ORIGINAL ARTICLES

Association Between the Forced Midexpiratory Flow/Forced Vital Capacity Ratio and Bronchial Hyperresponsiveness

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OBJECTIVE: A long-standing hypothesis is that a low ratio of airway caliber to lung size is associated with bronchial hyperresponsiveness (BHR). The aim of our study was to measure the association between airway caliber relative to lung size (expressed as the ratio between forced expiratory flow, midexpiratory phase, divided by forced vital capacity [$FEF_{25\%-75\%}$/FVC]) and BHR measured by a methacholine challenge test, adjusting for age, height, sex, smoking history, geographic area, respiratory symptoms, and baseline forced expiratory volume in 1 second (FEV_1).

MATERIAL AND METHODS: We carried out a multicenter cross-sectional study of the general Spanish population in 2647 subjects from the European Community Respiratory Health Survey (ECRHS I). The ECRHS questionnaire was administered, total and specific immunoglobulin E were measured, and skin tests, spirometry, and a methacholine challenge test were performed.

RESULTS: We show the relationship of the various clinical and sociodemographic variables with the 2 parameters indicative of a positive methacholine test. The lower the $FEF_{25\%-75\%}$/FVC ratio was, the greater the risk of HRB, after adjustment for variables (odds ratio [OR]=0.09; 95% confidence interval [CI], 0.04-0.018 for the concentration provoking a 20% decrease in FEV_1, and OR=0.06; 95% CI, 0.03-0.12 for the dose provoking a 20% decrease in FEV_1).

CONCLUSIONS: There is a significant association between the $FEF_{25\%-75\%}$/FVC ratio and BHR after adjustment for age, atopy, smoking, geographic area, respiratory symptoms, and initial FEV_1.

Key words: *Bronchial hyperresponsiveness. Lung size. $FEF_{25\%-75\%}$/FVC.*

Asociación entre el cociente $FEF_{25-75\%}$/FVC y la hiperreactividad bronquial

OBJETIVO: La desproporción entre el calibre de la vía aérea y el parénquima pulmonar tiene una relación negativa con la presencia de hiperreactividad bronquial (HRB).

El objetivo del presente estudio es medir la asociación entre el calibre de la vía aérea relativa a la talla pulmonar, expresado por el cociente entre el flujo mesoespiratorio entre el 25 y el 75% de la capacidad vital forzada dividido por la capacidad vital forzada ($FEF_{25-75\%}$/FVC), con la HRB medida por el test de metacolina, ajustando por edad, altura, sexo, consumo de tabaco, área geográfica, síntomas respiratorios y volumen espiratorio forzado en el primer segundo previo.

MATERIAL Y MÉTODOS: Estudio multicéntrico transversal sobre población general española (2.647 sujetos) del Estudio de Salud Respiratoria de la Comunidad Europea (ECRHS-I). Se aplicó un cuestionario llamado ECRHS, se determinó la inmunoglobulina E total y específica, y se realizaron pruebas cutáneas, espirometría y test de metacolina.

RESULTADOS: Se presenta la relación entre las diferentes variables sociodemográficas y clínicas con los 2 parámetros de positividad del test de metacolina. Hay aumento del riesgo de HRB a menor cociente $FEF_{25-75\%}$/FVC ajustado por diferentes variables (*odds ratio* = 0,09; intervalo de confianza del 95%, 0,04-0,18, para PC_{20}, y *odds ratio* = 0,06; intervalo de confianza del 95%, 0,03-0,12 para PD_{20}).

CONCLUSIONES: El cociente $FEF_{25-75\%}$/FVC está asociado significativamente a la HRB, independientemente de la edad, la existencia de atopia, el consumo de tabaco, el área geográfica, los síntomas respiratorios y el volumen espiratorio forzado en el primer segundo.

Palabras clave: *Hiperreactividad bronquial. Talla pulmonar. $FEF_{25-75\%}$/FVC.*

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Introduction

Bronchial hyperresponsiveness (BHR) is defined as an exaggerated response of the bronchi to a wide variety of stimuli, in the form of increased resistance to the passage of air.[1] There has long been interest in BHR, and in 1960 Orie et al[2] proposed that airway hyperresponsiveness was a "host factor" associated with increased risk of chronic bronchitis or nonspecific lung disease. Since then considerable effort has gone into testing the hypothesis that people with airway hyperresponsiveness are more likely to experience gradual and irreversible worsening of airway obstruction than those with less airway responsiveness,[3] and that airway hyperresponsiveness precedes symptoms and diagnosis of asthma in children[4] and in adults.[5]

Given the repercussions of BHR, it is important to know what variables can affect its severity. The relation between BHR and atopy,[6] childhood respiratory diseases,[7] low birth weight,[8] occupation,[9] age,[10] and smoking status[11] have been well studied. In addition to such "biological" associations, part of airway responsiveness can be attributed to "geometric variables." There is a long-standing hypothesis that a low ratio of airway caliber to lung size is associated with the presence of BHR.[12] The problem lies in knowing what measure to use to assess the ratio. In a study that evaluated the ratios between the diameter of the main bronchus and the area of the lung, between the trachea and the area of the lung obtained by chest radiography, and between forced expiratory flow, midexpiratory phase and forced vital capacity ($FEF_{25\%-75\%}$/FVC), the authors suggested using the latter as a surrogate measure for airway caliber relative to lung size. Furthermore, they also demonstrated that this measure was associated with BHR in a population of men with a mean age of 60 years.[13]

Our objective was to study the association between the ratio of airway caliber to lung size expressed as $FEF_{25\%-75\%}$/FVC and BHR measured by a methacholine challenge test, after adjusting for age, height, sex, smoking status, geographic area, respiratory symptoms, and baseline forced expiratory volume in 1 second (FEV_1) in a sample of young adult men and women.

Material and Methods

Population

The method of the European Community Respiratory Health Survey (ECRHS-I) has been described in previous studies.[14,15] Briefly, that multicenter cross-sectional study of the general population was carried out in 48 geographic areas, predominantly in western Europe. In Spain, the study was carried out in Albacete, Barcelona, Galdakao, Huelva, and Oviedo. In the first phase, a sample was selected by simple random sampling from the municipal records of each area, except for Oviedo, where the electoral census was used. A sample of 1500 individuals of each sex between the ages of 20 and 44 years was taken. The measurement instrument used was a short questionnaire adapted from the bronchial symptoms questionnaire of the International Union Against Tuberculosis and Lung Disease (IUATLD).[16] Later, another simple random sampling was done to obtain 20% of the initial sample, and those selected were asked to participate in a second phase of the study to be carried out in hospitals. After informed consent was obtained, the tests mentioned below were performed. Refusals to participate ranged from 2.4% to 14.8% in the various areas. The distributions of refusals by sex and age group were similar in most centers, with the exception of significant differences according to sex in Albacete and Barcelona (more women) and Huelva (more men).[15]

Questionnaire and Respiratory Symptoms Groups

The ECRHS questionnaire was created from various questionnaires used in other international studies.[16] Based on answers to the questionnaire, each subject was placed in one of the following groups: asthma-related symptoms (nighttime awakenings due to dyspnea, and/or asthma attacks, and/or need for asthma medication within the previous 12 months), chronic bronchitis (cough with phlegm for more than 3 months in the previous 2 years), minor respiratory symptoms (wheezing with dyspnea and/or chest tightness, and/or breathlessness in the previous 12 months), chronic cough (cough with phlegm that does not meet criteria for chronic bronchitis), and no respiratory symptoms (negative response for all symptoms).

Other Variables

Smoking status. Subjects who had never smoked or who had smoked fewer than 20 packs in their lives were considered nonsmokers. Subjects who had been smoking for a month and who were still smoking were considered current smokers. Smokers were categorized by number of cigarettes per day: 1-9, 10-20, or more than 20 cigarettes per day. Subjects who had been exposed regularly (most days and nights) to tobacco smoke in the previous 12 months were considered passive smokers. Subjects who had smoked more than 20 packs in their lives but who did not currently smoke were considered ex-smokers.

Immunoglobulin E (IgE) and atopy. A positive IgE finding was recorded whenever the concentration exceeded 100 U/mL. An individual with specific IgE exceeding 0.35 U/mL to any of the 9 respiratory allergens tested was considered atopic.[14]

Baseline spirometry. The aim of spirometry was to record a precise value for FVC and $FEF_{25\%-75\%}$ for each individual. In the case of individuals who reported symptoms of respiratory infection, spirometry was delayed 3 weeks.

Identical bell spirometers (Stead-Wells Baires System; Biomedin; Padua, Italy) were used in all 5 centers. All maneuvers were performed according to criteria of the European Community for Steel and Coal (ECSC)[17] and of the American Thoracic Society.[18] Spirometry was performed by duly trained professionals with university qualifications in nursing, with at least a year of experience in a lung function laboratory.

Lung function. FEV_1 and FVC were both expressed in liters, and $FEF_{25\%-75\%}$ was expressed in liters per second.

Methacholine challenge test. Bronchial response was measured by a methacholine challenge test. The methacholine dilutions (Hoffmann La Roche, Basel, Switzerland) were prepared centrally for all the Spanish areas at the Pharmaceuticals Department, Hospital Clínic, in Barcelona. A saline diluent was used, buffered with phosphate to obtain physiological pH. The methacholine was administered during maneuvers of maximal inspiration to total lung capacity using a programmable pressurized dosimeter (Mefar, MB3, Bovezzi, Italy) connected to nebulizers with increasing concentrations of methacholine. Baseline spirometry was performed as described above. The best FEV_1 was recorded as percent of predicted value. The control or post-diluent value was obtained by measuring FEV_1 immediately after 4 inhalations of the diluent. If the best post-diluent FEV_1 was less than 90% of the best baseline value, the methacholine challenge test was not performed. The test was performed with a long protocol (doubling doses of methacholine) if the subject responded affirmatively to some questions concerning asthma-related symptoms on the ECRHS second phase questionnaire. In the event there were no symptoms, a short protocol (4-fold increases in methacholine concentration) was used. The short protocol was changed to the long protocol if during the test the FEV_1 fell below 90% of the best post-diluent value, and the test was interrupted if FEV_1 fell below 80% of the best post-diluent value or if the maximum cumulative dose of 1 mg (5.117 μmol) was reached. The test maneuvers conformed to the guidelines established by ECSC.[19]

Bronchial hyperresponsiveness. The concentration causing a 20% or more decrease in FEV_1 (PC_{20}) in comparison with the best post-diluent FEV_1 observed during the test was recorded, the maximum cumulative dose permitted being 5.117 μmol of inhaled methacholine. Subjects in whom this occurred were considered positive for BHR.

Subjects were also considered positive for BHR, even if they did not present a 20% or greater decrease in FEV_1 during a challenge test, if such a decrease could be predicted to a cumulative provocation dose (PD_{20}) of up to 8 μmol by extrapolating. In all cases the slope of the dose-response curve was calculated as percentage of decrease in FEV_1/cumulative dose of methacholine (μmol).

Quality Control

A fieldwork quality control plan was designed for all the participating centers. The plan included the supervision of each step of the study by an experienced technician from the coordinating center. An external quality control team also audited the degree of adherence to established guidelines *in situ* on at least 2 occasions during the study.[14]

Statistical Analysis

We present descriptive data with means (SD), frequencies, and percentages. For the study of the association of sociodemographic and clinical variables with a positive methacholine test we used the χ^2 test for categorical variables and the Student *t* test for continuous variables. For the study of the relation of $FEF_{25\%-75\%}$/FVC to BHR we used 2 logistic regression models. BHR was considered a dichotomous variable, that is, the presence or absence of bronchial response to a methacholine concentration causing a decrease in FEV_1. For the examination of the dose-response ratio, we applied the Beibull model described in detail in other articles.[20]

The independent variable was the $FEF_{25\%-75\%}$ /FVC ratio, which was adjusted for smoking status, atopy, geographic area, age, sex, IgE more than 100 U/mL, baseline FEV_1, and respiratory symptoms. Subjects from Galdakao served as the reference group for the geographic area variable, nonsmokers for the smoking status variable, and subjects with no respiratory symptoms for the respiratory symptoms variable.

Results

We studied a total of 2647 subjects, 51.83% of whom were women, with a mean age of 32 years for both sexes (Table 1). Subjects lived in Albacete, Barcelona, Galdakao, Huelva, and Oviedo. The largest group was the one with no respiratory symptoms, followed by the groups with minor respiratory symptoms, asthma-related symptoms, chronic cough, and chronic bronchitis. There was a high percentage of smokers, especially among men. More women than men had a positive methacholine challenge test, but more men had an IgE concentration more than 100 U/mL and evidence of atopy.

In the univariate analysis of the data shown in Table 2, we studied the relation between the various sociodemographic and clinical variables and the 2

TABLE 1
Study Variables*

Number of Subjects	Women 1372 (52%)	Men 1275 (48%)
Mean age, years	32.41±7.20	32.19±7.50
Height, cm	159±5.9	172±6.92
Area		
Albacete	320 (23)	306 (24)
Barcelona	292 (21)	224 (17)
Galdakao	292 (21)	300 (23)
Huelva	203 (15)	191 (15)
Oviedo	265 (19)	254 (20)
Smoking status		
Nonsmoker	214 (16)	120 (9)
Passive smoker	369 (27)	225 (18)
Ex-smoker	190 (14)	174 (14)
Smoker, 1-9 cigarettes/day	175 (13)	118 (9)
Smoker, 10-20 cigarettes/day	346 (25)	405 (32)
Smoker >20 cigarettes/day	78 (6)	212 (17)
Respiratory symptoms		
Asthma-related symptoms	291 (21)	264 (21)
Chronic bronchitis	58 (4)	102 (8)
Minor respiratory symptoms	319 (23)	307 (25)
Chronic cough	130 (9)	157 (12)
No respiratory symptoms	574 (42)	445 (35)
FEV_1, L	3.048±0.479	4.095±0.743
FEV_1/FVC	83.9±6.92	81.74±7.23
BHR†	146 (16)	128 (13)
Atopy‡	253 (29)	373 (40)
IgE>100 U/mL	210 (22)	296 (31)

*FEV_1 indicates forced expiratory volume in the first second; FVC, forced vital capacity; BHR, bronchial hyperresponsiveness; IgE, immunoglobulin E.
Numbers are frequencies with percentages in parentheses for all variables except age and FEV_1, and $FEF_{25\%-75\%}$, which are means ±SD.
†Expressed as the number of subjects presenting a decrease in FEV_1 of 20% or more compared to the best post-diluent FEV_1 observed during the methacholine challenge test.
‡Subject with a positive skin test or specific IgE test.

TABLE 2
Results of Positive Methacholine Tests According to Clinical and Sociodemographic Variables*

	PC_{20}	*P*	PD_{20}	*P*
IgE>100 U/mL	101 (23.7)	<.001	130 (32.7)	<.001
Atopy	133 (21.2)	<.001	173 (29.7)	<.001
Smoking status				<.001
Nonsmoker	28 (13.3)		33 (16.8)	
Passive smoker	60 (14.4)		72 (18.51)	
Ex-smoker	28 (11.5)		46 (19.9)	
Smoker, 1-9 cigarettes/day	30 (13.7)		39 (19.1)	
Smoker, 10-20 cigarettes/day	91 (16.9)		118 (23.7)	
Smoker, >20 cigarettes/day	36 (17.4)		57 (30.6)	
Respiratory symptoms		<.001		<.001
Asthma-related symptoms	109 (28.4)		134 (37.5)	
Chronic bronchitis	25 (20.4)		39 (34.2)	
Minor respiratory symptoms	68 (15.4)		94 (23.3)	
Chronic cough	21 (9.95)		31 (15.7)	
No respiratory symptoms	51 (7.3)		70 (10.7)	
Geographic area		<.001		<.001
Barcelona	48 (19.4)		62 (25.4)	
Galdakao	51 (11.6)		50 (11.4)	
Albacete	107 (22.5)		147 (34.7)	
Oviedo	40 (11.1)		71 (19.8)	
Huelva	28 (8.4)		38 (14.8)	
Mean age, years	31.44±7.38		31.42±7.3	
FEV_1, mL	3424±0.78	<.001	3448±0.74	<.001
$FEF_{25\%-75\%}$/FVC	82.01±27.46	<.01	82.31±26.59	<.001

*FEV_1 indicates forced expiratory volume in the first second; FVC, forced vital capacity, IgE, immunoglobulin E; $FEF_{25\%-75\%}$, forced expiratory flow, midexpiratory phase. Numbers are frequencies with percentages in parentheses for all variables except age, FEV_1, and $FEF_{25\%-75\%}$, which are means ±SD.
The χ^2 test was used for categorical variables and the Student *t* test for continuous variables.
The *P* value refers to the comparison between subjects with positive tests and those with negative tests.

TABLE 3
Association Between $FEF_{25\%-75\%}$/FVC and Bronchial Hyperresponsiveness*

	OR	PC_{20} 95% CI	–2 log L	OR	PD_{20} 95% CI	–2 log L
$FEF_{25\%-75\%}$/FVC	0.97	0.96-0.98†	84.85	0.97	0,96-0.97†	110.63
FEV_1	0.51	0.40-0.64†	20.11	0.49	0.39-0.60†	27.2
Smoking status			9.59			3.83
Passive smoker	0.99	0.54-1.81		1.15	0.64-2.04	
Ex-smoker	0.91	0.47-1.77		1.43	0.77-2.64	
Smoker, 1-9 cigarettes/day	0.92	0.46-1.84		1.11	0.58-2.13	
Smoker, 10-20 cigarettes/day	1.04	0.58-1.86		1.1	0.63-1.93	
Smoker >20 cigarettes/day	1.11	0.56-2.16		1.47	0.77-2.78	
Respiratory symptoms			73.65			73.87
Asthma-related symptoms	3.25	2.12-4.99†		3.37	2.26-5.01†	
Chronic bronchitis	2.42	1.29-4.54†		3.42	1.88-6.21†	
Minor respiratory symptoms	1.66	1.06-2.61†		1.91	1.27-2.88†	
Chronic cough	0.94	0.49-1.79		1.09	0.62-1.92	
Atopy	1.73	1.22-2.44†	9.39	1.85	1.34-2.23†	14.14
IgE>100 U/mL	2.09	1.48-2.95†	175.75	2.73	1.99-3.75†	207.04
Age, years	0.94	0.92-0.97†	19.86	0.93	0.91-0.95†	31.01
Geographic area			38.79			82.57
Barcelona	1.31	0.75-2.29		2.54	1.48-4.34†	
Albacete	2.03	1.32-3.11†		3.42	1.88-6.21†	
Oviedo	0.82	0.49-1.37		1.91	1.27-2.88	
Huelva	0.47	0.26-0.84†		1.09	0.62-1.92	

*$FEF_{25\%-75\%}$/FVC indicates ratio between forced expiratory flow, midexpiratory phase, divided by forced vital capacity; OR, *odds ratio;* CI, confidence interval; FEV_1, forced expiratory volume in the first second; IgE, immunoglobulin E.
Logistic regression models with PC_{20} as the dependent variable in the first model and PD_{20} in the second. The independent variable was the $FEF_{25\%-75\%}$/FVC ratio, adjusted for baseline FEV_1, smoking status, atopy, geographic area, age, sex, IgE more than 100 U/mL, and respiratory symptoms.
†*P*<.05.

parameters indicative of a positive methacholine test. All of them showed significant differences, except for age. The frequency of a positive test result was found to increase as the number of cigarettes smoked per day increased and also correlated with the presence of asthma-related symptoms.

Table 3 shows the association (expressed as odds ratio with 95% confidence interval) between the $FEF_{25\%-75\%}$/FVC ratio and BHR. After adjusting for the value of baseline FEV_1, smoking status, atopy, geographic area, age sex, high IgE concentrations, and respiratory systems, we noted that the lower the $FEF_{25\%-75\%}$/FVC ratio, the higher the risk of BHR. Of all the variables included for adjustment, the first to be entered into the model was the $FEF_{25\%-75\%}$/FVC ratio as a continuous variable, followed by respiratory symptoms, IgE concentrations, and geographic area. The variables that correlated least with BHR were atopy and smoking status, which were not statistically significant. This was also the case for PC_{20} and PD_{20}.

Discussion

In the present study, our primary interest was to verify whether the ratio between airway caliber and lung size had an effect on the degree of bronchial responsiveness. It has long been hypothesized that a low ratio of airway caliber to lung size was associated with BHR.[12] This has important implications for epidemiological studies evaluating its prevalence.

Our results indicated that in a sample of men and women between the ages of 20 and 44 years a lower $FEF_{25\%-75\%}$/FVC ratio, taken as a surrogate measure for airway caliber relative to lung size, was associated with greater BHR after adjusting for the various factors known to affect airway responsiveness.

To assess this disproportion, Mead[21] developed a formula consisting of the ratio of maximal expiratory flow at 50% of vital capacity ($\dot{V}_{max50}$) divided by vital capacity (VC) and the static recoil pressure of the lung at 50% of vital capacity ($Pst[L]_{50}$): $\dot{V}_{max50}/(VC \times Pst[L])_{50}$). Other authors later showed that the $FEF_{25\%-75\%}$/FVC ratio was a reasonable approximation of this formula and pointed out that basal bronchomotor tone contributed relatively little to variability in peak expiratory flow in flow-volume curves—peak flow being negatively associated with the presence of BHR in a sample of children and young adults.[22] The $FEF_{25\%-75\%}$/FVC ratio adjusted for initial FEV_1, age, smoking status, eosinophil count, and IgE concentration was studied in a sample of 929 men with a higher mean age (60.5 [77.5] years) and a significant association was found between that ratio and the degree of airway responsiveness to methacholine.[13] These results are similar to the ones obtained in our analysis of findings adjusted for respiratory symptoms in a sample of younger men and women.

The mechanisms by which lung size influences airway responsiveness are unknown. A study of 1613 children between the ages of 7 and 12 years and 2398 adults between the ages of 25 and 50 years using FVC as a surrogate measure for lung size and FEV_1 as the measure of the airway showed small but significant effects on airway responsiveness. The authors point out that both lung size and airway caliber should be taken into account when airway response measurements are compared, as the effective quantity and the concentration of agonist received by the lungs may differ.[12] Thus, studies of the prevalence of BHR among different age groups and sexes may not be comparable, as subjects with smaller lungs will be receiving a proportionally larger dose than those with larger lungs.[23] It is therefore difficult to determine whether the apparently significant differences in the prevalence of BHR among children and adults are due to lung size.[24]

The positive associations between BHR and variables of our analysis other than $FEF_{25\%-75\%}$/FVC, such as respiratory symptoms, baseline FEV_1, and elevated IgE concentrations are understandable. The differences between geographic areas may be due to the way the dosimeters were calibrated, with evaporation loss leading to overestimation of the nebulized dose, or to the effect of seasonal differences.[15]

The limitations of the present study are chiefly due to the fact that as a cross-sectional study, it could not be used to determine the implications of dysanapsis on the etiology of BHR. We hope that once the study of this cohort done in 1999-2001 has been analyzed, it will be possible to verify whether subjects with a low $FEF_{25\%-75\%}$/FVC ratio develop BHR.

Our results show that $FEF_{25\%-75\%}$/FVC is significantly associated with airway responsiveness to methacholine, independent of age, atopy, smoking status, geographic area, respiratory symptoms, and baseline FEV_1. We feel, therefore, that airway size relative to lung size should be adjusted for when carrying out epidemiological studies to evaluate the prevalence of BHR, especially when different age groups are compared. Such an adjustment would make it possible to specify and measure the other risk factors involved in BHR.

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