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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 M E R I C A N C O L L E G E O F



P H Y S I C I A N S ®

Abbreviations:

ATS: American Thoracic Society

BAL: Bronchoalveolar Lavage

CI: Confidence Interval

COPD: Chronic obstructive pulmonary disease

CS: Corticosteroids

FeNO: Fractional exhaled nitric oxide

FEV1: Forced expiratory volume in one second

FRC: Functional Reserve Capacity

FVC: Forced vital capacity

HU: Hounsfield Units

ICS: Inhaled corticosteroids

ICU: Intensive Care Unit

%LAA: Percent Lung Attenuating Area

MDCT: Multi-detector computed tomography

NIH: National Institutes of Health

NO: Nitric oxide

OR: Odds Ratio

PC₂₀: Provocative Concentration of methacholine causing a 20% decline in forced expiratory volume in one second

RV: Residual Volume

SARP: Severe Asthma Research Program

TLC: Total Lung Capacity

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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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ABSTRACT

Background: Severe asthma subjects have increased physiologically measured air trapping. However, a similar study using CT measures of air trapping has not been performed.

This study was designed to address two hypotheses: 1) air trapping, measured by multi-detector CT 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: Multi-detector CT scanning of a subset of the Severe Asthma Research Program subjects was performed at functional residual capacity. Air trapping was defined as 9.66% or more of the lung tissue less than -850 HU. Subjects who were defined as air trappers were then compared to non-trappers on clinical and demographic factors using both univariate and multivariate statistical analysis.

Results: Air trappers were significantly more likely to have a history of asthma-related hospitalizations, ICU visits and/or mechanical ventilation. Duration of asthma (OR 1.42, 95% CI 1.08-1.87), history of pneumonia (OR 8.55, 95% CI 2.07-35.26), high levels of airway neutrophils (OR 8.67, 95% CI 2.05-36.57), air flow obstruction (FEV₁/FVC) (OR 1.61, 95% CI 1.21-2.14) and atopy (OR 11.54, 95% CI 1.97-67.70), 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 with a high risk of severe disease. Several independent risk factors for the presence of this phenotype were identified, perhaps most interestingly history of pneumonia, neutrophilic inflammation, and atopy.

INTRODUCTION

Physiologically defined air-trapping has long been considered a risk factor for severe forms of obstructive airways disease.^{1,2} 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 multi-detector 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, inflamed parenchyma, etc.³⁻¹⁹ In emphysema, previous studies 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 which were respectively identified on pathologic specimens.^{3,4,16,19} The normal specific volume of the lung at TLC is 6.0 ml/gm, corresponding to a CT density of -856 HU.^{3,13} 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.⁵ If pulmonary airways within the lung borders 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 FEV₁ values and RV,²⁰⁻²² 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, co-morbid 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 hundred twenty well-characterized asthmatic and normal subjects from the NIH Severe Asthma Research Program (SARP) underwent MDCT scans at FRC and TLC (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.

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 exhaled nitric oxide (FeNO) testing, completed questionnaires on demographic factors, medication use and medical history, and had a 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.²³ The study was approved by each site's Institutional Review Board and monitored by an independent Data and Safety Monitoring Board.

Human subjects

SARP subjects who underwent MDCT imaging studies were included into this study. The number is much lower than the total number of SARP subjects, as not all SARP sites were performing MDCT. Subjects were 13-60 years old and non-smokers (smoking history <5 pack-years and no smoking within 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 forced expiratory volume in one second (FEV₁) (PC₂₀) > 16 mg/ml). All asthmatics had physician diagnosed asthma, no concurrent lung disease, and a positive methacholine bronchoprovocation (PC₂₀ ≤ 8mg/ml) or ≥ 15% improvement in FEV₁ post-bronchodilator. Asthma subjects were classified as severe or non-severe as previously described.²³ Severe asthma subjects met ATS workshop refractory asthma criteria.²⁴ All asthmatics who did not meet criteria for severe asthma were classified as non-severe asthmatics.

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). Suspended expiratory measurements at FRC were obtained at the following settings: GE: 1.675-1.75 pitch, 0.6 sec rotation time, 120 kV, 50-100 mAs, detector collimation 0.625 and 1.25 mm, 0.625-1.25 mm reconstructed slice thickness, medium smooth “standard” reconstruction algorithm; Siemens: 1.5 pitch, 0.5 sec rotation time, 120 kV, 50 mAs, detector collimation of 0.75 mm, 1mm reconstructed slice thickness, slice interval = field of view (mm)/512, and a medium smooth reconstruction algorithm (Siemens B31f) – effective mAs = 33 (low radiation dose). The radiation dose from the low dose CT scans (one at TLC and at FRC) ranged from 1.55 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 ef-

fective 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 about 300 mrem or 3 mSv per year.²⁵ 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 percent of lung tissue between different MDCT voxel numbers, expressed in HUs (Pulmonary Profiler, VIDA Diagnostics, Iowa City, IA).²⁶ A review of the software capabilities and a validation has been published elsewhere.²⁷ The specific MDCT measurements used in the data analysis included percent low attenuating area (%LAA) less than - 850 HU, %LAA - 900 HU, %LAA - 950 HU. The measurements were performed by a trained technician at the University of Iowa, Carver College of Medicine in a blinded manner. In Figure 1, a CT image of air trapping in a non-severe (upper row) and severe (lower row) asthmatic is illustrated. Trapped air defined as voxels within the lung field falling below -850 are highlighted in both images. There is a marked increase in air trapping in the severe asthmatic.

Subject classification

The lung percentage less than -850 HU units 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^{5,14,28-30} it is expected that all subjects will have some voxels falling within range of interest. Subjects above the median were defined as air trappers and compared to those below the median (non-trappers). Airway neutrophil and eosinophil variables were calculated based on sputum and bronchoalveolar lavage (BAL) data. Sixty-six of the 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.

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=28), and the predicted probabilities used to classify these subjects as neutrophil positive or negative.

Association with lung function

Initial correlations between lung function (specifically FEV₁/FVC as the most definitive parameter to measure airflow limitation) and the percent of lung at -850, -900 and -950 HU (at both FRC and TLC) were evaluated using Spearman's 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 percent 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 or -950 HU. Therefore, further studies were performed using -850 HU at FRC.

Chi-square tests determined associations between air trapping and severe asthma and its outcomes (such as intensive care unit 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.³¹ Table 5 (online supplement) illustrates variables of interest and their univariate associations with air trapping. All analyses were conducted with SAS (version 9.1).

RESULTS

One hundred-twenty SARP subjects were studied (60 severe persistent asthma, 34 not-severe asthma subjects, and 26 normal controls). Subject demographics are listed in Table 1.

Air trapping and severity of illness

The relationship of severe asthma and its outcomes with air trapping is illustrated in Figure 2. More subjects who were air trappers were severe asthmatics, although the relationship was not statistically significant ($p = 0.058$). However, air trappers were significantly more likely to have a history of asthma-related hospitalizations, intensive care unit (ICU) visits, and/or mechanical ventilation compared to subjects classified as non-trappers. 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 considered air trappers were compared to the non-trapping group using univariate odds ratios (Table 3). Air trapping subjects had greater air flow limitation (FEV₁ and FVC percent predicted and FEV₁/FVC). Subjects with air trapping were likely to be male, older, and have a longer duration of asthma. Air trappers were more likely to report a clinical history of pneumonia and to be atopic than subjects who were not classified as air trappers. 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: 0.72-0.995 for each 10 ppb increase) 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.

Multivariate logistic regression analysis

Duration of asthma, history of pneumonia, high levels of neutrophils in the airway, air flow obstruction as measured by FEV₁/FVC and atopy were 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 FEV₁/FVC corresponded to a 61% increase in the odds of air trapping. Subjects with a history of pneumonia were at increased risk of 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 be air trappers than non-atopic subjects. Although the estimates were relatively large, the confidence intervals 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).

Air trapping in normal controls

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 FEV₁/FVC values were within the normal range. Females were less likely to be air trappers than males although the difference was not statistically significant (p=0.11). No other variables associated with air trapping in asthmatics were associated with air trapping in the normal group.

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, Coralville Iowa) based on the density mask, but which employs a more sophisticated method for identifying lung boundaries.²⁶ Muller et al.³⁰ developed the original concept for the density mask based on early observations which demonstrated that lung volume³² and regional air content, or density,³³ 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 in²⁸ and, in the case of this

study, trapped air when the lung is imaged at low lung volumes.¹⁴ 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, air trapping subjects 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, previous reports suggest that this degree of hyperlucency (< -850 HU) should only be seen at TLC as this density is measuring a fully distended alveolus.³ 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. As 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 ATS 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 previous reports for physiologic measures of air trapping.¹ A recent study, from this cohort, reported that severe asthmatics had a greater component of physiologically measured air trapping relative to airflow limitation than milder subjects and concluded that air trapping is broadly associated with severe asthma.²² Further, Mitsunobu et al. assessed air trapping using MDCT and reported that the relative area of the lungs less than -950 HU correlated with air flow limitation and with severity of asthma. Therefore, our findings are not completely unexpected.³⁴ Unlike previous studies, the SARP database contains a multitude of variables which 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 FEV₁/FVC. We chose FEV₁/FVC (among the multiple related spirometric values available) as the FEV₁% predicted is low in restrictive, as well as obstructive disease, while the FEV₁/FVC decreases only with increasing airflow limitation. This relationship has been reported in physiologically measured air trapping¹ and in air trapping measured by MDCT— albeit, based on univariate analysis.³⁴ 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 asthmatics have lower FEV₁, as well as lower FEV₁/FVC, than females.³⁵ The relationship of air trapping with lower FeNO is surprising but may suggest that, in this cohort, NO has a bronchodilating effect³⁶ 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, eosinophils were not associated with air trapping. The relationship of eosinophils to airway obstruction has been variable across studies,^{1,37-40} 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, FEV₁/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 can not 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:1.92-5.69).²³ More severe disease may increase the risk for developing pneumonia due to poor secretion clearance and immunosuppression by corticosteroids (CS). An analysis of a large healthcare database found that asthmatics are at higher risk of development of pneumonia.⁴¹ Inhaled CS (ICS) as a risk factor for pneumonia is also becoming increasingly identified. ICS use has been associated with an increased risk for pneumonia in prospective studies of COPD.^{42,43} All severe asthma subjects 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 by-product of high corticosteroid use in this population. Corticosteroids inhibit neutrophil apoptosis and enhance their activity and survival which may explain their increase.^{44,45} Unfortunately, despite greater than 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.⁴⁶⁻⁴⁸

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.⁴⁹

The final risk factor of interest was atopy. Had the analysis included non-asthmatics, this association would not have been surprising, as atopy is strongly associated with asthma. However, the analysis was restricted to asthmatics, 82% of whom were atopic. Non-atopic asthmatics are a mix of individuals including aspirin sensitive to post-viral adult onset asthmatics.^{38,50} The multivariate analysis is adjusted for asthma duration so the relationship cannot be attributed to non-atopic asthmatics having a shorter disease duration. The relationship between atopy and air trapping has not been extensively evaluated. One study reported more extensive airway remodeling (assessed by high resolution CT) among non-atopic individuals than atopic individuals.⁵¹ 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 non-atopic differs from atopic asthma, leading to differences in radiologic and physiologic changes.

Finally, a large percentage of normal controls 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 which induced these changes. Although these subjects had normal pulmonary function testing and negative methacholine challenges, they had a lower FEV₁/FVC and tended to be males, both seen in the asthmatics 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 healthcare 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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Figure Legend

Figure 1. CT image of air trapping. Example comparison of two asthmatic subjects falling in the non-severe (upper row) or severe (lower row) categories. Depicted here are selected Coronal (first column), Transverse (second column), Sagittal sections (third column) along with a Volume Rendering of the whole lung viewed from the ventral/left lateral aspect (fourth column). Trapped air defined as voxels within the lung field falling below -850 are highlighted in yellow (sectional views) or green (volume rendered view). The severe asthma subject has 10% of lung less than -850 HU as compared to the non-severe asthma subject with 4% of lung less than -850 HU.

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

Table 1. Summary statistics of demographic and clinical variables for severe asthmatics, mild/moderate asthmatics, and normal controls

Demographic and Clinical Variables	Severe Asthmatics	Non-Severe Asthmatics	Normal Controls
Number of study subjects	60	34	26
Categorical Variables	Number (Percent)	Number (Percent)	Number (Percent)
Female gender	33 (55.0%)	20 (58.8%)	17 (65.4%)
Percent of Lung Less than -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 Inhaled Steroids	59 (98.3%)	18 (52.9%)	0 (0%)
Continuous Variables	Mean (Standard Deviation)	Mean (Standard Deviation)	Mean (Standard Deviation)
Age	37.5 (13.3)	34.3 (10.7)	30.3 (7.8)
Percent less -850	20.2 (16.7)	12.1 (12.0)	12.3 (16.7)
FEV ₁ percent predicted	62.7 (22.1)	79.7 (16.6)	99.7 (10.0)
FEV ₁ /FVC (x 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)

Table 2. Summary statistics of demographic and clinical variables by air trapping status

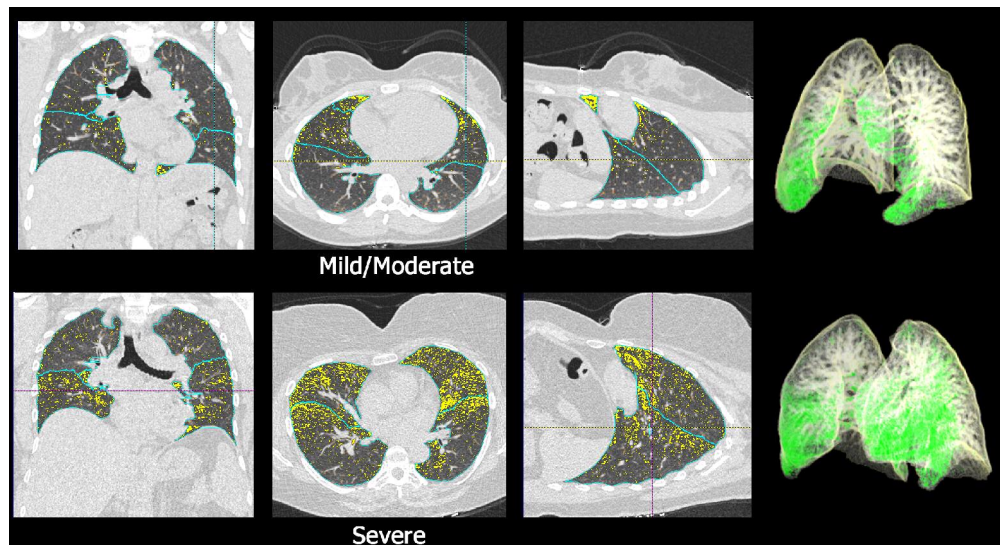
Demographic and Clinical Variables	Trappers	Non-trappers
Number of study subjects	51	43
Categorical Variables	Number (Percent)	Number (Percent)
Female gender	24 (47.1%)	29 (67.4%)
Current use of oral steroids	17 (33.3%)	9 (20.9%)
Current use of inhaled steroids	41 (87.2%)	36 (76.7%)
High level of neutrophils	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 GERD	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 (Standard Deviation)	Mean (Standard Deviation)
Age	39.8 (12.1)	32.3 (11.8)
Percent less -850	28.0 (13.9)	4.5 (2.4)
Duration of asthma	27.2 (13.7)	17.9 (10.6)
Age at onset of asthma	12.6 (14.2)	14.3 (14.9)
FEV ₁ percent predicted	59.4 (21.0)	80.1 (16.9)
FVC percent predicted	78.6 (20.8)	90.2 (15.7)
FEV ₁ /FVC x 100	59.5 (11.8)	72.3 (10.8)
Positive skin reactions (number)	4.1 (2.6)	3.1 (3.2)
Percent eosinophils (sputum)	4.1 (5.5)	6.2 (19.5)
Percent eosinophils (BAL)	1.9 (7.1)	0.8 (1.4)
Percent neutrophils (sputum)	41.8 (22.6)	22.6 (19.1)
Percent neutrophils (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)

Table 3. Univariate Odds Ratios-Among Asthmatics for Air Trapping

Variable	Odds Ratio (95% Confidence Interval)	Unit increase
FEV ₁ /FVC	1.64 (1.31-2.05)	5% decrease
Asthma Duration	1.36 (1.13-1.64)	5 year increase
Neutrophils above the median	2.21 (0.75-0.55)	
History of Pneumonia	3.54 (1.45-8.60)	
Atopy	5.09 (1.52-17.09)	
Sex	0.43 (0.19-0.996)	
FEV ₁ % 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 unit 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)	
GERD	2.07 (0.85-5.08)	
Age	1.68 (1.17-2.40)	10 year increase
Oral Steroid Use	1.88 (0.74-4.82)	

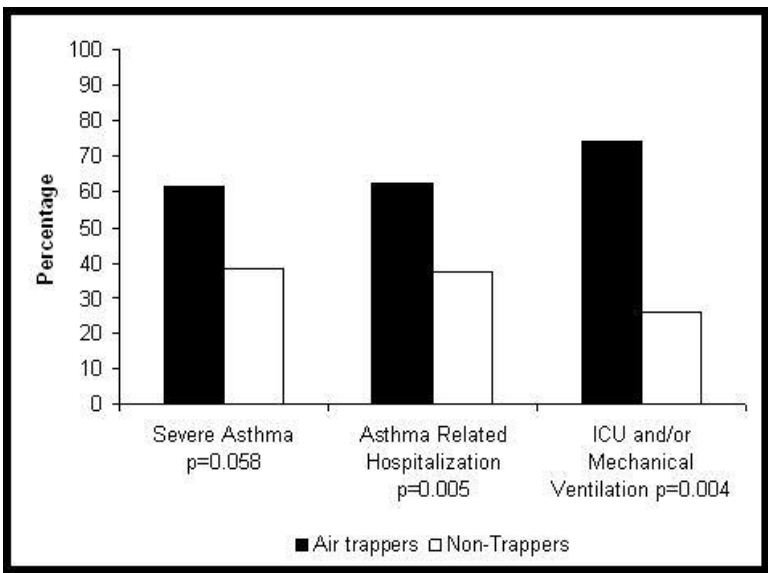
Table 4. Results From Multivariate Logistic Regression Model

Variable	Odds Ratio (95% Confidence Interval)
Duration of Asthma (5 year increase)	1.42 (1.09-1.87)
FEV ₁ /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)



CT image of air trapping. Example comparison of two asthmatic subjects falling in the non-severe (upper row) or severe (lower row) categories. Depicted here are selected Coronal (first column), Transverse (second column), Sagittal sections (third column) along with a Volume Rendering of the whole lung viewed from the ventral/left lateral aspect (fourth column). Trapped air defined as voxels within the lung field falling below -850 are highlighted in yellow (sectional views) or green (volume rendered view). The severe asthma subject has 10% of lung less than -850 HU as compared to the non-severe asthma subject with 4% of lung less than -850 HU.

181x98mm (300 x 300 DPI)



Methods

Bronchoscopy with Endobronchial Biopsy and Lavage

The subject receives two intramuscular injections of Atropine (0.6 mg) and codeine (45 mg) intramuscularly and then is given 2 ml of nebulized albuterol were given prior to the procedure. Lidocaine (<400 mg total) was used for local anesthesia in the upper and lower airways. Just prior to and during the bronchoscopy, midazolam and fentanyl were given intravenously for conscious sedation. The subjects received oxygen and vital signs were monitored throughout the procedure. Spirometry was performed pre- and postprocedure. The bronchoscope was passed orally or nasally through the vocal cords and into the trachea/bronchi. Endobronchial biopsies were taken from the first or second subcarinae of the right or left lower lobes. The bronchoscope was then repositioned in the opposite lung where bronchoalveolar lavage (BAL) was performed in subsegments of the lingula or right middle lobe using four 60-ml aliquots of warmed sterile saline, with sequential instillation and manual aspiration.

Statistical Methods

For the multivariate model, all covariates of interest that were associated with air trapping at the 0.20 significance level in univariate analyses were retained for possible inclusion in the final multivariable logistic regression model.

Results

Table 5 illustrates the associations between clinical variables of interest and air trapping among asthma subjects. Associations with a p-value<0.20 were considered as candidate variables in the model building process.

Table 5. Univariate Odds Ratios-Among Asthmatics for Air Trapping

Variable	Unit increase	Odds Ratio	Lower CI	Upper CI	p-value
FEV1/FVC	-5	1.64	1.31	2.05	<0.0001
FEV1 % predicted	-5	1.32	1.16	1.5	<0.0001
FEV % predicted	-5	1.2	1.05	1.36	0.006
Asthma duration	5	1.36	1.13	1.64	0.0012
Sex (female compared to male)		0.43	0.19	0.996	0.049
FeNO	10	0.85	0.72	0.995	0.04
Fraternal history of asthma		1.1	0.36	3.61	0.88
Fraternal history of allergies		0.57	0.23	1.4	0.22
Maternal history of asthma		0.81	0.31	2.13	0.67
Maternal history of allergies		0.52	0.21	1.27	0.15
History of pneumonia		3.54	1.45	8.6	0.005
History of GERD		2.07	0.85	5.08	0.11
Age	10	1.68	1.17	2.4	0.004
Airway neutrophilic inflammation above the mean (no imputed data)		2.21	0.75	6.55	0.15
Airway eosinophilic inflammation above the mean (no imputed data)		0.94	0.32	2.73	0.91
Oral Steroid Use		1.89	0.74	4.82	0.18
BMI	1	0.99	0.94	1.05	0.83
Age of diagnosis	5	0.96	0.83	1.1	0.56
Race (white vs. non-white)		1	0.43	2.32	0.996
PC20		0.93	0.78	1.12	0.45
Smoking History (yes/no)		1.29	0.44	3.73	0.64
Nasal Steroid use (yes/no)		1.35	0.6	3.06	0.47
Eosinophil count from blood		1.61	0.33	7.81	0.56
History of sinusitis		0.72	0.31	1.65	0.44

A Multivariate Analysis of Risk Factors for the Air-Trapping Asthmatic Phenotype as Measured by Quantitative CT Analysis.
Ashley Busacker, John D. Newell, Jr., Thomas Keefe, Eric A. Hoffman, Janice Cook Granroth, Mario Castro, Sean Fain and Sally Wenzel
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