ORIGINAL ARTICLE

Heterogeneity of Airway Smooth Muscle Remodeling in Asthma

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Abstract

Rationale: Ventilatory defects in asthma are heterogeneous and may represent the distribution of airway smooth muscle (ASM) remodeling.

Objectives: To determine the distribution of ASM remodeling in mild–severe asthma.

Methods: The ASM area was measured in nine airway levels in three bronchial pathways in cases of nonfatal ($n = 30$) and fatal asthma ($n = 20$) and compared with control cases without asthma ($n = 30$). Correlations of ASM area within and between bronchial pathways were calculated. Asthma cases with 12 large and 12 small airways available ($n = 42$) were classified on the basis of the presence or absence of ASM remodeling (more than two SD of mean ASM area of control cases, $n = 86$) in the large or small airway or both.

Measurements and Main Results: ASM remodeling varied widely within and between cases of nonfatal asthma and was more widespread and confluent and more marked in fatal cases. There were weak correlations of ASM between levels within the same or separate bronchial pathways; however, predictable patterns of remodeling were not observed. Using mean data, 44% of all asthma cases were classified as having no ASM remodeling in either the large or small airway despite a three- to 10-fold increase in the number of airways with ASM remodeling and 81% of asthma cases having ASM remodeling in at least one large and small airway.

Conclusions: ASM remodeling is related to asthma severity but is heterogeneous within and between individuals and may contribute to the heterogeneous functional defects observed in asthma. These findings support the need for patient-specific targeting of ASM remodeling.

The variable and excessive airway narrowing that characterizes asthma can be demonstrated by the inhalation of agents that cause airway smooth muscle (ASM) shortening (1). The thickness of the ASM layer is related to the degree of narrowing in isolated airway segments from patients with asthma (2) and to the clinical severity of asthma (3). Therefore, ASM represents an important target for the treatment of asthma.

It has been suggested that phenotypes of asthma exist, defined by the distribution of ASM remodeling in the large and/or small airways (4, 5), and localized functional abnormalities in patients with asthma suggest regions of localized remodeling. Heterogeneity of airway narrowing occurs with histamine challenge (6), and

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At a Glance Commentary

Scientific Knowledge on the Subject: Although the role of excess airway smooth muscle (ASM) is recognized in asthma, and mean data show that it is increased in relation to asthma severity, little is known about the distribution of the increased smooth muscle throughout the small and large airways of people with mild and severe asthma. The presence of regional heterogeneity of ventilation in patients with asthma suggests a possible structural basis that may act locally or influence the behavior of the distal airways or lungs.

What This Study Adds to the Field: This study shows that using mean data to compare cases of asthma with control subjects greatly underestimates the extent and potential functional impact of ASM remodeling in asthma. ASM remodeling is heterogeneous within and between cases of mild to moderate asthma but more confluent and more severe in fatal (severe) cases of asthma. This may explain the benefits of bronchial thermoplasty in severe cases. The distribution of ASM remodeling points to a need for specific identification of remodeling and targeting and monitoring of current and new treatments for ASM remodeling.

intraindividual heterogeneity of airway tone is greater in patients with asthma (7). Functional magnetic resonance imaging (MRI) in patients with asthma shows reasonably stable areas of reduced ventilation (8). Although deficits in ventilation may correspond to regions of ASM remodeling, it is recognized that remodeling in large airways may give rise to abnormal airway behavior in structurally normal small airways (9).

Currently, direct treatment of ASM in asthma is confined to selected patients using bronchial thermoplasty (10, 11), and side effects and duration of treatment can be reduced if treatment is directed to areas of ikely focal ASM remodeling (12, 13). The prospect of imaging the ASM *in vivo* using optical coherence tomography (14–16) to direct treatment and measure the effects of new treatments raises practical problems of protocols for assessing the bronchial tree during bronchoscopy (i.e., not all airways can be assessed). Whether ASM remodeling is related to airway size, bronchial pathways, or anatomic position in the lung or occurs in discrete, randomly distributed regions of the lung is largely unknown. We mapped the distribution of ASM remodeling in individuals with mild–severe asthma and the effect of random sampling on the classification of ASM remodeling phenotypes. The hypothesis for this study was that ASM remodeling in asthma would be evident in specific patterns related to airway size and bronchial pathways and that specific phenotypes of ASM remodeling could be distinguished.

Methods

Subjects

Postmortem airway samples used in this study were obtained from six centers contributing to the Airway Disease Biobank (17). Subjects were defined as: cases of fatal asthma, in which the primary cause of death was asthma; cases of nonfatal asthma, in which the cause of death was nonrespiratory and there was a history of asthma; and control cases in which the cause of death was nonrespiratory and there was no history of asthma or evidence of other respiratory disease. Age at the time of death, sex, and when available, smoking history, clinical severity (on the basis of admissions to hospital for asthma, time from work or school, frequency of asthma symptoms, and use of oral corticosteroids), duration of asthma, age of onset of asthma, and current treatment requirements were recorded. Ethics committee approval was granted from all participating centers and the Sir Charles Gairdner Hospital Human Research Ethics Committee (HREC No: 2015-053).

Tissue Preparation

In left lungs from the Prairie Provinces study (18, 19), fixed in inflation via the main bronchus and pulmonary artery with glutaraldehyde, nine equidistant cross-sections of airways were cut along three bronchial pathways from the origins of the upper lobe, lower lobe posterior segment, and lower lobe anterior segment to the lung periphery (Figure 1A). Additional control cases and cases from other centers were sampled in a systematic stratified manner after fixation in inflation via the trachea with formaldehyde (20) or chosen at random at the discretion of a pathologist and fixed by immersion. Tissue blocks of large and small airways were embedded in paraffin wax, sectioned at 5 μm, and stained with hematoxylin and eosin or with the Masson's or Gomori trichrome techniques.

ASM Measurements

On airways cut in cross-section, the area of the ASM layer was measured using planimetry on stereological software (newCAST version 4.2.1; Visiopharm A/S) or by point count (*see* online supplement). The basement membrane perimeter (Pbm) was used as a marker of airway size, with airways classified as small (Pbm $<$ 6 mm) or large (Pbm $>$ 6 mm) (17). The average thickness of the ASM layer was calculated as ASM area/Pbm^2 and log-transformed for comparisons between groups.

Analysis

To visualize the distribution of ASM remodeling in large and small airways, each of the nine levels of the three bronchial pathways from the Prairie Provinces Study asthma cases (Table 1) was assigned a color on the basis of its ASM area/Pbm^2 value relative to the mean value for the same level in the control group, from pale blue ($\leqslant$3 SD) to pale yellow ($\geqslant$3 SD), log-normal *z*-score equivalent (Figure 1B). For each case, the three bronchial pathways were laid horizontally to form a heat map (Figure 1C) of ASM remodeling. The effects of the pathway on remodeling were examined using Cohen's *d* effect size. For clarity, the distribution of remodeling was also presented in binary form as either less than or more than the upper 95% confidence interval of the control mean value (Figure 2B). The percent of large and small airways with ASM area/Pbm^2 above the upper 95% confidence interval of the control mean value was calculated for each case, and differences between group means were compared using one-way ANOVA with *post hoc* Tukey's test. To examine the regional distribution of remodeling along bronchial pathways or at specific airway levels (peripheral vs. central), the Pearson correlation coefficients of ASM area/Pbm^2 between adjacent levels from the same

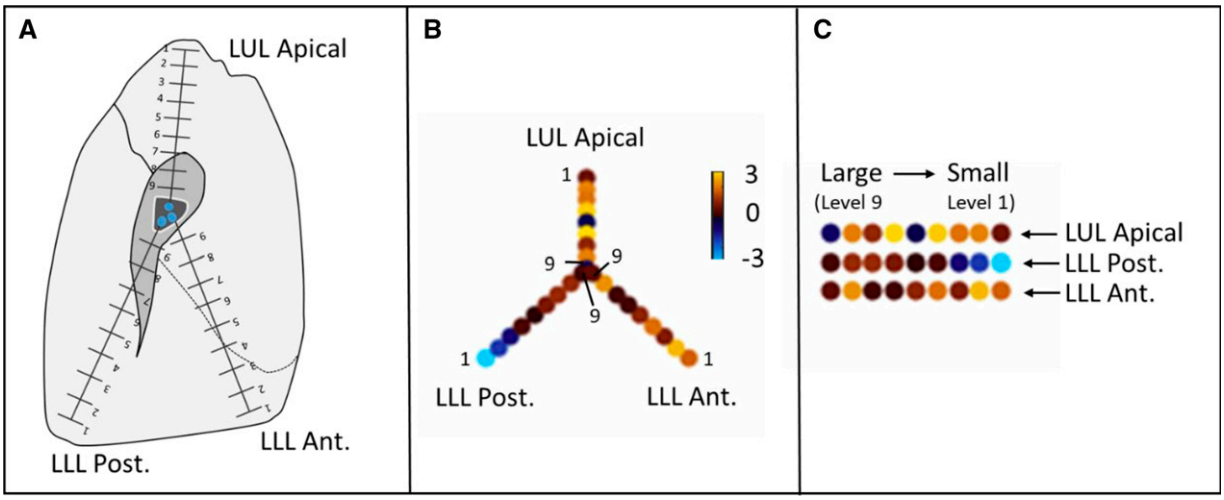

Figure 1. (*A*) Medial view of left lung showing sampling strategy of nine levels of airway (level nine being most central and level one being most peripheral) in three bronchial pathways used in the Prairie Provinces Study (18, 19). (*B*) In each case, the area of airway smooth muscle measured on a section from each level was assigned a color on the basis of its value relative to the mean and SD derived from control cases without asthma (Table 1). Pale blue and pale yellow represent airway smooth muscle areas three SDs below or above the control mean value, respectively. (*C*) The three bronchial pathways were aligned to form a heat map for visual comparisons between the same levels in different bronchial pathways and between adjacent levels within the same bronchial pathways. The example represents a single case of nonfatal asthma (from Figure 2). LLL Ant. = anterior segment of the left lower lobe; LLL Post. = posterior segment of the left lower lobe; LUL Apical = apical segment of the left upper lobe.

branching pathway and between the same levels (one through nine) in different branching pathways were calculated.

The effect of sampling frequency and definition of remodeling on the classification of cases into remodeling categories was assessed in cases of asthma ($n = 42$) with both 12 large and 12 small airways available for measurement and compared with mean and SD of the ASM area/Pbm^2, established in 86 control cases (Table 2) from large ($n = 1{,}237$) and small ($n = 688$) airways. Cases of asthma were then classified on the basis of the presence of ASM remodeling in the large and/or small airways as large and small airways (LS), large airways only (LO), small airways only (SO), or cases with ASM remodeling in neither large nor small airways (NI). ASM remodeling was defined in separate analyses as present if either: *1*) the ASM area/Pbm^2 of any large or small airway was greater than two SD above the control mean ASM area/Pbm^2; or *2*) the mean ASM area/Pbm^2 of the sampled large or small airways in each case was greater than two SD above the control mean values. The percentage of cases classified into each category was calculated, initially on the basis of the ASM area/Pbm^2 of only one large airway and one small airway (chosen at random without replacement), then successively recalculated after the addition of the ASM area/Pbm^2 of another large and another small airway, continuing until the ASM area/Pbm^2 of a total of 12 large and 12 small airways for each case had been included. This process was repeated 1,000 times to estimate the confidence of the estimates of classification.

Case means were compared between case groups (control, nonfatal asthma, and fatal asthma) and airway size groups using one-way ANOVA or Student's *t* test and appropriate *post hoc* tests. Nonparametric tests were used to compare subject groups in which data were not normally distributed or could not be normalized.

Table 1. Subject Characteristics Pathway and Level Analysis for Figures 1–3

Subject Characteristics	No Asthma ($n = 30$)	Nonfatal Asthma ($n = 30$)	Fatal Asthma ($n = 20$)
Sex (M/F), *n*	19/11	14/16	10/10
Age, yr	38 ± 10	36 ± 11	32 ± 13
Height (cm),* median (IQR); *n*	175 (172–190);15	173 (166–186); 18	167 (165–186); 11
Weight (kg),* median (IQR); *n*	75 (69–91)†; 14	101 (84–123); 19	76 (60–85)†; 11
Ever smoked,* n (%)	25 (72)	20 (55)	14 (64)
Age at onset of asthma,* *n* (yr)	—	19 (19 ± 14)	14 (14 ± 17)
Duration of asthma,* *n* (yr)	—	19 (18 ± 11)	14 (17 ± 9)
Asthma severity,* mild–moderate/severe, *n*	—	12/9	2/10†
Corticosteroid oral or inhaled,* *n* (%)	—	17 (59)	14 (79)†

Definition of abbreviation: IQR = interquartile range.
*Data not available for all cases.
†$P < 0.05$ compared with nonfatal asthma cases.

Figure 2. (*A*) Heat maps for all control cases and cases of asthma, derived as per Figure 1, of airway smooth muscle area/Pbm^2 for each of the cases, grouped as NA, cases of NFA, and cases of FA. Color scale shows variation from pale blue (equivalent to −3 or less standard deviations below the control value) through black (equivalent to the mean value of the control cases) to pale yellow (equivalent to three or more standard deviations above the control value). Red vertical bars represent medium or greater differences between pairs of pathways (Cohen's $d > 5$). Note: Using this scale, approximately 2% of airways are truncated. (*B*) Airways as for *A*, but shown in binary form as not remodeled (below the 95% confidence interval [blue]), or remodeled (above the 95% confidence interval), of the control value (brown). The percentage of remodeled airways is shown in Table 3. FA = fatal asthma; NA = control cases without asthma; NFA = nonfatal asthma.

Statistical analyses were undertaken using SigmaStat version 14.0 (Systat Software, Inc.) and Matlab R2020b (Mathworks).

Results

The subject characteristics are shown in Tables 1 and 2. On the basis of the available clinical data, the cases of fatal asthma were more severe and more often used oral and/or inhaled corticosteroids. Figure 2 shows the distribution of the remodeled airway sections, at nine levels (large to small airways, left to right), along the three bronchial pathways in each control and each asthma case. As expected, the control cases showed a distribution of colors around the mean value (black). There was considerable interindividual variability between and within individuals and between sections. In each group, there were medium or greater effects of the pathway (Cohen's d) observed in less than 20% of cases (Figure 2A).

In the nonfatal and fatal cases of asthma, there were more airways with ASM remodeling both in relation to case group and airway size (Figure 2B and Table 3). The airways sampled at the nine levels were of a similar size on the basis of Pbm (*see* Table E1 in the online supplement), and the mean area of the ASM was increased at most levels in cases of asthma (*see* Table E2). There were no apparent trends between levels or between bronchial pathways. There was considerable interindividual variability

Table 2. Subject Characteristics for Effect of Sampling Analysis (Figure 4)

Subject Characteristics	Control Cases ($n = 86$)	Nonfatal Asthma ($n = 21$)	Fatal Asthma ($n = 21$)
Sex (M/F), *n*	56/30	10/11	13/8
Age, yr (range)	35 (19–48)	29 (21–37)	31 (20–46)
Height,* cm (range); *n*	173 (162–180); 54	173 (164–177); 12	170 (165–180); 15
Weight,* kg (range); *n*	70 (58–81); 48	86 (76–141)†; 13	72 (64–79); 14
Ever smoked,* *n* (%)	40 (67)	16 (50)	17 (52)
Age at onset of asthma (yr),* median (IQR); *n*	—	9.5 (2–19.5); 16	12 (2.5–39); 17
Duration of asthma (yr),* median (IQR); *n*	—	12 (8–28); 15	16 (7–20); 17
Asthma severity (*n*),* mild–moderate/severe	—	10/6	5/11
Corticosteroid: oral or inhaled,* *n* (%)	—	13 (38)	16 (88)

For definition of abbreviation, *see* Table 1.
*Data not available for all cases.
†$P < 0.05$ compared with control cases.

Table 3. Percent of Airways with Smooth Muscle Remodeling*

	No Asthma (*N* = 30)	Nonfatal (*N* = 30)	Fatal Asthma (*N* = 20)
Large airways, *n*	5.5 ± 9; 568	18 ± 17†; 542	56 ± 25†‡; 348
Small airways, *n*	4.7 ± 8.7; 237	22 ± 24†; 256	50 ± 23†‡; 189

*Remodeling is defined as airway smooth muscle area/(perimeter of basement membrane)^2 above the upper 95% confidence interval of the control mean value. Percent of cases shown as mean ± SD.
†$P < 0.05$ compared with control cases.
‡$P < 0.05$ compared with nonfatal asthma cases.

in the nonfatal cases, but this was reduced in the fatal asthma cases (Figure 2).

The correlations of ASM area/Pbm^2 in cases of asthma between the same levels (one through nine) in different bronchial pathways and between adjacent levels within three bronchial pathways in the same lobes are shown in Figure 3 and Tables E3 and E4. Significant correlations were observed in the midsized airways, particularly at levels five and six, and within branching pathways there were no clear trends between adjacent levels.

The effect of sampling between 1 and 12 airways using any large or small airway with ASM area/Pbm^2 greater than two SDs above the mean control value to classify cases is shown in Figures 4A–4C (and Tables E5–E10). For all asthma cases (Figure 4A), categories of remodeling were largely established once eight or more large and small airways were sampled. After sampling 12 large and 12 small airways, 81% of cases were classified as LS, 5% as LO, 10% as SO, and 4% as NI. For nonfatal cases of asthma (Figure 4B), a similar pattern was seen, and 62%, 11%, 19%, and 8% were finally classified as LS, LO, SO, or NI, respectively. For fatal cases of asthma (Figure 4C), 99% of cases were finally classified as LS, less than 1% as LO or SO, and none as NI.

The analyses using the mean value of ASM thickness greater than two SDs of the mean control value to define ASM remodeling are shown in Figures 4D–4F. For all cases of asthma (Figure 4D), the proportion of cases classified as NI cases was 41%, with a slight increase up to 44% as more airways were sampled. There was a steady increase in cases classified as LS from 16% to 22% and a steady decrease in cases classified as LO to 22% and SO to 12%. For nonfatal cases of asthma (Figure 4E), cases classified as NI increased to 73%, LS increased to 8%, and LO and SO decreased to 2% and 17%, respectively. For fatal cases of asthma (Figure 4F), cases classified as LS increased to 37% with a corresponding decrease in NI to 15% and little change overall in LO and SO to 40% and 7%, respectively. This suggests that as more airways are sampled, it is increasingly likely that markedly remodeled airways (particularly large airways) are contributing to an increase in the mean value of ASM area/Pbm^2.

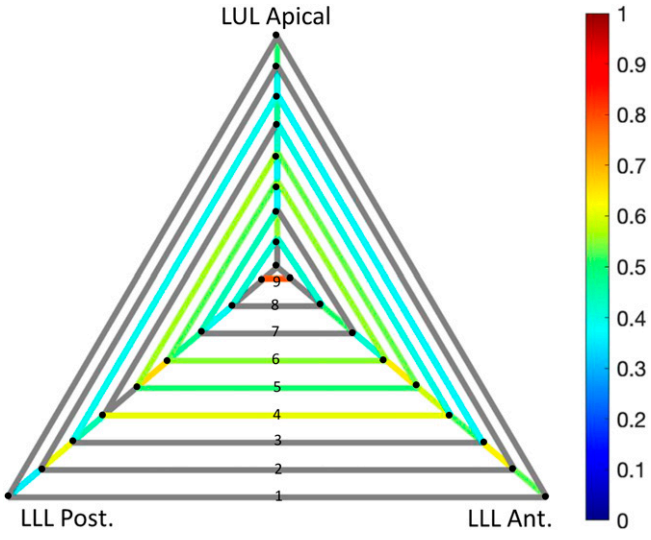

Figure 3. Correlations of airway smooth muscle area/Pbm^2 between levels (*see* Figure 1) within and between three branching pathways of the left lung in 50 cases of asthma (as seen in Figure 2). Levels one are the small, peripheral airways, and levels nine are the proximal bronchi of the LUL Apical, LLL Post., and LLL Ant. The three radial arms show the correlations between adjacent airway levels (one and two, two and three, three and four, … , eight and nine) within the same bronchial pathways. The concentric triangles show the correlations between each of the airway levels (one through nine) in different branching pathways. The color scale represents the *r* values of the pairwise comparisons. Gray segments are not statistically significant ($P > 0.05$, after Bonferroni correction). The *r* values and *P* values for all comparisons are shown in Tables E3 and E4. For definition of abbreviations, *see* Figure 1.

Discussion

We found that compared with control cases, cases of nonfatal asthma (mostly clinically mild–moderate) had more large and small airways with ASM remodeling, even if their mean ASM thickness was not increased. Remodeling of the ASM was more widespread and more severe in cases of fatal asthma. The area of ASM in cases with and without asthma varied between levels of the bronchial tree within and between individuals. Using mean data for the area of ASM, categories of remodeling were evident on the basis of the distribution of remodeling in the large and small airways. In cases of nonfatal asthma, approximately one in five large and small airways, and in cases of fatal asthma, approximately one in two large and one in 1.8 small airways, ASM remodeling was observed. There were weak correlations of ASM area between airways of similar size in different lobes of the lung and between different levels within lobes; however, other than those related to asthma severity, no predictable patterns of remodeling within or between lobes were observed. These findings extend previous studies by showing that although the frequency of remodeled airways is related to disease severity, a significant degree of heterogeneity exists, particularly in patients with mild to moderate asthma.

Previously, ASM remodeling was defined as the mean area of ASM only greater than one SD of the control mean

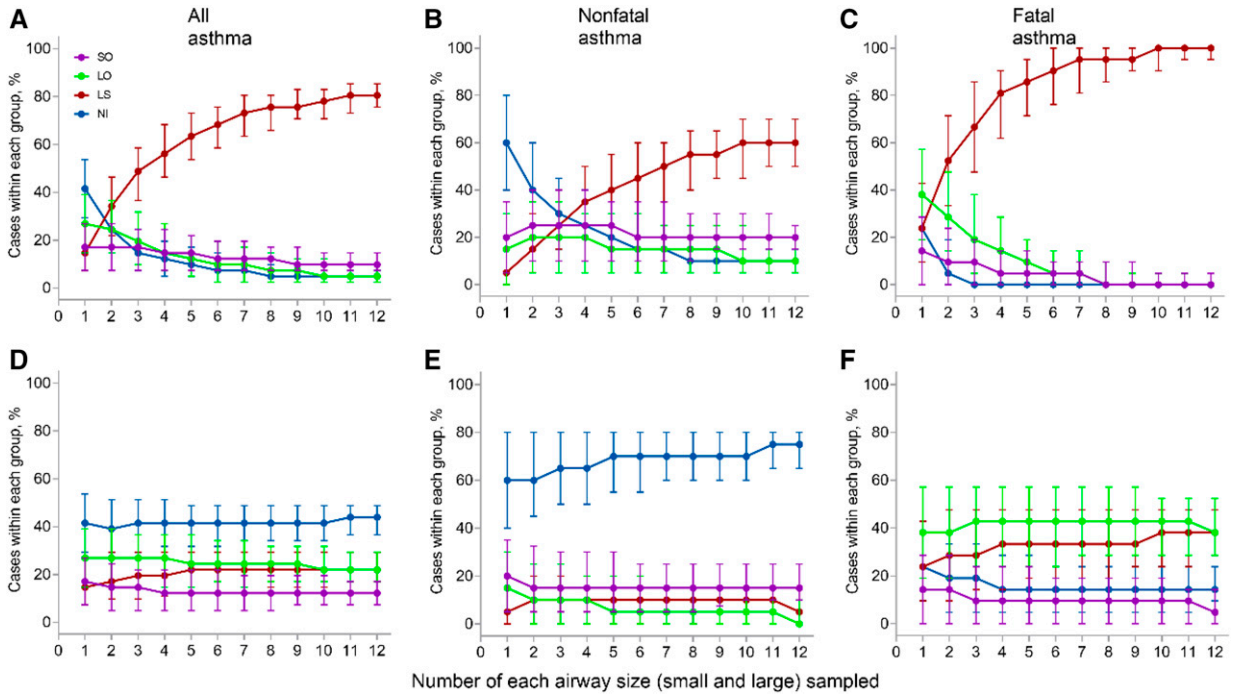

Figure 4. The effect of the number of large and small airways sampled (from 1 to 12) on the classification of cases into remodeling groups on the basis of airway smooth muscle (ASM) remodeling being present in both the large and small airways, the large airways only, the small airways only, or in neither the large or small airways. ASM remodeling was defined in two ways: *1*) (*A–C*) if the area of ASM in any large or small airway was greater than two SDs above the mean value for the control cases (Table 2); or *2*) (*D–F*) if the mean value for the large or small airway was greater than two SDs above the mean value for the control cases. Results are shown (percentages of each remodeling group, median ± 95% confidence interval) for all cases of (*A* and *D*) asthma, (*B* and *E*) nonfatal cases of asthma, and (*C* and *F*) fatal cases of asthma. Data for the graphs are shown in Tables E5–E10. LO = large airways only; LS = large and small airways; NI = neither large nor small airways; SO = small airways only.

value (5). In the present study, remodeling was defined as ASM thickness greater than two SDs of the mean control value; 12 large and 12 small airways were sampled from each case of asthma. The 1,000 iterations of computed samplings of any one large and one small airway would be expected to predict a stable classification of cases when sampling 1–12 airways and defining remodeling on the basis of the mean value. The falling percent of large-only cases in the nonfatal cases (Figure 4E) is consistent with the observation that the majority of large airways do not have ASM remodeling. In the fatal cases (Figure 4F), however, the steady increase in the percent of cases classified as large and small, with a corresponding decrease in the percent of small-only cases, is likely a result of the inclusion of more markedly remodeled large airways. The relative stability of the proportion of large-only cases is consistent with the observation that, on the basis of mean data, the ASM remodeling affects a greater percentage of the large airways than the small airways. Therefore, in fatal asthma, not only do more airways (particularly large airways) have ASM remodeling, but the remodeling is also more severe.

In a study of the variation of ASM remodeling (21), sampling from whole lungs from eight cases of fatal asthma and four cases of nonfatal asthma showed only a small increase in mean ASM area compared with control cases, although there was a shift to the right in the distribution of ASM area/Pbm with a tail of more severe remodeling. These results are consistent with our findings, which demonstrate marked heterogeneity and individual airways with more marked remodeling (greater than three SDs above the control mean). In the same study (21), heterogeneity was expressed as the coefficient of variation (CV) (SD / mean × 100), which was high in both cases without asthma (70.2%) and cases with asthma (98.0%). These values for the coefficient of variation are much higher than those observed within short airway segments of 1 mm (CV = 2–5%) (22), 0.6 mm (CV = 5–10%) (23), or 2 mm (CV = 25–34%) (24) in control cases and fatal asthma.

A further study of the regionality of ASM remodeling (25) showed that spatial correlations of ASM remodeling were present in airways separated by short distances, either in the same transverse plane or in the same branching pathway. In our analysis, we examined the correlations of ASM area in airways that were adjacent in a branching pathway and the correlations between airways that were not adjacent but at similar levels (and sizes) in separate branching pathways (Figure 3). We found that overall correlations were low, although they tended to be higher in adjacent sections in the same branching pathway. These findings support spatial correlation. This may not be surprising, however, because any proposed mechanism of hypertrophy or hyperplasia of smooth muscle, if heterogeneous, is still likely to be regional to some extent. Although we did observe the effect of a pathway in some cases (Figure 2A), this was in a minority of cases, and no clear patterns were evident.

In the present study, the cases of fatal asthma were distinguished by having ASM that involved more airways (particularly large airways), was more severe, and was more confluent. However, there was some overlap between the two asthma groups. Although the amount of smooth muscle around the airways is a determinant of how much the airways can narrow (2), other factors likely contribute to fatal asthma. In addition to more regions of extreme ASM remodeling, these factors include the degree of stimulation of the ASM by inhaled irritants, allergens, or agonists, perception of airway narrowing, and the underlying severity of other pathologies, such as mucus gland hypertrophy and inflammation (26). The degree of stimulation of the ASM by an inhaled allergen is independently related to the dose of the allergen, sensitivity to the allergen, and nonspecific airway responsiveness (27). Therefore, it is possible that a person with mild or unrecognized asthma or no previous asthma symptoms (and presumably very little ASM remodeling) could develop symptoms for the first time or even die of a fatal asthma attack if exposed to a strong enough stimulus, as has been observed in thunderstorm asthma (28).

The strengths of the present study are the large number of asthma cases and control cases, the distribution of asthma severity, and the systematic, extensive sampling of airways. This approach has facilitated the comparison of airways between lobes, within the same pathways (contiguous vs. noncontiguous), and between airway sizes. The availability of whole airway sections reduced the effects of sampling artifacts and allowed the comparison of airways of similar size between individuals. The cases of fatal asthma in this study included those with poorly controlled asthma, undertreated asthma, and those with severe asthma on maximum available therapy. However, in this postmortem study, apart from including or excluding the diagnosis of asthma, clinical details such as current medications, doses and adherence, and objective measures of lung function were not available in all cases.

The causes or mechanisms of the increased ASM in asthma remain unknown. ASM remodeling is related to the severity but not the duration of asthma (3) and is present in early life (29). Asthma is associated with reduced lung function (30) that is present even in infancy (31). These observations suggest that ASM remodeling arises very early in individuals with asthma. The present study did not uncover any specific pattern of ASM remodeling with regard to lobe, bronchial pathway, or airway size that might suggest possible mechanisms of ASM remodeling.

Models of airway narrowing show that the increased ASM mass observed in asthma has the greatest effect on maximal airway narrowing (32). The present study shows that ASM remodeling in asthma is not evenly distributed across the bronchial tree. Incorporating the variability of airway structure and random degrees of maximal airway narrowing into a model of airway narrowing results in marked heterogeneity of reduced ventilation in the lung (33–35). Extending these observations, subsequent modeling has shown that heterogeneity of airway narrowing of central airways may lead to abnormal ventilation in the structurally normal distal lung (9).

Using physiological tests and new imaging techniques, including high-resolution computer-assisted tomography and MRI, numerous studies have demonstrated the marked heterogeneity of ventilation observed in asthma (36–39). The degree of heterogeneity of ventilation is related to asthma severity and airway responsiveness (40–42). Regions of ventilation heterogeneity may vary over time, possibly because of relatively random distal effects of airway narrowing (9, 43). However, many regions are constant over time (8, 44, 45). The persistence of regional heterogeneity suggests a structural basis (39, 46, 47) for these regions that is independent of airway inflammation (39) and is supported by the findings of the present study.

The unpredictable heterogeneous distribution of ASM remodeling that we observed mandates more specific measures to identify airways or lung regions that might be targeted for treatment, such as functional MRI (12, 48). This technique identifies regions of abnormal ventilation but does not identify airway segments with ASM remodeling. Relating sites of ASM remodeling to functional changes more precisely await reliable means of measuring ASM thickness *in vivo* (28, 42). Both the distribution and the absolute increase of ASM mass within the bronchial tree are likely to have additive functions (34).

The widespread and severe ASM remodeling observed in the large airways in severe cases of asthma explains the effectiveness of bronchial thermoplasty, despite its application in a uniform manner (13, 16). The considerable heterogeneity of ASM remodeling of both the large and small airways may explain why bronchial thermoplasty is not effective in all cases and why the more targeted application of bronchial thermoplasty achieves similar results with fewer side effects and fewer treatment sessions (12). Imaging studies using computed tomography and ultrasound can identify localized increased airway wall thickness in midsized and large airways. However, these techniques are unable to distinguish ASM from other airway wall components to accurately localize ASM remodeling. Optical coherence tomography has been shown to define the layer of smooth muscle within the airway wall (14, 15) and this technique offers the possibility of more precisely targeted bronchial thermoplasty (49).

The present study has shown widespread remodeling of the ASM, involving both large and small airways, in cases of severe asthma. In cases of mild–moderate asthma, remodeling of the ASM is more piecemeal yet is likely to contribute to regional functional abnormalities and to airway hyperresponsiveness, which is characteristic of cases of even mild asthma (1). Therefore, approaches to identifying, treating, and assessing the effects of current and new treatments of ASM remodeling may need to be more localized. ■

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