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Potential role of pentosidine on susceptibility to small airway closure in elderly and smoking asthma

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Summary
Background: Small airway closure in asthma is determined by a complex interaction of structural and functional characteristics including lung elastic recoil. Recently, we determined that loss of elastic recoil might be attributable to pentosidine level in the airways. This study was designed to investigate the influences of aging and smoking on small airway closure in asthma.
Methods: Sixty-one patients with asthma (20 non-smoking young adult, 23 non-smoking elderly, and 18 smoking young adult) and 36 control subjects (12 non-smoking young adult, 11 non-smoking elderly, and 13 smoking young adult) were included. We assessed airway responses during methacholine provocation and calculated the closing index. In addition, we measured pentosidine levels in induced sputum from all study subjects.
Results: Pentosidine levels in induced sputum were markedly higher in asthmatic patients than in controls. In control subjects, the intergroup differences in pentosidine level among 3 subgroups were significant. Similarly, pentosidine levels were significantly higher in non-smoking elderly and smoking young adult asthmatics than in non-smoking young adult asthmatics. There was no significant difference in pentosidine levels between non-smoking elderly and smoking young adult asthmatics. The closing index was also significantly higher in non-smoking elderly and smoking young adult asthmatics than in non-smoking young adult asthmatics. Moreover, pentosidine levels in non-smoking elderly and smoking young adult asthmatics were closely correlated with closing index.

Abbreviations: delta N_2, slope of the nitrogen alveolar plateau; DRS, dose–response slope; DTT, dithiothreitol; FEV_1, forced expiratory volume in one second; FVC, forced viral capacity; IQR, interquartile range; NO, nitric oxide; PC20 methacholine, provocative concentration causing a 20% fall in FEV_1 with methacholine.

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Conclusions: We determined the correlation of pentosidine level with susceptibility to small airway closure in elderly and smoking asthmatics. Our results might facilitate the understanding of elderly and smoking asthma.

Introduction

Asthma is a chronic inflammatory airway disease characterized by variable airway obstruction attributed to an underlying inflammatory process and airway remodeling [1]. In general, the pathophysiology of asthma has been based on these inflammatory and structural changes occurring predominantly in the large airways [2]. However, these histopathologic changes also occur in the small airways, resulting in functional consequences such as small airway closure [3]. Increased small airway closure has been associated with a greater risk of severe asthma exacerbations and correlated with the severity of asthma [4]. Small airway closure in asthma is determined by a complex interaction of structural and functional characteristics including the thickness and elastic properties of the airway wall [5]. Several studies have determined that reduced elastic recoil is primarily responsible for small airway closure in asthma [6—8]. These findings indicate that the relative contribution of reduced elastic recoil to small airway closure is of high importance [9]. Interestingly, reduced elastic recoil has been observed in stable, asymptomatic asthmatic patients as well as in patients with severe exacerbations of the disease. Moreover, it is also reported that even asthmatic patients with no actual airway obstruction have reduced elastic recoil [10].

Pentosidine is well established as an intermolecular cross-linking type of advanced glycation end products, and it accumulates with aging in various connective tissues including collagen [11—14]. It is formed through a series of non-enzymatic reactions between glucose and proteins resulting in a highly stable cross-linked product. One of the contributing factors to its production is oxidative stress. Although all proteins are prone to pentosidine formation, deleterious pentosidine accumulation occurs in tissues with low turnover, including collagen. This accumulation subtly alters collagen structure and function, increasing stiffness in arteries, skin, bone, and lung [15,16]. In human studies, pentosidine has also been found to be responsible for collagen cross-linking in lung tissues [17]. Recently, we demonstrated that pentosidine levels in induced sputum were significantly higher in asthmatic patients than in normal controls, and that loss of elastic recoil might be attributable to pentosidine level in the airways [18].

An aging population will result in increased prevalence of elderly asthma; therefore, it is important to clarify the pathophysiological features of this condition. To date, difficulties have been encountered in differentiating asthma and COPD [19]. Cigarette smoking is a major diagnostic confounder in elderly populations, and published descriptions of elderly asthma are derived from cohorts that include smokers [20]. Because of the confounding effects of smoking, these descriptions might not truly reflect elderly asthma. A previous study reported that small airway closure in elderly asthmatics was increased compared with younger asthmatics [7]. Although age-related loss of elastic recoil is likely the main cause of this phenomenon, the precise mechanism remains undetermined. In order for a population of elderly asthmatic patients to serve as a model in which to examine small airway closure, the confounding effects of smoking must be eliminated. Therefore, this study was designed to investigate the influences of aging and smoking on susceptibility to small airway closure in asthma.

Methods

Study subjects

Sixty-one patients with asthma (20 non-smoking young adult, 23 non-smoking elderly, and 18 smoking young adult) and thirty-six control subjects (12 non-smoking young adult, 11 non-smoking elderly, and 13 smoking young adult) were included in this study. Young adult subjects were aged 20—40 years, and elderly subjects were more than 60 years of age. Smokers were aged 20—40 years, and had more than a 10 pack-year history (control smokers, range: 10—19 pack-years; asthmatic smokers: 10—21 pack-years). All control subjects were volunteers who had no history of lung diseases. All asthmatic patients had been newly diagnosed with asthma at the respiratory outpatient clinics of our university hospital on entry into this study. All asthmatics had: (1) episodic cough, wheeze and dyspnea; (2) normal chest roentgenograph; (3) reduction of forced expiratory volume in 1 s (FEV_1) in case of asthma attack and increase of 20% or greater in FEV_1 in response to a bronchodilator; (4) airway hyperresponsiveness to methacholine. In addition, all of them were atopy; total serum immunoglobulin E (IgE) levels were more than 250 IU/mL, and one or more common aeroallergens were determined by specific IgE. At the time of the study, all asthmatic patients were solely receiving salbutamol for as-needed relief of symptoms without controller medications (*i.e.*, long-acting β2-agonists, leukotriene modifiers, and oral or inhaled corticosteroids). Exhaled nitric oxide (NO) levels were measured with a chemiluminescence analyzer with a resolution of 1 parts per billion (ppb) in accordance with the American Thoracic Society standards [21]. All asthmatic patients were clinically stable, and none had a history of respiratory infection for at least the 4-week period preceding the study. All subjects provided written informed consent for participation in the study, which was approved by the Ethics Committee of Osaka City University.