Bronchodilator responsiveness and serum total IgE levels in families of probands with severe early-onset COPD

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ABSTRACT: Bronchodilator responsiveness has been associated with a subsequent accelerated decline in forced expiratory volume in one second (FEV1). Therefore, bronchodilator responsiveness and total serum immunoglobulin E(IgE) levels were assessed in 184 adult first-degree relatives of probands with severe early-onset chronic obstructive pulmonary disease (COPD) and a control group.

Greater bronchodilator responsiveness was found among current smokers or exsmokers who were first-degree relatives of early-onset COPD probands than in currently or exsmoking controls, expressed as increase in FEV1 as a percentage of baseline (5.8±8.1 *versus* 2.9±5.1%, p<0.01), absolute increase in FEV1 from baseline (120±130 *versus* 60±110 mL, p<0.05), and increase in FEV1 as a percentage of the predicted value (3.6±4.1 *versus* 2.2±3.9%, p<0.05). However, elevated total serum IgE levels were not found in first-degree relatives of early-onset COPD probands compared with control subjects.

The increased bronchodilator responsiveness among currently smoking/exsmoking first-degree relatives of early-onset COPD probands suggests that these individuals may have enhanced susceptibility to the detrimental effects of cigarette smoking.
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Chronic obstructive pulmonary disease (COPD), the fourth leading cause of death in the USA [1, 2] and a growing international problem, is strongly associated with cigarette smoking [3]. Even though tobacco use is a well-known risk factor for COPD [4], the development of airflow obstruction in response to smoking is highly variable [5], and it has been postulated that individuals may vary in their genetic susceptibility to COPD [3]. In a previous report on individuals without severe α_1-antitrypsin deficiency, increased risk of airflow obstruction and chronic bronchitis was found in current smokers and exsmokers who were first-degree relatives of probands with severe early-onset COPD, compared with appropriate control subjects [6]. Thus, the findings of the authors and others [7–13] suggest that familial factors, probably genetic, contribute to the development of COPD.

Bronchodilator responsiveness, a physiological response that differs from airway responsiveness to bronchoconstrictors, has been associated with a subsequent accelerated decline in forced expiratory volume in one second (FEV1) [14–17]. Thus, bronchodilator responsiveness may be associated with an increased risk of either acquiring COPD or developing the disease at an earlier age in susceptible individuals who smoke.

Higher total serum immunoglobulin E (IgE) levels have previously been demonstrated in first degree relatives of PI Z subjects with COPD than in first-degree relatives of PI Z subjects without COPD [18]. This report presents a comparison of bronchodilator responsiveness and total serum IgE levels in 184 adult first-degree relatives of 44 probands with severe early-onset COPD (without severe α_1-antitrypsin deficiency) and 83 adult control subjects.

Methods

Study participants

The screening and enrolment procedures for subjects participating in the study have been described elsewhere [6]. In brief, 44 probands with severe early-onset COPD were identified from lung transplant programmes, lung volume reduction surgery programmes and pulmonary clinics at participating hospitals. The enrolment criteria for probands with COPD included: FEV1 <40% of the predicted value, age <53 yrs, and the absence of severe α_1-antitrypsin deficiency (*e.g.*, PI Z, PI null-null). Subjects were excluded if they had already undergone lung volume reduction surgery or lung transplantation.

For the 44 probands with early-onset COPD, all available first-degree relatives were invited to enroll; 203 first-degree relatives (28 parents, 91 siblings and 84 children) of COPD probands were recruited.

Control probands, all of whom were current smokers or exsmokers, were recruited from prior population-based studies in Watertown and East Boston, MA, USA [19, 20]. The spouses and first-degree relatives of the control probands were asked to participate. Twenty control probands, 54 first-degree relatives and nine spouses comprised the comparison group for first-degree relatives of early-onset COPD probands.

Since there were no subjects younger than 18 yrs of age in the control group, first-degree relatives of early-onset COPD probands who were <18 yrs of age (n=19) were excluded from this analysis.

After giving written informed consent, all study subjects completed a protocol that included a questionnaire, spirometry and giving a blood sample. Over 90% of the protocols were performed at the subjects' homes. The study protocol was approved by the Human Research Committee of Brigham and Women's Hospital in Boston.

Questionnaire

Each participant completed a modified version of the 1978 American Thoracic Society Division of Lung Diseases Respiratory Disease Questionnaire including questions on passive smoking and diet [21]. The intensity of cigarette smoking in pack-yrs was calculated as the product of the period of tobacco use (in yrs) and the average number of cigarettes smoked per day, which was divided by 20 to convert to packs.

Spirometry

A Survey Tach Spirometer (Warren E. Collins, Braintree, MA, USA) was used to perform spirometry in a standardized manner, with subjects seated and wearing a nose-clip. As many as eight attempts were performed by each participant in order to obtain three acceptable measures. Spirometry was performed in accordance with American Thoracic Society specifications [22]; the FEV_1/forced vital capacity from the best test effort and the highest FEV_1 value are reported. Height was measured in stockinged feet to the nearest 0.5" (1.3 cm). Subjects were told to avoid bronchodilator use for ≥4 h prior to the test, unless significant respiratory symptoms required bronchodilator treatment.

Spirometry was repeated after inhalation of 180 μg (2 puffs) albuterol using a spacer device. The time elapsed between the last effort measured prior to bronchodilator challenge and the first effort following administration of albuterol was recorded. A subject's response to bronchodilator challenge was expressed as [1] a percentage of baseline FEV_1, calculated using change in (Δ) FEV_1=((postbronchodilator FEV_1 - baseline FEV_1)/baseline FEV_1) × 100; 2) an absolute value in mL, calculated using: ΔFEV_1=postbronchodilator FEV_1 -baseline FEV_1; and 3) a percentage of the predicted value of FEV_1, calculated using ΔFEV_1=((postbronchodilator FEV_1 - baseline FEV_1)/predicted FEV_1) × 100.

Pulmonary function test results were expressed as a percent of the predicted values using the equations of CRAPO *et al.* [23].

Total serum immunoglobulin E levels

Serum total IgE levels were determined by means of the UniCAP 100 system (Pharmacia & Upjohn, Kalamazoo, MI, USA). All values obtained were transformed to a log10 scale for analysis, in accordance with the recognized logarithmic distribution of total serum IgE levels in the general population.

Statistical methods

Student's t-tests and simple linear regression were performed using the SAS statistical package (SAS Statistical Institute, Cary, NC, USA) on a Sun microsystem (Sun Microsystems, Mountain View, CA, USA). Since multiple subjects from each family were included, standard regression analysis was not appropriate for assessing the influence of relationship to a proband with early-onset COPD on the phenotypes of interest [6]. Therefore, generalized estimating equations (GEEs) from the SAS Statistical Institute (GEE Version 2.03, Hiedelberg Macro), adjusting for various covariates, were employed to study the differences in bronchodilator responsiveness and total serum IgE levels (expressed as quantitative traits) between first-degree relatives of early-onset COPD probands and control subjects.

Results

Comparison of adult first-degree relatives of probands with severe early-onset chronic obstructive pulmonary disease and control subjects

The 184 adult first-degree relatives of probands with severe early-onset COPD (mean FEV_1=83.1±20.3% pred) were compared with 83 control family members (mean FEV_1=91.0±14.4% pred) (table 1). There were no differences in total serum IgE levels between first-degree relatives of early-onset COPD probands and control subjects (p= 0.07). There was greater bronchodilator responsiveness in

Table 1. – Demographics, bronchodilator responsiveness and serum immunoglobulin E (IgE) levels of adult first-degree relatives of chronic obstructive pulmonary disease (COPD) probands compared with controls

	Subjects n	Age yrs	Smoking duration pack-yrs	ΔFEV_1 % baseline	ΔFEV_1 % pred	ΔFEV_1 L	Log10 IgE IU·mL^{-1}
First-degree relatives of COPD probands	184	43.7±17.4	17.3±25.0	4.9±7.2	3.3±4.1	0.11±0.14	1.53±0.69
All controls	83	45.0±16.3	12.8±20.0	3.2±5.5*	2.5±3.9	0.08±0.12*	1.69±0.63

Data are presented as mean±SD. ΔFEV_1: change in forced expiratory volume in one second. *: p<0.05 *versus* first-degree relatives of COPD probands.

first-degree relatives of early-onset COPD probands than in control subjects, expressed as ΔFEV1 as a percentage of baseline (p<0.05) or as an absolute value (p<0.05).

In order to determine whether tobacco use influenced bronchodilator responsiveness and total serum IgE levels, first-degree relatives of early-onset COPD probands and control subjects were compared after stratification by smoking (table 2). There were no significant differences in bronchodilator responsiveness and total serum IgE levels between nonsmoking first-degree relatives of COPD probands and nonsmoking control subjects. In contrast, currently smoking or exsmoking first-degree relatives of COPD probands had greater bronchodilator responsiveness than currently or exsmoking control subjects, expressed as ΔFEV1 as a percentage of baseline (p<0.01), an absolute value (p=0.01), or a percentage of the predicted value (p<0.05).

Figure 1 illustrates the relationship between the absolute value of ΔFEV1 and measured baseline FEV1 among current/exsmoking first-degree relatives of COPD probands and currently smoking/exsmoking controls. Figure 2 illustrates the same relationship among nonsmoking first-degree relatives of COPD probands and nonsmoking control subjects. In both first-degree relatives of COPD probands and control subjects, the absolute value of ΔFEV1 and measured baseline FEV1 were not significantly correlated, regardless of smoking habits.

Multivariate analysis of the association between bronchodilator responsiveness and relationship to probands with severe, early-onset chronic obstructive pulmonary disease

GEEs were employed to study the association between bronchodilator responsiveness and relationship to an early-onset COPD proband (table 3). After adjustment for age, sex, and intensity of smoking (in pack-yrs), there was no significant difference in ΔFEV1 as a percentage of the predicted value between first-degree relatives of early-onset COPD probands and control subjects (model 1). Former or current smokers who were first-degree relatives of early-onset COPD probands had a greater ΔFEV1 as a percentage of the predicted value than current smokers or exsmoking controls (model 2). No significant difference in ΔFEV1 as a percentage of the predicted value was observed when nonsmoking first-degree relatives of early-onset COPD probands and nonsmoking controls were compared (model 3).

Multivariate analyses with ΔFEV1 as an absolute value and as a percentage of baseline as outcomes were also per-
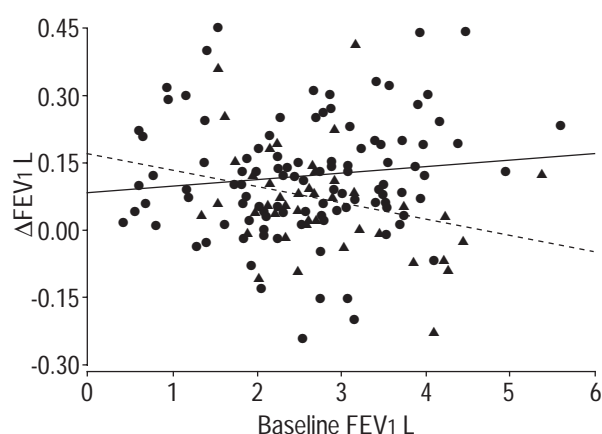

Fig. 1. – Correlation between change in (Δ) forced expiratory volume in one second (FEV1) following bronchodilator challenge and measured baseline FEV1 in current/exsmoking adult first-degree relatives of chronic obstructive pulmonary disease probands (●: ——: regression line; Spearman=0.14, p=0.14) and current/exsmoking controls (▲; - - -: regression line=0.22, p=0.14).

formed. After adjustment for age, sex, height and intensity of smoking, currently smoking or exsmoking first-degree relatives of early-onset COPD probands had a significantly greater ΔFEV1 than currently smoking or exsmoking controls (difference in ΔFEV1 54 mL, 95% confidence interval (CI) 10.5–96.7 mL, p=0.01; 3.4%, 95% CI 1.1–5.8%, p<0.01). The addition of measured baseline FEV1 to these multivariate models did not appreciably change the difference in ΔFEV1 as an absolute value between the two groups; however, there was no longer a significant difference in ΔFEV1 as a percentage of baseline when measured baseline FEV1 was included in the models.

Because the control group included 18 subjects with physician-diagnosed asthma, multivariate analyses of the association between bronchodilator responsiveness and relationship to early-onset COPD probands, adjusting for age, sex, duration of smoking and measured baseline FEV1 were repeated after excluding asthmatic subjects from the control group. Former or current smokers who were first-degree relatives of early-onset COPD probands had greater bronchodilator responsiveness than currently smoking or exsmoking control subjects, expressed as ΔFEV1 as an absolute value or as a percentage of the predicted value (difference 55 mL, 95% CI 13.7–96.0 mL, p<0.01; 1.4% pred, 95% CI 0.1–2.7% pred, p=0.03), and a trend for ΔFEV1 as a percentage of baseline (1.9%, 95% CI -0.3–4.1%, p=0.08).

Table 2. – Demographics, bronchodilator responsiveness and total serum immunoglobulin E (IgE) levels of adult first-degree relatives of chronic obstructive pulmonary disease (COPD) probands compared with controls stratified by smoking

	Subjects n	Age yrs	Smoking duration pack-yrs	ΔFEV1 % baseline	ΔFEV1 % pred	ΔFEV1 L	Log10 IgE
Smoking first-degree relatives	111	46.2±17.1	28.7±26.6	5.8±8.1	3.6±4.1	0.12±0.31	1.56±0.73
Smoking controls	48	48.6±13.9	22.1±22.1	2.9±5.1**	2.2±3.9*	0.06±0.11*	1.70±0.65
Nonsmoking first-degree relatives	73	39.9±17.3	0.0±0.0	3.4±5.3	2.9±4.1	0.10±0.15	1.48±0.63
Nonsmoking controls	35	39.9±18.2	0.0±0.0	3.6±6.1	2.8±3.8	0.09±0.14	1.69±0.60

Data are presented as mean±SD. ΔFEV1: change in forced expiratory volume in one second. *: p<0.05, **: p<0.01 *versus* first-degree relatives of COPD probands with similar smoking history.

Table 3. – Multivariate analysis of the association between change in forced expiratory volume in one second after bronchodilator challenge, expressed as a percentage of the predicted value and relationship to chronic obstructive pulmonary disease (COPD) probands

GEE model	Variables	Regression coefficient (95% CI)	p-value
Model 1: all adult first-degree relatives of COPD probands compared with all controls	First-degree relatives of COPD probands	1.01 (-0.14–2.16)	0.08
	Female sex	0.72 (-0.43–1.87)	0.22
	Age	-0.01 (-0.05–0.03)	0.72
	Smoking intensity*	0.01 (-0.02–0.03)	0.60
Model 2: smoking adult first-degree relatives of COPD probands compared with smoking controls	First-degree relatives of COPD probands	1.60 (0.17–3.00)	0.03
	Female sex	1.60 (0.34–2.87)	0.02
	Age	-0.01 (-0.06–0.04)	0.82
	Smoking intensity*	0.004 (-0.02–0.03)	0.74
Model 3: nonsmoking adult first-degree relatives of COPD probands compared with nonsmoking controls	First-degree relatives of COPD probands	0.31 (-1.61–1.71)	0.68
	Female sex	0.54 (-2.43–1.34)	0.57
	Age	-0.01 (-0.06–0.04)	0.64

*: in pack-yrs. CI: confidence intervals.

Multivariate analysis of the association between total serum immunoglobulin E level and relationship to probands with severe early-onset chronic obstructive pulmonary disease

Using GEEs, the association between total serum IgE levels and relationship to early-onset COPD probands was examined. After adjustment for sex, duration of smoking and age, there were no significant differences in $\log_{10}$ IgE between first-degree relatives of early-onset COPD probands and controls. These results were not appreciably changed after excluding the 18 asthmatic subjects from the control group.

Discussion

Even though the natural history of COPD is distinctly influenced by tobacco use, only a minority of smokers
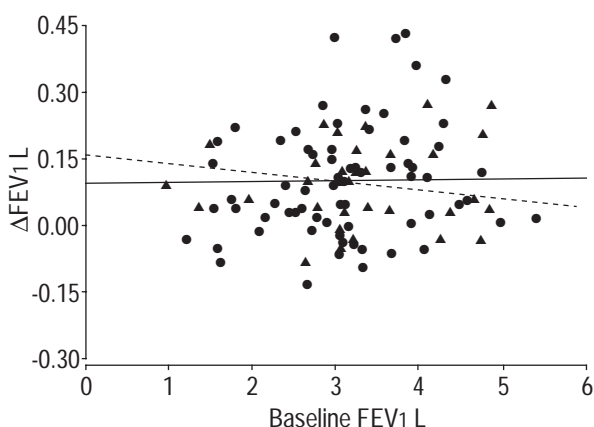

Fig. 2. – Correlation between change in (Δ) forced expiratory volume in one second (FEV1) following bronchodilator challenge and measured baseline FEV1 in nonsmoking adult first-degree relatives of chronic obstructive pulmonary disease probands (●; ——: regression line; Spearman=0.09, p=0.46) and current/exsmoking controls (▲; - - -: regression line=0.03, p=0.88).

develop COPD [24]. α_1-Antitrypsin deficiency is a well-documented genetic risk factor for COPD, but it accounts for only a small proportion of cases [25]. In order to identify genetic risk factors for COPD other than α_1-antitrypsin deficiency, a group of 44 probands with severe early-onset COPD and 203 of their first-degree relatives was assembled [6]. Efforts were concentrated on subjects without severe α_1-antitrypsin deficiency developing severe COPD at an early age, since the likelihood of finding a significant genetic contribution to their disease may be greater, analogous to other complex illnesses [26]. In currently smoking or exsmoking adult first-degree relatives of early-onset COPD probands, increased bronchodilator responsiveness was found compared with currently smoking or exsmoking adult controls. In contrast. there was no significant difference in bronchodilator responsiveness between nonsmoking first-degree relatives of probands with severe early-onset COPD and nonsmoking controls.

The results of the population-based retrospective cohort study of VOLLMER *et al.* [14] did show a positive correlation between bronchodilator response and the subsequent yearly decline in FEV1, which remained unchanged after restricting the analysis to subjects with abnormal FEV1 at baseline. Five longitudinal case-series studies that prospectively examined the relationship of bronchodilator responsiveness to the rate of decline in FEV1 among patients with chronic airflow obstruction have yielded conflicting results, finding either positive [15–17] or negative correlations [27, 28]. Possible explanations for the disagreement among these studies include confounding by baseline FEV1, treatment effects and analytical differences [29]. Since direct assessment of airway responsiveness to methacholine or histamine was impractical for probands and relatives with severe airflow obstruction, bronchodilator response was measured as a potential intermediate (disease-related) phenotype of COPD.

In the Lung Health Study (LHS), a large prospective cohort study of smokers with mild-to-moderate airflow limitation, TASHKIN *et al.* [30] observed ΔFEV1 ranging

from 75±85 mL in females without airway hyperresponsiveness to 132±151 mL in males with airway hyperresponsiveness. In the currentt study, the authors observed a $\Delta FEV1$ of 120±130 mL among 111 currently smoking and exsmoking first-degree relatives of early-onset COPD probands that were not selected on the basis of their lung function. In a large health survey of children and adults conducted in Alberta (Canada), DALES *et al.* [31] observed a $\Delta FEV1$ of 68±129 mL among 2,609 participants. In the present study a $\Delta FEV1$ of 80±120 mL was observed among the 83 adult controls, which is consistent with the survey findings of DALES *et al.* [31]. The observed $\Delta FEV1$ in the present smoking controls (60±110 mL) was lower than the $\Delta FEV1$ among the LHS participants, probably reflecting differences in the selection processes of the study samples. However, the possibility of having unintentionally selected former and current smokers with decreased bronchodilator responsiveness into the control group of the present study cannot be completely excluded.

The increased bronchodilator responsiveness in current smokers or exsmokers who were first-degree relatives of early-onset COPD probands may be related to their lower level of lung function. However, the inclusion of measured baseline FEV1 in the multivariate models did not appreciably change the observed difference in bronchodilator responsiveness between the groups, particularly after excluding asthmatic subjects from the control group. Thus, heightened bronchomotor tone and/or undefined inflammatory processes may be partially responsible for the greater response to bronchodilator administration among former and current smokers who are first-degree relatives of early-onset COPD probands [29].

The increased bronchodilator responsiveness in currently smoking or exsmoking first-degree relatives of probands with severe early-onset COPD may be caused by genetic or shared environmental factors. Even though smoking-related exposures were adjusted for, it is possible that other unmeasured factors (*e.g.* childhood home passive smoke exposure) may explain the increased bronchodilator responsiveness in currently smoking or exsmoking first-degree relatives of COPD probands; however, no strong evidence was found that they are critical determinants of COPD in the present pedigrees [6].

In previous work, increased total serum IgE levels were found in first-degree relatives of PI Z subjects with COPD [18]. Elevated total serum IgE levels in first-degree relatives of early-onset COPD probands were not found compared with control subjects, even after excluding asthmatic subjects from the control group. Thus, the present findings suggest that families of probands with severe early-onset COPD are not highly atopic.

In summary, increased bronchodilator responsiveness was found among current smokers or exsmokers who are first-degree relatives of probands with severe early-onset chronic obstructive pulmonary disease. Relative risks for forced expiratory volume in one second <60% pred, forced expiratory volume in one second <80% pred, and chronic bronchitis of approximately three for currently smoking or exsmoking first-degree relatives of probands with severe early-onset chronic obstructive pulmonary disease have previously been reported [6]. All of these findings suggest that first-degree relatives of subjects with severe, early-onset chronic obstructive pulmonary disease show increased susceptibility to the effects of cigarette smoking.

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