Bronchial hyperreactivity in systemic sclerosis patients: influence of associated Sjögren’s syndrome

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Abstract

Objective—To determine the frequency and relative risk of bronchial hyperreactivity to methacholine in systemic sclerosis patients with or without associated Sjögren’s syndrome.

Methods—A prospective study of 56 patients with systemic sclerosis (42 with the diffuse and 14 with the limited variant; 24 with associated Sjögren’s syndrome), 57 with primary Sjögren’s syndrome, and 61 healthy controls.

Results—Bronchial hyperreactivity (BH) was present in 6.5% of the healthy controls, 25% of the systemic sclerosis patients without associated Sjögren’s syndrome, 42.2% of those with primary Sjögren’s syndrome, and in 50% of those with systemic sclerosis with associated Sjögren’s syndrome. The presence of BH did not correlate with age, disease duration, chest radiograph abnormalities, respiratory, and immunological data. The subgroup of subjects with the limited variant of systemic sclerosis more frequently had associated BH than did those with the diffuse variant of the disease; coexisting Sjögren’s syndrome further increased this frequency.

Conclusions—In agreement with previous studies, we have confirmed the high prevalence of bronchial hyperreactivity in primary Sjögren’s syndrome; systemic sclerosis likewise appears to be associated with an increased frequency of bronchial hyperreactivity compared with healthy control subjects. There is evidence also that the coexistence of Sjögren’s syndrome and systemic sclerosis further increases the frequency and the calculated relative risk of developing bronchial hyperreactivity.

(Bronchial hyperreactivity is characteristic of asthma, but is also found at a lower frequency in chronic obstructive pulmonary disease (COPD). The underlying pathology of BH is understood incompletely in asthma and COPD, and even less in the connective tissue diseases. While direct evidence is lacking, mechanisms similar to those demonstrated in asthma patients may be involved. After bronchial glandular atrophy has occurred, possible changes in the lining bronchial fluid (qualitative, quantitative, or both) may account for BH in SS. Similarly in SSc, bronchial glandular atrophy caused by the infiltrating fibrotic process may result in a modification of the bronchial lining fluid, thus leading to development of BH. In patients with asthma, however, the cellular chronic inflammatory infiltrate in the bronchial mucosa and submucosa is also responsible for BH. In SS also, the lymphocytic infiltrate may play a central role in BH through the local release of cytokines. SSc and SS may share a common histopathological lesion accounting for BH.

To clarify the mechanisms underlying BH in the connective tissue diseases, we performed a bronchial provocation test with methacholine in four groups of patients: those with SSc, with or without SS; those with primary SS; and healthy control subjects.

Subjects and methods

We studied 56 patients with SSc (24 of them with associated SS), 57 patients with primary SS, and 61 healthy control subjects. None of the subjects included in the study had ever smoked.

The diagnosis and classification of SSc were based on the criteria of Le Roy et al. Fourteen patients were classified as affected by the diffuse form (four with associated SS), and 42 had the limited variant (20 with associated SS). Diagnosis of SS followed the European Community Study Group on Diagnostic Criteria for SS, according to which the absence of sicca symptoms excluded a diagnosis of SS. In all patients complaining of sicca symptoms, a lip biopsy specimen was obtained and objective tests for xerophthalmia and xerostomia were performed. The presence of a ‘Tarpley scale’ grade >1 in the lip biopsy specimen and objective signs of xerostomia or xerophthalmia were necessary for the diagnosis of SS. Objective criteria for the presence of xerostomia were a positive salivary gland scintigraphy pattern, a positive Saxon’s test (<2.7 g/2 min), or both. Objective criteria for
Bronchial hyperreactivity in systemic sclerosis with or without Sjögren’s syndrome

The presence of xerophthalmia were a positive Schirmer test (<5 mm/5 min), positive break up time (>10 s) and positive fluorescein staining test; xerophthalmia was diagnosed if two of these three tests were positive.

All patients (but not the controls) underwent serological examination: antinuclear antibodies (ANA) and ant centromere antibodies (ACA) using Hep-2 cells as substrate (positive if >1/80); extractable nuclear antigens (ENA) (SS-A, SS-B, Scl-70, ribonucleoprotein (RNP)) were determined by double immunodiffusion using calf and human spleen extracts as the antigen source; rheumatoid factor (RF) was measured by nephelometry (positive if >50 IU/ml).

All subjects also underwent a clinical examination, respiratory function tests, and chest radiograph (not performed in controls). Lung function tests included forced vital capacity (FVC), forced expiratory volume curves in one second (FEV1), and flow volume curves recording the expiratory flow volume curves at 50% of vital capacity (FEF50). Total lung capacity was measured with the helium dilution technique and the single breath carbon monoxide diffusing capacity (Dco) was determined using the single breath method. Pulmonary function tests were performed using the Transfer Screen (Erich Jager, Germany) and the results expressed as percentage of predicted values.10

Inhalation challenge with methacholine

After informed consent was obtained, airway responsiveness to aerosolised methacholine was assessed in all subjects according to a modified procedure of Chai et al11 described in detail previously,12 using a Mefar dosimeter (Ballini, Brescia, Italy) connected to a Mefar jet nebuliser. None of the subjects was taking drugs known to modify bronchial reactivity (α2 agonist or β blockers, theophylline, diuretics), and steroids and calcium antagonists were stopped at least 48 hours before methacholine testing.

Ventilatory function was monitored by FEV1 measurements. No subject had an FEV1 less than 60% of the predicted value. Baseline FEV1 was taken as the best of two spirometric tracings obtained three minutes after the beginning of each set of five inhalations of aerosolised methacholine. Inhalations were continued until the FEV1 had decreased to more than 20% below baseline.

To assess airway responsiveness, methacholine dose-response curves were constructed as reported previously.13 14 Values above the cumulative delivered dose of 1.4 mg methacholine (obtained after a set of five inhalations of 16 mg/ml) were considered normal, in accordance with previous studies using similar or comparable methods.15-17

Statistical analysis

All values are presented as mean (SD). Statistical comparisons were made with one way analysis of variance (parametric or non-parametric as appropriate) for unpaired data. The χ2 test was used for contingency tables. Logistic analysis was performed to calculate the relative risk of developing BH in all groups. A probability level of 5% was considered significant.

Results

Table 1 shows the demographic data and the main immunological parameters. No significant differences were found among the groups in age and disease duration. As expected, ACA and Scl-70 antibodies were present only in SSc patients, whereas SS-A and SS-B antibodies and RF were found mainly in patients with primary SS except for one SSc patient (with associated SS) who was positive for SS-A antibodies. Five other SSc patients were positive for RF (three with associated SS).

A large number of SSc patients had chest radiographs showing an interstitial lung pattern; however, no difference in frequency was found between SSc patients with and without SS (33.3% and 43.7%, respectively). In contrast, an interstitial lung pattern was more frequent (p < 0.05) in patients having SSc without SS than in those with primary SS (12.2%). Dry cough in primary SS (24.5%) and dyspnoea in SSc patients (17.8%) were the most frequent respiratory symptoms; the frequency of these symptoms did not differ significantly among the groups (data not shown).

Figure 1 shows the results of the methacholine test. BH was present in 62% (four of 61) of the healthy controls, in 25% (eight of 32) of patients having SSc without SS, in 42.2% (24 of 57) of those with primary SS, and in 50% (12 of 24) of patients having SSc with SS. In both SSc and primary SS there was no

<table>
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<tr>
<th>Table 1</th>
<th>Main clinical and immunological data</th>
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<tr>
<td></td>
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<tr>
<td>No of patients</td>
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<td>Disease duration (yr)</td>
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<tr>
<td>ACA</td>
<td>14 [4-3]</td>
</tr>
<tr>
<td>RF positive</td>
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Values are mean (SD) or No [%].

SSc = Systemic sclerosis; pSS = primary Sjögren’s syndrome; SS = Sjögren’s syndrome; C = healthy controls; ANA = antinuclear antibodies; ENA = extractable nuclear antigens; Scl-70 = Scl-70 antibodies; ACA = anticientromere antibodies; RF = rheumatoid factor.

*Patient with RNP antibodies.

Figure 1: Bronchial responsiveness in control and disease groups. SSc = Systemic sclerosis; SS = Sjögren’s syndrome; pSS = primary Sjögren’s syndrome; n = number of patients.
correlation between the presence of BH and ANA, ENA, RF, age, disease duration, chest radiograph abnormalities, and respiratory symptoms, although dry cough was quite a frequent symptom in the patients with SS who had bronchial BH.

Figure 2 shows the prevalence of BH in the diffuse and limited forms of SSc with or without SS. Interestingly, only in the diffuse form did patients with associated SS have a higher prevalence of BH than controls (numbers too small for statistical analysis), while the limited variant seemed, per se, to be associated with an increased frequency of BH and the coexistence of SS further enhanced this frequency. The two subsets were similar for age and disease duration.

The prevalence of BH was associated with lower values of FEV₁, % and FEF₂⁵, % in all groups of patients, but the differences reached statistical significance only in the pSS group (table 2).

The relative risks of developing BH adjusted for age, disease duration, and respiratory functional pattern ( obstructive, restrictive, isolated small airways obstruction) compared with controls, calculated with logistic analysis, were: ×6.1 for SSc without SS (confidence interval (CI) 1.8- to 41.5); ×26.4 for SS with SS (CI 5.2- to 132.2); ×21.5 for primary SS (CI 5.3- to 87.8).

Discussion

Primary and secondary SS are associated with an increased bronchial responsiveness to methacholine challenge.¹⁻³ In a previous study we found that only in the presence of SS did patients with systemic connective tissue diseases have a significant prevalence of BH (in almost 50% of the cases), whereas in the absence of associated SS the frequency of BH was comparable to that in the healthy population.³ Such evidence supports the hypothesis that BH is correlated with the presence of SS.

Interestingly, patients with SSc were more likely to develop BH than other patients. This finding was confirmed in a small cohort of patients in a subsequent preliminary study,⁴ and has now been validated further in a larger number of SSc patients.

The present data appear to confirm that SSc is itself related to an increase in bronchial reactivity in 25% of cases. Moreover, the coexistence of SS further enhanced the frequency of BH, up to 50%. Assessment of the relative risk of developing BH supports these results; however, the confidence intervals were too wide to permit unequivocal prediction of risk.

In these patients, BH is a subclinical condition detected by a provocative test. The mechanisms involved in the development of BH in SSc are unknown. As in primary SS, a reduction in secretions may be present in SSc as a result of the fibrosis which causes a loss of bronchial glands. It has been reported that sicca symptoms present in SSc patients who lack any biological and immunological evidence of SS.¹⁰ The bronchial secretions may be altered both quantitatively and qualitatively, such as in their ion and macromolecular composition. Although there are no data on the characteristics of bronchial secretions in patients with SS, tears⁹ and saliva²⁰ are hyperosmolar in such patients, and thus the airway fluid may also have an altered ion and macromolecular composition. It is known that hyperosmolar solutions can cause bronchoconstriction and increased bronchial responsiveness in asthma patients;¹¹ other factors, such as chronic inflammatory reactions related to autoimmune disease, may also be involved in the development of BH. The observation that BH patients show lower mean values of baseline FEV₁ and FEF₂⁵ may suggest that bronchial Airways may be affected and hyperresponsive to external stimuli. It is possible that inflammatory changes within the Airways may sensitize the bronchial smooth muscle to inhaled methacholine. Mucosal oedema, together with alteration of secretions, may lead to a narrowing of the bronchial lumen. As the bronchial mucosa and secretions were not studied in these patients, these hypotheses remain unconfirmed.

It is interesting to note that the incidence of BH was greater in the limited form of SSc than in the diffuse form. This was partly attributable to the greater incidence of SS in the former variant, previously noted also by others,¹⁰ but even in the absence of SS, BH was more frequent in the limited form of SSc. We have no explanation for this observation, though the presence of BH could be evidence of a different pathogenetic mechanism in SSc subsets.

In conclusion, BH may be a sign of bronchial involvement in SS and SSc. These two diseases may represent a novel model for the study of
Bronchial hyperreactivity in systemic sclerosis with or without Sjögren’s syndrome

BH. Further studies are required to confirm these observations and to examine the underlying mechanisms of BH.

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