

Understanding the pathophysiology of the asthma–chronic obstructive pulmonary disease overlap syndrome

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Key words: Asthma, emphysema, COPD, asthma-COPD overlap syndrome

This article will address the landmark publications leading to the identification of asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS). The accompanying contributions in this issue of the *Journal* are likewise invaluable. We have also taken the liberty of including our sentinel observations with respect to the possible mechanisms responsible for loss of lung elastic recoil and persistent expiratory airflow limitation in 4 treated patients with chronic asthma who never smoked and had unexpected mild centrilobular emphysema at autopsy.

There are many patients with a longstanding history of chronic cigarette smoking with persistent expiratory airflow obstruction despite partial reversibility with therapeutic intervention. Furthermore, approximately 15% to 20% can have phenotypic clinical features of both asthma and chronic obstructive pulmonary disease (COPD).¹ In some cases a history of asthma has presumably preceded the development of cigarette-related COPD.¹ Recently, this epiphenomenon has been labeled ACOS.¹ In 1961, during the first Bronchitis Symposium held in Groningen, The Netherlands, the intuitive Orie et al² hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, should be considered not as separate diseases but as different clinical and phenotypic expressions of one common disease origin, namely chronic nonspecific lung disease. They proposed that multiple exogenous and endogenous factors, including atopy and hyperresponsiveness, influenced pathogenesis.² Subsequently, at the Third International Bronchitis Symposium in The Netherlands in 1969, Fletcher and Pride³ suggested the term “Dutch hypothesis” for the original proposal of Orie et al.² Needless to say, this ensured the legacy of Orie. Alternatively, in 1991, Vermeire and Pride⁴ emphasized that despite common clinical and phenotypic features in patients with COPD and those with asthma, the origins were distinctly different. In 2006, Monica Kraft⁵ and Peter J. Barnes⁶ debated the clinical and pathophysiologic similarities (Dutch hypothesis) versus differences (British hypothesis) between asthma and

COPD. In this issue of the *Journal* Postma et al⁷ provide the interested reader with an in-depth analysis of the multiple endogenous and exogenous factors that influence the phenotypic homogeneity and heterogeneity in asthma versus COPD and ACOS.

Sputum cytokine and proinflammatory mediators⁸ and airway epithelial genomic⁹ studies that identify T_H2 inflammatory markers, including periostin, *SERPINE2*, and *CLCA1*, have reported overlap results in subsets of patients with asthma and COPD. Furthermore, T_H2-mediated eosinophilic inflammation, bronchodilator reversibility, and corticosteroid responsiveness identify a COPD subset, even in the absence of a clinical history of asthma.⁹ Alternatively, other studies did not identify common genetic signatures in asthmatic patients and patients with COPD.^{10,11}

However, more importantly, ACOS studies have not specifically addressed the unique pathophysiologic mechanism or mechanisms responsible for persistent expiratory airflow limitation in nonsmoking patients with chronic asthma with a COPD phenotype. In nonsmoking asthmatic patients we^{12,13} and other investigators have reported reversible loss of lung elastic recoil and hyperinflation at total lung capacity during acute asthma attacks that were either spontaneous or induced by exercise or antigen challenge. Loss of lung elastic recoil has also been reported in patients with chronic asthma with only partially reversible airway obstruction despite treatment and also in patients with mild asthma.^{12,13} The sentinel study in 1967 by Gold et al¹⁴ reported the reversible loss of lung elastic recoil in patients with acute asthma. In 1968, Woolcock and Read¹⁵ noted the sentinel chronic loss of lung elastic recoil in patients with stable moderate-to-severe asthma and persistent expiratory airflow limitation with a further parallel shift to the left of the pressure-volume curve during asthma exacerbation. The unexpected loss of lung elastic recoil in nonsmoking asthmatic patients contributes greatly to exaggerate any expiratory airflow limitation because of intrinsic peripheral airways bronchoconstriction.^{12,13} We have noted that nonsmoking asthmatic patients with loss of lung elastic recoil compared with nonsmoking, age-matched control subjects have normal diffusing capacity corrected for alveolar volume and near-normal lung computed tomographic results, despite persistent maximal expiratory airflow limitation.^{12,13} There was only mild parenchymal attenuation of lung density with voxel quantification on high-resolution, thin-section (1 mm) lung computed tomography at full inspiration.^{12,13} However, the limited resolution of lung computed tomography might not be capable of discriminating between mild emphysema and hyperinflation. Because structure-function studies of inflated lungs in asthmatic patients are infrequently published, the pathophysiologic mechanism or mechanisms responsible for the reversible loss of lung elastic recoil in patients with acute and persistent loss in patients with chronic asthma have remained unexplained until recently.^{12,13}

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Disclosure of potential conflict of interest: A. F. Gelb has received research support from AstraZeneca, GlaxoSmithKline, Forest, Pearl Therapeutics, and Novartis and has received payment for lectures from Boehringer Ingelheim and Forest. J. A. Nadel declares that he has no relevant conflicts of interest.

Received for publication June 10, 2015; accepted for publication June 12, 2015.

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J Allergy Clin Immunol 2015;136:553-5.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2015.06.013>

Our pathophysiologic observations in 4 treated patients with moderate-to-severe chronic asthma who never smoked and had persistent expiratory airflow obstruction despite partial reversibility have been reported recently.^{12,13} All 4 asthmatic patients had a significant decrease in lung elastic recoil compared with that seen in nonsmoking age-matched control subjects. Unsuspected diffuse microscopic mild centrilobular emphysema was noted in formalin-inflated lungs obtained at autopsy in all 4 cases, despite normal diffusing capacity. Moreover, the lung tissue breakdown was not consistent with senile emphysema, as described by Verbeke et al,¹⁶ and only trivial to mild emphysema was identified on high-resolution, 1-mm, thin-section lung computed tomography including voxel quantification. There were also concurrent microscopic findings of typical asthma-induced changes in the large and small airways, including mucosal goblet cell metaplasia and thickening of both the basement membrane and airway smooth muscle layers.^{12,13} These pathophysiologic findings are sentinel and extend earlier novel pathologic observations by Mauad et al,¹⁷ who described localized peritermal bronchiolar emphysema with breakdown of alveolar attachment in patients with fatal asthma without lung function studies. Furthermore, investigators have emphasized the alveolar inflammatory response, as reported by Dolhnikoff et al and de Magalhaes Simoes et al who described increased eosinophil, mast cell, and neutrophil counts in the peribronchiolar parenchyma.^{12,13} The outer wall of small membranous bronchioles was the main site of inflammatory changes in patients with fatal asthma.^{12,13} Recently, Senhorini et al¹⁸ noted younger adults with fatal asthma had thicker basement membrane, smooth muscle, and outer wall areas in both the small and large airways when compared with both patients with COPD and older asthmatic patients. In older asthmatic patients there was an overlap in basement membrane thickness and airway structure in the small airways. The inner wall layers in the large and small airway levels and submucosal gland areas were similar among groups. Older patients with fatal asthma had overlapping airway structural features with younger adults with fatal asthma and patients with severe COPD.¹⁸

The original description of emphysema by Leopold and Gough¹⁹ suggested that the terminal bronchioles were the nascent site of lung tissue breakdown that led to centrilobular emphysema. As recently summarized,^{12,13} we suggest that recurrent asthma attacks might produce bronchiolar inflammation with activation of a predominantly T_H2 proinflammatory pathway and subsequent proteolytic cascade, leading to lung tissue destruction.^{12,13} This might be mediated by an autocrine proinflammatory, perhaps epidermal growth factor receptor–initiated signaling cascade stimulated by inhaled invaders in epithelial cells, as we previously suggested.^{12,13,20} Subsequently, protective mucociliary responses occur in the airway epithelium through IL-17 and IL-18, which activate IL-8 to induce mucin production and neutrophil recruitment, especially in patients with mild-to-moderate asthma.^{12,13,20} Moreover, proteases, such as neutrophil elastase and cathepsin G, or membrane metalloproteases, activated eosinophils, macrophages, and mast cells might all induce mucin production through proteolytic activation of the epidermal growth factor receptor ligand–initiated signaling cascade.^{12,13,20} Furthermore, neutrophil elastase and cathepsin G are potent secretagogues for submucosal gland epithelial cells.^{12,13,20} Additionally, treated patients with mild-to-moderate chronic asthma often have persistently noneosinophilic and predominantly

neutrophilic inflammation,²¹ potentially leading to neutrophil elastase secretion in lung tissue. Together with activated matrix metalloproteinases, this proteolytic cascade has the potential to cleave and disrupt the normal connective tissue integrity of the attachments linking the lung parenchyma to adjacent terminal bronchioles, leading to potential loss of anatomic and physiologic interdependence.^{12,13} This asthma pathway is proposed to uncouple terminal bronchiolar attachments to lung parenchyma in smokers with early emphysema, resulting in loss of lung elastic recoil, as described by Saetta et al.²² Gelb et al²³ previously described chronic smokers with significant obstructive disease of the small airways who had clinically unsuspected moderate centrilobular emphysema confirmed on inflated lungs obtained from lobectomy or pneumonectomy. They all had normal FEV₁ (in liters) but reduced expiratory airflow at low lung volumes, with reduction in both lung elastic recoil and diffusing capacity.

The identification and treatment of the patient with ACOS has been recently addressed in a joint initiative from the Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease.²⁴ Moreover, the in-depth review of Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease and other published guidelines for treatment of ACOS by Helen K. Reddel²⁵ in the current issue of the *Journal* emphasizes the conflicting data and limitations of specific therapeutic recommendations related to varying phenotypes. The excellent contribution from Peter J. Barnes,²⁶ also in this issue of the *Journal*, emphasizes putative stratified pharmacologic intervention to counter the inflammatory and proteolytic cascade in addition to long-acting β -agonists, long-acting muscarinic antagonists, inhaled corticosteroids, and omalizumab. The goal is to prevent airway and parenchymal structural changes that can become irreversible. Barnes²⁶ describes the anti-eosinophil blocking antibodies against IL-5, IL-13, IL-33, and thymic stromal lymphopoietin and oral chemoattractant receptor–homologous molecule expressed on T_H2 lymphocytes antagonist. Furthermore, anti-neutrophil intervention could include macrocyclics, CXCR2 antagonists, phosphodiesterase-4 inhibitors, p38 mitogen-activated protein kinase inhibitors, and antibodies against IL-1 and IL-17.

Herein we have focused on treated patients with chronic asthma who never smoked and had persistent expiratory airflow obstruction and associated loss of lung elastic recoil because of unsuspected emphysema, with in part shared pathophysiologic structural changes seen in patients with COPD.^{12,13} This is probably a consequence of a predominantly T_H2 proinflammatory and proteolytic cascade. Furthermore, unsupervised cluster analyses of gene expression and the transcriptomic data set also reveal an overlap of genome endotypes in patients with asthma and those with COPD.^{8,9} Further studies are needed to confirm these observations and the underlying mechanisms, and hopefully, this will lead to more successful targeted pharmacologic interventions.

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