Airway Wall Thickening in Patients With Cough Variant Asthma and Nonasthmatic Chronic Cough*

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Background: **Chronic cough, which may be of asthmatic or nonasthmatic origin, is an important clinical issue. Airway inflammation, and remodeling demonstrated by subbasement membrane thickening has been associated with cough variant asthma (CVA) as well as with nonasthmatic chronic cough (NAC). CT studies have shown airway wall thickening in patients with asthma who wheeze. We examined airway wall thickness by CT in adult patients with chronic cough and examined its pathophysiologic implication.**

Methods: **Nonsmoking, steroid-naïve patients with CVA (n = 27), NAC (n = 26), and healthy control subjects (n = 15) were studied. Airway dimensions were assessed by a validated CT technique, in which we measured airway wall area (WA) corrected by body surface area (BSA), the ratio of WA to outer wall area (percentage of wall area [WA%]), absolute wall thickness (T)/$\sqrt{}$BSA, and airway luminal area/BSA of a segmental bronchus. Correlations between CT parameters and clinical indexes such as disease duration and cough sensitivity were examined.**

Results: **In patients with CVA, WA/BSA, WA%, and T/$\sqrt{}$BSA were all significantly greater than those in control subjects. In patients with NAC, WA/BSA and T/$\sqrt{}$BSA were significantly greater than in control subjects. The increase of WA/BSA and T/$\sqrt{}$BSA of NAC patients was less than that of CVA patients. In a subset of patients with NAC, WA% correlated with capsaicin cough sensitivity (n = 9, r = 0.75, p = 0.034).**

Conclusions: **Walls of central airways are thickened in patients with CVA, and also to a lesser degree in patients with NAC. Airway wall thickening in NAC may be associated with cough hypersensitivity.** ***(CHEST 2007; 131:1042–1049)***

Key words: airway wall thickening; cough sensitivity; cough variant asthma; CT; nonasthmatic chronic cough

Abbreviations: Ai = luminal area; BSA = body surface area; C5 = cough threshold, the lowest concentration of capsaicin that induces five or more coughs; CVA = cough variant asthma; Dmin = cumulative dose of inhaled methacholine at the inflection point at which respiratory resistance begins to increase; GERD = gastroesophageal reflux disease; NAC = nonasthmatic chronic cough; PICC = postinfectious chronic cough; SBS = sinobronchial syndrome; T = absolute airway thickness; WA = airway wall area; WA% = percentage of wall area

Airway wall thickening has been observed in postmortem studies of patients with status asthmaticus. The wall thickening is accompanied by airway structural changes, such as subbasement membrane thickening, mucous gland and goblet-cell hyperplasia, increased vascularity, and smooth-muscle hyper-

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trophy and hyperplasia, as well as with chronic inflammation such as mucosal edema and inflammatory cell infiltration.[1–4] These changes have been further confirmed by studies[5–7] using bronchial biopsy in living patients. With the advent of high-resolution CT, noninvasive assessment of airway dimensions in asthma has become available.[8] We and others[9–13] have quantitatively assessed airway wall thickening and its clinical implication in asthma.

Chronic cough is a common problem for which patients seek medical attention from primary care physicians and pulmonologists.[14] Although chronic cough itself is not fatal, it severely impairs quality of life.[15] One of the most common causes of chronic cough is cough variant asthma (CVA),[16] which lacks the typical manifestation of asthma such as wheezing or dyspnea but presents airway hyperresponsiveness and bronchodilator responsive coughing.[17] CVA is clinically considered as a variant type of asthma as well as a precursor of classic asthma with wheezing.[18,19] Pathologically, CVA shares common features such as eosinophilic inflammation and remodeling changes, including subbasement membrane thickening and goblet-cell hyperplasia with classic asthma.[20–23]

Chronic cough due to other causes, such as gastroesophageal reflux disease (GERD) and postnasal drip syndrome, which is currently referred to as *upper airway cough syndrome*,[16] is often grouped as nonasthmatic chronic cough (NAC).[22] Patients with NAC also have features of airway inflammation and remodeling. In a study[24] examining BAL fluid of patients with NAC, mast cells, eosinophils, and histamine levels were increased; while in another study,[25] sputum neutrophilia and increased levels of interleukin-8 and tumor necrosis factor-α were observed. Increase of bronchoalveolar lymphocytes in idiopathic chronic cough is also reported.[26] In terms of remodeling, the presence of submucosal fibrosis in the airways of patients with NAC was first described by Boulet and colleagues.[27] A biopsy study[22] of NAC has further demonstrated an increase of submucosal mast cells, subbasement membrane thickness, goblet-cell area, vascularity, and smooth-muscle area. Nonasthmatic eosinophilic bronchitis, another cause of chronic cough characterized by airway eosinophilia and absence of airway hyperresponsiveness, also involves subbasement membrane thickening.[28] Regardless of the accumulating evidence of airway remodeling based on bronchial biopsies in patients with chronic cough, only one study[29] of nonasthmatic eosinophilic bronchitis has examined whole airway wall thickness using CT scans, and has shown that in contrast with the biopsy study,[28] wall area of large airways in patients with nonasthmatic eosinophilic bronchitis is not different from that of healthy control subjects and is less than that of intermittent or mild persistent asthmatics with sputum eosinophilia,[29] suggesting the importance of assessment by CT that may extend and compensate the information of endobronchial biopsy studies in chronic cough.

In this study, we examined airway dimensions by CT in patients with CVA and those with NAC. Correlations between the CT parameters and clinical indexes, such as age, disease duration, pulmonary function, cough sensitivity, and sputum cell differentials, were also studied.

Materials and Methods

Subjects

We studied adult patients with CVA (n = 27), and those with NAC (n = 26) from the Asthma and Cough Clinic of Kyoto University Hospital, and healthy control subjects (n = 15). None were current smokers. The patients included all had recent diagnoses, were steroid naïve, and had normal chest radiographic findings. Their cough persisted for > 8 weeks.

Diagnosis of CVA was based on the following criteria[20]: an isolated chronic cough without wheezing or dyspnea, airway hyperresponsiveness to methacholine, and symptomatic improvement of coughing with the use of inhaled β_2-agonists, sustained-release theophylline, or both. Wheezing or rhonchi were not audible on chest auscultation, even with forced expiration. The subjects had no history of asthma, or upper respiratory tract infection within the past 8 weeks. No other apparent causes of cough such as GERD, sinobronchial syndrome (SBS), or medication with angiotensin-converting enzyme inhibitors were present.

Causes of NAC were as follows: SBS (n = 8), diagnosed based on a positive result of sinus images and improvement of cough, as well as the symptom related to chronic sinusitis with macrolides[30]; GERD (n = 3), based on a positive result of 24-h pH monitoring of the esophagus (pH Digitrapper MarkII Gold 6200; Synetics Medical Company; Stockholm, Sweden) and response to treatment with proton-pump inhibitor[31]; postinfectious chronic cough (PICC) [n = 3]; and idiopathic or unexplained cough (n = 11), in whom extensive examinations and intensive therapeutic trials for CVA, GERD, and SBS including inhaled corticosteroids and antireflux treatment were negative or failed. In the remaining patient, both GERD and SBS were considered to be causes of chronic cough. Five patients with CVA, three patients with SBS, one patient with PICC, and two patients with unexplained chronic cough reported sputum production. Other patients produced none or minimal amounts of sputum. Bronchiectasis was observed on CT scans in one patient with SBS. The Ethics Committee of our institution approved the study protocol, and written informed consent was obtained from each participant.

Clinical Measurements

Patients underwent a workup including questionnaire, physical examination, blood tests, chest and sinus radiographs, pulmonary function and airway responsiveness tests, sputum induction, cough sensitivity testing, and CT scanning. These were done in this order within 1 month. FEV_1 and FVC were tested using a spirometer (Chestac-65V; Chest; Tokyo, Japan).