

Original articles

Bronchial responsiveness and acute bronchodilator response in chronic obstructive pulmonary disease and diffuse panbronchiolitis

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Abstract

Background – Diffuse panbronchiolitis (DPB) is characterised clinically by chronic airflow limitation and respiratory tract infection, and pathologically by chronic bronchiolar inflammation. To elucidate the functional differences between chronic obstructive pulmonary disease (COPD) and DPB the bronchial responsiveness to methacholine was compared in 64 patients with COPD and 32 patients with DPB, and the bronchodilator response was compared in 72 patients with COPD and 49 with DPB.

Methods – Bronchial responsiveness to methacholine was determined by the dosimeter method and expressed as $PD_{20}FEV_1$, and bronchodilator response was measured as the change in percentage predicted response with 5 mg nebulised salbutamol.

Results – Baseline FEV_1 was similar in the two groups of patients. Patients with COPD were more responsive to methacholine than were those with DPB (geometric mean $PD_{20}FEV_1$ 8.87 v 48.0 cumulative units). Reversibility of air flow obstruction, expressed as the difference between the percentage predicted postbronchodilator FEV_1 and prebronchodilator FEV_1 , was significantly larger in patients with COPD than in those with DPB (7.87 (6.52)% v 4.16 (4.43)%).

Conclusions – The observation that patients with DPB differ substantially in bronchial responsiveness from those with COPD is thought to reflect the difference in the mechanisms of these two diseases – that is, airway disease in DPB and more parenchymal disease in the group of patients with COPD. The nature of bronchiolar inflammation in COPD and DPB is also different, possibly explaining the difference in bronchial responsiveness. More fixed airflow limitation as a result of structural bronchiolar lesions in DPB will explain the smaller reversibility of airflow obstruction.

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Diffuse panbronchiolitis (DPB) is characterised clinically by chronic airflow limitation and lower respiratory tract infection often associated with paranasal sinusitis. Pathologically it is a chronic inflammatory disease of the airways and the predominant sites are the bronchiolar and centrilobular regions.¹⁻³ This disease was first described in 1969, and many patients with DPB have since been reported, predominantly in Japan, with several cases elsewhere.⁴⁻⁶ On the other hand, chronic obstructive pulmonary disease (COPD) is defined as a disorder characterised by an abnormality of expiratory flow that does not change markedly over periods of several months.⁷ The pathology of COPD is described as a mixture of inflammation of the central and peripheral airways and emphysema to varying degrees.⁸ Chronic inflammatory changes related to prolonged cigarette consumption are accepted as the primary cause of these pathological changes.⁹

Many patients with DPB suffer from chronic cough, copious sputum, and exertional dyspnoea, and have bilateral small nodular shadows and hyperinflation of the lungs on chest radiography.¹⁻³ The major symptom of COPD is exertional dyspnoea, and many patients complain of productive cough. In addition, both diseases are characterised by chronic airflow limitation. These two diseases therefore show some similarity in their clinical presentation.

Bronchial hyperresponsiveness to non-specific stimuli is a feature of COPD, and increased bronchial responsiveness is associated with the accelerated annual decline of FEV_1 , even after adjusting for the baseline level of lung function.^{10,11} The acute bronchodilator response has also been shown to correlate with prognosis.¹⁰ These observations may reflect an important relation between functional or structural abnormalities, or both, and the pathogenesis of bronchial hyperresponsiveness and bronchodilator response in COPD.

To elucidate the functional differences between COPD and DPB we have evaluated the bronchial responsiveness and bronchodilator response in patients with these diseases.

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Table 1 Mean (SD) baseline pulmonary function in patients with chronic obstructive pulmonary disease (COPD) and diffuse panbronchiolitis (DPB)

	n	COPD	n	DPB	p
Age (years)	75	66.0 (6.8)	51	52.1 (15.0)	<0.001
Sex (male:female)		75:0		30:21	
Smoking history*	75	75	50	11	<0.001
VC (l)	74	3.28 (0.71)	50	2.49 (1.00)	<0.001
%predicted		91.6 (19.6)		69.0 (21.2)	<0.001
FVC (l)	74	2.94 (0.78)	50	2.27 (1.04)	<0.001
FEV ₁ (l)	74	1.38 (0.53)	50	1.35 (1.04)	NS
%predicted		52.1 (18.5)		48.2 (19.5)	NS
FEV ₁ /FVC (%)	74	46.4 (10.5)	50	58.2 (12.3)	<0.001
TLC (l)	64	7.76 (1.41)	33	6.38 (1.50)	<0.001
%predicted		138.9 (22.4)		132.8 (23.0)	NS
RV (l)	64	4.46 (1.28)	33	3.85 (1.10)	NS
%predicted		225.7 (64.1)		250.1 (67.8)	NS
RV/TLC (%)	64	57.0 (9.2)	33	60.8 (11.8)	NS
TLCO (mmol/min/kPa)	74	5.73 (1.74)	47	7.91 (4.02)	<0.001
TLCO/VA (mmol/min/kPa/l)	74	1.20 (0.40)	47	1.88 (0.39)	<0.001
Cst (l/kPa)	65	4.59 (2.24)	35	2.96 (1.53)	<0.001
Raw (kPa/l/s)	55	0.483 (0.226)	24	0.538 (0.250)	NS
IgE-RIST (IU/ml)†	72	106.6	48	73.1	NS

VC = vital capacity; FVC = forced vital capacity; FEV₁ = forced expiratory volume in one second; TLC = total lung capacity; RV = residual volume; TLCO = gas transfer factor for the lung; TLCO/VA = transfer coefficient; Cst = static compliance; Raw = airways resistance; IgE-RIST: immunoglobulin E measured by radioimmunosorbent test.

* Current smokers + ex-smokers.

† Geometric mean.

Methods

PATIENTS

The study population consisted of 75 patients with COPD and 51 with DPB who visited the Chest Disease Research Institute Hospital, Kyoto University from 1985 to 1992 (table 1).

Chronic obstructive pulmonary disease

The diagnosis of COPD was based on the definition of the American Thoracic Society.⁷ The patients with COPD in the present study fulfilled the following criteria: (1) a maximum ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) of less than 70% over several measurements of postbronchodilator spirometry; (2) a smoking history of more than 20 pack years; (3) no history consistent with asthma such as paroxysmal dyspnoea and wheezing; and (4) chest radiographic findings compatible with pulmonary emphysema. In addition, most patients had low attenuation areas on high resolution computed tomography, indicating the presence of centrilobular emphysema.¹²

Diffuse panbronchiolitis

The diagnosis of DPB was made according to the clinical diagnostic guidelines established for DPB in the nationwide survey by the Welfare and Health Ministry of Japan.¹ The criteria can be summarised as follows: (1) symptoms of chronic cough, sputum, and dyspnoea on exertion; (2) physical signs of crackles or rhonchi; (3) chest radiographic findings of diffusely disseminated small nodular shadows with hyperinflation of the lung; and (4) lung function studies giving more than three of the following: FEV₁/FVC < 70%, slow vital capacity < 80% of the predicted value, residual volume (RV) > 150% of the predicted value, RV/total lung capacity > 45% or Pao₂ < 10.5 kPa. In addition, chronic paranasal sinusitis and high resolution computed tomographic findings compatible with DPB – that is, centrilobular nodules¹³ – were confirmed in

all patients with DPB. In nine patients, including those who did not fulfil the above stated clinical guidelines, the diagnosis was confirmed by open lung biopsy. The specimen exhibited focal lesions of panbronchiolitis consisting of an aggregate of foamy macrophages and lymphoid cells within the wall of respiratory bronchioles and adjacent alveolar ducts and alveoli.^{2,14,15} Because long term low dose erythromycin is an effective treatment for DPB,^{16,17} all measurements were performed before initiating erythromycin treatment in these patients.

Based on the baseline prebronchodilator spirometric measurements, the severity of the obstructive abnormality in patients with COPD and DPB was graded as follows¹⁸: mild, %pred FEV₁ < 100 and ≥ 70; moderate, %pred FEV₁ < 70 and ≥ 60; moderately severe, %pred FEV₁ < 60 and ≥ 50; severe, %pred FEV₁ < 50 and ≥ 34; very severe, %pred FEV₁ < 34.

All patients were stable for at least two months before performing the baseline pulmonary function tests, the acute bronchodilator test, and the methacholine inhalation challenge test. With a few exceptions the methacholine inhalation challenge test and the acute bronchodilator test were performed within a month of each other. Inhalation of β receptor agonists or anticholinergic drugs were withheld for at least 12 hours and oral theophylline for 48 hours before performing the three tests. No subjects had taken oral or inhaled steroids. All subjects were informed of the purpose of this study.

Methods

METHACHOLINE INHALATION CHALLENGE TEST

Methacholine challenge tests were performed in patients who had an FEV₁ of > 34% of the predicted value using the method described by Chai and coworkers.¹⁹ Methacholine chloride was dissolved in phosphate buffered saline (pH 7.0). Phosphate buffered saline and methacholine solutions were delivered by a dosimeter (Rosenthal French, Baltimore, USA) using a No 646 DeVilbiss nebuliser (DeVilbiss Co, Somerset, USA) at a pressure of 139 kPa (20 psi). Subjects performed spirometric tests correctly on a heat spirometer (AS-600, Minato Medical Equipment Co. Tokyo, Japan) three times before inhalation and twice after inhalation of each concentration of methacholine. The largest value for each measurement was used. The results were expressed as the dose of methacholine required to produce a 20% fall in FEV₁ (PD₂₀FEV₁). The doses of methacholine were expressed as cumulative units where one inhalation of 1 mg/ml methacholine solution = one cumulative unit, and the PD₂₀FEV₁ values were determined by linear interpolation of the log cumulative dose-response curve.

BRONCHODILATOR RESPONSE

Five milligrams of salbutamol with 2 ml of saline was inhaled using a DeVilbiss No 646

Table 2 Mean (SD) bronchial responsiveness to methacholine (expressed as log PD₂₀ FEV₁) in patients with chronic obstructive pulmonary disease (COPD) and diffuse panbronchiolitis (DPB) in relation to obstructive abnormality

Grade*	n	COPD	n	DPB	p
Mild	12	1.592 (0.577)	8	1.886 (0.382)	NS
Moderate	11	1.170 (0.624)	3	2.115 (0.410)	<0.05
Moderately severe	18	0.809 (0.618)	8	1.685 (0.731)	<0.01
Severe	23	0.614 (0.660)	13	1.453 (0.736)	<0.01
Total	64	0.948 (0.713)	32	1.681 (0.652)	<0.01

* Mild = %pred FEV₁ <100 and ≥70; moderate = %pred FEV₁ <70 and ≥60; moderately severe = %pred FEV₁ <60 and ≥50; severe = %pred FEV₁ <50 and ≥34.

nebuliser. Spirometric testing was performed before and 15 minutes after each inhalation. To minimise the effect of the baseline airway calibre results were expressed as the difference between percentage predicted postbronchodilator FEV₁ and prebronchodilator FEV₁.²⁰⁻²² The largest FVC and the largest FEV₁ of at least three acceptable measurements were used.²³

PULMONARY FUNCTION TESTING

Diffusion capacity was measured by the single breath method using carbon monoxide (Chestax 65VH, Chest Co, Tokyo, Japan).²⁴ Total lung capacity was calculated as the sum of the volume of thoracic gas determined by pressure corrected flow type body plethysmography²⁵ (model MBR 2000M, Nihon Kohden Co, Tokyo, Japan), the inspiratory residual volume and the tidal volume. The residual volume (RV) was calculated as the thoracic gas volume minus the expiratory residual volume. Static compliance was measured by the single breath interrupted technique. The predicted values for FEV₁ and vital capacity were those established by the Japan Society of Chest Diseases.²⁶

SERUM IMMUNOGLOBULIN E

Serum immunoglobulin E was measured by radioimmunosorbent test.

STATISTICAL ANALYSIS

The data were analysed by the Kruskal-Wallis test and Mann-Whitney U test; $p < 0.05$ was considered significant. Spearman correlation coefficients were used for the analysis of the relation between baseline FEV₁ and bronchial responsiveness to methacholine. Data are expressed as mean (SD).

Table 3 Mean (SD) acute bronchodilator response (expressed as difference between % predicted FEV₁ before and after bronchodilator) in patients with chronic obstructive pulmonary disease (COPD) and diffuse panbronchiolitis (DPB) in relation to obstructive abnormality

Grade*	n	COPD	n	DPB	p
Mild	12	7.39 (5.27)%	7	2.94 (3.24)%	NS
Moderate	11	4.76 (4.28)%	4	6.12 (4.58)%	NS
Moderately severe	17	12.49 (8.96)%	10	4.15 (6.39)%	<0.05
Severe	23	6.95 (5.07)%	17	4.66 (4.61)%	NS
Very severe	9	5.96 (4.32)%	11	3.48 (2.75)%	NS
Total	72	7.87 (6.52)%	49	4.16 (4.43)%	<0.001

* Mild = %pred FEV₁ <100 and ≥70; moderate = %pred FEV₁ <70 and ≥60; moderately severe = %pred FEV₁ <60 and ≥50; severe = %pred FEV₁ <50 and ≥34; very severe = %pred FEV₁ <34.

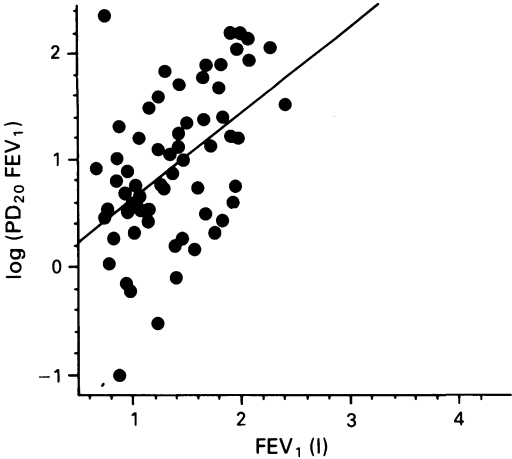


Figure 1 Relation between baseline FEV₁ and bronchial responsiveness to methacholine in patients with chronic obstructive pulmonary disease. $r_s = 0.473$, $p < 0.001$.

Results

Seventy five patients with COPD and 51 patients with DPB were included in the study. Baseline pulmonary function and other characteristics are summarised in table 1. Airway resistance and RV/TLC were in the same range for both diseases. Both groups of patients had similar serum IgE levels. All of the patients with COPD were smokers as a smoking history was an entry criterion. On the other hand, 78% of patients with DPB had never smoked.

Bronchial responsiveness was determined in 64 patients with COPD and 32 with DPB, and bronchodilator response was obtained in 72 of the patients with COPD and 49 of those with DPB. No significant differences in baseline FEV₁ values between the two groups were observed before the bronchial responsiveness and bronchodilator response tests (1.38 (0.45) l v 1.57 (0.86) l, and 1.33 (0.48) l v 1.27 (0.70) l, respectively). The patients with COPD showed significantly greater bronchial responsiveness and bronchodilator response than those with DPB (tables 2 and 3, respectively). Five of the 49 patients with DPB and 21 of the 72 patients with COPD had a bronchodilator response of more than 15%.

To exclude the possible effect of baseline airway calibre on bronchial responsiveness^{27 28} and bronchodilator response²⁹ we analysed separately patients subdivided according to the severity of their airflow limitation (tables 2 and 3). Patients with COPD with moderate to severe airflow limitation were significantly more responsive to methacholine than were patients with DPB. There were no statistically significant differences in bronchodilator response between patients with COPD and DPB, except for those who had moderately severe airflow limitation. However, the bronchodilator response tended to be greater in general in the patients with COPD than those with DPB.

Whereas a strong correlation between baseline FEV₁ and bronchial responsiveness was noted in patients with COPD (fig 1, $r_s = 0.473$, $p < 0.001$), the correlation was weaker, but still significant, in patients with DPB (fig 2,

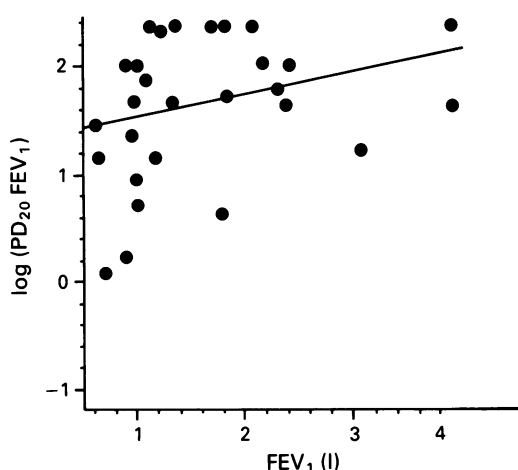


Figure 2 Relation between baseline FEV_1 and bronchial responsiveness to methacholine in patients with diffuse panbronchiolitis. $r_s = 0.414$, $p < 0.05$.

$r_s = 0.414$, $p < 0.05$). There were significant differences in intercepts (-0.168 v 1.331 , $p < 0.001$) and slopes (0.807 v 0.209 , $p < 0.01$) between these two regression lines. There were no significant correlations between baseline FEV_1 and bronchodilator response in patients with either disease.

Discussion

Bronchial responsiveness to methacholine in patients with COPD is related to the baseline airway calibre. Geometric factors³⁰ and an increased deposition of bronchoconstrictor aerosols in the central airways³¹ are thought to contribute to this phenomenon. Although no significant difference in baseline FEV_1 was observed in the present study, the patients with COPD showed greater bronchial responsiveness. This indicates that increased bronchial responsiveness in patients with chronic airflow limitation is determined not only by baseline airway calibre but also by other factors.

Airway inflammation is regarded as an important factor in the pathogenesis of bronchial hyperresponsiveness in asthma,^{32,33} and chronic bronchiolar inflammation which is associated with prolonged cigarette consumption contributes to the pathogenesis of bronchial hyperresponsiveness in COPD.³⁴ However, inhaled steroids or non-steroidal anti-inflammatory drugs do not attenuate bronchial hyperresponsiveness in patients with COPD.^{35,36} We also found that patients with DPB, an inflammatory bronchiolar disease, were less responsive to methacholine than those with COPD. These results suggest that airway inflammation is not the major cause of bronchial hyperresponsiveness in COPD. However, in contrast to COPD, inflammation in DPB is associated with chronic lower respiratory tract infection and is unrelated to smoking. This difference in the nature of bronchiolar inflammation may lead to the dissimilarity in bronchial responsiveness.

Some factors other than bronchiolar inflammation, such as a decreased interaction between the airways and parenchyma, have

been proposed to contribute to the pathogenesis of bronchial hyperresponsiveness in COPD. This suggestion is further supported by our observation that patients with COPD had an increased static lung compliance relative to those with DPB, which may reflect destruction of alveolar septal attachment to airways and allow airway collapse.

A strong relation was found between baseline FEV_1 and bronchial hyperresponsiveness in our patients with COPD, and this observation is compatible with previous reports.^{27,28} In addition, since we found a weak but significant correlation between baseline FEV_1 and bronchial responsiveness in patients with DPB, baseline airway calibre appears to influence bronchial responsiveness in patients with chronic airflow limitation. Since patients with DPB exhibited a smaller bronchodilator response than the patients with COPD, structural bronchiolar lesions in DPB seem to cause more fixed airflow limitation. In contrast, airways in patients with COPD are better preserved, and factors other than airway lesions such as the decreased interaction between airway and parenchyma probably cause airflow limitation.³⁷ In fact, bronchiolar and peribronchiolar changes in COPD are much milder than in DPB.² Whilst only a few patients with DPB (five out of 49) showed a bronchodilator response of more than 15%, many patients with COPD responded to inhaled salbutamol.

DPB has similarities to cystic fibrosis and bronchiectasis, conditions also characterised by chronic lower respiratory tract infection and obstructive changes. Pathological findings in advanced DPB have shown airway dilatation progressing to the more proximal bronchi, and some investigators have pointed out this resemblance between DPB and diffuse bronchiectasis. Increased bronchial responsiveness also occurs in patients with cystic fibrosis,^{38,39} and bronchiectasis.^{40,41} The response to methacholine in the patients with DPB in the present study was similar to that seen in patients with cystic fibrosis reported by Eggleston *et al.*³⁸

Most of the patients with COPD in our study had CT findings compatible with emphysema, probably because few patients with COPD in Japan have predominantly intrinsic airways disease without significant emphysema. Thus, there might be racial differences in the effects of smoking related airway inflammation causing a variable pattern in chronic bronchitis in our country.

In conclusion, our observation that patients with DPB differ substantially in bronchial responsiveness and bronchodilator response from those with COPD is thought to reflect the distinct mechanisms of these two diseases – that is, airway disease in DPB and parenchymal disease in COPD with emphysema. The nature of bronchiolar inflammation in COPD and DPB is also quite different, possibly explaining the difference in bronchial hyperresponsiveness.

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