Bronchial Hyperresponsiveness to Methacholine Is Associated With Increased Common Carotid Intima-Media Thickness in Men

Mahmoud Zureik, Sabine Kony, Catherine Neukirch, Dominique Courbon, Bénédicte Leynaert, Daniel Vervloet, Pierre Ducimetière, Françoise Neukirch

Background—Respiratory alterations have been associated with subsequent coronary heart diseases in numerous population-based studies. The underlying mechanisms remain largely unknown. The objective of this study was to examine the association between bronchial hyperresponsiveness (BHR) to methacholine (which reflects local inflammation in the bronchus) and common carotid intima-media thickness (CCA-IMT).

Methods and Results—As part of the European Community Respiratory Health Survey follow-up, in Paris Center, we assessed BHR to methacholine (‡20% decrease in FEV1 for a maximum methacholine dose of 4 mg) and measured CCA-IMT by ultrasonography in 255 adults free of cardiovascular diseases aged 29 to 56 years (123 men, 132 women; mean age 44.5 years, 43.5% never smokers). In men, CCA-IMT mean value was higher in subjects with BHR than in those without (0.68±0.11 versus 0.62±0.09 mm, P=0.002). No association was found in women. Multivariate analysis confirmed the independent association between BHR and CCA-IMT in men (adjusted odds ratio for a 0.10-mm increase in CCA-IMT=2.1, 95% confidence interval: 1.1 to 4.3; P=0.02). These results remained similar after exclusion of asthmatic subjects (n=11). In each strata of smoking status (nonsmoker, ex-smoker, and current smokers), CCA-IMT mean values tended to be higher in subjects with BHR than in those without, although the difference between the 2 groups was more pronounced in current smokers.

Conclusions—The results of the present study suggest that BHR is independently associated with CCA-IMT in men. The interrelationships between cardiovascular and respiratory alterations should be further investigated. (Arterioscler Thromb Vasc Biol. 2004;24:1098-1103.)

Key Words: epidemiology ■ atherosclerosis ■ carotid ■ pulmonary disease ■ imaging

Several population-based studies have shown that impaired lung function is a powerful predictor of nonfatal ischemic heart disease and of mortality caused by cardiovascular disease.1–4 The physiopathological mechanisms underlying these associations remain largely unknown. We have previously reported, in a 4-year longitudinal study performed in a large sample of relatively aged subjects, that low values of peak expiratory flow relative to the predicted ones were associated with increased carotid atherosclerotic plaques occurrence detected by ultrasonography, even after adjustments for conventional cardiovascular risk factors (including smoking habits).5 In another study performed in men free of coronary heart diseases (aged between 30 and 70 years), forced expiratory volume in 1 second (FEV1) was negatively associated with aortic stiffness, a major component of arterial function.6 These results suggest that both atherosclerosis and arterial stiffness might be involved in the associations between respiratory impairment and cardiovascular risk. However, the modifications on vascular structure associated with respiratory impairment need to be further investigated.

B-mode ultrasound measurements of intima-media wall thickness (IMT) in the extracranial carotid arteries are generally considered as early markers of systemic atherosclerosis and vascular hypertrophy. Increased IMT has been shown to be associated with the main cardiovascular risk factors,7,8 the presence of other localizations of atherosclerosis,9,10 and an increased risk of coronary heart disease and stroke.11,12 However, IMT probably also reflects a hypertrophic response of arterial intima and medial cells to high blood pressure and hypertension.13,14

Bronchial hyperresponsiveness (BHR) to a nonspecific stimulus (eg, cold, 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 nonasthmatic population.15 Because airway hyperresponsiveness is associated with reduced lung function and more rapid
than normal decrease in lung function,15,16 it might be involved in the interrelationships between respiratory and cardiovascular alterations.

In this population-based study, we assessed the associations of BHR to methacholine with common carotid IMT in middle-aged subjects (123 men and 132 women) free of cardiovascular diseases.

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 protocol of this study has been described elsewhere.17,18 Briefly, 660 subjects aged 20 to 44 years were randomly selected from the electoral rolls of Paris (18th district). These subjects were examined at the hospital between 1992 and 1993 (ECRHS-I). Three-hundred sixty subjects were recontacted and agreed to be reexamined 10 years later for ECRHS-II.17 There were no significant differences between subjects examined in 1992 and 1993 and those reexamined a second time in terms of sex, age, body mass index (BMI), respiratory symptoms, and diseases, but the frequency of individuals who had never smoked was higher among subjects who were reexamined than among those examined only once (67.6% versus 57.5%; P=0.008).

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.

Study Protocol

Each subject answered a standardized questionnaire administered by trained interviewers and underwent lung function tests and blood tests. FEV1 was determined with a water-sealed bell spirometer (Biomedin srl, Padova, Italy) and the best of 5 satisfactory maneuvers was used for the analysis. For each subject, FEV1 relative to the predicted value (FEV1 %pred) was calculated, with predicted values being obtained from previously published sex-specific regression equations of FEV1 on age and height.19

Bronchial responsiveness 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, in particular, history of heart disease, use of β-blockers, a baseline FEV1 of <70% predicted value or of <1.5 L, or a baseline FEV1 of <90% of initial FEV1, epilepsy, pregnancy and breast-feeding. A Mefar MB3 dosimeter (Mefar srl, Bovezi, Italy) was used to administer methacholine. After phosphate-buffered saline was inhaled, methacholine was administered until FEV1 had decreased by ≥20% from the postsaline 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, and 4 mg, changing to 2-fold steps if FEV1 decreased by ≥10%. BHR was defined as a decrease in FEV1 of at least 20% with respect to the postsaline value for a maximum methacholine dose of 4 mg. We also used the dose-response slope as a continuous measure of bronchial responsiveness to methacholine.20 The dose-response slope was calculated as the percent decrease in FEV1 from the postsaline value to that at the final cumulative dose administered divided by the final cumulative dose.20

Smoking status was assessed in 3 classes: never-smokers, ex-smokers, and current smokers. The participants were also asked to complete a standardized questionnaire on conventional cardiovascular risk factors. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, and subjects were classified as being hypertensive when their SBP was at least 140 mm Hg and/or their DBP was at least 90 mm Hg, and/or they reported using an antihypertensive treatment.21 High-sensitivity measurements of serum C-reactive protein (CRP) concentrations were made by means of immunonephelometric assays on a BN II analyzer (Dade Behring). Nonfasting total plasma cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels were determined by standard methods. Hypercholesterolemia was defined as total cholesterol level ≥280 mg/dL or use of lipid-lowering drugs. Subjects who reported medical history of diabetes, use of antidiabetic drugs, or had a nonfasting plasma glucose level ≥2.0 g/L were considered as having diabetes.22 BMI was calculated as weight in kilograms divided by the square of height in meters. For physical activity, the subjects were asked, “How many hours per week do you usually exercise so much that you get out of breath or sweat?” Response options were none, ≈30 minutes, 1 hour, 2 to 3 hours, 4 to 6 hours, and 7 hours or more.

Carotid Ultrasonography

Ultrasound examinations were performed, before spirometry tests and methacholine challenge, by 2 trained physicians using the Aloka SSD-650 with a transducer frequency of 7.5 MHz. Acquisition, processing, and storage of B-mode images were computer-assisted with the new version of a software previously described (MATHIS; Metris, France).23 The protocol, which was similar to those applied in the other ultrasound studies conducted by our team,1,2,4,25 involved scanning of the common carotid arteries (CCAs), the carotid bifurcations (CBs), and the origin (first 2 cm) of the internal carotid arteries (ICA). The near and far walls of these arterial segments were scanned longitudinally and transversally to assess, at the time of the examination, the presence of plaques. The presence of plaques was defined as localized echo-structures encroaching into the vessel lumen for which the distance between the media- adventitia interface and the internal side of the lesion was ≥1 mm.

For IMT, far and near walls of the right and the left CCAs 2 to 3 cm proximal to bifurcation were imaged. For each side, at least 2 optimal longitudinal images were frozen and stored for off-line analysis. All measurements were performed by 1 reader (1 of the physicians). The IMT was measured at a site free of any discrete plaques along a 10-mm-long segment of the far wall of the CCA and measured as the distance between the lumen–intima interface and the media–adventitia interface using an automated edge detection algorithm. A mean of 50 measurements was automatically performed on each image (2 images by side) and on each side (left and right). The mean of the right and left CCA-IMT measurements was used in the analysis.

A blinded rereading study was made on a random subsample of images of CCAs (n=50). Mean absolute difference, coefficient of variation, and correlation coefficient between repeated readings of CCA-IMT were, respectively, 0.04 mm, 6.1%, and 0.93.

Statistical Analysis

The study population consisted of 255 subjects free of cardiovascular diseases, comprising 123 men and 132 women for whom all the data were available (360 subjects minus 36 subjects for whom carotid ultrasonography was not performed for technical and logistic reasons [the first 6 subjects and the last 30 subjects]), 15 subjects who did not undergo respiratory testing or blood pressure measurement, and/or 54 subjects for whom complete methacholine challenge was not possible because of refusal (n=8), fatigue (n=5), or exclusion criteria (use of β-blockers, n=13; history of heart disease, n=12; baseline FEV1 of <70% of predicted value or of <1.5 L, or postsaline FEV1 of <90% of initial FEV1, n=9; others, n=7).

Standard procedures from the Statistical Analysis System (SAS, Cary, NC) were used for univariate and multivariate analyses. All analyses were separately performed in men and women. Associations of BHR with CCA-IMT and potential risk factors were assessed by χ2 tests and by t test. Potential risk factors considered in the analysis were age, smoking habits, BMI, vigorous exercise, hypertension (or systolic blood pressure), diabetes, hypercholesterolemia, CRP (in logarithmic-transformed values), asthma, FEV1%pred, and FEV1/forced vital capacity. For multivariate analysis, a stepwise
Results

The characteristics of the study population, according to sex, are presented in Table 1. BMI, SBP, DBP, CRP, and CCA-IMT were significantly lower in women than in men. Hypertension was less frequent and BHR was more frequent in women than in men. Only 15 men and 6 women had carotid plaques (P = 0.02).

In men, CCA-IMT was positively associated with age (correlation coefficient r = 0.44, P < 0.001) and SBP (r = 0.20, P = 0.03), and negatively associated with FEV1/FVC (r = -0.22, P = 0.01). CCA-IMT and FEV1 % pred were negatively, but not significantly, associated (r = -0.13, P = 0.17). The CCA-IMT means (± SD) in never-smokers, ex-smokers, and current smokers were, respectively, 0.60 ± 0.08 mm, 0.67 ± 0.08 mm, and 0.65 ± 0.10 mm (P for overall differences = 0.003). Higher means of CCA-IMT were observed in men with hypercholesterolemia compared with those without (0.67 ± 0.10 versus 0.62 ± 0.09 mm, P = 0.009), and in asthmatics compared with nonasthmatics (0.69 ± 0.11 versus 0.63 ± 0.09 mm, P = 0.04). In women, only age (r = 0.47, P < 0.001), BMI (r = 0.20, P = 0.02), and SBP (r = 0.17, P = 0.05) were positively associated with CCA-IMT.

The relationships of BHR with risk factors is shown in Table 2. Both in men and in women, asthma, FEV1 % pred and FEV1/FVC were associated with BHR (Table 2). CRP and BHR were positively related, although the differences reached statistical significance only in women (Table 2). In men, CCA-IMT was higher in subject with BHR than in those without (0.68 ± 0.10 versus 0.62 ± 0.09 mm, P = 0.002). The unadjusted odds ratio (OR) of BHR for a 0.10-mm increase of CCA-IMT (≈ 1 SD) was 2.3 (95% CI = 1.2 to 4.6, P = 0.004). No association between BHR and CCA-IMT was observed in women (Table 2). Multivariate analysis confirmed the independent association of BHR and CCA-IMT in men (Table 3). The multivariate-adjusted OR of BHR for 0.10-mm increase of CCA-IMT was 2.1 (95% CI = 1.1 to 4.3, P = 0.02). The substitution of cigarette pack-years (as continuous variable with never smokers assigned the value of zero) for smoking habits categories did not markedly modify the results. In this model, the multivariate-adjusted OR of BHR for 0.10-mm increase of CCA-IMT was 2.2 (95% CI = 1.1 to 4.4, P = 0.02).

When the dose-response slope (as continuous variable) was used instead of BHR, the correlation coefficients between CCA-IMT and O’Connor slope (logarithmic values) were 0.31 (P < 0.001) in men and -0.01 (P = 0.92) in women.

Subgroups Analyses

The exclusion of subjects with asthma (n = 11) did not alter the association of BHR and CCA-IMT in men (Table 4). Analyses were also repeated according to smoking habits categories. In all these categories, CCA-IMT mean values tended to be higher in subjects with BHR than in those without, although the difference between the 2 groups was more pronounced in current smokers (Table 4).

Discussion

In this population-based study, BHR was associated with increased CCA-IMT in men, even after adjustment for conventional cardiovascular risk factors including smoking habits. No association was observed in women. To our knowledge, this is the first study that reports the relationship between bronchial hyperresponsiveness and carotid IMT.

Several explanations could be formulated to explain the observed association of BHR with carotid IMT. Inflammatory mechanisms may act as a contributing factor to this association. Previous studies have suggested that BHR may reflect not only a local inflammation in the bronchus but also a nonspecific systemic inflammation. Immune complexes and abnormal inflammatory responses have also been shown to be implicated of arterial injury. Inflammation mediates a key role in the pathogenesis of atherosclerosis.26 Various cytokines, growth factors, and inflammatory cells are abundant in atheromatous plaques.26
The investigation of the interrelationships of systemic markers of inflammation with both CCA-IMT and BHR may thus clarify this hypothesis. CRP, a major inflammation-sensitive plasma protein in humans, was measured in our study. CRP tended to be positively related to BHR, but CCA-IMT and CRP were not associated (correlation coefficient $\rho = 0.04$, $P = 0.55$), which is in agreement with the results of some other investigations. In addition, when CRP was forced into the final multivariate model, the association between BHR and CCA-IMT was not modified. The multivariate-adjusted OR of BHR for a 0.10-mm increase of CCA-IMT was 2.2 (95% CI = 1.1 to 4.4, $P = 0.03$). These findings thus do not entirely support the systemic inflammation hypothesis.

Leukotrienes, which are inflammatory mediators generated from arachidonic acid by the enzyme 5-lipoxygenase, may be also involved in the association between arterial thickening and BHR. Leukotrienes are obviously implicated in bronchial asthma and blockers of the cysteinyl leukotriene receptor CysLT1 or of 5-lipoxygenase are used as antiasthmatic medications. Leukotrienes may contribute to arterial injury and atherosclerosis by promoting nonspecific leukocyte chemotaxis.

### TABLE 2. Associations of Bronchial Hyperresponsiveness with Risk Factors by Sex

<table>
<thead>
<tr>
<th>Bronchial Hyperresponsiveness (BHR)</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 102)</td>
<td>Yes (n = 21)</td>
<td>$P$</td>
<td>No (n = 77)</td>
<td>Yes (n = 55)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>$45.3 \pm 7.4^*$</td>
<td>$45.2 \pm 7.4$</td>
<td>0.9</td>
<td>$43.5 \pm 7.4$</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>$24.8 \pm 3.0$</td>
<td>$24.0 \pm 3.1$</td>
<td>0.3</td>
<td>$23.0 \pm 3.7$</td>
</tr>
<tr>
<td>Smoking habits, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smokers</td>
<td>44.1</td>
<td>23.8</td>
<td></td>
<td>45.5</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>24.5</td>
<td>33.3</td>
<td></td>
<td>24.7</td>
</tr>
<tr>
<td>Current smokers</td>
<td>31.4</td>
<td>42.9</td>
<td></td>
<td>29.9</td>
</tr>
<tr>
<td>Vigorous exercise, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>29.7</td>
<td>47.6</td>
<td></td>
<td>35.1</td>
</tr>
<tr>
<td>Up to 1 h/wk</td>
<td>29.7</td>
<td>33.3</td>
<td></td>
<td>36.4</td>
</tr>
<tr>
<td>$&gt; 1$ h/wk</td>
<td>40.6</td>
<td>19.1</td>
<td></td>
<td>28.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>$125.3 \pm 12.9$</td>
<td>$126.9 \pm 14.9$</td>
<td>0.6</td>
<td>$114.7 \pm 15.1$</td>
</tr>
<tr>
<td>Hypertensive medication, %</td>
<td>11.8</td>
<td>14.3</td>
<td>0.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>3.9</td>
<td>4.8</td>
<td>0.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>23.5</td>
<td>28.6</td>
<td>0.6</td>
<td>23.4</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>$2.0 \pm 2.6$</td>
<td>$2.6 \pm 2.5$</td>
<td>0.1$\dagger$</td>
<td>$1.2 \pm 2.1$</td>
</tr>
<tr>
<td>Asthma, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.9</td>
<td>28.6</td>
<td>&lt; 0.001</td>
<td>9.1</td>
<td>23.6</td>
</tr>
<tr>
<td>FEV$_1$, % pred (%)</td>
<td>$107.2 \pm 14.7$</td>
<td>$99.9 \pm 12.7$</td>
<td>0.04</td>
<td>$106.6 \pm 12.9$</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>84.8 $\pm$ 6.3</td>
<td>81.3 $\pm$ 6.5</td>
<td>0.02</td>
<td>85.5 $\pm$ 5.8</td>
</tr>
<tr>
<td>CCA-IMT (mm)</td>
<td>$0.62 \pm 0.09$</td>
<td>$0.68 \pm 0.10$</td>
<td>0.002</td>
<td>$0.61 \pm 0.09$</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; FEV$_1$, forced expiratory volume increase second; FVC, forced vital capacity; BHR, bronchial hyperresponsiveness; CCA-IMT, common carotid intima-media thickness.

*Mean $\pm$ SD.

$\dagger$Based on log-transformed values.

### TABLE 3. Multivariate Analysis of Bronchial Hyperresponsiveness with Risk Factors in Men (Stepwise Logistic Regression Model)

<table>
<thead>
<tr>
<th>Bronchial Hyperresponsiveness (BHR)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma, %</td>
<td>6.2</td>
<td>1.3–28.9</td>
<td>0.01</td>
</tr>
<tr>
<td>CCA-IMT (per 0.10-mm increase$\dagger$)</td>
<td>2.1</td>
<td>1.1–4.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking habits*, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smokers</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>2.7</td>
<td>0.6–12.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Current smokers</td>
<td>2.2</td>
<td>0.5–8.9</td>
<td>0.27</td>
</tr>
</tbody>
</table>

BHR indicates bronchial hyperresponsiveness; CCA-IMT, common carotid intima-media thickness.

*Smoking habits variables were forced into the model.

$\dagger$Approximately 1 SD.

### TABLE 4. Means of Common Carotid Intima-Media Thickness ($\pm$SD) According to Bronchial Hyperresponsiveness in Nonasthmatic Groups and in Smoking Habits Groups (Analysis Limited to Men)

<table>
<thead>
<tr>
<th>Bronchial Hyperresponsiveness (BHR)</th>
<th>No</th>
<th>Yes</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA-IMT, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In nonasthmatics (n = 112)</td>
<td>$0.62 \pm 0.09$</td>
<td>$0.68 \pm 0.10$</td>
<td>0.02</td>
</tr>
<tr>
<td>In never-smokers (n = 50)</td>
<td>$0.59 \pm 0.08$</td>
<td>$0.64 \pm 0.10$</td>
<td>0.07</td>
</tr>
<tr>
<td>In ex-smokers (n = 32)</td>
<td>$0.66 \pm 0.09$</td>
<td>$0.68 \pm 0.10$</td>
<td>0.75</td>
</tr>
<tr>
<td>In current smokers (n = 41)</td>
<td>$0.64 \pm 0.11$</td>
<td>$0.71 \pm 0.10$</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CCA-IMT indicates common carotid intima-media thickness.
motaxis and by increasing vascular permeability. In a recent study, it has been shown that variant 5-lipoxygenase genotypes were associated with common carotid IMT in 470 healthy middle-aged women and men. However, this result, which is of particular interest, should be confirmed by other studies, and the potential role of leukotrienes in atherosclerosis merits further investigations.

Another plausible explanation is that bronchial responsiveness and arterial structure are dependent, in part, on the same systemic histopathological and physiopathological processes. This fact, if true, would lead to the observation of a parallelism between BHR and arterial thickening. Thickening changes in the arterial wall include smooth muscle cell proliferation and hypertrophy, and deposition of lipid and accumulation of collagen, elastin, and proteoglycans. Structural changes (airway remodeling) are seen in the asthmatic lung. These changes include hypertrophy of bronchial smooth muscle, transformation of fibroblasts to myofibroblasts, and deposition of subepithelial collagen.

Another explanation is that the observed association between BHR and CCA-IMT could be because of the relation of confounding factors, especially smoking habits, with both alterations. To test this hypothesis, analyses were conducted taking into account major conventional cardiovascular risk factors. Main findings were the apparent independent association of BHR with CCA-IMT in men. Although the association between CCA-IMT and BHR seems to be more pronounced in current smokers, CCA-IMT was higher in subjects with BHR in all smoking habits groups. Despite our efforts to take into account the potential risk factors in the statistical analyses, residual effects of them and the effects of unknown or, to a lesser extent, unmeasured factors could not be entirely ruled out.

In our study conducted in middle-aged subjects, the association between BHR and CCA-IMT was observed only in men. This differential association is not surprising. Women have relatively low rates of cardiovascular morbidity before menopause, and cardiovascular risk factors are less frequent. CCA-IMT mean was lower in women compared with men (Table 1), in agreement with the results of previous studies, and CCA-IMT might be less sensitive to cardiovascular risk factors (other than blood pressure and hypertension) in middle-aged women than in men. However, higher prevalence of BHR was reported in women in our study and in many others. Specific factors such as sexual hormones and more susceptibility of women to various irritants might be involved in bronchial responsiveness in women. This suggests that BHR in women might be a more heterogeneous condition, leading to the dilution of its eventual association with carotid thickening. The relatively small number of subjects (and the potential lack of adequate statistical power) may also explain in part the differential association of CCA-IMT with BHR in men and women. However, bronchial responsiveness to methacholine is an invasive test that should be performed in France at the hospital level and therefore cannot be performed in large-scale population-based studies.

Thickening of the intima-media at the common carotid should not be only considered as a marker of generalized atherosclerosis. Its pathophysiological significance with regard to the atherosclerotic process is questionable. First, the interpretation of results provided by ongoing studies is largely dependent on the methodology used to assess the intima-media thickness, especially on the site of measurement and the inclusion or not of atherosclerotic plaques in the measurement interval. Second, because of the inability of B-mode ultrasonography to differentiate the intimal from the medial layer, the anatomic structure involved in the arterial wall thickening cannot be determined. Third, IMT less than certain levels may not reflect atherosclerosis, but may merely be an adaptive intimal thickening to physiological and hemodynamic variations in shear and tensile forces along the length of arteries. Fourth, traditional atherosclerotic risk factors explain very modest variations of IMT in contrast to the greater variations explained by these factors of other phenotypes of confirmed atherosclerosis such as burden of carotid plaque area.

One limitation of the present study is its cross-sectional study design. However, cross-sectional findings for carotid IMT are generally consistent with what is observed longitudinally. Nevertheless, we cannot discount the possibility that genetic or other constitutional factors may have influenced the present cross-sectional findings. The cross-sectional nature could not also indicate the direction and time-dependent relationships of BHR with arterial thickening. B-mode ultrasound is a noninvasive technique that can directly visualize and assess the wall thickness on several arterial segments of the carotids. However, there are large variations in IMT according to the arterial site. The internal carotid artery and the bifurcation show greater IMT and more pronounced right skewness than the common carotid artery. However, assessing and quantification of the IMT in the internal carotid artery and the bifurcation are more difficult for various technical and methodological reasons (tortuosity, proximity to the mandible, reproducibility, etc). Good-quality images of the far wall of the straight part of the CCA are easy to obtain and IMT can be reliably measured in nearly all subjects. Our results were obtained from an observational population-based study. The interrelationships between the cardiovascular and respiratory alterations should be complemented by the use of other research techniques and methods.

Strengths of the study, however, were its single-center nature, the accurate assessment of IMT, and the quality of the data collected in the European Community Respiratory Health Survey. The factors we found to be associated with IMT and BHR were reported to be so in numerous other studies. In conclusion, our results suggest that bronchial hyperresponsiveness was independently associated with carotid arterial wall thickness. The nature of these associations remains unclear and merits further investigations.

Acknowledgments

The authors thank the Center of Clinical Investigations (CIC) of Bichat Teaching Hospital for its collaboration.

References


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Arterioscler Thromb Vasc Biol. 2004;24:1098-1103; originally published online April 8, 2004; doi: 10.1161/01.ATV.0000128128.65312.05

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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