ORIGINAL ARTICLE

Pruning of the Pulmonary Vasculature in Asthma

The Severe Asthma Research Program (SARP) Cohort

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Abstract

Rationale: Loss of the peripheral pulmonary vasculature, termed vascular pruning, is associated with disease severity in patients with chronic obstructive pulmonary disease.

Objectives: To determine if pulmonary vascular pruning is associated with asthma severity and exacerbations.

Methods: We measured the total pulmonary blood vessel volume (TBV) and the blood vessel volume of vessels less than 5 mm^2 in cross-sectional area (BV5) and of vessels less than 10 mm^2 (BV10) in cross-sectional area on noncontrast computed tomographic scans of participants from the Severe Asthma Research Program. Lower values of the BV5 to TBV ratio (BV5/TBV) and the BV10 to TBV ratio (BV10/TBV) represented vascular pruning (loss of the peripheral pulmonary vasculature).

Measurements and Main Results: Compared with healthy control subjects, patients with severe asthma had more pulmonary vascular pruning. Among those with asthma, those with poor asthma control had more pruning than those with well-controlled disease. Pruning of the pulmonary vasculature was also associated with lower percent predicted FEV_1 and FVC, greater peripheral and sputum eosinophilia, and higher BAL serum amyloid A/lipoxin A_4 ratio but not with low-attenuation area or with sputum neutrophilia. Compared with individuals with less pruning, individuals with the most vascular pruning had 150% greater odds of reporting an asthma exacerbation (odds ratio, 2.50; confidence interval, 1.05–5.98; $P = 0.039$ for BV10/TBV) and reported 45% more asthma exacerbations during follow-up (incidence rate ratio, 1.45; confidence interval, 1.02–2.06; $P = 0.036$ for BV10/TBV).

Conclusions: Pruning of the peripheral pulmonary vasculature is associated with asthma severity, control, and exacerbations, and with lung function and eosinophilia.

Keywords: severe asthma; eosinophilia; pulmonary vascular; pruning

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At a Glance Commentary

Scientific Knowledge on the Subject: Loss of the peripheral pulmonary vasculature seen on computed tomography, often termed vascular pruning, has been shown to be associated with emphysema and with disease severity in patients with chronic obstructive pulmonary disease. It is unknown if it is present in asthma.

What This Study Adds to the Field: In this study, we demonstrate that not only is pulmonary vascular pruning present in the computed tomography scans of individuals with asthma, it is also associated with disease severity and is independently associated with an increased odds and rate of asthma exacerbations.

Although asthma and chronic obstruction pulmonary disease (COPD) are often thought of as diseases of the airways, both are also associated with changes in the other lung compartments including the pulmonary vasculature (1–15). COPD in particular is associated with radiologic and pathologic changes in the pulmonary vasculature that are, in turn, associated with mortality and disease severity (1–6). For example, we have shown that a smaller relative volume of the peripheral pulmonary vasculature, often termed vascular pruning, measured using computed tomographic (CT), is associated with COPD disease severity and cardiac dysfunction (16, 17).

Although there are fewer studies on pulmonary vascular involvement in asthma, in certain cases asthma is associated with significant vascular involvement, such as in eosinophilic granulomatous polyangiitis (18). In addition, several animal models of asthma develop inflammation and remodeling of the pulmonary vessels, raising the question of whether vascular involvement may be present in patients with asthma who do not meet the clinical criteria for eosinophilic granulomatous polyangiitis (7–13). Based on these findings and our prior work on COPD, we hypothesized that CT measures of pruning of the pulmonary vasculature may be associated with disease severity in asthma.

Some of these results have previously been reported in the form of an abstract (19).

Methods

Cohort and Clinical Measurements

The Severe Asthma Research Program (SARP) is an NIH-sponsored multicenter study designed to improve the understanding of severe asthma (20, 21). For this study we used data from adult participants with both severe and nonsevere asthma from the third phase of SARP (SARP III) and from a smaller group of participants characterized as healthy control subjects (20). Severe asthma was defined based on the American Thoracic Society/European Respiratory Society guidelines, and mild-moderate asthma was defined based on the National Asthma Education and Prevention Program guidelines (20–23). Individuals were defined as having well-controlled asthma if they had an asthma control test (ACT) score greater than or equal to 20, an asthma control questionnaire score less than or equal to 0.75, and one or fewer exacerbations in the past year. They were defined as being suboptimally controlled if they had an ACT score of between 16 and 19 and/or two to three exacerbations in the past year, and were defined as poorly controlled if their ACT score was less than or equal to 15 or their asthma control questionnaire score was greater than or equal to 1.5 or if they had three or more exacerbations in the past year. All subjects had fewer than 5 pack-years of smoking history and none had smoked within the prior 5 years (20). All participants provided informed consent and the study was approved by the institutional review board at each center.

At the baseline visit, participants provided an extensive questionnaire-based history that included asthma control surveys. They also underwent lung function testing including measurement of the fractional exhaled nitric oxide and a bronchodilator challenge (24–34). Peripheral (blood) eosinophilia and sputum eosinophilia were also measured, and those individuals without a contraindication underwent methacholine challenge and bronchoscopy (20, 35, 36). At the second baseline visit, adult participants were given 40 mg of intramuscular triamcinolone to determine their response to systemic steroids (37). The asthma control surveys, spirometry, bronchodilator response, and sputum and peripheral eosinophilia measures were then repeated 18 $\pm$ 3 (mean $\pm$ SD) days later, and for this study changes in these measures are expressed as absolute differences from baseline (24). Participants returned for annual follow-up visits that included spirometry and an updated questionnaire-based history with questions regarding interval asthma exacerbations, which were defined as respiratory events that required at least 3 days of an oral or intravenous steroid burst (a dose $>$10 mg or double the individual's chronic daily steroid dose). For our study, a participant was defined as having an asthma exacerbation if at least one was reported during follow-up.

CT Imaging and Analysis

Volumetric CT scans of the chest were performed on a subgroup of individuals from three clinical centers (the Universities

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Author Contributions: The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. S.Y.A., F.N.R., B.D.L., R.S.J.E., E.I., and G.R.W. designed the initial study and wrote the initial manuscript. S.Y.A. and F.N.R performed the literature search and the statistical analyses, and created the figures. F.N.R. and R.S.J.E. developed the vascular analysis tool and deployed it in the available data. S.Y.A., F.N.R., C.E.C., J.C.R., A.G.C., J.C.C.-G., E.M.D., E.R.B., M.C., J.V.F., S.B.F., B.M.G., E.A.H., N.N.J., D.T.M., and S.E.W. contributed to the final study design and to the production of the final manuscript.

Table 1. Cohort Characteristics

		n Available
Clinical characteristics		
Age, yr, mean ± SD	46.0 ± 14.8	237
Female, *n* (%)	157 (66.2)	237
Nonwhite, *n* (%)	93 (39.2)	237
Body mass index, kg/m^2, mean ± SD	32.8 ± 9.0	237
Spirometric characteristics		
Percent predicted FEV_1, mean ± SD	73.2 ± 20.8	237
Percent predicted FVC, mean ± SD	84.9 ± 18.1	237
Percent change in FEV_1 with bronchodilator, mean ± SD	17.4 ± 17.3	237
Methacholine challenge PC_{20}, mean ± SD	2.9 ± 3.5	103
Asthma category, *n* (%)		
Healthy control	11 (4.6)	237
Nonsevere	68 (28.7)	237
Severe	158 (66.7)	237
Asthma control		
Asthma control test score, mean ± SD	16.4 ± 5.0	226
Poor asthma control, *n* (%)	131 (58.0)	226
Eosinophilia		
Peripheral eosinophil, %, mean ± SD	4.1 ± 3.5	233
Sputum eosinophil, %, mean ± SD	4.2 ± 9.4	176
Fractional exhaled nitric oxide, mean ± SD	29.7 ± 27.4	234
Steroid response		
Change in peripheral eosinophil, %, mean ± SD	−1.9 ± 2.9	121
Change in sputum eosinophil, %, mean ± SD	−2.6 ± 8.1	141
Change in fractional exhaled nitric oxide, mean ± SD	−7.1 ± 20.6	218
Change in FEV_1, mean ± SD	0.09 ± 0.27	223
Other sputum characteristics		
Sputum neutrophil, %, mean ± SD	55.0 ± 24.7	176
BAL		
BAL neutrophil, %, mean ± SD	2.0 ± 3.0	93
BAL eosinophil, %, mean ± SD	1.6 ± 5.4	93
BAL serum amyloid A/lipoxin A_4 ratio, mean ± SD	109.1 ± 340.3	58
Quantitative CT measures		
CT measured lung volume, L, mean ± SD	5.0 ± 1.2	237
Percent low-attenuation area, mean ± SD	2.0 ± 2.3	237
Percent air trapping on expiratory CT, mean ± SD	10.8 ± 2.8	187
Measures of pulmonary vasculature		
BV5, ml, mean ± SD	111.0 ± 28.4	237
BV10, ml, mean ± SD	134.8 ± 31.6	237
TBV, ml, mean ± SD	188.7 ± 42.6	237
BV5/TBV, mean ± SD	0.587 ± 0.066	237
BV10/TBV, mean ± SD	0.714 ± 0.050	237
Longitudinal exacerbation analyses		
Duration of follow-up, yr, mean ± SD	2.6 ± 1.2	214
Number of exacerbations per yr, mean ± SD	1.2 ± 1.6	214
Participants who reported at least 1 exacerbation during follow-up, *n* (%)	87 (40.7)	214

Definition of abbreviations: BV5 = aggregate vessel volume for vessels less than 5 mm^2 in cross-sectional area; BV10 = aggregate vessel volume for vessels less than 10 mm^2 in cross-sectional area; CT = computed tomography; PC_{20} = provocative concentration causing a 20% fall in FEV_1; TBV = total pulmonary blood vessel volume.
Low-attenuation area is defined as the percentage of lung occupied by tissue with attenuation less than −950 Hounsfield units on inspiratory CT obtained.
Percentage of area with air trapping is defined as the percentage of lung occupied by tissue with attenuation less than −856 Hounsfield units on expiratory CT.

of Pittsburgh and Wisconsin and Washington University in St. Louis). CT scanning was performed using the protocol established by the SPIROMICS (Subpopulations of Intermediate Outcome Measures in Chronic Obstructive Pulmonary Disease) study, which includes contiguous images to enable vascular segmentation. For this study, the primary analyses, including the measurements of the pulmonary vasculature, were performed using baseline scans acquired at TLC (38, 39). Expiratory CT images were obtained in a subset of individuals and were acquired at FRC for consistency with prior SARP studies (39). We applied previously described fully automated methods to segment the lungs from the chest wall and other thoracic structures and to segment the pulmonary vasculature from the lung parenchyma (40, 41).

We also performed automated measurements of the percentage of lung occupied by low-attenuation area (LAA) (on images acquired at TLC), which is a densitometric measure of airspace dilation and destruction correlated with emphysema, and of the percentage of lung with air trapping (on images acquired at FRC). For the purposes of this study LAA was defined as area with an attenuation less than −950 Hounsfield units based on prior work suggesting that tissue with a density less than this threshold is most closely associated with the histopathologic presence of emphysema, and air trapping was defined as the percentage of lung with an attenuation of less than −856 Hounsfield units (42–47).

Summary measures of the pulmonary vasculature included the total blood vessel volume (TBV) and the blood vessel volume of the smaller pulmonary blood vessels using two different thresholds: those less than 5 mm^2 in cross-sectional area and those less than 10 mm^2 in cross-sectional area (BV5 and BV10, respectively) (16, 48, 49). These volumes are the combined volumes of the pulmonary arteries and veins, and because of variations in blood vessel volume based on overall body size, all analyses were performed using the ratio of either BV5 or BV10 to TBV (BV5/TBV and BV10/TBV, respectively). Lower values of these ratios suggest CT imaging evidence of vascular pruning (i.e., a smaller proportion of the blood vessel volume comprised of small peripheral pulmonary blood vessels) (16). All of the quantitative image analyses were performed using the Chest Imaging Platform (https://chestimagingplatform.org/) and implemented using 3D Slicer (https://www.slicer.org/), both of which are open source image processing tools (50, 51).

Statistical Analysis

Summary statistics are presented as means and SD where appropriate. The measures

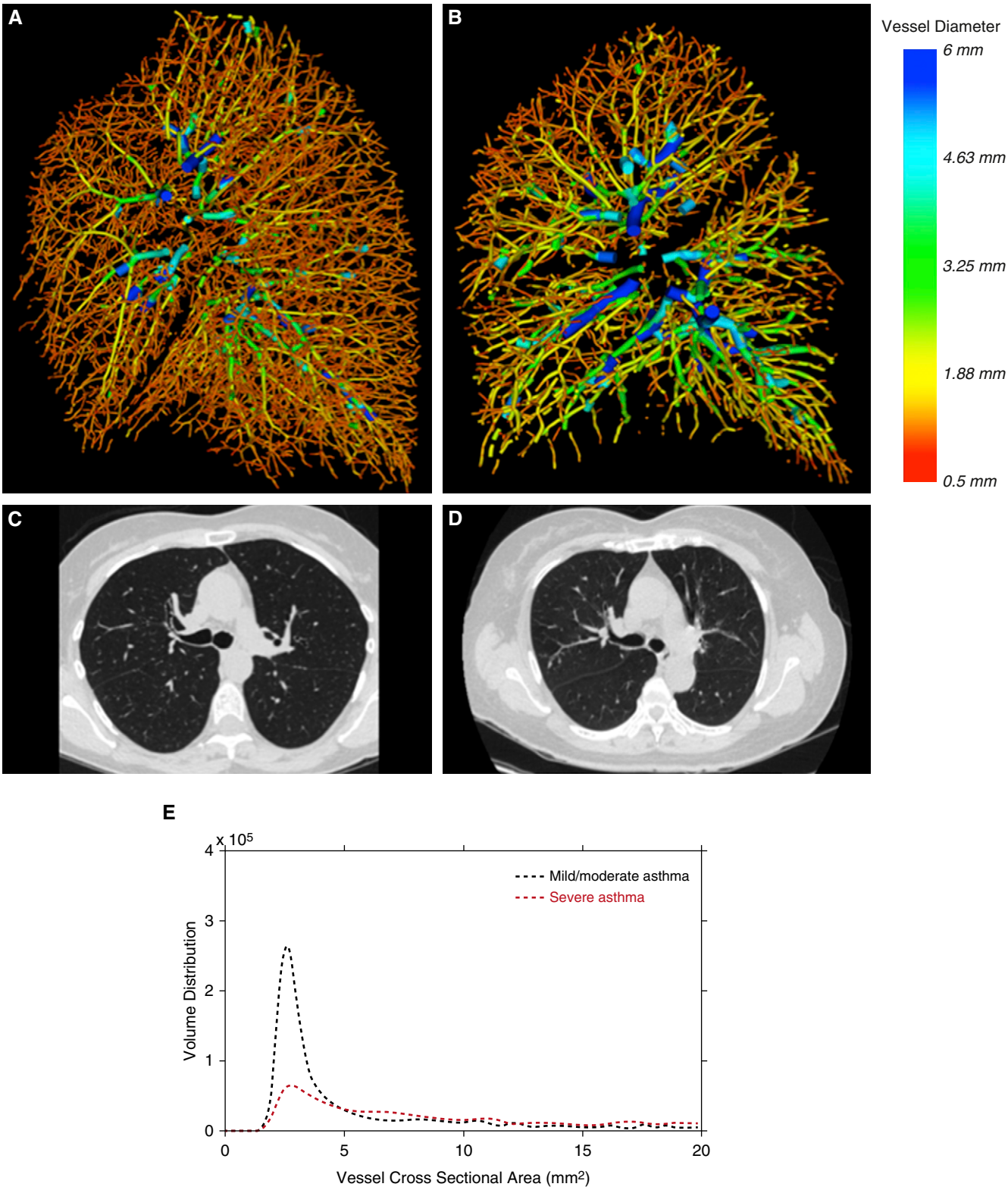

Figure 1. Sagittal view of the three-dimensional quantitative reconstruction of the pulmonary vasculature in the right lung of (*A*) a subject without evidence of pruning and normal lung function (FEV_1 percent predicted, 97%), and (*B*) a subject with evidence of pruning and impaired lung function (FEV_1 percent predicted, 75%). The color red corresponds to smaller vessels, and blue corresponds to larger vessels. (*C* and *D*) Representative axial computed tomography images from the same two participants. (*E*) Quantitative profiles of blood volume distribution of the same two participants.

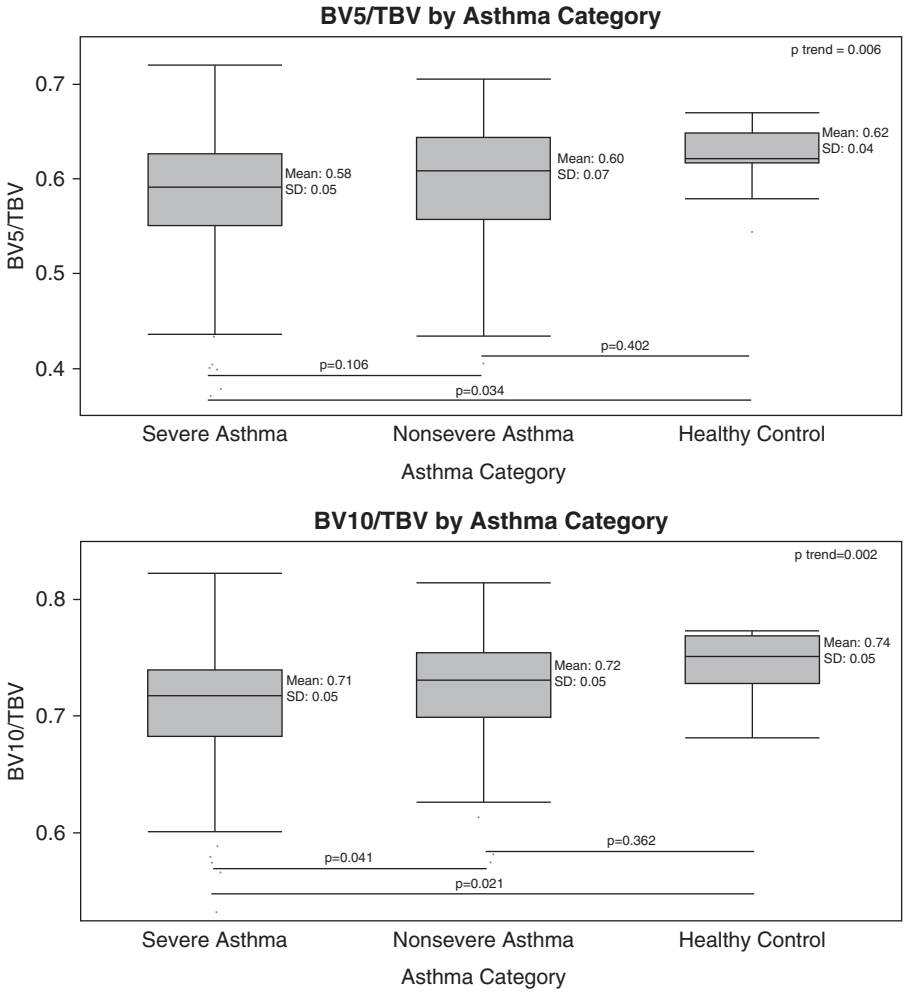

Figure 2. Pruning by asthma disease severity. Severe asthma was defined on the basis of American Thoracic Society/European Respiratory Society guidelines, and mild–moderate asthma was defined on the basis of National Asthma Education and Prevention Program guidelines (20–23). In box plots, the box portion represents the 25th to the 75th percentile with the solid mid-line representing the mean, and the whisker portion represents the 2.5th to the 97.5th percentile. *P* values for pairwise comparisons shown below the box plots are based on the Steel-Dwass-Critchlow-Fligner method (53). *P* trend values are based on the Jonckheere-Terpstra test. BV5 = blood vessel volume of vessels less than 5 mm^2 in cross-sectional area; BV10 = blood vessel volume of vessels less than 10 mm^2 in cross-sectional area; TBV = total pulmonary blood vessel volume.

of vascular pruning were analyzed as continuous variables except for the analyses of the odds of a prospective asthma exacerbation as discussed later. Pearson correlation and multivariable linear regression were used to determine the associations between the measures of vascular pruning and other continuous clinical and radiographic measurements. The latter analyses were adjusted for age, sex, race, body mass index, LAA, CT measured lung volume, and prebronchodilator percent predicted FEV_1 (FEV_1 pp), except for the models for the baseline spirometric measures, which were not adjusted for prebronchodilator FEV_1 pp and the models for the densitometric CT measures (LAA and air trapping), which were not adjusted for LAA. Bonferroni correction was applied to the multivariable analyses to account for multiple testing as indicated, but not to the univariate correlations because these were believed to be descriptive.

Because we hypothesized that greater asthma severity and worse asthma control would be associated with more pulmonary vascular pruning, the Jonckheere-Terpstra test, a rank based nonparametric test for ordered differences among classes, was used to test the associations between asthma severity category (ordered as healthy control, mild-moderate asthma, severe asthma) and vascular pruning, and for the association between and asthma control category (ordered as well-controlled, suboptimally controlled, poorly controlled) and vascular pruning (52). In addition, pair-wise comparisons were made between asthma severity categories and asthma control categories using the Steel-Dwass-Critchlow-Fligner method, a nonparametric approach based on pair-wise two-sample Wilcoxon comparisons corrected for multiple testing (53).

Multivariable logistic regression was used to assess the associations between BV5/TBV and BV10/TBV and the odds of reporting a prospective asthma exacerbation, and zero inflated negative binomial regression was used to assess the associations between BV5/TBV and BV10/TBV and the rate of prospective asthma exacerbations (54). The latter was chosen to account for the large number of participants who reported no exacerbation during follow-up. For these analyses the odds ratios and incidence rate ratios are expressed as the odds or rate of those with the most vascular pruning (those in the lowest 25% of BV5/TBV or BV10/TBV) versus those with less vascular pruning (those in the highest 75% of BV5/TBV or BV10/TBV). The multivariable exacerbation analysis models were adjusted for age, sex, race, body mass index, prebronchodilator FEV_1 pp, baseline ACT score, and a reported history of exacerbation in the year before the baseline visit. All analyses were performed using SAS 9.4 or JMP 13 Pro (SAS Institute), all statistical tests were two-sided, and P less than 0.05 were considered statistically significant.

Results

The clinical and imaging characteristics of the 237 participants who had CT imaging and clinical data available are shown in Table 1. Of note, the cohort was largely comprised of individuals with severe asthma who had a relatively small amount (mean ± SD, 2.0 ± 2.3%) of LAA or emphysema-like tissue on CT. Figure 1 provides examples of the pulmonary vasculature of the right lung from individuals with mild and severe asthma, and demonstrates loss of the peripheral pulmonary vasculature in the individual

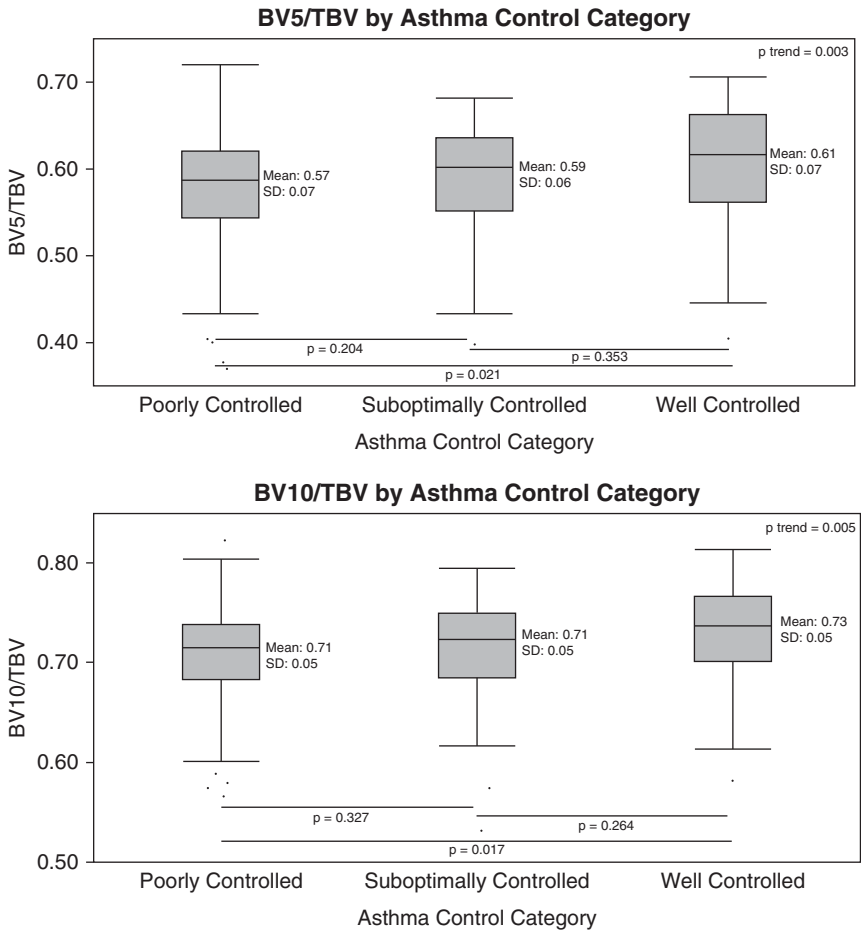

Figure 3. Pruning by asthma control category. The categories are: well controlled—ACT ⩾20 and ACQ ⩽0.75 and one or fewer exacerbations in the past year; suboptimally controlled—ACT 16–19 and/or 2–3 exacerbations in the past year; and poorly controlled—ACT ⩽15 or ACQ ⩾1.5 or three or more exacerbations in the past year. In box plots, the box portion represents the 25th to the 75th percentile with the solid mid-line representing the mean, and the whisker portion represents the 2.5th to the 97.5th percentile. *P* values for pairwise comparisons shown below the box plots are based on the Steel-Dwass-Critchlow-Fligner method (53). *P* trend values are based on the Jonckheere-Terpstra test. ACQ = asthma control questionnaire; ACT = asthma control test; BV5 = blood vessel volume of vessels less than 5 mm^2 in cross-sectional area; BV10 = blood vessel volume of vessels less than 10 mm^2 in cross-sectional area; TBV = total pulmonary blood vessel volume.

with more severe disease. As shown in Figure 2, greater asthma severity was associated with a trend toward greater pruning of the pulmonary vasculature (i.e., lower BV5/TBV and BV10/TBV; *P* for trend = 0.006 and 0.002 for BV5/TBV and BV10/TBV, respectively), but pairwise differences were only present between those with severe disease and healthy control subjects ($P = 0.034$ and 0.021 for BV5/TBV and BV10/TBV, respectively) and between those with severe asthma and those with mild-moderate disease (BV10/TBV only, $P = 0.041$). Similarly, as shown in Figure 3 worse asthma control was associated with a trend toward more vascular pruning (*P* for trend = 0.003 and 0.005 for BV5/TBV and BV10/TBV, respectively), but pairwise differences were only present between those with well-controlled asthma and those with poorly controlled asthma ($P = 0.021$ and $P = 0.017$ for BV5/TBV and BV10/TBV, respectively).

The univariate correlations between vascular pruning and continuous clinical and radiologic measures are shown in Table 2 and Figure 4. Notably, loss of the peripheral pulmonary vasculature was correlated with lower lung function, lower ACT score, more air trapping (BV10/TBV only), greater peripheral eosinophilia and sputum eosinophilia (BV10/TBV only for sputum eosinophilia), higher BAL white blood cell count, and a higher BAL serum amyloid A to lipoxin A_4 ratio (SAA/LXA_4).

In the multivariable analyses, loss of the peripheral pulmonary vasculature was associated with lower FEV_1 pp and percent predicted FVC (FVC pp), and higher BAL SAA/LXA_4. It was also associated with greater peripheral and sputum eosinophilia, and a greater reduction in peripheral eosinophils in response to triamcinolone (BV10/TBV only). The largest changes in vascular pruning were associated with the SAA/LXA_4 ratio. For every 1 SD increase in BAL SAA/LXA_4 BV5/TBV decreased by 0.0233 (confidence interval [CI], 0.0124–0.0341; $P < 0.001$) and BV10/TBV decreased by 0.0208 (CI, 0.0123–0.0294; $P < 0.001$) (Table 3). Strong associations were also seen with lung function and peripheral and sputum eosinophilia. For example, for every 1 SD decrease in FEV_1 pp BV5/TBV decreased by 0.0170 (CI, 0.0078–0.0261; $P < 0.001$) and BV10/TBV decreased by 0.0143 (CI, 0.0071–0.0214; $P = 0.001$), and for every 1 SD increase in peripheral eosinophilia BV5/TBV decreased by 0.0138 (CI, 0.0039–0.0237; $P = 0.001$) and BV10/TBV decreased by 0.0130 (CI, 0.0053–0.0206; $P < 0.001$).

Finally, compared with individuals with less pruning, individuals with the most vascular pruning (i.e., those in the lowest quartile of BV10/TBV) had a 150% greater odds of reporting an asthma exacerbation during follow-up (BV10/TBV only: odds ratio, 2.50; CI, 1.05–5.98; $P = 0.039$) (Table 4), and had a 45% higher exacerbation rate during follow-up (BV5/TBV incidence rate ratios, 1.45; CI, 1.00–2.11; $P = 0.049$) (BV10/TBV incidence rate ratios, 1.45; CI, 1.02–2.06; $P = 0.036$) (Table 5).

Discussion

In this study of patients with severe and mild-moderate asthma, we found that loss of the peripheral pulmonary vasculature on CT scan was associated with a trend toward worse asthma severity and control. In addition, pulmonary vascular pruning, measured as a lower small vessel volume fraction, was associated with worse lung function, greater eosinophilic inflammation, and a higher BAL SAA/LXA_4 ratio. Finally, compared with those with less pruning, those who had the most pruning had a higher odds of having an asthma

Table 2. Univariate Correlations

Parameter	BV5/TBV		BV10/TBV	
	r	*P* Value	*R*	*P* Value
Prebronchodilator FEV_1 pp	0.41	<0.001	0.44	<0.001
Prebronchodilator FVC pp	0.44	<0.001	0.45	<0.001
Percent change in FEV_1 with bronchodilator	−0.12	0.057	−0.12	0.061
Methacholine challenge PC_{20}	0.10	0.333	0.09	0.387
Asthma control test score	0.25	<0.001	0.22	0.001
Low-attenuation area	0.06	0.320	0.07	0.280
Percent air trapping on expiratory CT	−0.14	0.063	−0.16	0.033
Peripheral eosinophil, %	−0.15	0.022	−0.22	0.001
Sputum eosinophil, %	−0.16	0.033	−0.21	0.005
Fractional exhaled nitric oxide	−0.01	0.831	−0.05	0.449
Sputum neutrophil, %	−0.03	0.682	−0.06	0.413
BAL neutrophil, %	−0.07	0.520	−0.09	0.384
BAL eosinophil, %	0.14	0.180	0.14	0.186
BAL serum amyloid A/lipoxin A_4 ratio	−0.57	<0.001	−0.59	<0.001
Steroid response				
Change in prebronchodilator FEV_1	0.00	0.975	−0.01	0.877
Change in peripheral eosinophil, %	0.20	0.028	0.30	0.001
Change in sputum eosinophil, %	0.05	0.552	0.12	0.163
Change in fractional exhaled nitric oxide	−0.07	0.315	−0.04	0.523

Definition of abbreviations: BV5 = blood vessel volume for vessels less than 5 mm^2 in cross-sectional area; BV10 = blood vessel volume for vessels less than 10 mm^2 in cross-sectional area; CT = computed tomography; PC_{20} = provocative concentration causing a 20% fall in FEV_1; pp = percent predicted; TBV = total pulmonary blood vessel volume.
n = 237 for all analyses except for: methacholine challenge (*n* = 103), sputum eosinophil % (*n* = 176), BAL neutrophil % (*n* = 92), BAL eosinophil % (*n* = 92), BAL serum amyloid A/lipoxin A_4 (*n* = 58), FEV_1 steroid response (*n* = 223), peripheral eosinophil steroid response (*n* = 121), sputum eosinophil steroid response (*n* = 141), fractional exhaled nitric oxide steroid response (*n* = 218), and air trapping (*n* = 187).

exacerbation during follow-up and had a higher rate of asthma exacerbations during follow-up.

Our data suggest that pulmonary vascular pruning is associated with increased asthma severity and reduced lung function as well as eosinophil specific inflammation. Whether pruning contributes to this severity or is a physiologic or pathophysiologic result of the severity is unclear. Much of the prior work on the vasculature within the lung in patients with asthma has focused on the bronchial circulation, whereas the involvement of the pulmonary circulation is less well characterized (7, 14, 15, 18, 55–59). In a small autopsy study, Saetta and coworkers (60) examined the muscular pulmonary arteries adjacent to peripheral airways from patients with fatal asthma and found that the pulmonary arteries did not differ in size, intimal thickness, medial thickness, or adventitial thickness compared with those from control subjects, but did have more adventitial eosinophilic inflammation. In a series of studies, Rydell-Törmänen and coworkers (8, 12) found that allergic airway inflammation was associated with increased eosinophilic vascular inflammation,

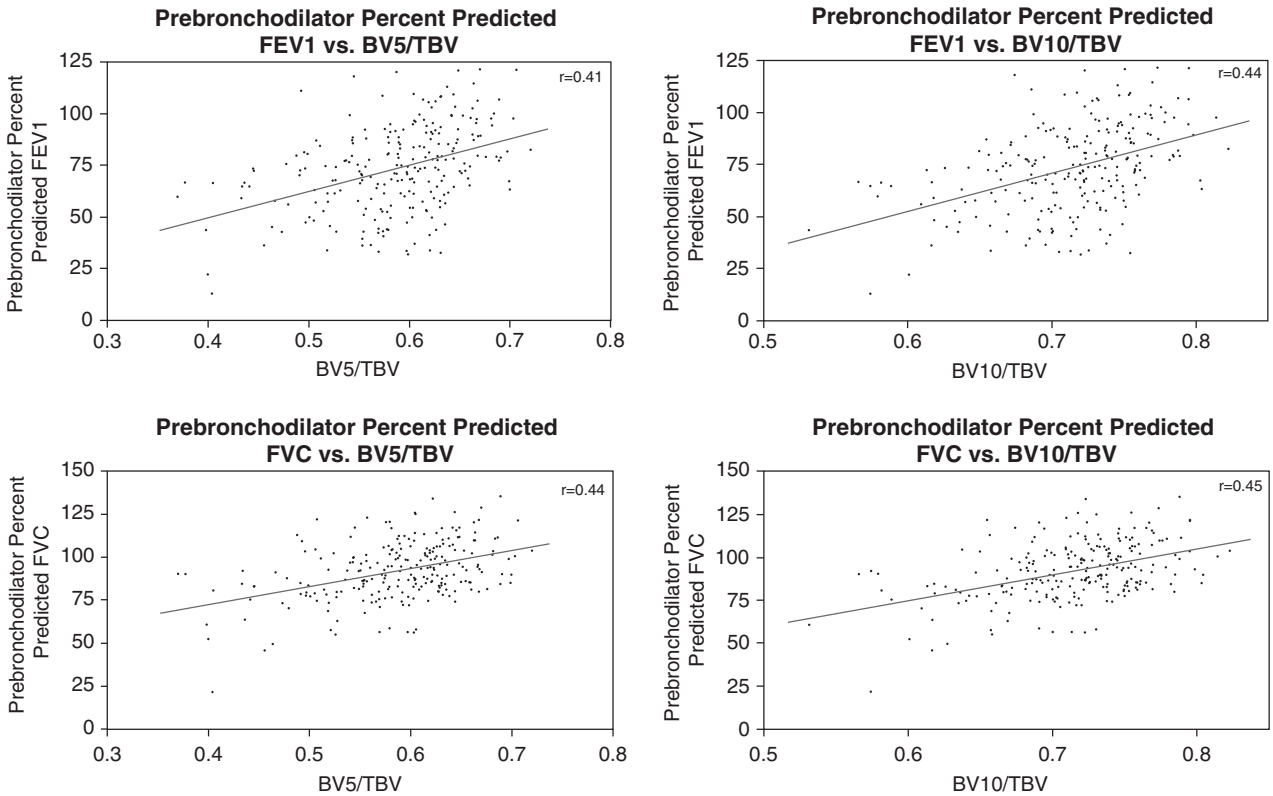

Figure 4. Pruning and lung function. *r* values are based on Pearson correlation. For definition of abbreviations, *see* Figure 2.

Table 3. Multivariable Associations

Parameter	BV5/TBV			BV10/TBV		
	Change Per 1 SD	Confidence Interval	*P* Value	Change Per 1 SD	Confidence Interval	*P* Value
Effect on clinical parameter expressed per 1 SD change in pruning						
Prebronchodilator FEV_1 pp	7.10	3.28 to 10.92	<0.001	7.28	3.55 to 10.73	0.001
Prebronchodilator FVC pp	4.71	1.59 to 7.84	<0.001	4.77	1.83 to 7.71	<0.001
Percent change in FEV_1 with bronchodilator	**2.05**	**−1.01 to 5.10**	**0.370**	**2.18**	**−0.72 to 5.08**	**0.237**
Methacholine challenge PC_{20}	**−0.15**	**−1.37 to 1.06**	**1.000**	**−0.20**	**−1.37 to 0.96**	**1.000**
Asthma control test score	0.23	−0.71 to 1.17	1.000	0.18	−0.72 to 1.07	1.000
Low-attenuation area	**0.12**	**−0.34 to 0.58**	**1.000**	**0.23**	**−0.21 to 0.67**	**0.732**
Percent air trapping on expiratory CT	**−2.09**	**−4.87 to 0.69**	**0.238**	**−1.55**	**−4.24 to 1.13**	**0.584**
Peripheral eosinophil, %	−1.12	−1.91 to −0.32	0.001	−1.27	−2.02 to −0.52	<0.001
Sputum eosinophil, %	−3.05	−5.73 to −0.38	0.015	−3.28	−5.82 to −0.74	0.004
BAL eosinophil, %	0.52	−2.01 to 3.05	1.000	0.45	−1.92 to 2.82	1.000
Fractional exhaled nitric oxide	−3.73	−10.39 to 2.92	0.985	−4.60	−10.92 to 1.72	0.367
Sputum neutrophil, %	**0.03**	**−6.97 to 7.03**	**1.000**	**−0.49**	**−7.19 to 6.21**	**1.000**
BAL neutrophil, %	**0.13**	**−1.21 to 1.48**	**1.000**	**−0.01**	**−1.27 to 1.25**	**1.000**
BAL serum amyloid A/lipoxin A_4 ratio	**−269.7**	**−441.3 to −98.1**	**<0.001**	**−268.6**	**−418.9 to −118.2**	**<0.001**
Steroid response						
Change in prebronchodilator FEV_1	−0.01	−0.08 to 0.06	1.000	−0.01	−0.07 to 0.06	1.000
Change in peripheral eosinophil, %	0.72	−0.16 to 1.60	0.197	0.94	0.12 to 1.76	0.014
Change in sputum eosinophil, %	1.46	−1.33 to 4.26	1.000	1.96	−0.64 to 4.56	0.306
Change in fractional exhaled nitric oxide	1.04	−4.01 to 6.09	1.000	1.77	−3.04 to 6.58	1.000
Effect on pruning measure expressed per 1 SD change in clinical parameter						
Prebronchodilator FEV_1 pp	0.0170	0.0078 to 0.0261	<0.001	0.0143	0.0071 to 0.0214	0.001
Prebronchodilator FVC pp	0.0173	0.0058 to 0.0288	<0.001	0.0147	0.0056 to 0.0237	<0.001
Percent change in FEV_1 with bronchodilator	**0.0069**	**−0.0034 to 0.0172**	**0.370**	**0.0061**	**−0.0020 to 0.0142**	**0.237**
Methacholine challenge PC_{20}	**−0.0017**	**−0.0148 to 0.0115**	**1.000**	**−0.0018**	**−0.0121 to 0.0085**	**1.000**
Asthma control test score	0.0020	−0.0063 to 0.0103	1.000	0.0013	−0.0052 to 0.0078	1.000
Low-attenuation area	**0.0023**	**−0.0069 to 0.0116**	**1.000**	**0.0039**	**−0.0034 to 0.0111**	**0.732**
Percent air trapping on expiratory CT	**−0.0080**	**−0.0186 to 0.0026**	**0.238**	**−0.0048**	**−0.0131 to 0.0035**	**0.584**
Peripheral eosinophil, %	−0.0138	−0.0237 to −0.0039	0.001	−0.0130	−0.0206 to −0.0053	<0.001
Sputum eosinophil, %	−0.0119	−0.0223 to −0.0015	0.015	−0.0104	−0.0185 to −0.0023	0.004
BAL eosinophil, %	0.0022	−0.0086 to 0.0130	1.000	0.0016	−0.0070 to 0.0102	1.000
Fractional exhaled nitric oxide	−0.0051	−0.0143 to 0.0040	0.985	−0.0052	−0.0123 to 0.0019	0.367
Sputum neutrophil, %	**0.00004**	**−0.0100 to 0.0100**	**1.000**	**−0.0006**	**−0.0084 to 0.0072**	**1.000**
BAL neutrophil, %	**0.0013**	**−0.0117 to 0.0142**	**1.000**	**−0.0001**	**−0.0104 to 0.0103**	**1.000**
BAL serum amyloid A/lipoxin A_4 ratio	**−0.0233**	**−0.0380 to −0.0085**	**<0.001**	**−0.0208**	**−0.0325 to −0.0092**	**<0.001**
Steroid response						
Change in prebronchodilator FEV_1	−0.0012	−0.0106 to 0.0083	1.000	−0.0007	−0.0081 to 0.0067	1.000
Change in peripheral eosinophil, %	0.0117	−0.0026 to 0.0259	0.197	0.0126	0.0016 to 0.0236	0.014
Change in sputum eosinophil, %	0.0058	−0.0052 to 0.0168	1.000	0.0065	−0.0021 to 0.0152	0.306
Change in fractional exhaled nitric oxide	0.0020	−0.0078 to 0.0119	1.000	0.0028	−0.0049 to 0.0105	1.000

For definition of abbreviations, *see* Table 2.

For effect on clinical parameter expressed per 1 SD change in pruning, change is expressed as an absolute amount per 1 SD increase in BV5/TBV or BV10/TBV. For instance, for 1 SD increase in BV5/TBV the prebronchodilator FEV_1 pp increases by 7.10.

For effect on pruning measure expressed per 1 SD change in clinical parameter, change is expressed as an absolute amount per 1 SD increase in clinical, laboratory, or imaging parameter. For instance, for 1 SD increase in the prebronchodilator FEV_1 pp the BV5/TBV increases by 0.0170.

Models were adjusted for age, sex, race, body mass index, percentage of lung occupied by low-attenuation area, CT-measured lung volume, and prebronchodilator FEV_1 pp except for the models for the baseline spirometric measures, which were not adjusted for prebronchodilator FEV_1 pp, and the models for the densitometric CT measurements, which were not adjusted for low-attenuation area.

P values and confidence intervals given are corrected for multiple comparisons within each group/family as represented by boldface, using the Bonferroni correction. For example, for the spirometric analyses the *P* values given are adjusted for a total of four comparisons (BV5/TBV with FEV_1 and FVC, and BV10/TBV with FEV_1/FVC). Confidence intervals are similarly corrected. For example, for the spirometric analyses, the confidence intervals given are the 98.75% confidence intervals.

$n = 237$ for all analyses except for: methacholine challenge ($n = 103$), sputum eosinophil % ($n = 176$), BAL neutrophil % ($n = 92$), BAL eosinophil % ($n = 92$), BAL serum amyloid A/lipoxin A_4 ($n = 58$), peripheral eosinophil steroid response ($n = 121$), sputum eosinophil steroid response ($n = 141$), fractional exhaled nitric oxide steroid response ($n = 218$), and air trapping ($n = 187$).

Table 4. Association between Vascular Pruning and Prospective Asthma Exacerbations

	Odds Ratio for Reporting Asthma Exacerbation during Follow-up	Confidence Interval	*P* Value
BV5/TBV (low vs. high)	1.51	0.65 to 3.54	0.341
BV10/TBV (low vs. high)	2.50	1.05 to 5.98	0.039

Definition of abbreviations: BV5 = aggregate vessel volume for vessels less than 5 mm^2 in cross-sectional area; BV10 = aggregate vessel volume for vessels less than 10 mm^2 in cross-sectional area; TBV = total pulmonary blood vessel volume.
BV5/TBV and BV10/TBV dichotomized at 25th percentile. That is, effect estimates are expressed as odds of those with the most pruning (top 25%) vs. those with less pruning (bottom 75%).
All models were adjusted for baseline values of age, sex, race, body mass index, prebronchodilator FEV_1 percent predicted, and asthma control test score as well as for a reported history of exacerbation in the year before the baseline visit.
n with longitudinal data available = 214. *n* who reported exacerbation during follow-up = 87 (40.7%).

vascular smooth muscle remodeling, perivascular alterations in collagen synthesis, and increase in endothelial cell proliferation in allergen-exposed BALB/C mice. Their work also suggests that some of this vascular remodeling may be irreversible (10, 11).

Although these studies generally examined vasculature much smaller than described in our current work, they suggest possible biologic plausibility for our findings. Namely, severe asthma may have a previously unappreciated "small vessel" component, even in the absence of clinically apparent eosinophilic granulomatous polyangiitis. This may be in addition to or associated with the "small airways" aspect of the disease. Additional studies that include both CT imaging and biopsy or autopsy specimens are needed to demonstrate if this is the case. If it is, then it would be important to determine if in severe asthma these vascular changes are present in the small vessels of other organ systems as they are in other chronic diseases (61, 62).

The very strong association between the SAA/LXA_4 ratio and pulmonary vascular pruning is also intriguing. SAA is associated with BAL neutrophilia, and recently a high SAA, low LXA_4 endotype has been described that is associated with neutrophilic lung inflammation and poor asthma control (63, 64). However, SAA is also increased in severe allergic asthma, and may function as an adjuvant to promote allergy to an innocuous inhaled allergen (65, 66). LXA_4 is an arachidonic acid–derived specialized proresolving mediator, which is protective in murine models of lung inflammation and is decreased in the sputum and BAL of patients with severe asthma (67). Moreover, LXA_4 administration in ovalbumin-allergic mice decreases airway hyperresponsiveness and reduces lung tissue eosinophilia and vascular injury (68). It is therefore conceivable that increased SAA induced inflammation in the setting of low LXA_4 in severe asthma is associated with pulmonary vascular injury and pruning.

Although these pathophysiologic mechanisms for our finding are possible, alternative mechanisms for our observation of increased vascular pruning in severe asthma certainly exist and include functional rather than anatomic causes of decreased regional blood flow. For instance, airway constriction or occlusion, possibly caused by mucus plugging, may result in regional hypoventilation and hypoxia, which in turn may lead to hypoxic vasoconstriction of the small pulmonary vessels in that region. Although this likely occurs to some extent, recent work using positron emission tomography/CT imaging suggests that it is not the sole mechanism for regional perfusion redistribution in bronchoconstricted patients with asthma, and other functional explanations are also likely to exist (60, 69). For instance, regional hypoventilation results in regional hyperinflation that may lead to increased alveolar pressure and compression of the pulmonary vasculature similar to what occurs in West's zone 1 (69–71). The lack of association between measures of vascular pruning and CT densitometry measured air trapping on expiratory imaging in the adjusted analyses in this study argue against this being the primary explanation for our findings. However, BV10/TBV was associated with CT-measured air trapping in the univariate analyses, a trend existed for the association between BV5/TBV and CT air trapping in the adjusted analyses, and expiratory imaging was only available in a subset of the participants. In addition, although correlated, air trapping on expiratory imaging and regional hyperinflation do not always overlap (72). Thus, further work that combines measurements of the pulmonary vasculature with regional measures of ventilation, air trapping, and hyperinflation, such as magnetic resonance imaging, parametric response mapping, and positron emission tomography, is needed to investigate these functional possibilities more fully (69, 70, 73–76).

Other potential explanations for our findings include a direct mechanical effect of airway constriction on the pulmonary vasculature or that asthma and pulmonary

Table 5. Association between Vascular Pruning and Prospective Asthma Exacerbation Rate

	Incidence Rate Ratio for Asthma Exacerbations during Follow-up	Confidence Interval	*P* Value
BV5/TBV (low vs. high)	1.45	1.00 to 2.11	0.049
BV10/TBV (low vs. high)	1.45	1.02 to 2.06	0.036

For definition of abbreviations, *see* Table 4.
BV5/TBV and BV10/TBV dichotomized at 25th percentile. That is, effect estimates are expressed as the rate of those with the most pruning (top 25%) vs. those with less pruning (bottom 75%).
All models were adjusted for baseline values of age, sex, race, body mass index, prebronchodilator FEV_1 percent predicted, and asthma control test score as well as for a reported history of exacerbation in the year before the baseline visit.
n with longitudinal data available = 214. *n* who reported exacerbation during follow-up = 87 (40.7%).

vascular remodeling share certain signaling pathways (69, 77). For instance, activation of the transcription factor NFAT (nuclear factor of activated T cells) has been implicated in the pathogenesis of both asthma and pulmonary arterial hypertension (7). If these diseases do share this mechanism of pathogenesis then stimulation of vasoactive intestinal peptide, or another inhibitor of NFAT activation, could be useful in the treatment of both (7).

One striking finding from our study is the lack of association between vascular pruning and a radiologic measure of emphysema, LAA (78). Although we were unable to definitively demonstrate a lack of emphysema in patients with severe asthma using histopathology, the absence of an association between LAA and pruning suggests that loss of the distal pulmonary vasculature in severe asthma is unlikely to be caused by clinically occult emphysema, or by misclassification of COPD. That said, in the absence of direct evaluation of patients' histopathology we are unable to say definitively that emphysema is not present. In addition, more broadly, without pathologic evaluation we are unable to definitely answer the question of whether there are pathologic changes to the distal pulmonary vasculature in the individuals with severe asthma who had vascular pruning. Future work that involves pathologic evaluation in combination with additional functional imaging is needed to better determine the precise mechanisms of our findings. Additional work is also needed using arterial-venous segmentation to determine if the associations seen in our study are differentially driven by arterial or venous pruning.

With regard to other limitations, the resolution of the CT scanning may limit the detection of the very small vasculature, which may partially explain our more robust findings with BV10/TBV than with BV5/TBV. Finally, the differences in pruning measures between asthma groups were relatively small and given the cohort size we were unable to demonstrate pairwise differences in pruning between each of the asthma severity and control groups. Similarly, although many of the correlations between pruning and the continuous measures of disease severity were statistically significant, the correlation coefficients themselves were relatively low. This may be caused in part by the heterogeneity of the disease and the imprecision of some of the measurement techniques. Further work is needed in other cohorts to determine if this is the case.

Using quantitative CT analysis, in the SARP III cohort, we found that individuals with severe asthma had more pruning of the pulmonary vasculature than those with mild-moderate asthma or healthy control subjects. In addition, pulmonary vascular pruning was associated with worse lung function and eosinophilia, and increased odds of asthma exacerbation. If these findings are replicated and found to have pathologic correlates they may suggest that asthma is not only an airways disease but a pulmonary vascular one as well. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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