[Original Research]

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Further Studies of Unsuspected Emphysema in Nonsmoking Patients With Asthma With Persistent Expiratory Airflow Obstruction

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BACKGROUND: Previously, we and other investigators have described reversible loss of lung elastic recoil in patients with acute and persistent, moderate-to-severe, chronic, treated asthma who never smoked, and its adverse effect on maximal expiratory airflow. In four consecutive autopsies, the pathophysiologic mechanism(s) has been unsuspected mild, diffuse, middle and upper lobe centrilobular emphysema.

METHODS: We performed prospective studies (5 to 22 years) in 25 patients (12 female) with chronic asthma, age 55 ± 15 years, who never smoked, with persistent moderate-to-severe expiratory obstruction. Studies included measuring blood eosinophils, IgE, total exhaled nitric oxide (NO), central airway NO flux, peripheral airway/alveolar NO concentration, impulse oscillometry, heliox curves, lung elastic recoil, and high-resolution thin-section (1 mm) lung CT imaging at full inspiration with voxel quantification.

RESULTS: In 25 patients with stable asthma with varying type 2 phenotype, after 270 μg of aerosolized albuterol sulfate had been administered with a metered dose inhaler with space chamber, FVC was 3.1 ± 1.0 L (83% ± 13% predicted) (mean ± SD), FEV_1 was 1.8 ± 0.6 L (59% ± 11%), the FEV_1/FVC ratio was 59% ± 10%, and the ratio of single-breath diffusing capacity of the lung for carbon monoxide to alveolar volume was 4.8 ± 1.1 mL/min/mm Hg/L (120% ± 26%). All 25 patients with asthma had loss of static lung elastic recoil pressure, which contributed equally to decreased intrinsic airway conductance in limiting expiratory airflow. Lung CT scanning detected none or mild emphysema. In all four autopsied asthmatic lungs previously reported and one unreported explanted lung, microscopy revealed unsuspected mild, diffuse centrilobular emphysema in the upper and middle lung fields, and asthma-related remodeling in airways. In eight cases, during asthma remission, there were increases in measured static lung elastic recoil pressure-calculated intrinsic airway conductance, and measured maximal expiratory airflow at effort-independent lung volumes.

CONCLUSIONS: As documented now in five cases, unsuspected microscopic mild centrilobular emphysema is the sentinel cause of loss of lung elastic recoil. This contributes significantly to expiratory airflow obstruction in never-smoking patients with asthma, with normal diffusing capacity and near-normal lung CT scan results.

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ABBREVIATIONS: Gus = conductance of upstream airway; TLC = total lung capacity; $V\,max_{exp}$ = maximal expiratory airflow

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We[1] and other investigators[2-9] have previously reported reversible loss of lung elastic recoil and hyperinflation at total lung capacity during acute attacks of asthma that were either spontaneous[1-5] or induced by exercise[6,7] or by antigen challenge.[8,9] Furthermore, loss of lung elastic recoil has been reported in chronic moderate to severe asthma with only partially reversible airway obstruction despite treatment[2,3,5,10-13] and also in mild asthma.[14] We have reported that nonsmoking, treated patients with asthma, with loss of lung elastic recoil and persistent limitation of maximal expiratory airflow, have normal diffusing capacity and normal or only mild parenchymal attenuation of lung density on high-resolution, thin-section (1 mm) lung CT imaging at full inspiration,[10-12] with trivial emphysema scores ≤ 15.[15,16] Furthermore, the limited resolution of lung CT scanning may not be capable of discriminating between mild emphysema and hyperinflation.[17-19] Because structure-function studies of the lungs in asthma are rarely available, the pathophysiologic mechanism(s) responsible for the loss of lung elastic recoil in acute asthma[1-9] and especially in chronic asthma[2,3,5,10-14] remain an enigma. We published two studies of 11 patients with chronic asthma who never smoked, with persistent expiratory airflow limitation, despite treatment, and unexplained loss of lung elastic recoil.[20,21] Autopsies of all four patients with asthma revealed unsuspected upper and middle lung, mild, diffuse centrilobular emphysema in addition to asthma-related changes in the central and peripheral airways.[20,21]

We now report our fifth case of unsuspected mild, diffuse centrilobular emphysema, detected in a left lung explant following unilateral lung transplantation in a nonsmoking patient with asthma with very severe expiratory airflow limitation. These ongoing pathophysiologic observations of unsuspected emphysema in never-smoking patients with asthma with loss of lung elastic recoil are sentinel, and we present whole-slide pathologic images that can be viewed as PDFs or with a QR code reader.

Methods

Study Design and Selection of Patients With Asthma

We studied 25 nonsmoking adults with asthma monitored in a tertiary referral asthma clinic for moderate-to-severe cases with persistent maximal expiratory airflow limitation despite treatment.[10-12,20,21]

Within the previous 2 years of study, all patients with asthma satisfied the spirometric criteria for at least partial reversibility, with an increase in $FEV_1 > 200$ cm^3 and 12% after administration of 270 μg of aerosolized albuterol sulfate via spacer chamber when off all long-acting and short-acting β_2-agonist and muscarinic antagonist (by metered dose inhaler) for 24 and 6 hours, respectively. All individuals studied gave informed consent for participation.

Lung CT Imaging

Patients with asthma underwent high-resolution thin-section scanning of the lungs at full inspiration, using a helical 64-slice multidetector row CT scanner (model Sensation 64; Siemens) with reconstruction focal resolution, 1 mm; rotation time, 0.5 s; pitch, 1.0 mm; kVp, 120; slice thickness, 0.75 mm and 0.5-mm interval; and reconstruction kernel B35.[20,21] We used the Thurlbeck emphysema template[15,16] to score macroscopic extent of attenuation of lung density, that is, hyperinflation/emphysema. Our confidence in this template[16] was based on our previous experience in 18 cases[15] with high correlation for scoring emphysema in formalin-fixed, inflated whole lungs obtained at autopsy versus premortem lung CT scanning. Lung CT voxel quantification of < -910 HU and < -950 HU, consistent with hyperinflation and emphysema, respectively, was determined with Apollo software and 1.0-mm reconstruction slice thickness and kernel B35 at Vida Diagnostics, Inc. (vidadiagnostics.com). Interpretation of the lung CT scans was determined by one of the authors (M. J. S.), who had no knowledge of the results of the clinical and physiologic studies.

Lung Function and Other Studies

When these 25 patients with asthma were clinically stable for $\geq$ 6 weeks, and tapered off oral corticosteroid $\geq$ 6 weeks, they continued all medications, except for the withholding of inhaled albuterol sulfate and/or ipratropium bromide for 6 h, and of long-acting β_2-agonist and muscarinic antagonist bronchodilators for 24 h, prior to testing. Lung function studies have been previously described in detail.[10-12,20-24]

The Asthma Control Test[24] was used as a validated measure for quantitation of clinical status, and blood total eosinophil count, IgE, total exhaled nitric oxide, central airway nitric oxide flux, and peripheral airway/alveolar nitric oxide concentration were obtained as potential markers of the type 2 phenotype.[25] Maximal expiratory airflow at 50% FVC was determined before and after inhaling combined 20% oxygen and 80% helium (heliox) for 10 minutes. Impulse oximetry results were also obtained.

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