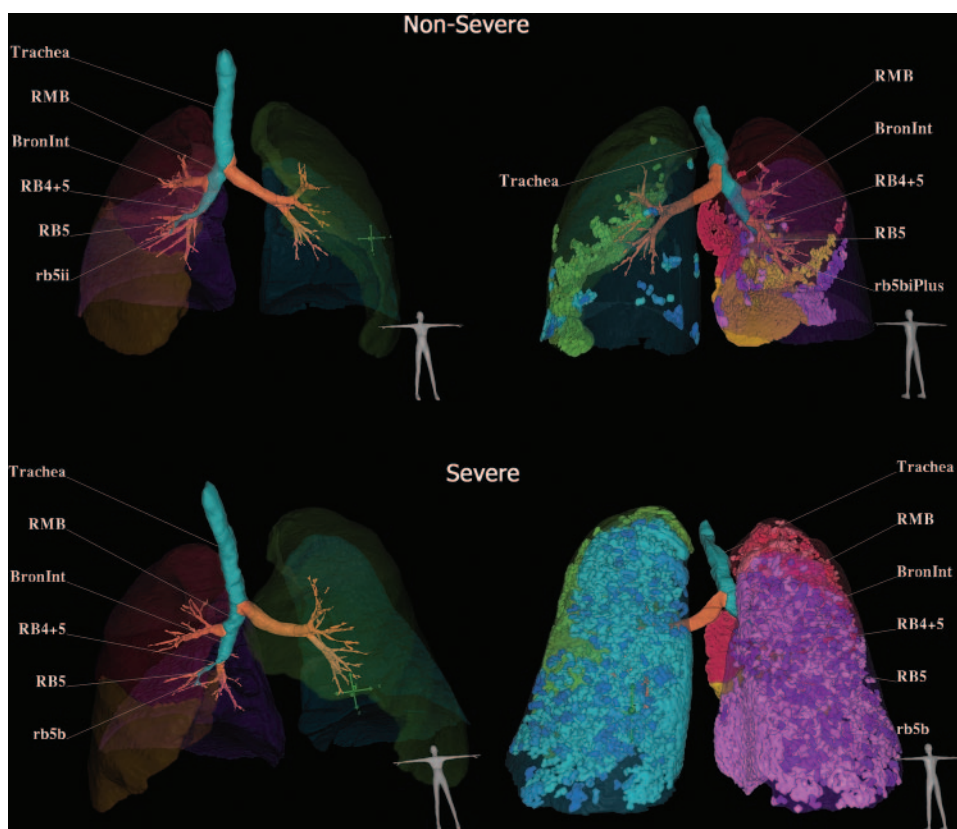


FIGURE 1. CT-derived three-dimensional display of the lungs, airways, and regions of air trapping. Example comparison of two asthmatic subjects falling in the nonsevere (*upper row*) or severe (*lower row*) categories. In the *left column*, the lung lobes and airway tree are shown from a ventral view. In the *right column*, the air trapping is depicted, color coded by lobe and displayed from the dorsal aspect. Software allows one to click on an airway path of interest, and airway segment labels are automatically generated. Trapped air, defined as voxels within the lung field falling < - 850 HU, are highlighted and coded by lobe in the *left column*. The patient with severe asthma has 21.0% of lung < - 850 HU as compared to the patient with nonsevere asthma, with 4.75% of lung < - 850 HU. Images are from the Pulmonary Workstation 2.0 (Vida Diagnostics).

that all subjects will have some voxels falling within range of interest. Subjects above the median were defined as having air trapping and were compared to subjects below the median (no air trapping). Airway neutrophil and eosinophil variables were calculated based on sputum and BAL data. Sixty-six of 90 asthma subjects had either sputum or BAL inflammatory data and were classified as neutrophil positive if either sputum or BAL neutrophils were above the asthmatic median of either distribution (sputum or BAL). If levels were below the median, subjects were considered neutrophil negative. Subjects were classified as eosinophil positive and negative in the same manner. Atopy was defined by the presence of one or more positive allergy skin test results.

#### Imputation of Cellular Data

For subjects with lung inflammatory cell data, logistic regression analysis identified variables that significantly predicted neutrophilic inflammation. The model was applied to subjects with missing neutrophil data ( $n = 25$ ) and the predicted probabilities used to classify these subjects as neutrophil positive or negative.

#### Association With Lung Function

Initial correlations between lung function (specifically FEV<sub>1</sub>/FVC as the most definitive parameter to measure airflow limitation) and the percentage of lung at  $-850$  HU,  $-900$  HU, and  $-950$  HU (at both FRC and TLC) were evaluated using Spearman correlations in the asthma subjects (FRC:  $-850$  HU:  $-0.583$ ;  $-900$  HU:  $-0.514$ ;  $-950$  HU:  $-0.403$ ,  $p < 0.0001$  for each; TLC:  $-850$  HU:  $-0.362$  [ $p < 0.001$ ];  $-900$  HU:  $-0.318$  [ $p = 0.002$ ];  $-950$  HU:  $-0.199$  [ $p = 0.06$ ]). Correlations between lung function and percentage of lung density were stronger at all densities in FRC scans (indicative of air trapping) as compared to TLC scans. Additionally, correlations at  $-850$  HU were stronger than at  $-900$  HU and  $-950$  HU. Therefore, further studies were performed using  $-850$  HU at FRC.

$\chi^2$  tests determined associations between air trapping and severe asthma and its outcomes (such as ICU admission). Logistic regression analysis was used to evaluate univariate associations among variables for air trapping and to determine a group of risk factors associated with air trapping in asthmatic subjects. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated between air trapping and significant covariates ( $p < 0.05$ ). Confounding was examined as change in magnitude of the estimates.<sup>31</sup> All analyses were conducted using statistical software (SAS, version 9.1; SAS Institute; Cary, NC).

## RESULTS

One hundred twenty SARP subjects were studied (60 with severe persistent asthma, 34 with nonsevere asthma, and 26 normal control subjects). Subject demographics are listed in Tables 1, 2.

#### Air Trapping and Severity of Illness

The relationship of severe asthma and its outcomes with air trapping is illustrated in Figure 2. More subjects with air trapping had severe asthma, although the relationship was not statistically significant ( $p = 0.058$ ). However, subjects with air trap-

**Table 1—Summary Statistics of Demographic and Clinical Variables for Subjects With Severe Asthma, Subjects With Mild-to-Moderate Asthma, and Normal Control Subjects**

Variables	Severe Asthma	Nonsevere Asthma	Normal Control Subjects
Subjects, No.	60	34	26
Categorical variables, No. (%)			
Female gender	33 (55.0)	20 (58.8)	17 (65.4)
Percentage of lung $< -850$ HU above median	37 (61.7)	14 (41.2)	9 (34.6)
Atopic	46 (76.7)	31 (91.2)	8 (30.8)
Current use of oral steroids	26 (43.3)	0 (0)	0 (0)
Current use of ICS	59 (98.3)	18 (52.9)	0 (0)
Continuous variables, mean (SD)			
Age, yr	37.5 (13.3)	34.3 (10.7)	30.3 (7.8)
Percentage of lung $< -850$ HU above median	20.2 (16.7)	12.1 (12.0)	12.3 (16.7)
FEV <sub>1</sub> % predicted	62.7 (22.1)	79.7 (16.6)	99.7 (10.0)
FEV <sub>1</sub> /FVC, $\times 100$	62.6 (13.0)	70.1 (11.6)	84.9 (6.3)
IgE level	441.6 (694.8)	229.7 (295.0)	93.5 (171.5)

ping were significantly more likely to have a history of asthma-related hospitalizations, ICU visits, and/or mechanical ventilation compared to subjects without air trapping. These differences suggest that MDCT-measured air trapping may identify a different and more severe phenotype of asthma. We therefore built an explanatory model of air trapping to identify clinical variables that were risk factors for air trapping.

#### Univariate Analysis of Risk Factors Associated With Air Trapping

Subjects with air trapping were compared to subjects without air trapping using univariate ORs (Table 3). Subjects with air trapping had greater airflow limitation (FEV<sub>1</sub> and FVC percentage of predicted and FEV<sub>1</sub>/FVC). Subjects with air trapping were likely to be male, older, and have a longer duration of asthma, and were more likely to report a clinical history of pneumonia and to be atopic than subjects without air trapping. The presence of airway neutrophils was marginally associated with air trapping, while airway eosinophils were not associated. The risk of air trapping was inversely associated with FeNO (OR, 0.85; 95% CI, 0.72 to 0.995 for each increase of 10 parts per billion) in a subset of subjects ( $n = 60$ ), but due to the low number of subjects with FeNO values, it was not considered when determining the final model.

**Table 2—Summary Statistics of Demographic and Clinical Variables by Air-Trapping Status**

Variables	Air Trapping	No Air Trapping
Subjects, No.	51	43
Categorical variables, No. (%)		
Female gender	24 (47.1)	29 (67.4)
Current use of oral steroids	17 (33.3)	9 (20.9)
Current use of ICS	41 (87.2)	36 (76.7)
High level of neutrophils	25 (78.1)	21 (61.8)
High level of eosinophils	9 (28.1)	10 (29.4)
Ever smoked	10 (20.0)	7 (16.3)
History of gastroesophageal reflux disease	22 (44.9)	11 (28.2)
History of pneumonia	33 (70.2)	16 (40.0)
Severe asthma	37 (72.6)	23 (53.5)
Atopic	47 (92.2)	30 (69.8)
Continuous variables, mean (SD)		
Age, yr	39.8 (12.1)	32.3 (11.8)
Percentage of lung < - 850 HU above median	28.0 (13.9)	4.5 (2.4)
Duration of asthma, yr	27.2 (13.7)	17.9 (10.6)
Age at onset of asthma, yr	12.6 (14.2)	14.3 (14.9)
FEV <sub>1</sub> % predicted	59.4 (21.0)	80.1 (16.9)
FVC % predicted	78.6 (20.8)	90.2 (15.7)
FEV <sub>1</sub> /FVC, × 100	59.5 (11.8)	72.3 (10.8)
Positive skin reactions	4.1 (2.6)	3.1 (3.2)
Percentage of eosinophils in sputum	4.1 (5.5)	6.2 (19.5)
Percentage of eosinophils in BAL	1.9 (7.1)	0.8 (1.4)
Percentage of neutrophils in sputum	41.8 (22.6)	22.6 (19.1)
Percentage of neutrophils in BAL	6.0 (6.1)	1.3 (1.9)
IgE level	257.8 (327.5)	450.5 (735.6)
FeNO	30.7 (26.2)	52.9 (48.2)

**Multivariate Logistic Regression Analysis**

Duration of asthma, history of pneumonia, high levels of neutrophils in the airway, airflow obstruction as measured by FEV<sub>1</sub>/FVC, and atopy were

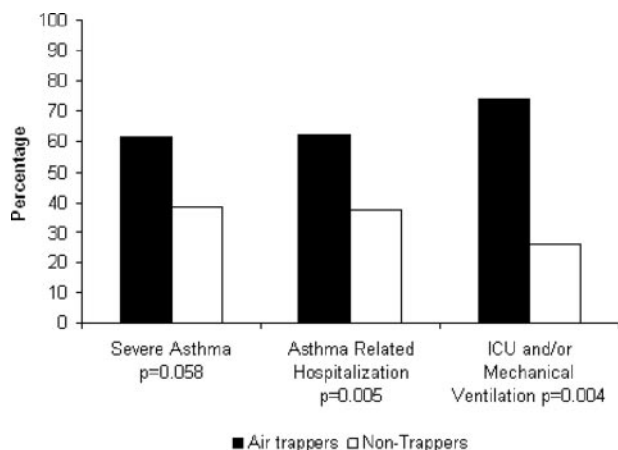


FIGURE 2. Association between air trapping and presence of severe asthma or severe asthma exacerbations.

**Table 3—Univariate ORs in Asthma Patients for Air Trapping**

Variables	OR (95% CI)	Unit Increase
FEV <sub>1</sub> /FVC	1.64 (1.31–2.05)	5% decrease
Asthma duration	1.36 (1.13–1.64)	5-yr increase
Neutrophils above the median	2.21 (0.75–6.55)	
History of pneumonia	3.54 (1.45–8.60)	
Atopy	5.09 (1.52–17.09)	
Sex	0.43 (0.19–0.996)	
FEV <sub>1</sub> % predicted	1.32 (1.16–1.50)	5% decrease
FVC % predicted	1.20 (1.05–1.36)	5% decrease
FeNO	0.85 (0.72–0.995)	10-U increase
Smoking	1.29 (0.44–3.73)	
Eosinophils above the median	0.80 (0.24–2.68)	
Paternal history of allergies	0.58 (0.21–1.59)	
Paternal history of asthma	1.07 (0.43–2.63)	
Gastroesophageal reflux disease	2.07 (0.85–5.08)	
Age	1.68 (1.17–2.40)	10-yr increase
Oral steroid use	1.88 (0.74–4.82)	

identified as risk factors associated with the air-trapping phenotype (Table 4). For each 5-year increase in asthma duration, there was a 42% increase in the odds of air trapping. A 5% decrease in FEV<sub>1</sub>/FVC corresponded to a 61% increase in the odds of air trapping. Subjects with a history of pneumonia were at increased risk for air trapping compared to those with no history. Airway neutrophils above the median in sputum or BAL were also associated with an increased risk of air trapping. Atopic subjects were more likely to have air trapping than nonatopic subjects. Although the estimates were relatively large, the CIs were wide for pneumonia, neutrophils, and atopy, all reflective of the relatively small sample size. The model building process was also completed using only those subjects with measured neutrophil data; the terms were identical, and coefficients were not different from those in the presented model (data not shown).

**Table 4—Results From Multivariate Logistic Regression Model**

Variables	OR (95% CI)
Duration of asthma (5-yr increase)	1.42 (1.09–1.87)
FEV <sub>1</sub> /FVC (5% decrease)	1.61 (1.21–2.15)
History of pneumonia	8.55 (2.07–35.26)
Neutrophilic inflammation in airway above the median	8.66 (2.05–36.57)
Atopy	11.54 (1.97–67.70)

## Air Trapping in Normal Control Subjects

Almost 35% of the normal subjects were classified as air trappers (Table 1). Power limited the analysis of clinical variables with air trapping using multivariate models. However, the odds of air trapping increased significantly with increasing levels of airway obstruction even though FEV<sub>1</sub>/FVC values were within the normal range. Female subjects were less likely to have air trapping than male subjects, although the difference was not statistically significant ( $p = 0.11$ ). No other variables associated with air trapping in asthmatic subjects were associated with air trapping in the normal group. Variables of interest and their univariate associations with air trapping are shown in Table 5 (shown in online supplement).

## DISCUSSION

This is the first large study of CT-measured air trapping in a range of extensively characterized asthmatic subjects to identify independent risk factors for the air-trapping phenotype, a phenotype associated with the most severe form of asthma. This assessment of air trapping was quantitatively and objectively performed using a histogram based assessment of lung densities (VIDA Diagnostics) based on the density mask but which employs a more sophisticated method for identifying lung boundaries.<sup>26</sup> Müller et al<sup>30</sup> developed the original concept for the density mask based on early observations that demonstrated that lung volume<sup>32</sup> and regional air content, or density,<sup>33</sup> could be accurately assessed via CT. This density mask method identified the lung field and a density threshold within the lung field to count emphysema-like lung voxels. Since then, the histogram of voxel density within the lung field has been widely used to identify emphysema-like lung and fibrosis, as reviewed by Hoffman et al<sup>28</sup> and, in the case of this study, trapped air when the lung is imaged at low lung volumes.<sup>14</sup> The histogram-based assessment of the lung used here replaces the former “density mask” approach, but the essence of the measurement remains the same.

In this study, subjects with air trapping were defined as individuals with  $\geq 9.66\%$  of their total lung volume at FRC  $< -850$  HU. While this density is not as extreme as the  $-910$ - to  $-970$ -HU threshold applied to COPD/emphysema, a previous report suggests that this degree of hyperlucency ( $< -850$  HU) should only be seen at TLC because this density is measuring a fully distended alveolus. Additionally, higher correlations with lung function were seen at the  $-850$ -HU threshold than at either  $-900$  HU or  $-950$  HU, suggesting that  $-850$  HU may be a more appropriate threshold for asthma. Because

asthma, even in severe cases, is not pathologically an “emphysematous” process involving alveolar septal destruction, the better discrimination of our data at this higher cut-off is not surprising.

This threshold applied to asthma identified a marginally more severe cohort using the American Thoracic Society refractory asthma definition, but who were much more likely to have had a history of a severe and/or near-fatal asthma event, similar to a previous report<sup>1</sup> for physiologic measures of air trapping. A recent study<sup>22</sup> from this cohort reported that patients with severe asthma had a greater component of physiologically measured air trapping relative to airflow limitation than subjects with milder asthma and concluded that air trapping is broadly associated with severe asthma. Further, Mitsunobu et al<sup>34</sup> assessed air trapping using MDCT and reported that the relative area of the lungs  $< -950$  HU correlated with airflow limitation and with severity of asthma. Therefore, our findings are not completely unexpected. Unlike previous studies, the SARP database contains a multitude of variables that were then utilized to determine risk factors for air trapping on MDCT scan using a multivariate modeling approach.

Based on univariate analysis, numerous factors were associated with the air trapping phenotype including airway obstruction, measured by FEV<sub>1</sub>/FVC. We chose FEV<sub>1</sub>/FVC (among the multiple related spirometric values available) because the percentage of predicted FEV<sub>1</sub> is low in restrictive disease, as well as in obstructive disease, while the FEV<sub>1</sub>/FVC decreases only with increasing airflow limitation. This relationship has been reported in physiologically measured air trapping<sup>1</sup> and in air trapping measured by MDCT, albeit based on univariate analysis.<sup>34</sup> A variety of other factors, including longer duration of disease, male sex, and lower FeNO, were either marginally or significantly related. The association of air trapping with increased age and longer disease duration suggest a contribution of remodeling over time, while the relationship with male sex could be explained by the greater prevalence of asthma in early childhood in boys than in girls or a greater susceptibility to elements of the remodeling process. Interestingly, when matched for severity, male subjects with asthma have lower FEV<sub>1</sub> as well as lower FEV<sub>1</sub>/FVC than female subjects.<sup>35</sup> The relationship of air trapping with lower FeNO is surprising but may suggest that, in this cohort, nitric oxide has a bronchodilating effect<sup>36</sup> that limits the degree of air trapping seen. However, because of its limited sample size, FeNO was not considered in the multivariate analysis. Further studies are needed to determine if it is protective against air trapping. Despite the potential relationship with FeNO, eosin-

ophils were not associated with air trapping. The relationship of eosinophils to airway obstruction has been variable across studies<sup>1,37–40</sup>; therefore, further study of this relationship is required.

A multivariate analysis was undertaken selecting factors in the univariate analyses associated with air trapping ( $p < 0.20$ ). In the multivariate analysis, FEV<sub>1</sub>/FVC, duration of disease, reported history of pneumonia, neutrophilic airway inflammation, and atopy were identified as independent risk factors. Some univariately associated variables were not significant in the multivariate model, likely due to the overlapping nature of these variables. Among the risk factors, perhaps the most interesting are history of pneumonia, neutrophilic inflammation, and atopy. Because this is a cross-sectional study, causal relationships cannot be presumed, with the observed relationships as likely to be a consequence of air trapping as causes. Despite these uncertainties, the results remain provocative. Consistent with our finding of an association of the more severe air-trapping phenotype with history of pneumonia, analysis of the entire SARP database ( $> 400$  subjects) determined pneumonia to be independently associated with asthma severity (OR, 3.30; 95% CI, 1.92 to 5.69).<sup>23</sup> More severe disease may increase the for pneumonia due to poor secretion clearance and immunosuppression by corticosteroids. An analysis of a large healthcare database found that asthmatics are at higher risk of development of pneumonia.<sup>41</sup> Inhaled corticosteroids (ICS) as a risk factor for pneumonia are also becoming increasingly identified. ICS use has been associated with an increased risk for pneumonia in prospective studies of COPD.<sup>42,43</sup> All subjects with severe asthma in this study were on high ICS doses, which could have contributed to a higher pneumonia risk. Only longitudinal studies will confirm (or refute) that relationship.

Another interesting risk factor was airway neutrophilia. The observation that pneumonia and neutrophils are independent risk factors for air trapping suggests that historical pneumonia is not driving the neutrophilia, nor is the neutrophilia likely a residual of pneumonia. It is possible that neutrophilia is a byproduct of high corticosteroid use in this population. Corticosteroids inhibit neutrophil apoptosis and enhance their activity and survival, which may explain their increase.<sup>44,45</sup> Unfortunately, despite  $> 100$  patients in this trial, power limitations restricted our ability to adjust the model for corticosteroids. Whether caused by more severe disease or its treatment, higher levels of lung neutrophils could lead to air trapping. Neutrophils produce enzymes, including elastases and metalloproteinases, which contribute to elastin (and other matrix elements) breakdown observed in fatal asthma and severe cases

of asthma.<sup>46–48</sup> These airway and perhaps parenchymal changes could alter elastic recoil properties and lead to a more “emphysematous-like” pattern and increased air trapping. An emphysematous-like pattern seen on CT in chronic asthma subjects has been reported in other studies.<sup>49</sup>

The final risk factor of interest was atopy. Had the analysis included nonasthmatic subjects, this association would not have been surprising because atopy is strongly associated with asthma. However, the analysis was restricted to asthmatics, 82% of whom were atopic. Nonatopic asthma patients are a mix of individuals including aspirin sensitive to post-viral adult onset asthma.<sup>38,50</sup> The multivariate analysis is adjusted for asthma duration, so the relationship cannot be attributed to nonatopic asthmatics having a shorter disease duration. The relationship between atopy and air trapping has not been extensively evaluated. One study<sup>51</sup> reported more extensive airway remodeling (assessed by high-resolution CT) among nonatopic individuals than atopic individuals. This study did not specifically assess air trapping, and only qualitative analyses were conducted. Further studies are needed to determine whether the remodeling process associated with nonatopic differs from atopic asthma, leading to differences in radiologic and physiologic changes.

Finally, a large percentage of normal control subjects met the threshold for air trapping. It is unclear whether these subjects are at increased risk for asthma, have genetic predisposition to air trapping, or had some past insult that induced these changes. Although these subjects had normal pulmonary function test and negative methacholine challenge results, they had a lower FEV<sub>1</sub>/FVC and tended to be male, both seen in the asthmatic subjects with air trapping. Studies of air trapping in normal subjects are needed to determine if air trapping is a risk factor for asthma development.

There are limitations to this report. Although one of the largest MDCT studies of asthma, a larger sample size would have provided increased power perhaps resulting in more stable estimates and ability to evaluate other factors. Additionally, airway neutrophil data were unavailable for 23% of subjects. We imputed missing airway neutrophil data to consider this variable in the multivariate logistic regression model. The imputation may have resulted in misclassification; however, including imputed values did not change the results obtained using subjects with actual neutrophil data. In contrast, the strengths include the large well-characterized and diverse population, the availability of lung inflammatory markers and the quantitative measure of air trapping. Finally, the multivariate analysis included a range of data allowing for examination of confounding.

This study supports the utility of MDCT scanning to identify a group of asthmatics at risk of severe disease, particularly intensive health-care utilization. Independent risk factors were identified, including history of pneumonia, neutrophilic inflammation, and atopy. Further prospective studies to evaluate the role of these factors in development of this phenotype are needed.

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**A Multivariate Analysis of Risk Factors for the Air-Trapping Asthmatic Phenotype as Measured by Quantitative CT Analysis**

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