RESPIRATORY PHYSIOLOGY

Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): a population based study

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Background: C-reactive protein (CRP), a marker of systemic inflammation, is a powerful predictor of adverse cardiovascular events. Respiratory impairment is also associated with cardiovascular risk. Although some studies have found an inverse relationship between lung function and markers of systemic inflammation, only one study has reported a relationship between lung function and CRP levels. In contrast, little is known about the relationship between bronchial hyperresponsiveness (BHR) and systemic inflammation. The association between lung function and CRP and between BHR and CRP has been investigated.

Methods: As part of the European Community Respiratory Health Survey follow up study serum CRP levels, forced expiratory volume in 1 second (FEV_1), and BHR to methacholine ($\geq$20% decrease in FEV_1 to $<$4 mg methacholine) were measured in 259 adults aged 28–56 years free of cardiovascular disease or respiratory infection.

Results: Mean (SD) FEV_1 (adjusted for age, sex, height, and smoking status) was lower in subjects with a high CRP level (high tertile) (3.29 (0.44) l/s *v* 3.50 (0.44) l/s; $p<0.001$) and BHR was more frequent (41.9% *v* 24.9%; $p=0.005$) than in subjects with lower CRP levels (low+middle tertiles). Similar results were obtained when the potential confounding factors were taken into account. Similar patterns of results were found in non-smokers and in non-asthmatic subjects.

Conclusions: Increased CRP levels are strongly and independently associated with respiratory impairment and more frequent BHR. These results suggest that both respiratory impairment and BHR are associated with a systemic inflammatory process.

C-reactive protein (CRP) is a major inflammation sensitive plasma protein in humans. Its synthesis by the liver is regulated to a large extent by the pro-inflammatory cytokine interleukin (IL)-6. The measurement of CRP levels in the blood is simple and has been used for decades in clinical practice to follow the progression of inflammatory processes. CRP may also actively contribute to the formation of atherosclerotic lesions,[1] and its concentration in the blood—particularly now that high sensitivity dosages are available—has recently been recognised in numerous prospective studies as a particularly powerful marker of systemic inflammation for predicting risk of cardiovascular events in initially healthy subjects.[2–5] CRP could therefore become a crucial tool in clinical practice in cardiovascular disease.

Impaired respiratory function (expressed by forced expiratory volume in 1 second (FEV_1) and/or peak expiratory flow) is strongly associated with cardiovascular risk factors,[6] atherosclerosis,[7] arterial stiffness,[8] cardiovascular disease and mortality,[9 10] although the physiopathological mechanisms underlying these associations are largely unknown. Some hypotheses have been put forward, including the possibility that respiratory and cardiovascular alterations may share common risk factors such as ageing and smoking status. Systemic inflammation is also a possible element in the link between respiratory impairment and cardiovascular events. Reduced lung function has been associated with various inflammation sensitive plasma proteins[11–13] but, to date, only one study has reported an association between lung function and CRP levels.[14]

Although bronchial hyperresponsiveness (BHR) is known to be linked to decline in respiratory function,[15 16] only limited data are available as to whether BHR is associated with systemic inflammation, and the relationship between BHR and CRP levels has never been investigated. BHR to a non-specific stimulus such as cold or pharmaceutical agents reflects local inflammation in the bronchus. It is a key characteristic of asthma but is also present in a significant fraction of the non-asthmatic population.

A population based study was undertaken to evaluate the relationship between BHR and systemic inflammation (assessed by serum CRP levels).

METHODS

Study participants

Data were collected at Bichat Hospital, Paris, France between October 1999 and May 2001 as part of the follow up phase of the European Community Respiratory Health Survey (ECRHS-II). The general objective of the ECRHS was to study the risks factors, the prevalence and incidence of asthma and asthma-like symptoms in Europe. The protocol of this study has been described elsewhere.[17 18] Briefly, at the time of the first phase (ECRHS-I) in 1991–2, 660 subjects aged 20–44 years were randomly selected from the electoral rolls of Paris (18th district) and examined at the hospital. Three hundred and sixty subjects were contacted again and agreed to be re-examined 10 years later for ECRHS-II.[18]

Abbreviations: BHR, bronchial hyperresponsiveness; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Study protocol

Each subject answered a standardised questionnaire administered by trained interviewers and underwent lung function tests and blood tests. Subjects who had suffered from respiratory infection in the 3 weeks immediately preceding the examination were asked to postpone their examination, as this was a criterion for exclusion.

FEV_1 and forced vital capacity (FVC) were determined with a water sealed bell spirometer (Biomedin srl, Padova, Italy) and the best of five satisfactory manoeuvres was used for the analysis. BHR was measured by a methacholine challenge for all subjects with none of the exclusion criteria defined in the international ECRHS protocol. The exclusion criteria were: history of heart disease, use of β blockers, baseline FEV_1 <70% predicted value or <1.5 l,[19] or a post-saline FEV_1 of <90% of initial FEV_1, epilepsy, pregnancy and breastfeeding. A Mefar MB3 dosimeter (Mefar srl, Bovezzi, Italy) was used to administer methacholine. After inhalation of phosphate buffered saline, methacholine was administered until FEV_1 had fallen by 20% or more from the post-saline value or until a maximum cumulative dose of 4 mg had been given. Subjects with a history of asthma or wheezing were initially given a dose of 0.0078 mg which was doubled for each subsequent administration. In other subjects the following cumulative doses were administered: 0.0156, 0.0625, 0.25, 1, 2, 4 mg, changing to twofold steps if FEV_1 fell by 10% or more. BHR was defined as a decrease in FEV_1 of at least 20% with respect to the post-saline value for a maximum methacholine dose of 4 mg.

Smoking status was assessed in three classes: never smokers, ex-smokers, and current smokers. Chronic bronchitis was defined as bringing up phlegm from the chest on most days for as much as 3 months each year.[20]

In addition to the general ECRHS-II protocol, high sensitivity measurements of serum CRP concentrations were made by immunonephelometric assays on a BN II analyser (Dade Behring, Marburg, Germany). The detection range was 0.18–1100 mg/dl. The participants were also asked to complete a standardised questionnaire on conventional cardiovascular risk factors. Systolic and diastolic blood pressures (SBP and DBP) were measured and hypertension was assessed as described elsewhere.[21] Subjects were also asked if they had a history of cardiovascular events, and the nature and the date of these events.

Non-fasting total plasma cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels were determined by standard methods. Patients were considered to have hypercholesterolaemia if they answered yes to at least one of the following questions: ''Have you ever been told your cholesterol level was too high?'' and ''Do you currently use any lipid lowering drugs?'' Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres.

Written informed consent was obtained from each subject before inclusion in the study. The protocol was approved by the French ethics committee for human research and by the National Committee for Data Processing and Freedom.

Statistical analysis

The study population consisted of 259 subjects free of heart disease (117 men, 142 women) for whom all the data were available. In 32 patients blood samples were not collected due to refusal or for technical reasons, 15 subjects did not undergo respiratory testing or blood pressure measurement, and in 54 subjects the complete methacholine challenge was not possible due to refusal (n = 8), fatigue (n = 5), or exclusion criteria (use of β blockers, n = 13; heart medication ± β blockers or history of heart disease, n = 12; baseline FEV_1 <70% predicted value or <1.5 l, or post-saline FEV_1 <90% initial FEV_1, n = 9; other, n = 7). When the baseline demographic characteristics of the study subjects were compared with those of subjects who could not be included in the analyses (either because they met exclusion criteria or because they did not participate in ECRHS-II), there were no differences with regard to sex distribution and BMI. Study subjects were slightly older (1 year on average), finished education when slightly older (1 year on average), and were

Table 1 Characteristics of subjects included in the analysis in 1999–2001 by sex

	Men (n = 117)	Women (n = 142)
Age (years)*	45.5 (7.5)	44.0 (7.2)
BMI (kg/m^2)*	24.9 (3.0)	23.1 (3.8)
Age at leaving education (years)*	21.1 (3.8)	21.6 (3.5)
White ethnic group† (%)	94.8‡	95.1
Systolic blood pressure (mm Hg)*	125.8 (13.5)	114.3 (16.7)
Diastolic blood pressure (mm Hg)*	80.6 (8.7)	74.9 (11.0)
Hypertension (%)	23.9	11.3
Total cholesterol (mg/dl)*	242.1 (78.7)	263.5 (119.8)
HDL cholesterol (mg/dl)*	64.1 (21.3)	82.3 (39.7)
LDL cholesterol (mg/dl)*	145.6 (57.8)	153.2 (74.9)
Hypercholesterolaemia (%)	24.8	22.5
Smoking status		
Never smokers (%)	40.2	43.7
Ex-smokers (%)	26.5	27.5
Current smokers (%)	33.3	28.9
Chronic bronchitis (%)	3.4	2.8
Asthma (%)	9.4	14.1
Adjusted¶ FEV_1 (l/s)*	3.83 (0.54)	3.10 (0.53)
FEV_1 (% pred)*	106.9 (14.3)	104.2 (13.3)
Adjusted¶ FVC (l/s)*	4.51 (0.68)	3.76 (0.66)
FEV_1 % FVC*	84.0 (6.2)	83.0 (6.6)
BHR (%)	18.0	40.9
CRP (mg/l)*	2.01 (2.7)	1.48 (2.1)

BMI, body mass index; HDL, high density level; LDL, low density level; BHR, bronchial hyperresponsiveness; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
*Values are mean (SD).
†Both parents of white ethnic origin.
‡On 115 subjects.
¶Adjusted for age, sex, height, and smoking status.

Table 2 Associations between C-reactive protein (CRP) and demographic, cardiovascular, biological, and respiratory factors

	CRP		
	Lower tertiles (n = 173)	High tertile (n = 86)	p value
Age (years)*	44.4 (7.6)	45.4 (6.8)	0.30
Men (%)	54.9	54.7	1.00
BMI (kg/m^2)*	22.9 (3.0)	25.8 (3.9)	<0.001
Age at leaving education (years)*	21.5 (3.4)	21.0 (4.0)	0.30
White ethnic origin† (%)	95.3‡	94.2	0.70
Systolic blood pressure (mm Hg)*	118.9 (16.5)	121.5 (15.9)	0.20
Diastolic blood pressure (mm Hg)*	77.0 (10.3)	78.5 (10.5)	0.30
Hypertension (%)	12.7	25.6	0.009
Total cholesterol (mg/dl)*	249.6 (97.6)	262.4 (114.9)	0.40
HDL cholesterol (mg/dl)*	75.3 (2.6)	71.5 (3.7)	0.40
LDL cholesterol (mg/dl)*	147.0 (62.9)	155.4 (76.6)	0.40
Hypercholesterolemia (%)	21.4	27.9	0.20
Smoking status			
Never smokers (%)	43.9	38.4	0.10
Ex-smokers (%)	29.5	22.1	
Current smokers (%)	26.6	39.5	
Chronic bronchitis (%)	4.1	7.0	0.30
Asthma (%)	11.0	14.0	0.50
Adjusted¶ FEV_1 (l/s)*	3.50 (0.44)	3.29 (0.44)	<0.001
FEV_1 (% pred)*	107.60 (13.56)	101.14 (13.39)	<0.001
Adjusted¶ FVC (l/s)*	4.16 (0.55)	3.97 (0.55)	0.01
FEV_1 % FVC*	84.31 (6.02)	83.29 (7.20)	0.20
BHR (%)	24.86	41.86	0.005

Tertiles are sex dependent (tertile limits in men: <0.7 mg/l, 1.3 mg/l, 1.4–12.5 mg/l; in women: <0.4 mg/l, 1.2 mg/l, 1.3–11.7 mg/l).
BMI, body mass index; HDL, high density level; LDL, low density level; BHR, bronchial hyperresponsiveness; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
*Values are mean (SD).
†Both parents of white ethnic origin.
‡On 171 subjects.
¶Adjusted for age, sex, height, and smoking status.

more likely to have both parents of white ethnic group (95% *v* 90%).

Data were analysed with SAS software version 8.1 (SAS Institute Inc, Cary, USA). CRP was mainly used as a qualitative variable: it was treated as a binary variable. Because our interest was focused on subjects with the highest CRP values versus the lower ones with regard to lung function and BHR, we compared subjects with CRP values in the highest tertile with those with CRP values in the lower tertiles (low+middle tertiles). Tertiles were sex specific. Lung function was expressed as ''adjusted'' FEV_1 (observed FEV_1 adjusted for age, sex, height, and smoking status). FEV_1 percentage predicted (FEV_1 % pred),[19] FEV_1 as a percentage of FVC (FEV_1% FVC), and adjusted FVC (adjusted for age, sex, height, and smoking status) were also considered.

In univariate analysis the relationship between two quantitative variables was assessed by calculating Pearson's correlation coefficient (r). CRP as a quantitative variable was normalised by log transformation. Respiratory characteristics and other factors were compared between the two groups of subjects according to their CRP levels (high tertile *v* lower tertiles) using t tests and χ^2 tests for quantitative and qualitative variables, respectively. In multivariate analyses the relationship between FEV_1 and CRP was analysed by analysis of covariance. The relationship between BHR and CRP was expressed as an odds ratio (OR) with 95% confidence interval (CI) determined by logistic regression. p values of <0.05 were considered significant.

RESULTS

The characteristics of the study population according to sex are shown in table 1. BMI, arterial blood pressure, and CRP were lower in women than in men. As expected, the HDL cholesterol level was higher in women than in men, observed FEV_1 was lower in women than in men, and BHR was more frequent in women than in men. Only a few subjects (n = 8) had chronic bronchitis.

As expected, FEV_1 was significantly associated with age (p<0.001), sex (p<0.001), and height (p<0.001). Adjusted FEV_1 was negatively associated with BHR (p = 0.002). As expected, BHR was more frequent in asthmatic subjects than in non-asthmatic subjects (p<0.001). CRP was positively associated with BMI and hypertension, and tended to be associated with smoking status (table 2).

Adjusted FEV_1 was significantly lower in subjects with high CRP levels than in those with lower CRP levels (table 2), and this was still the case after adjustment for additional potential confounding factors (BMI, age at leaving education, hypercholesterolaemia, and hypertension: 3.31 (0.47) l/s *v* 3.49 (0.45) l/s, p = 0.05). When BHR was added to the multivariate model, adjusted FEV_1 remained significantly lower in subjects with high CRP levels than in those with lower CRP levels (3.32 (0.47) l/s *v* 3.48 (0.47) l/s, p = 0.02).

Although the relationship between adjusted FEV_1 and CRP was more marked in never smokers than in current and ex-smokers in whom this relationship did not reach statistical significance, the interaction between CRP and smoking status was not statistically significant (p = 0.08, multivariate analysis). When FEV_1 % predicted was used instead of adjusted FEV_1, similar results were obtained in univariate analysis (table 2) as in multivariate analysis. Lower adjusted FVC values were observed in subjects with high CRP values than in those with lower CRP values, but a significant association was no longer found in multivariate analysis (results available on request).

BHR was significantly positively associated with CRP levels (table 2) and this was still the case after multivariate adjustment (table 3). CRP and sex were the only variables significantly associated with BHR (table 3). When asthma was added to the multivariate model, BHR was still

Table 3 Multivariate analysis: association between CRP levels and bronchial hyperresponsiveness by logistic regression

	Bronchial hyperresponsiveness		
Covariates	**OR**	**95% CI**	**p value**
CRP (high tertile *v* lower tertiles)	2.27	(1.20 to 4.28)	0.01
Age (per 10 year increase)	1.17	(0.77 to 1.76)	0.50
Women	3.60	(1.93 to 6.72)	<0.001
BMI (per 4 kg/m^2 increase)	0.95	(0.67 to 1.35)	0.80
Current+ex-smokers	1.16	(0.66 to 2.08)	0.60
Age at leaving education (per 4 year increase)	0.97	(0.70 to 1.34)	0.80
Hypercholesterolaemia	0.74	(0.37 to 1.47)	0.40
Hypertension	1.66	(0.75 to 3.64)	0.20

CRP, C-reactive protein; OR, odds ratio; CI, confidence interval; BMI, body mass index.

associated with CRP (adjusted OR 2.04 (95% CI 1.06 to 3.94), p = 0.03). When adjusted FEV_1 was included in the multivariate analysis, BHR remained significantly associated with CRP (adjusted OR 1.98 (95% CI 1.03 to 3.79), p = 0.04).

Similar patterns of results were obtained either for the relationships between adjusted FEV_1 and CRP and between BHR and CRP after exclusion of asthmatics (n = 31), subjects of non-white ethnic origin (n = 13), subjects with chronic bronchitis (n = 13), heavy smokers (≥20 g tobacco a day) (n = 20), or non-smokers exposed to tobacco smoke (n = 53).

DISCUSSION

A reduced FEV_1 and a higher frequency of BHR were strongly associated with high CRP levels in this epidemiological study. Multivariate analyses suggested that these associations were independent of the potential confounding factors, particularly smoking and asthma status.

The validity of our results is supported by the quality of the data collected in the European Community Respiratory Health Survey.[17 18] The factors we found to be associated with FEV_1 and BHR were reported to be so in numerous other studies.[22–24] In the present study CRP was associated with BMI and smoking status, consistent with previously published results.[25]

We found that FEV_1 was independently associated with CRP. BHR was inversely associated with FEV_1 (in agreement with results of previously published studies[15 16]), but FEV_1 was still significantly associated with CRP after adjustment for BHR in multivariate analysis, suggesting that this association cannot be accounted for by BHR.

The association between FEV_1 and CRP found in our study is consistent with previous studies that have found a relationship between lung function and other markers of systemic inflammation. Kauffmann *et al* found a negative association between FEV_1 and haptoglobin levels in men.[11] In line with this result, Dahl *et al* reported that a lower FEV_1 and increased risk of chronic obstructive pulmonary disease were associated with increased plasma fibrinogen levels.[12] Finally, Engström *et al* showed in men that the FVC was inversely associated with levels of inflammation sensitive plasma proteins (fibrinogen, α_1-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid). They also showed that the levels of these inflammation markers partially accounted for the relationship between lung function and cardiovascular events.[13] Only one study investigated the relationship between FEV_1 and CRP, but this was performed only in men and only a crude association was reported as it was not the major aim of that study.[14] Our study and previous ones support the hypothesis that systemic inflammation may be the missing link in the association between pulmonary and cardiovascular alterations.[6–10]

The present study provides the first evidence of an association between a higher frequency of BHR and higher CRP levels. This result is consistent with those of studies showing that asthmatic patients—who commonly present with BHR—have both systemic inflammation and local inflammation in the bronchus.[26–28] However, most of these studies included small numbers of subjects and used markers of inflammation usually associated with an allergic inflammatory response such as eosinophils and interferon-γ.[26 27] Closer to our study is the recent population based study of Jousilahti *et al*[28] showing that CRP levels were higher in asthmatic subjects than in non-asthmatic ones.

A few epidemiological studies have investigated the relationship between BHR and other systemic inflammation sensitive proteins or cytokines. Kauffmann *et al*[11] found a positive association in men between BHR and haptoglobin levels and Tsunoda *et al*[29] recently reported a positive association in pregnant women between BHR (methacholine challenge tests were performed a few weeks after delivery) and some cytokines including IL-6 and granulocyte-macrophage colony stimulating factor.

Our population based study in both men and women and these previous studies suggest that BHR may reflect not only local inflammation in the bronchus but also non-specific systemic inflammation. The mechanisms underlying the association between respiratory function and BHR with systemic inflammation are unknown and our cross sectional study does not shed light on the nature of this association. A number of hypotheses have been suggested. It has been reported that α_1-antitrypsin is inversely associated with an alteration of gas exchanges in the lungs.[30] As the pro-inflammatory IL-6 is largely implicated in the synthesis of CRP and also in that of α_1-antitrypsin, fibrinogen and haptoglobin, IL-6 may play a particularly important role in the mechanisms leading to reduced pulmonary function. The higher level of CRP observed in some subjects may also result from higher exposure to some irritant or infectious agents—for example, in an occupational environment—and may therefore reflect the effects of theses agents in the lungs.[13] The genetic determinants of systemic markers of inflammation and a predisposition to an exaggerated inflammatory response may also be involved in the association between lung function and CRP. Consistent with this hypothesis, a number of studies have provided evidence of heritability for CRP levels.[31 32] More generally, systemic inflammation may reflect a poorer general state of health, hence its association with respiratory and cardiovascular health—two vital functions. Interestingly, some recent studies have suggested that individuals who are able to produce high levels of IL-6 are disadvantaged for longevity.[33] The mechanisms underlying the association between BHR and CRP levels may involve environmental and genetic factors.

In conclusion, we found that FEV_1 impairment and a higher frequency of BHR were strongly associated with increased CRP levels, independent of potential confounding factors, which suggests that both reduced lung function and BHR are related to a systemic inflammatory process. Further studies are needed to determine the mechanisms underlying these associations.

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