Association Between Peak Expiratory Flow and the Development of Carotid Atherosclerotic Plaques

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Background: Numerous population-based studies have suggested that impaired lung function is associated with subsequent coronary heart disease–related mortality and cardiovascular disease–related mortality. The relative contribution of atherosclerosis in these associations is unknown.

Objective: To examine the association of peak expiratory flow (PEF) with the occurrence during 4 years of atherosclerotic plaques in the extracranial carotid arteries in a sample of 656 subjects (aged 59-71 years) free of coronary heart disease and stroke at baseline.

Methods: Peak expiratory flow was measured at the baseline examination. Peak expiratory flow values relative to the predicted values (relative PEF values) were calculated, predicted values being obtained from previously published sex-specific regression equations of PEF on age and height. A carotid B-mode ultrasonographic examination was performed at baseline and 2 and 4 years later. The occurrence of carotid plaques during follow-up was defined as the appearance of 1 plaque (or more) in previously normal carotid segments and/or the appearance of new plaques in the carotid segments that previously had plaques.

Results: The proportion of subjects who experienced an occurrence of carotid atherosclerotic plaques during follow-up was 16.8% (110/656). The unadjusted odds ratios from the highest to the lowest quintiles of relative PEF values were 1.00, 1.07 (95% confidence interval [CI], 0.69-2.79), 1.08 (95% CI, 0.52-2.24), 1.38 (95% CI, 0.69-2.79), and 3.07 (95% CI, 1.62-5.85) (P<.001 for trend).

Adjustment for major known cardiovascular risk factors did not markedly change the results, and the multivariate-adjusted odds ratio of carotid plaque occurrence in subjects with the lowest quintile of PEF compared with those with the highest quintile remained highly significant (odds ratio, 2.84; 95% CI, 1.45-5.71) (P=.002). Particularly in all smoking categories, carotid plaque occurrence was higher in subjects with the lowest relative PEF values. In never smokers, the multivariate-adjusted odds ratio of carotid plaque occurrence in subjects with the lowest quintile of PEF compared with those with the highest quintile was 2.80 (95% CI, 1.14-6.88).

Conclusions: Reduced lung function predicts the development of carotid atherosclerosis in elderly subjects. The nature of these associations remains largely unknown and merits further investigations. Nevertheless, assessment of lung function, which is simple and inexpensive, could help identify a population at high risk of atherosclerosis development and coronary heart disease.

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Established cardiovascular risk factors, such as advancing age, male sex, smoking, hypertension, and hypercholesterolemia, do not fully explain the risk of coronary heart diseases (CHDs) in the population. Other unrecognized factors could also contribute to the risk. Numerous prospective studies have suggested that impaired lung function is independently associated with subsequent myocardial infarction, cardiovascular disease– and CHD-related mortality, and all-cause mortality. However, the physiopathological mechanisms underlying these associations are not known and the relative contribution of atherosclerosis to the subsequent CHD events in subjects with reduced lung function remains speculative.

Atherosclerosis is obviously the main underlying pathologic feature of ischemic cardiovascular diseases. Until recently, direct assessment of atherosclerosis was principally restricted to autopsy and angiographic studies that were conducted in highly selected populations and in subjects with advanced atherosclerosis. These facts could explain, at least in part, the lack of population-based studies investigating possibly more-specific relationships of lung function with atherosclerosis development.
SUBJECTS AND METHODS

Details of the Etude sur le Vieillissement Arteriel study have been reported previously. The initial study population was composed of 1389 volunteers, aged between 59 and 71 years, who were recruited from the electoral rolls of Nantes, France. The study protocol was approved by the Comite d’Ethique du Centre Hospitalier Universitaire du Kremlin-Bicetre, and written informed consent was obtained from all participants. After the baseline visit, which took place in the morning between June 3, 1991, and July 2, 1993, subjects were invited to participate in 2- and 4-year follow-up examinations.

MEDICAL HISTORY AND STANDARD BIOLOGICAL PROCEDURES

Medical information, obtained at the baseline examination by a standardized questionnaire, included demographic background, education, occupation, medical history, drug use, and personal habits, such as cigarette and alcohol consumption. In addition to the 6 specified common diseases (myocardial infarction, angina, stroke, hypercholesterolemia, hypertension, and diabetes), each subject was asked whether he or she had ever had an asthma attack or had experienced other chronic medical conditions such as chronic bronchitis. “Respiratory diseases” used in the analysis regrouped subjects with a self-reported asthma attack or a history of chronic bronchitis.

The smoking habits’ questionnaire included detailed information on whether the subject had ever smoked cigarettes, the duration of cigarette smoking, the average daily number of cigarettes smoked, and the age at which smoking ceased (if applicable). Subjects were classified as never, former, or current smokers. For ever smokers, cigarette pack-years were also calculated by multiplying the number of years of smoking by the average number of cigarettes smoked per day, divided by 20. Two independent measurements of systolic and diastolic blood pressure were made with a digital electronic tensiometer (model SP9; Spengler, Frankfurt, Germany) after a 10-minute rest, and the mean value was used in the analysis. Subjects with a systolic blood pressure of 160 mm Hg or higher, those with a diastolic blood pressure of 95 mm Hg or higher, and/or those who were using antihypertensive drugs were considered to have hypertension. Hypercholesterolemia was defined as a total cholesterol level of 6.2 mmol/L or higher (≥240 mg/dL) or use of lipid-lowering drugs. Subjects who reported a medical history of diabetes, use of antidiabetic drugs, or a fasting plasma glucose level of 7.0 mmol/L or higher (≥126 mg/dL) were considered to have diabetes. The body mass index was computed as weight in kilograms divided by the square of height in meters.

PEF TEST

The PEF test was performed only at the baseline visit. Measurements of PEF were taken between 9 AM and 11 AM, before the ultrasonographic examination, by trained research assistants using the Mini Wright peak flowmeter. Subjects were asked to take a deep breath and blow as hard and as fast as they could into the instrument while they were standing. The cooperation of subjects in performing the PEF test was recorded (good or bad). Three measurements of PEF were taken. The coefficient of variation for PEF measurements was 8.9%. The maximum of the 3 measurements was used for analysis. The highest measurement was within 10% of the second highest for 95.1% of the subjects and within 15% for 98.4% of them.

The same device was used during the entire study period (14 months). This device might have lost accuracy after repeated use. Peak expiratory flow values were thus split according to examination periods (each 1 month), and no measurement drift was detected over time.

ULTRASONOGRAPHY

Ultrasonographic examinations at baseline and at the 2- and 4-year follow-up visits were performed using an ultrasonograph (model SSD-650; Aloka, Tokyo, Japan), with a transducer frequency of 7.5 MHz. Acquisition, processing, and storage of B-mode images were computer-assisted, with software specially designed for longitudinal studies (EUREQUA; TSI, Meudon, France).

Details of the protocol have been described elsewhere. At each examination, it involved scanning of the common carotid arteries (CCAs), of the carotid bifurcations, and of the origin (first 2 cm) of the internal carotid arteries. At the examination, the intima-media thickness (IMT) was measured on the far wall of the middle and distal CCA as the distance between the lumen-intima interface and the media-adventitia interface using an automated edge detection algorithm. One transversal and 2 longitudinal measurements of IMT (at a site free of any discrete plaques) were completed on the right and left CCAs; the mean of the 4 right and left longitudinal CCA IMT measurements was used in the analysis.

High-resolution B-mode ultrasonography is a noninvasive, valid, and reproducible method of directly visualizing and assessing carotid atherosclerosis, and it is used in many population-based studies. Angiographic and ultrasonographic studies have found that carotid atherosclerotic plaques are associated with the presence of other localizations of atherosclerosis and can be used as a marker of general atherosclerosis.

In the present report, based on the longitudinal data of the Etude sur le Vieillissement Artériel study, we assessed the associations of peak expiratory flow (PEF) measured at the first examination and carotid plaque occurrence during the 4-year follow-up of a population of 656 subjects aged between 59 and 71 years.

The associations of baseline population characteristics and baseline ultrasonographic examination findings with quintiles of relative PEF values are shown in Table 1. Subjects with the lowest relative PEF values (quintile 1) had a higher mean CCA IMT. They also tended to be older and to have a higher prevalence of carotid plaques, but the differences did not reach statistical significance. Alcohol con-
The near and far walls of all arterial segments (ie, CCA or bifurcation-origin of the internal carotid artery) were scanned longitudinally and transversely to assess 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 or greater.

The same 4 ultrasonographers performed the ultrasonographic examinations at baseline and at the 2- and 4-year follow-up visits. For each subject, we attempted to have the 2- and 4-year follow-up examinations performed by the ultrasonographer who had performed the baseline examination. This was the case for 76% of the subjects. The reproducibility of the scanning and reading procedures has been reported elsewhere. Briefly, to study the reproducibility of plaque detection, 75 baseline examination images of carotid bifurcation–internal carotid artery (52 longitudinal and 23 transversal images) with plaques, as defined by the ultrasonographers, and 80 images of carotid bifurcation–internal carotid artery (44 longitudinal and 36 transversal images) without plaques were randomly chosen and sent to a single expert ultrasonographer (P.-J.T.) to assess blindly the presence or absence of plaques. The $k$ coefficients for agreement between the 2 readings were 0.86 for longitudinal views and 0.91 for transverse views. To study the reproducibility of CCA IMT measurements, a rereading study was made on a random subsamples of images of CCAs ($n=81$). The mean absolute difference and the correlation coefficient between repeated readings of CCA IMT were 0.06 mm and 0.82, respectively.24

**DATA ANALYSIS**

The occurrence of carotid plaques during follow-up (at the 2- and/or the 4-year examination) was defined as the occurrence of 1 plaque (or more) in previously normal segments and/or the occurrence of new plaques in segments that previously had plaques.

For each subject, the PEF relative to the predicted value (relative PEF value) was calculated, predicted values being obtained from previously published sex-specific regression equations of PEF on age and height.23 The means of PEF in the whole population, in men, and in women were 410 mL/min (SD, 100 mL/min), 496 mL/min (SD, 92 mL/min), and 397 mL/min (SD, 62 mL/min), respectively. The means of relative PEF values in the whole population, in men, and in women were 86.6% (SD, 14.9%), 88.9% (SD, 15.9%), and 85.1% (SD, 14.1%), respectively. The relative PEF values were divided into 5 categories according to quintiles of sex-specific values. The cutoff points of the 20th, 40th, 60th, and 80th percentiles were 78.1%, 88.2%, 93.0%, and 100.0%, respectively, for men and 76.0%, 83.1%, 89.6%, and 96.4%, respectively, for women.

Standard procedures from SAS statistical software (SAS Institute Inc, Cary, NC) were used for univariate and multivariate analyses. Associations of the 5 categories (quintiles) of relative PEF values with 4-year carotid plaque occurrence and baseline cardiovascular risk factors were assessed by $\chi^2$ tests and analysis of variance. Baseline cardiovascular risk factors considered in the analysis were age, sex, smoking habits, alcohol consumption, body mass index, hypertension, hypercholesterolemia, diabetes, CCA IMT, and the presence of carotid plaques at baseline. For multivariate analyses, we used dichotomic multiple logistic regression models with plaque occurrence (yes or no) as the dependent variable and categories of PEF and baseline cardiovascular risk factors as independent variables. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of plaque occurrence according to quintiles of relative PEF values, independent of baseline cardiovascular risk factors, were estimated by a multivariate logistic regression model, using the group of subjects with the highest relative PEF values (quintile 5) as the reference.

The PEF protocol was implemented in the Etude sur le Vieillissement Arteriel study from the 11th month on (up to the end of the baseline examination, 14 months). For this reason, the PEF test was not performed in the first 604 subjects. The subjects who underwent the PEF test were slightly older than those who were recruited before implementation of the PEF protocol (65.2 vs 64.8 years; $P=.02$). No statistically significant differences were observed for the other baseline cardiovascular risk factors, the presence of carotid plaques at baseline, or 4-year carotid plaque occurrence. Furthermore, 57 subjects who reported at the baseline examination a history of angina, myocardial infarction, or stroke were excluded from the analysis. Of the 728 remaining subjects, 656 (90.1%) had complete data on baseline PEF and cardiovascular risk factors and underwent at least 1 follow-up B-mode ultrasonographic examination (389 underwent 2 and 67 underwent only 1). At baseline, there were no statistically significant differences between subjects who participated and those who did not in the 4-year follow-up survey for PEF, cardiovascular risk factors, and ultrasonographic examination findings.

After adjustment for age, sex, body mass index, hypertension, hypercholesterolemia, diabetes, smoking habits, alcohol consumption, CCA IMT, and presence of carotid plaques at baseline, the ORs did not markedly change and the multivariate-adjusted OR of carotid plaque occurrence in subjects with the lowest quintile of PEF compared with those with the highest quintile remained highly significant ($P<.001$). In the multivariate analyses, the substitution of cigarette pack-years (as a continuous variable, with never smokers assigned the value of 0) for smoking habits categories did not alter the results. In this model, the multivariate-adjusted OR of carotid plaque occurrence...
occurrence in subjects with the lowest quintile of relative PEF values compared with those with the highest quintile was 2.92 (95% CI, 1.51-5.86).

SUBGROUP ANALYSES

Analyses stratified according to baseline cardiovascular risk factors are presented in Table 3. In all categories of smoking habits, carotid plaque occurrence was higher in subjects with the lowest relative PEF values. In all other subgroups, carotid plaque occurrence was also higher in subjects with the lowest relative PEF values, although the association was weaker among hypertensive subjects.

A further multivariate analysis was performed in the group of never smokers (n=406) (Table 4). The multivariate-adjusted OR of carotid plaque occurrence in subjects with the lowest quintile of PEF compared with those with the highest quintile was 2.80. In never smokers without carotid plaques at baseline, this association was even slightly stronger (Table 4).

The exclusion of subjects who reported respiratory diseases at baseline (n=50) did not alter the results. The multivariate-adjusted ORs from the highest to the lowest PEF quintiles were 1.00, 1.09 (95% CI, 0.50-2.38), 1.21 (95% CI, 0.56-2.67), 1.39 (95% CI, 0.64-3.02), and 2.73 (95% CI, 1.32-5.63) (P<.001 for trend). The association of PEF categories with carotid plaque occurrence was also observed after the exclusion of subjects who had respiratory diseases, hypertension, hypercholesterolemia, and/or diabetes (data not shown).

When subjects with nonrepeatable measurements of PEF (>10% difference between the 2 highest values [n=32]) were excluded, the multivariate-adjusted ORs from the highest to the lowest PEF quintiles were 1.00, 1.14 (95% CI, 0.52-2.50), 1.40 (95% CI, 0.64-3.07), 1.56 (95% CI, 0.71-3.42), and 3.11 (95% CI, 1.42-6.81) (P<.001 for trend). The exclusion of subjects with apparent poor cooperation in performing the PEF test (n=25) did not modify the results (data not shown). We also divided our population into 3 groups according to examination periods (0-5, 6-10, and >10 months); the amplitude and mean of PEF measurements were not different in the 3 groups and the association of PEF with carotid occurrence was observed within each of them (data not shown).

FURTHER ANALYSES

Instead of quintiles, the relative PEF values were also divided into 2 categories usually used in asthma management and prevention26: greater than 80% (n=474) and 80% or less (n=182). The unadjusted ORs of plaque occurrence in the 2 groups were 1.00, 1.14 (95% CI, 0.52-2.50), 1.40 (95% CI, 0.64-3.07), 1.56 (95% CI, 0.71-3.42), and 3.11 (95% CI, 1.42-6.81) (P<.001 for trend). The exclusion of subjects who had respiratory diseases, hypertension, hypercholesterolemia, and/or diabetes (data not shown).

When defined, a posteriori, the carotid plaques as localized protrusions of the vessel wall into the lumen were categorized into 2 groups: localized protrusions (n=254) and nonlocalized protrusions (n=148). The ORs of plaque occurrence in the 2 groups were 1.00, 1.09 (95% CI, 0.50-2.38), 1.21 (95% CI, 0.56-2.67), 1.39 (95% CI, 0.64-3.02), and 2.73 (95% CI, 1.32-5.63) (P<.001 for trend). The exclusion of subjects with apparent poor cooperation in performing the PEF test (n=25) did not modify the results (data not shown). We also divided our population into 3 groups according to examination periods (0-5, 6-10, and >10 months); the amplitude and mean of PEF measurements were not different in the 3 groups and the association of PEF with carotid occurrence was observed within each of them (data not shown).
men with a thickness of 1.5 mm or greater instead of 1 mm or greater (102 subjects had a plaque thickness of $\geq 1.5$ mm), the multivariate-adjusted OR of carotid plaque occurrence in subjects with the lowest quintile of PEF compared with those with the highest quintile was 2.98 (95% CI, 1.48-5.47).

### Table 2. Association of Categories of Relative Peak Expiratory Flow With 4-Year Carotid Plaque Occurrence*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Peak Expiratory Flow Quintile†</th>
<th>Unadjusted OR (95% CI)</th>
<th>Sex and age adjusted OR (95% CI)</th>
<th>Multivariate adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 131)</td>
<td>2 (n = 131)</td>
<td>3 (n = 131)</td>
<td>4 (n = 132)</td>
</tr>
<tr>
<td>Carotid plaque occurrence, %</td>
<td>29.8</td>
<td>16.0</td>
<td>13.0</td>
<td>12.9</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex and age adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate adjusted§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P = .001 for trend for all analyses. OR indicates odds ratio; CI, confidence interval.
†Quintile 1 indicates the lowest relative peak expiratory flow values; 5, the highest values.
‡Referent.
§Adjusted for age, sex, body mass index, hypertension, hypercholesterolemia, diabetes, smoking habits, alcohol consumption, common carotid artery intima-media thickness, and the presence of carotid plaques at baseline (when applicable).

### Table 3. Distribution of 4-Year Carotid Plaque Occurrence According to Categories of Relative Peak Expiratory Flow Values Within Categories of Baseline Cardiovascular Risk Factors*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Peak Expiratory Flow Quintile†</th>
<th>P For Difference</th>
<th>P For Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2-4</td>
<td>5</td>
</tr>
<tr>
<td>Sex</td>
<td>38.0</td>
<td>19.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Men (n = 248)</td>
<td>38.0</td>
<td>19.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Women (n = 408)</td>
<td>24.7</td>
<td>10.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Age, y</td>
<td>.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 65) y (n = 341)</td>
<td>23.7</td>
<td>12.3</td>
<td>5.6</td>
</tr>
<tr>
<td>&gt; 65 y (n = 315)</td>
<td>54.7</td>
<td>16.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker (n = 406)</td>
<td>24.7</td>
<td>10.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Ex-smoker (n = 195)</td>
<td>38.9</td>
<td>18.6</td>
<td>16.7</td>
</tr>
<tr>
<td>Current smoker (n = 55)</td>
<td>36.4</td>
<td>22.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Alcohol consumption, mL/d</td>
<td>.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n = 210)</td>
<td>30.6</td>
<td>12.0</td>
<td>7.0</td>
</tr>
<tr>
<td>1-20 (n = 288)</td>
<td>25.0</td>
<td>12.6</td>
<td>10.6</td>
</tr>
<tr>
<td>&gt; 20 (n = 158)</td>
<td>35.3</td>
<td>20.7</td>
<td>21.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 470)</td>
<td>31.9</td>
<td>10.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Yes (n = 186)</td>
<td>25.0</td>
<td>21.8</td>
<td>19.4</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 197)</td>
<td>24.3</td>
<td>11.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Yes (n = 459)</td>
<td>31.9</td>
<td>15.2</td>
<td>14.4</td>
</tr>
<tr>
<td>Baseline CCA IMT, mm</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.75 (n = 944)</td>
<td>26.2</td>
<td>12.7</td>
<td>10.3</td>
</tr>
<tr>
<td>(\geq 0.75) (n = 112)</td>
<td>45.8</td>
<td>22.6</td>
<td>20.4</td>
</tr>
<tr>
<td>Baseline carotid plaque</td>
<td>.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 517)</td>
<td>24.5</td>
<td>9.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Yes (n = 139)</td>
<td>45.5</td>
<td>32.6</td>
<td>30.8</td>
</tr>
</tbody>
</table>

*Data are given as the percentage of subjects with 4-year carotid plaque occurrence unless otherwise indicated. CCA IMT indicates common carotid artery intima-media thickness.
†Quintile 1 indicates the lowest relative peak expiratory flow values; 5, the highest values.

In this 4-year longitudinal observational study performed in a large sample of relatively older subjects, low values of PEF relative to the predicted ones were associated with increased carotid plaque occurrence, even after adjustments for conventional cardiovascular risk factors. In a recent article on the Etude sur le Vieillissement Artériel study, it was reported that age, sex, smoking habits, hypertension, hypercholesterolemia, CCA IMT, and the presence of carotid plaques at baseline were also related to carotid plaque occurrence.

The association of PEF with carotid plaque occurrence was observed in several important subgroups, including men, women, and never smokers. The magni-
Reduced forced expiratory volume in 1 second, in subjects aged between 56 and 77 years, was associated with an increased CCA IMT and a higher prevalence of carotid plaques; the latter difference was not statistically significant. Our cross-sectional findings corroborated with these results (Table 1).

Several explanations could be formulated to explain the observed association of PEF with carotid plaque occurrence. The association could be due to the relation of confounding factors, especially smoking habits, with lung function and atherosclerosis. To test this hypothesis, analyses were conducted adjusting and stratifying for major conventional cardiovascular risk factors. The main findings were the apparent independent association of PEF with carotid atherosclerosis in the overall group and the observation in all subgroups of a higher plaque occurrence in subjects with reduced lung function. Furthermore, more than 60% of the subjects were never smokers and results were similar for all smoking categories. Despite our efforts to take into account the major conventional cardiovascular 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. However, the strength of the observed association of PEF with carotid plaque occurrence would make unlikely that these factors could account for more than a small part of the association between PEF and carotid atherosclerosis.

Vventilatory lung function, especially in elderly subjects, could be regarded as a measurement of the overall health status. Assessment of pulmonary function could be also dependent on the participant’s effort, willingness, and ability to give maximal performance. Reduced lung function may then be a sign or a symptom of other disease processes that could ultimately lead to atherosclerosis. However, our results were based on subjects free of CHD and stroke, and when we further excluded in the analysis subjects with chronic cardiovascular and respiratory conditions and those with apparent poor cooperation in performing the PEF test, the results were not altered and were similar to those observed in the whole population.

Another explanation of the observed association in our study is that reduced lung function and atherosclerosis are dependent, at least in part, on the same pathological processes, and decreased lung function might be then an earlier response to these processes than plaque formation. In regard to this hypothesis, inflammatory mechanisms may be of particular interest. On the one hand, poor lung function could result from increased airway responsiveness and allergy; both of them are prototypes of inflammatory diseases. On the other hand, an increasing body of evidence supports the hypothesis that atherosclerosis may be an inflammatory disease that shares many similarities with other inflammatory or autoimmune diseases, such as rheumatoid arthritis and idiopathic pulmonary fibrosis.

Another explanation of our results is that impaired pulmonary function itself may contribute to the causation of atherosclerosis. However, the mechanisms by which a low value of PEF confers an increased risk of plaque occurrence are not clear. Reduced lung function may result in chronic hypoxemia, and the imbalance between the demand and the supply of oxygen in the arterial wall has been suggested to be a key factor for the development of atherosclerotic lesions.

Our population consisted of volunteers with a relatively low prevalence of CHD who agreed to undergo follow-up examinations. Taking into account the high rate of participation in the follow-up survey (90%), the potential effects, on the observed associations, of selective survival and self-selection biases are probably small but could not be ruled out. The weaker association of PEF with carotid atherosclerosis observed in hypertensive subjects should be interpreted with caution since we performed, in this part of the analysis, multiple statistical comparisons and a chance finding could not be excluded.

Most of the studies that have suggested that lung function predicted overall mortality and mortality from cardiovascular diseases used forced vital capacity or forced expiratory volume in 1 second as the measure of lung function. Although PEF is widely considered and used as an indirect index of airway caliber, it might be a less sensitive measure of lung function than spirometric measures. However, the strong correlation between PEF and forced vital capacity and forced expiratory volume...
in 1 second is well-known\textsuperscript{1,60} and, as expected, reduced PEF in our study was associated with respiratory manifestations and smoking habits. Recent international guidelines\textsuperscript{31,61} support the use of PEF measurements for clinical and epidemiological purposes. Furthermore, several studies\textsuperscript{32,33} have reported an independent association of PEF with cardiovascular disease and death.

Peak expiratory flow measurements were obtained by the Mini Wright peak flowmeter, which is simple and easy to use in a population survey. We do not think that the device used lost accuracy during the study period. No PEF measurement drift was detected over time, and similar patterns of association of PEF with carotid occurrence were observed according to examination periods. Most established designs of portable PEF meters hold their calibration for longer than 3 years,\textsuperscript{62} and the Mini Wright PEF meters aged up to 14 years can give readings that are as good as new meters.\textsuperscript{63}

The reproducibility of the instantaneous measures of PEF was in agreement with the results of other studies,\textsuperscript{64,65} and the number of subjects with nonrepeatable measurements was low. Although the exclusion of these subjects yielded similar findings to those reported in this article, we preferred to present the results obtained from the whole population. In fact, several studies\textsuperscript{64,65} have shown that the application of rigid repeatability criteria for lung function tests may bias epidemiological findings by the exclusion of subjects with high risks of accelerated loss of lung function and mortality.

In accordance with other investigations,\textsuperscript{66,67} a definition of plaque as a localized protrusion of the vessel wall into the lumen with a thickness of 1 mm or greater was used in our protocol. One could argue that this value is relatively low and that a minor wall irregularity may be mistakenly considered as a plaque. However, the results of the reproducibility study, for the presence (or the absence) of plaque, were satisfactory, and a reanalysis of our data using a more restrictive definition of plaque thickness (\(\geq 1.5\) mm) also showed a strong association between baseline PEF and the occurrence of carotid plaques.

In conclusion, our results suggest that reduced lung function predicts the 4-year occurrence of carotid atherosclerotic plaques in elderly subjects. The nature of these associations remains unknown and merits further investigations. The increasing prevalence of asthma and chronic obstructive pulmonary disease worldwide,\textsuperscript{68-69} should push investigations. The increasing prevalence of asthma and chronic obstructive pulmonary disease worldwide\textsuperscript{48,49} should push healthcare providers to screen for such diseases in the elderly subjects. The nature of these associations remains unknown and merits further investigations.

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