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PHYSIOLOGY

Bronchial biopsy and reactivity in patients with chest tightness relieved with bronchodilator

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ABSTRACT

Objective: It has been hypothesized that some patients with chest tightness of unknown origin can be successfully treated with a bronchodilator and that they should be diagnosed with chest pain variant asthma. We conducted a prospective study to characterize newly diagnosed patients with chest tightness relieved with bronchodilator use and without characteristic bronchial asthma attacks. **Methods:** Eleven patients were registered following recurrent positive responses of chest tightness to inhalation of a β_2 -agonist. These patients underwent assessments of airway responsiveness to methacholine, bronchial biopsy and bronchial lavage under fiber-optic bronchoscopy before receiving treatment. **Results:** For the patients with chest tightness relieved with bronchodilator use, the bronchial biopsy specimens exhibited significant increases in lymphocyte and macrophage infiltration ($p < 0.05$) and no significant increase in eosinophils ($p = 0.2918$) compared with the control subjects. The bronchial responsiveness to methacholine was increased in two of the patients with chest tightness, and it was not increased in seven; in addition, increased percentages of eosinophils were detected in bronchial lavage fluid (5% or more) from two patients, but no increase was detected in eight patients. **Conclusions:** We suspect that the chest tightness was induced by airway constriction in these patients, but further study is necessary to validate this hypothesis. We propose that the chest tightness relieved with bronchodilator use was attributed to airway constriction resulting from inflammation with lymphocytes and macrophages and/or that the chest tightness was directly attributed to airway inflammation. This clinical trial is registered at www.umin.ac.jp (UMIN13994 and UMIN 16741).

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Introduction

Chest tightness is a common symptom of diverse diseases. Many patients who experience chest tightness consult their physicians, and they are usually diagnosed with a cardiovascular or gastrointestinal disease. However, many patients remain undiagnosed and untreated. We have reported that some patients with chest tightness of unknown origin can be successfully treated with a bronchodilator or other asthma drugs [1].

The Global Initiative for Asthma (GINA) is a medical guidelines organization that works with public health officials and health care professionals around the world to reduce asthma prevalence, morbidity, and mortality. The GINA states that chest tightness is an asthma symptom [2]. Chest tightness is more likely muscle tightness or physical difficulty with moving air that is sensed through proprioception and not through pain pathways. Chest

tightness in patients with bronchial asthma sometimes improves with use of a bronchodilator [1].

Whitney and co-workers reported on three patients who presented with chest tightness that was relieved with bronchodilator use. These patients were diagnosed with asthma [3]. Specifically, this disease was termed “chest pain variant asthma (CPVA),” and several articles in the medical literature have addressed this disease [1, 3–6]. No clear diagnostic criteria for CPVA have been established, but it should be defined as chest tightness without characteristic bronchial asthma attacks that improves with bronchodilator use [1]. CPVA is common in our experience. However, this disease is difficult to diagnose because it is poorly characterized and less well known. The mechanism of chest tightness remains unexplained.

In a previous study, we have hypothesized that patients' positive responses to chest tightness with bronchodilator use are indicative of a correct diagnosis of CPVA [1].

The purpose of the present study was to demonstrate the clinical characteristics, pathophysiology, pathology, and medical treatment of patients with chest tightness relieved with bronchodilator use and without characteristic bronchial asthma attacks, as well as to evaluate the appropriateness of diagnosing these patients with a variant form of asthma. There is no clear definition of “variant asthma”; however, the main clinical condition with bronchoconstriction is almost identical to typical bronchial asthma, and the symptoms and related physical findings are distinct from those of typical bronchial asthma to some extent.

Methods

Study oversight

We conducted this prospective study between 2014 and 2016 at the Toyama Prefectural Central Hospital. After patient screening and baseline assessments were performed, the participants underwent several examinations and treatment. This study conformed to the Declaration of Helsinki, and it was approved by the ethics committee of the Toyama Prefectural Central Hospital (numbers 2010-2 and 4903). This clinical trial is registered at www.umin.ac.jp (UMIN13994 and UMIN 16741).

Subjects

We recruited 11 patients with recurrent chest tightness that improved in response to treatment with a bronchodilator, five control subjects who had undergone bronchial biopsy, five patients with classic asthma, and five healthy subjects.

In the group of patients with chest tightness, all of the patients complained primarily of chest tightness and had normal breath sounds. These patients had not been diagnosed with bronchial asthma, with the exception of childhood asthma, before the first examination, and they had not presented with characteristic bronchial asthma attacks. All of the patients underwent chest X-rays, computed tomography imaging, laboratory diagnostic analyses, and electrocardiograms to verify the absence of pneumothorax, infection, and coronary disease. Most of the patients underwent upper gastrointestinal endoscopy to verify the absence of gastrointestinal disease. The patients were administered a short-acting β_2 -agonist (0.03 mg procaterol hydrochloride) via inhalation for chest tightness. All of the patients were selected following recurrent positive responses of chest tightness to inhalation of a β_2 -agonist.

All of the bronchial-biopsied control subjects had a peripheral small lung tumor (< 3 cm in diameter)

requiring bronchoscopic examination for diagnosis, no past history of asthma, no respiratory symptoms, and no smoking history.

All of the patients in the asthmatic group had a history of episodic dyspnea, wheezing and coughing. They exhibited at least 15% reversibility of forced expiratory volume in one second (FEV₁) after inhalation of a short-acting β_2 -agonist (0.03 mg procaterol hydrochloride). Their symptoms were well or fairly controlled by treatment with inhaled fluticasone propionate.

None of the healthy subjects had a past history of asthma, respiratory symptoms, or a smoking history. All of the subjects provided informed consent after the purpose of the study had been explained.

Clinical and pulmonary function data

All of the patients with chest tightness underwent measurement of pulmonary function, sputum examination of cell differentials, and measurements of peripheral blood eosinophil, serum-nonspecific immunoglobulin E (IgE) antibody, and serum-specific IgE antibody levels (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust, cockroach, cat fur, and dog hair) (Uni-CAP®, Pharmacia Ltd., Milton Keynes, UK).

Pulmonary function was measured using a spirometer (DISCOM21 FXIII Chest Co. Ltd., Nagoya, Japan). The highest value of at least three measurements was recorded. The flow volume curve patterns of the pulmonary function tests before the bronchodilator treatment were classified as follows: an upper-airway obstruction pattern, obstruction pattern, or normal pattern [7,8]. The classification was determined by subjective judgment by discussion among several of the authors. The predicted pulmonary function values were extracted from Reference [9]. All of the patients with chest tightness underwent pulmonary function testing before and after inhalation of a short acting β_2 -agonist (0.03 mg procaterol hydrochloride) at the first examination. The greatest levels of chest tightness were evaluated with a numerical rating scale (NRS) [10].

Bronchial reactivity

The healthy subjects, patients with chest tightness, and patients with classic asthma underwent the methacholine bronchial provocation test to assess airway hyperresponsiveness before bronchial biopsy was performed. Bronchial reactivity was tested with a buffered methacholine solution using a DeVilbiss no. 646 nebulizer (DeVilbiss Co., Somerset, PA) operated at an airflow of 5 L/min, as previously described [11]. The concentrations of the methacholine solutions were 39, 78, 156, 313, 625,

1250, 2500, 5000 and 10 000 $\mu\text{g}/\text{ml}$. Pulmonary function was assessed with a spirometer (DISCOM21 FXIII Chest Co. Ltd., Nagoya, Japan).

The test began with 2 minutes of inhalation of saline aerosol and continued with inhalation of methacholine solutions of successively higher concentrations until a 20% decrease in the FEV_1 relative to the postsaline control value was observed. The FEV_1 was measured with a spirometer (DISCOM21 FXIII Chest Co. Ltd., Nagoya, Japan) after each challenge and was compared with the value obtained after saline inhalation. Challenge testing was discontinued when the FEV_1 decreased by 20% or more. The provocative concentration of methacholine that caused a 20% decrease in the FEV_1 ($\text{PC}_{20}\text{-FEV}_1$) was calculated by interpolation.

Bronchial biopsies and lavages

All of the patients with chest tightness and the bronchial-biopsied control subjects were subjected to bronchial biopsy and bronchial lavage using a fiberoptic bronchoscope (BF-P260F, Olympus, Tokyo, Japan) under local anesthesia with lidocaine before treatment. These bronchoscopic procedures were performed between 8 a.m. and 11 a.m. The patients were also administered midazolam and fentanyl intravenously for sedation before the procedure. The bronchoscope was placed into the right bronchus, and biopsies were obtained from the airway mucosa from both the central and peripheral airways. The central biopsy specimens were collected at a bifurcation of the right upper lobe bronchus and intermediate bronchus, and the peripheral biopsy specimens were obtained from subsegmental airways to bronchioles in the right lower lobe. Two to three biopsies were examined from each airway level using forceps (Radial Jaw 4, Boston Scientific, Galway, Ireland).

Bronchial lavage fluid (BLF) collection was performed in the middle lobe bronchus using 20 ml of physiologic saline solution. Smears for differential leukocyte counts were prepared by May-Grünwald-Giemsa staining.

The bronchial-biopsied control patients underwent bronchial biopsy before peripheral lung tumor biopsy and collection of BLF.

Processing of biopsy specimens

Sections of the biopsy specimens were prepared for light microscopy. For pathological analysis, the specimens were fixed in 10% neutral-buffered formalin for 6 hours, embedded in paraffin, sliced into 4- μm thick sections, and stained with hematoxylin and eosin. The following antibodies were used for immunohistochemical analyses: anti-CD3 (A0452, Dako, High Wycombe, UK),

anti-CD4 (1F6, Leica, Newcastle upon Tyne, UK), and anti-CD8 (C8/144B M7103, Dako). Mast cells were detected using a polyclonal antibody against c-cit (A4502, Dako). Macrophages were detected using a polyclonal antibody against CD163 (10D6, Leica).

Light microscopy was performed with a Nikon Eclipse 80i (Nikon, Tokyo, Japan) and DS-Fi1 (Nikon). The numbers of eosinophils, mast cells, neutrophils, macrophages, and CD3-, CD4-, and CD8-positive cells among epithelial cells and in the submucosa were visually counted by one of the authors, who was unaware of the clinical findings. The most intact areas of the bronchial epithelium and submucosa were chosen for analyses of mast cells, macrophages, and CD3-, CD4-, and CD8-positive cells. Full visual fields of the bronchial epithelium and submucosa were selected for analyses of eosinophils, mast cells, and neutrophils, which were present at comparatively smaller numbers. Cells located inside of vessels were not counted. The total area of examined submucosa was calculated by delineating the area of the section using NIS Elements D3.2 (Nikon). The results were expressed as the number of cells per square millimeter of submucosa.

Treatment

Initially, we treated the patients with recurrent chest tightness with 400 μg per day inhaled fluticasone propionate and procaterol hydrochloride (short-acting β_2 -agonist) as needed. If the effect of inhaled fluticasone propionate was insufficient after a month of treatment, then we additionally prescribed a long-acting β_2 -agonist or leukotriene receptor antagonist or another asthma drug. If the patient felt that the inhaled fluticasone propionate was ineffective, then we stopped that treatment and alternatively prescribed a long-acting β_2 -agonist or leukotriene receptor antagonist or another asthma drug.

Statistics

The data are expressed as the mean $\pm$ SD. Between-group differences were determined using Student's *t*-test. Significance was based on a 95% confidence level ($p < 0.05$).

Results

Clinical data

Among the 11 patients with chest tightness, the average age at diagnosis was 56.5 ± 21.3 years, and the male:female ratio was 3:8 (Table 1). The primary complaints of the patients included retrosternal tightness in

Table 1. Clinical characteristics of patients with chest tightness relieved with bronchodilator use and without characteristic bronchial asthma attacks.

Patient no.	Age of diagnosis (years)	Age of onset (years)	Sex	History of allergic disease	History of smoking (pack-year)	Complication	Eosinophils in PB (/μL)	Serum IgE (U/mL)	UniCAP specific IgE*	Aspect of chest tightness	Greatest level of the tightness (NRS)
1	65	62	F	AR	6 (EX)	—	29	241	—	Retrosternal tightness with headache at all hours of the day, lasting from 10 minutes to a few hours	10
2	25	24	F	CA	0	—	242	173	HD, Mite	Tightness in various parts of the chest, lasting for approximately 10 minutes and occurring a few times a day	8
3	45	42	M	—	0	LC	151	110	HD, Mite	Retrosternal tightness at all hours of the day	8
4	61	58	F	—	0	—	0	54.5	—	Tightness from the throat to the entire chest, lasting for 5 minutes and occurring very often	8
5	17	14	F	AD	0	—	48	35.1	HD, Mite	retrosternal tightness with headache at all hours of the day	8
6	73	in youth	F	—	0	HT	201	< 5.0	—	Retrosternal tightness with headache at all hours of the day	5
7	63	63	F	—	0	—	301	59.9	—	Retrosternal tightness at all hours of the day	10
8	67	65	M	—	5 (EX)	OMI	283	18.2	—	Retrosternal tightness with headache at all hours of the day, exacerbation on effort	5
9	75	74	F	—	0	RA	94	51.6	—	Retrosternal tightness on effort	8
10	74	73	M	—	40 (EX)	HT	190	998	HD, Mite	Retrosternal tightness on effort	10
11	21	21	F	AR	0	—	265	321	HD, Mite	Retrosternal tightness at all hours of the day	10
Average	53.3	—	M:3, F:8				164				8.2

Note. M, male; F, female; AR, allergic rhinitis; CA, childhood asthma; AD, atopic dermatitis; EX, ex-smoker; LC, lung cancer; HT, hypertension; OMI, old myocardial infarction; RA, rheumatoid arthritis; PB, peripheral blood; HD, house dust; IgE, immunoglobulin E; NRS, numerical rating scale

* UniCAP specific IgE, fluoroimmunoanalysis-specific immunoglobulin E.

nine patients, tightness of various parts of the chest in one, and tightness from the throat throughout the entire chest in one.

Among the five bronchial-biopsied control patients, the average age at examination was 57.2 ± 7.7 years, and the male:female ratio was 1:4. Among the five bronchial asthma patients, the average age at examination was 59.6 ± 13.2 years, and the male:female ratio was 1:4. Finally, among the five healthy subjects, the average age at examination was 29.2 ± 9.0 years, and the male:female ratio was 3:2.

Pulmonary function data

Among the eleven patients with chest tightness, the predicted FEV₁ % was $125.3 \pm 21.9\%$, the predicted peak expiratory flow rate (PEF) % was $76.9 \pm 13.0\%$, and the FEV₁/forced vital capacity (FVC) ratio was 81.4 ± 4.8 on the initial pulmonary function test. The flow volume curve patterns for the initial pulmonary function tests revealed an upper-airway obstruction pattern in 3 patients, an obstruction pattern in one, and a normal pattern in 7.

Among the patients with chest tightness, nine experienced a chest tightness attack at the first examination and exhibited a positive response to inhalation of a β_2 -agonist. Two patients did not experience an attack at the first examination. With inhalation of the short-acting β_2 -agonist, the FEV₁ increased by $5.0 \pm 4.2\%$, and the PEF improved by $10.1 \pm 12.1\%$ (Figure 1).

Bronchial reactivity

Among the 11 patients with chest tightness, the bronchial responsiveness to methacholine was increased in two and was not increased in seven (Figure 2). The average PC₂₀-FEV₁ in these two patients with increased responsiveness was $1732 \mu\text{g/ml}$. Patients number 7 and 11 stopped the treatment because they experienced severe chest tightness after inhalation of the methacholine solutions without exhibiting a 20% decrease in the FEV₁ relative to the post-saline control value.

The bronchial responsiveness to methacholine was increased in all of the patients with bronchial asthma. The average PC₂₀-FEV₁ in these patients was $1722 \mu\text{g/ml}$. However, it was not increased in the five healthy subjects.

Significant increases in PC₂₀-FEV₁ were detected in the patients with chest tightness compared with those with bronchial asthma ($p = 0.0006$). However, no significant differences were observed between the patients with chest tightness and the control subjects ($p = 0.1690$).

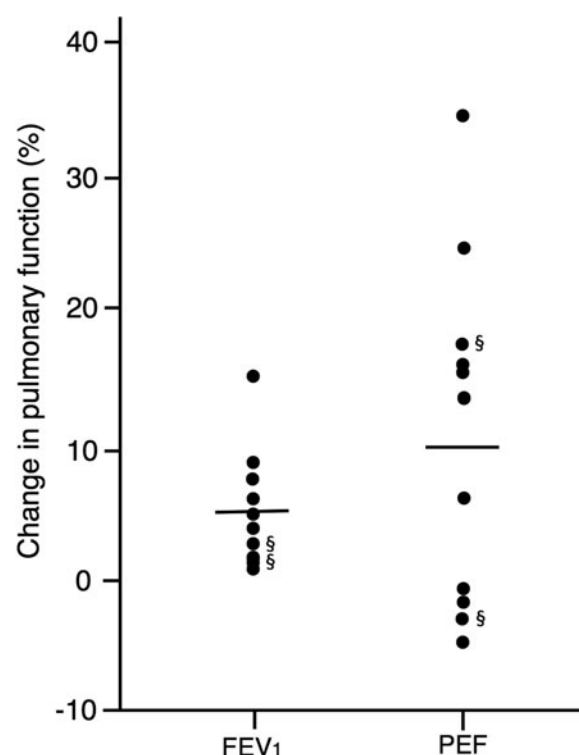


Figure 1. Changes in the forced expiratory volume in one second (FEV₁) and peak expiratory flow rate (PEF) observed on pulmonary function tests before and after inhalation of a short-acting β_2 -agonist (0.03 mg procaterol hydrochloride) at first examination in eleven patients with chest tightness relieved with bronchodilator use. Nine patients experienced a chest tightness attack at first examination, and two patients (§) did not experience such an attack.

Bronchial biopsies

Eleven central biopsy specimens and ten peripheral biopsy specimens were obtained from the patients with chest tightness. A central biopsy specimen only was collected from one patient. No significant differences in cell numbers were detected between the two airway levels studied. We used the average cell numbers at the two airway levels in statistical analyses.

Five central biopsy specimens and five peripheral biopsy specimens were obtained from the control subjects. No significant differences in cell numbers were observed between the two airway levels studied. We used the average cell numbers at the two airway levels in statistical analyses.

The numbers of cells in the biopsy specimens from the patients with chest tightness and the control subjects are presented in Figures 3 and 4. Significant increases in the numbers of CD3- ($p = 0.0098$), CD4- ($p = 0.0172$), and CD8-positive cells ($p = 0.0127$) and macrophages ($p = 0.0079$) were detected between the two groups. However, no significant differences in the number of eosinophils ($p = 0.2918$), mast cells ($p = 0.1976$), or

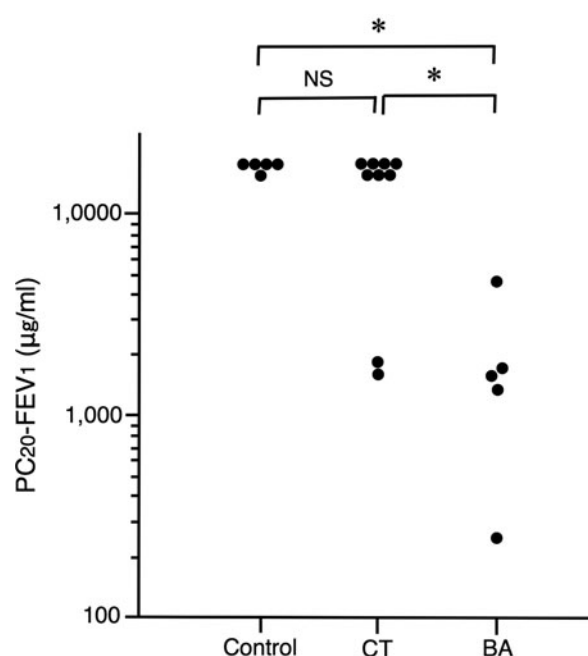


Figure 2. The provocative concentration of methacholine that produced a 20% decrease in the FEV₁ (PC₂₀) of the control subject ($n = 5$), patients with chest tightness (CT) ($n = 9$), and patients with classic bronchial asthma (BA) ($n = 5$). NS = nonstatistically significant. * $p < 0.05$ using Student's t -test.

neutrophils ($p = 0.2026$) were observed between the groups.

Eosinophils in bronchial lavages and sputum samples

A total of 10 BLF samples were obtained from the patients with chest tightness, and five were collected from the control subjects. We failed to obtain two BLF samples from patient number 1. An increased percentage of eosinophils in the BLF (5% or more) was detected in two patients with

chest tightness and in none of the control subjects ($p = 0.2050$, Figure 5).

A total of eight sputum samples were obtained from the patients with chest tightness, and five were collected from the control subjects. We failed to obtain sputum samples from three patients with chest tightness. No increase in the percentage of eosinophils in the sputum (3% or more) was detected in the patients with chest tightness or in the control subjects ($p = 0.3739$, Figure 5).

Treatment

The responses of the patients with chest tightness to the asthma drugs are shown in Table 2. The effects of each drug varied among the patients. Treatment with an inhaled corticosteroid for a month was recognized as effective for the control of chest tightness in seven patients but was considered ineffective in four. Changes in the FEV₁ and PEF observed on pulmonary function tests between the initial phase and the stable phase after treatment are presented in Figure 6, which shows that the FEV₁ increased by $2.3 \pm 5.7\%$ and that the PEF improved by $12.4 \pm 13.6\%$.

Discussion

In a previous report, we hypothesized that chest tightness in some patients can be relieved with a bronchodilator, while that in others can be relieved with a leukotriene receptor antagonist, thromboxane antagonist or systemic corticosteroid but not with a bronchodilator [1,12]. The chest tightness in the subset of patients who can obtain relief using a bronchodilator can also be relieved with the use of other asthma drugs. In this study, we assessed 11 patients presenting with no history of typical asthma

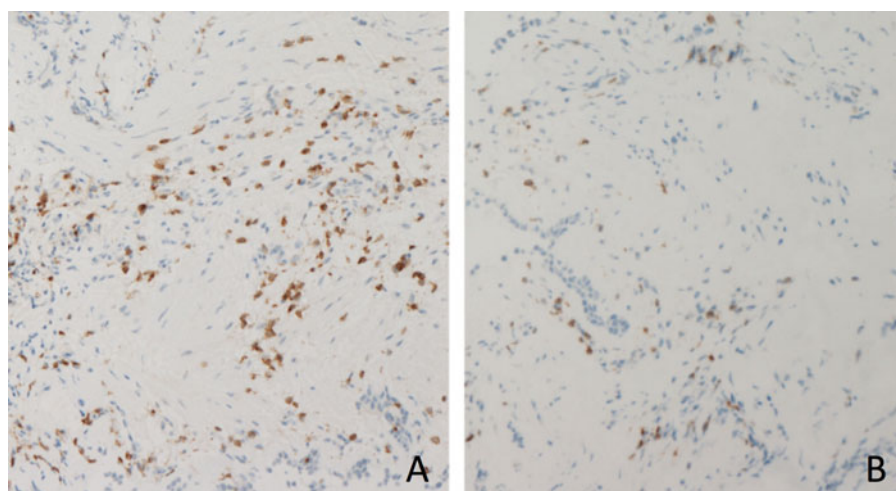


Figure 3. Typical bronchial biopsy specimens from a patient with chest tightness (A) and a control subject (B) stained with anti-CD3 antibody. The specimen from the patient with chest tightness contained many CD3-positive cells.

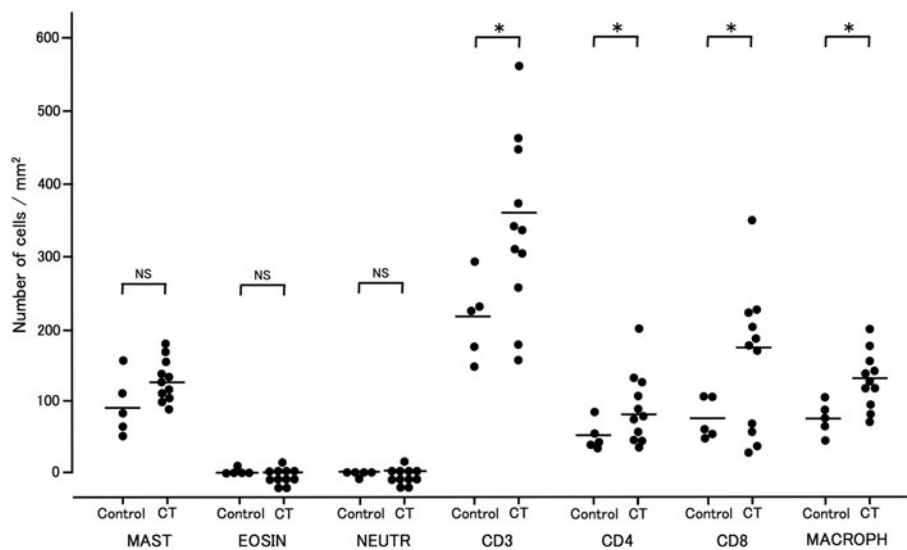


Figure 4. The numbers of mast cells (MAST), eosinophils (EOSIN), neutrophils (NEUTR), CD3-, CD4-, and CD8-positive cells, and macrophages (MACROPH) in the bronchial biopsy specimens of the control subjects ($n = 5$) and patients with chest tightness (CT) ($n = 11$) are presented per square millimeter. NS = nonstatistically significant. * $p < 0.05$ using Student's t -test.

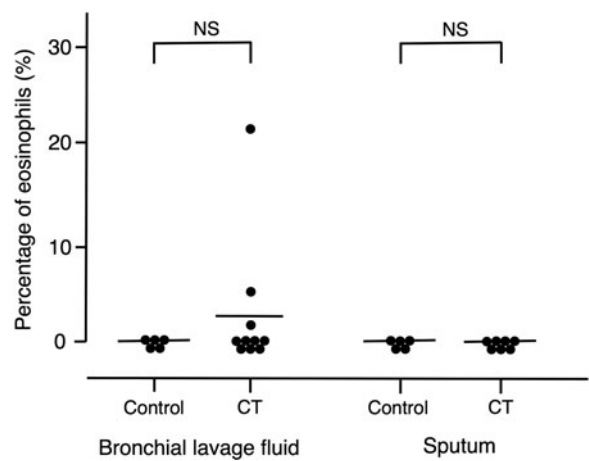


Figure 5. Percentages of eosinophils in bronchial lavage fluid and sputum from the control subjects and patients with chest tightness (CT). NS = nonstatistically significant.

attacks but with persistent or recurrent chest tightness that improved in response to inhaled β_2 -agonist use.

Retrosternal tightness or a heavy sensation in the chest has been previously described as a typical symptom of patients with chest tightness relieved with bronchodilator use and without characteristic bronchial asthma attacks [1]. This symptom is sometimes associated with coughing, sputum production, or tightness radiating to one side of the head, back, or chest. The severity, frequency, duration, and onset time of a chest tightness attack can vary among different patients. A subset of these patients has been found to have an upper-airway obstruction pattern on the pulmonary function test at first examination that exhibits improvement with bronchodilator inhalation [1,7]. These patients do not always have peripheral blood eosinophilia, an increase in the serum non-specific IgE level, or specific IgE positivity. In this study, very

Table 2. The responsiveness to asthma drugs of patients with chest tightness relieved with bronchodilator use and without characteristic bronchial asthma attacks.

Patient no.	SABA	ICS	LABA	LTRA	LAMA	THEO	TXI	SCS	CNI	A-IgE	Final control drugs
1	E	E	—	—	—	—	—	—	—	—	ICS
2	E	E	E	E	—	E	E	E	—	—	ICS/LABA, LTRA, TXI, THEO
3	E	E	E	E	—	—	—	—	—	—	ICS/LABA, LTRA
4	E	E	E	—	—	—	—	—	—	—	ICS/LABA
5	E	N	—	E	—	—	—	—	—	—	LTRA
6	E	E	—	—	—	—	—	—	—	—	ICS
7	E	E	—	E	—	—	—	—	—	—	ICS
8	E	E	E	—	—	—	—	—	—	—	ICS/LABA
9	E	N	E	N	—	N	E	—	—	—	LABA, TXI
10	E	N	E	—	—	—	—	—	—	—	LABA
11	E	N	E	N	N	N	N	N	N	E	ICS/LABA, A-IgE

Note. E, effective against chest tightness; N, not effective against chest tightness; SABA, short-acting β_2 -agonist; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; THEO, theophylline; TXI, thromboxane inhibitor; SCS, systemic corticosteroid; CNI, calcineurin inhibitor; A-IgE, anti-human immunoglobulin E antibody.

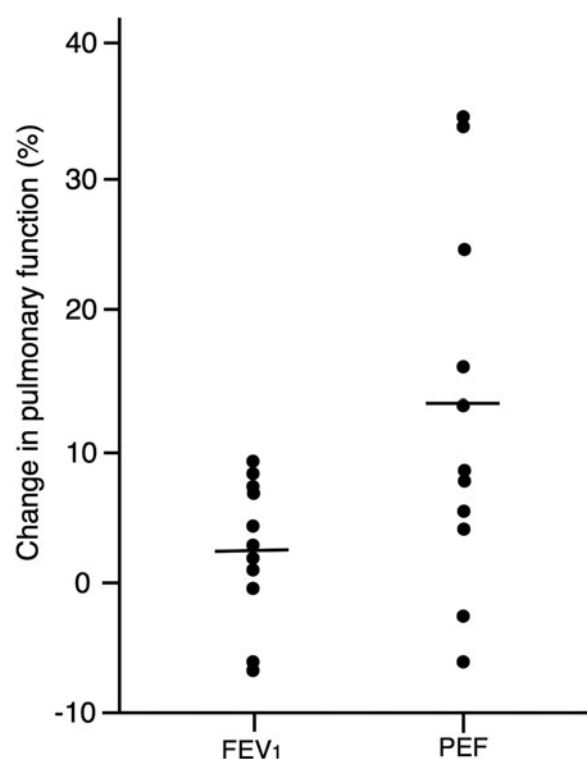


Figure 6. Changes in the forced expiratory volume in 1 second (FEV₁) and peak expiratory flow rate (PEF) observed on pulmonary function tests between the initial phase and the stable phase after treatment in 11 patients with chest tightness relieved with bronchodilator use.

similar findings were observed for the patients with chest tightness.

We suspected that the chest tightness was induced by airway constriction in these patients; this tightness decreased in response to administration of the bronchodilator in concordance with bronchodilation. However, it is difficult to demonstrate support of this hypothesis using the pulmonary function test results, which showed insignificant improvement with inhalation of the short-acting β_2 -agonist. It is possible that β_2 -agonists decrease chest tightness by other mechanisms such as inhibition of neurotransmission [13].

The most characteristic feature of classic bronchial asthma is bronchial inflammation leading to nonspecific hyperreactivity. There are several reports of increased inflammatory cells in the airway mucosa of asthmatic patients [14–19]. Influx of eosinophils into the airway mucosa may be a characteristic of asthma, but increased eosinophils are not always observed in the bronchoalveolar lavage fluid or bronchial tissues of patients of bronchial asthma.

Azzawi and coworkers have reported that the highest numbers of CD45-, CD3-, CD4-, and CD8-positive cells are present in asthma patients compared with

nonasthmatic atopic and healthy subjects [17]. Thus, the recruitment and activation of lymphocytes and eosinophils are important events in the pathogenesis of bronchial asthma. In this study, increases in the numbers of lymphocytes and macrophages were detected in the bronchial biopsy specimens of the patients with chest tightness, but no significant increase in the number of eosinophils was observed. In addition, no significant increase in the number of eosinophils was observed in the BLF samples from the patients with chest tightness. We propose that the chest tightness relieved with bronchodilator use was attributed to airway constriction resulting from inflammation with lymphocytes and macrophages and/or that the chest tightness was directly attributed to airway inflammation.

Bronchial reactivity is often increased in patients with typical bronchial asthma [20]. Assessment of bronchial reactivity is sensitive for diagnosis of asthma, but it has limited specificity. In this study, bronchial responsiveness to methacholine was enhanced in only two patients with chest tightness. Interestingly, these two patients experienced severe chest tightness after inhalation of the methacholine solutions without a 20% drop in the FEV₁ relative to the postsaline control value. They should not have experienced severe airway constriction after methacholine inhalation; however, the constriction was sufficient to induce chest tightness.

In similar patients, we have previously demonstrated bronchial responsiveness to histamines in six out of seven cases [1]. Bronchial responsiveness to histamine and methacholine is closely correlated with bronchial asthma [21]. The bronchial responsiveness of patients with chest tightness to methacholine and histamine may differ. We suspect that there are differences in the constricting regions of bronchi between bronchial asthma and chest tightness relieved with bronchodilator use [1,7] and that the difference in bronchial responsiveness between histamine and methacholine may result from variations in the targeted airway regions between these two drugs.

The GINA defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play roles. The chronic inflammation is associated with airway hyperresponsiveness, leading to a number of asthma symptoms. In this study, the bronchial biopsy specimens from the patients with chest tightness exhibited lymphocyte and macrophage infiltration. Chest tightness that is relieved with bronchodilator use in the absence of characteristic bronchial asthma attacks may be indicative of a variant form of asthma. However, the finding that bronchial responsiveness to methacholine was not greatly increased in the patients with chest

tightness does not support this hypothesis. Additionally, chest tightness that can be relieved with bronchodilator use may exhibit variable bronchial responsiveness to methacholine and asthma drugs.

There is a need for increased knowledge regarding the effective treatment of chest tightness with a bronchodilator or other asthma drugs in the absence of characteristic bronchial asthma attacks. Thus, this clinical condition should be further investigated. We hope to further assess the epidemiology, pathology, pathophysiology, and clinical characteristics of chest tightness that can be relieved with a bronchodilator and its associated disease. There is an apparent need for increased dissemination of knowledge concerning chest tightness that can be relieved with asthma drugs.

Declaration of interest

The authors report that there are no significant conflicts of interest regarding any companies/organizations whose products or services are discussed in this article. The authors alone are responsible for the content and writing of the article.

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