Difference in Carotid Artery Wall Structure Between Swedish and French Men at Low and High Coronary Risk

Nicolas Denarié, MD; Alain Simon, MD; Gilles Chironi, MD; Jérôme Gariepy, MD; Lars Kumlin, MD; Marc Massonneau, MD; Catherine Lanoiselée, MD; Lennart Dimberg, MD, PhD; Jaime Levenson, MD

Background and Purpose—We attempted to detect a group-specific north-south difference in carotid artery intima-media thickness (IMT), a marker of subsequent cardiovascular complication, by means of a case (high risk)–control (low risk) study in French and Swedish men.

Methods—The selection of high-risk and low-risk subjects was performed within the lower and upper percentiles of the Framingham risk distribution of 2 samples of 1000 white, male auto workers (45 to 50 years of age) in France (Renault) and Sweden (Volvo). In total, 299 men at low risk (79 French, 76 Swedish) and high risk (61 French, 83 Swedish), free from sustained hypertension, definite hypercholesterolemia, and cardiovascular disease, were included. Both common carotid arteries, by ultrasonography and central off-line computerized analysis, provided measurements of far wall media thickness, lumen diameter, and cross-sectional area IMT (CSA-IMT).

Results—As compared with low-risk status, high-risk status was associated with higher IMT (P<0.001), diameter (P<0.01), and CSA-IMT (P<0.001) in French men and higher CSA-IMT (P<0.05) in Swedish men. IMT, diameter, and CSA-IMT were higher in Swedish than in French men in the low-risk group (P<0.001) and in the high-risk group (P<0.01, P<0.001, P<0.001). The multivariate analysis of the whole population showed that IMT, diameter, and CSA-IMT were associated with risk status (P<0.01, P<0.01, P<0.001) and geographic status (P<0.001).

Conclusions—These findings show that the geographic status influences carotid artery structure independent of traditional cardiovascular risk factors and that this may affect the mortality and morbidity gradient between Northern and Southern Europe. (Stroke. 2001;32:1775-1779.)

Key Words: arterial wall ■ carotid arteries ■ geography

Data to explain higher cardiovascular mortality and morbidity rates in Northern than in Southern Europe are scarce. An explanation may be related to geographic difference, either in the burden of traditional cardiovascular risk factors or in the reactivity of arteries to risk factors. To explore these hypotheses, we have designed the Renault Volvo Cœur Study with the objective to compare the cardiovascular risk profile between similar types of auto workers in France (Renault) and in Sweden (Volvo). In a previous cross-sectional analysis, we have shown that the multifactorial risk burden, as estimated with the use of the Framingham index, was not different between French and Swedish groups, therefore excluding a geographic difference in the burden of traditional risk factors. In the present work, we tested the alternative hypothesis of a geographic difference in the arterial reactivity to traditional risk factors by comparing ultrasonographically assessed carotid artery structure, especially intima-media thickness (IMT), at the same level of cardiovascular risk, between French and Swedish samples of the Renault Volvo-Cœur Study.

Subjects and Methods
Two hundred ninety-nine white men, 45 to 50 years, at low and high risk, were selected among auto workers in France (Renault) and in Sweden (Volvo). Exclusive of those with blood pressure >170/100 mm Hg or antihypertensive treatment for ≥3 months, total cholesterol >6.5 mmol/L, or lipid-lowering drug treatment for ≥3 months and cardiovascular disease such coronary artery disease, stroke, or arteriopathy of the lower limbs. Subjects at low risk were chosen within the lower percentile of the distribution of the Framingham risk index (see below for estimation) of 1000 randomly selected subjects in each country to obtain an expected number of 90 individuals by country (see statistical issue). The so-chosen subjects were proposed to undergo ultrasound arterial investigation at the hospital (Broussais Hospital, Paris, France, or Östra Hospital, Goteborg, Sweden). They were classified by type of work into manual or clerical worker. Of these, 79 subjects in France (48% manual workers) and 76 subjects in Sweden (25% manual workers) agreed to undergo hospital investigation after being given detailed information on the protocol (Table 1).

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Subjects at high risk were chosen within the upper percentile of the distribution of the Framingham risk index of the 1000 previously mentioned subjects to obtain an expected number of 90 individuals (see statistical issue). Among these, 61 subjects in France (44% manual workers) and 83 subjects in Sweden (43% manual workers) agreed to undergo arterial investigation at the hospital after being given detailed information (Table 1). The study was approved by local ethics committees in both countries.

Ultrasound Investigation

In each country, all subjects were investigated by the same sonographers trained to the measurements required by the protocol. Carotid ultrasonography was performed with a real-time, B-mode ultrasound imager (Ultrasound 4 in Sweden and Ultramark 9 in France, Advanced Technologies Laboratories), with a 7.5-MHz probe. Longitudinal images of lumen diameter and far-wall IMT of the right and left common carotid arteries, 2 to 3 cm distal to the bifurcation, were performed according to a standardized procedure.

Once the lumen diameter and the two parallel echogenic interfaces (lumen-intimal and medial-adventitial) defining IMT were adequately visualized, the carotid image was frozen in end diastole by ECG R-triggering, transferred to a computer (Apple Macintosh), digitized, and stored on optical disk for off-line central reading.

Central Reading

The same reader, blinded to the risk and geographic status of the patient, performed the analyses of all ultrasound images obtained in both countries by means of an automated computerized program (Ió, IóDP). The program automatically located the two interfaces defining far-wall IMT and calculated their average distance along at least 1 cm of longitudinal length. The program also located the two leading edges of lumen-intimal interfaces of the near and far walls defining the lumen diameter and calculated their distance along the same length as the IMT. The IMT cross-sectional area (CSA-IMT) was calculated from IMT and lumen diameter (D) as π×IMT×(IMT+D). The final values of IMT, diameter, and CSA-IMT considered in the study were the average of left and right measurements.

Risk Factors

Risk factors were evaluated concomitantly with the ultrasound investigation, including body mass index (weight/height²); resting blood pressure (sphygmomanometry); fasting values of total cholesterol, HDL cholesterol after LDL and VLDL precipitation; and blood glucose (enzymatic methods); and current smoking (regular smoking for the previous 3 months irrespective of the amount smoked). The Framingham risk index (percent of coronary event at 10 years) was estimated by entering into the Framingham model equations the following variables: age, male sex, systolic pressure, total to HDL cholesterol ratio, current smoking, and diabetes defined as glycemia ≥7.8 mmol/L, the use of antidiabetic drugs, or both.

Statistical Issues

We targeted a group of 4×90 subjects to reach 4×75 subjects, which, based on our power estimate, would give a 90% chance to show a 10% difference for IMT.

Univariate comparisons of cardiovascular risk factors by risk and geographic status in Table 1 were done with an unpaired t test for continuous variables and by χ² test for qualitative variables. In Table 2, carotid arterial parameters were adjusted for age, work type, and body mass index in the 4 study groups (defined according to risk and geographic status) by using a multivariate linear regression with the arterial parameter as the dependent variable and the type of group (0, 1), age, body mass index, and work type (0, 1) as independent variables. For comparing carotid artery parameters between groups 2 by 2 in Table 2, a multivariate linear regression analysis was used with the arterial parameter as the dependent variable and the type of group (0, 1, 2, 3), age, body mass index, and work type (0, 1) as independent variables. A separate analysis of the whole study population in Table 3 used multivariate linear regressions to assess associations between carotid arterial parameters (dependent variable) and age, the type of work, 0, 1, body mass index, the risk status (0, 1) and the geographic status (0, 1) as independent variables. The distributions of the 3 independent variables (IMT, diameter, CSA-IMT) were analyzed, and the nonstatistical significance of the test for normality (Shapiro-Wilk W test) showed that the distributions were normal.

Results

Table 1 shows that, as expected, high-risk subjects had a higher Framingham risk index than did low-risk subjects in both countries (P<0.001). As compared with low-risk status, high-risk status was associated with (1) higher smoking

Table 1. Cardiovascular Risk Factors by Risk and Geographic Status

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th></th>
<th>High Risk</th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>France (n=79)</td>
<td>Sweden (n=76)</td>
<td>France (n=61)</td>
<td>Sweden (n=83)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.7 (1.7)</td>
<td>49.3 (1.6)†</td>
<td>51.0 (1.7)</td>
<td>49.7 (1.1)†</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Type of work, %</td>
<td>Manual</td>
<td>38 (48)</td>
<td>19 (25)†</td>
<td>27 (44)</td>
<td>36 (43)</td>
</tr>
<tr>
<td></td>
<td>Clerical</td>
<td>41 (52)</td>
<td>57 (75)</td>
<td>34 (56)</td>
<td>47 (57)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3 (2.6)</td>
<td>23.8 (2.6)†</td>
<td>26.5 (3.1)</td>
<td>27.2 (3.7)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>125 (8.2)</td>
<td>121 (10.1)†</td>
<td>133 (15.1)</td>
<td>136 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total-to-HDL cholesterol ratio</td>
<td>3.41 (0.62)</td>
<td>3.34 (0.73)</td>
<td>5.19 (0.97)</td>
<td>5.72 (1.28)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>5.61 (0.59)</td>
<td>4.35 (0.47)†</td>
<td>5.91 (1.11)</td>
<td>4.64 (1.66)†</td>
<td>&lt;0.05 NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>13 (16)</td>
<td>1 (1)†</td>
<td>40 (66)</td>
<td>42 (51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Framingham risk (% at 10 y)</td>
<td>5.5 (2.1)</td>
<td>4.1 (1.5)†</td>
<td>13.7 (5.0)</td>
<td>14.3 (5.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD) or number (n) with percentages (%). Between-group comparisons were done by unpaired t test for continuous variables and by χ² test for qualitative variables.

*Comparison between low and high risk.
†,‡Mean P<0.01, P<0.001 for comparing France with Sweden.
frequency and higher systolic pressure and total to HDL cholesterol ratio in both countries \((P<0.001)\); (2) higher body mass index in France \((P=0.01)\) and in Sweden \((P<0.001)\); (3) higher blood glucose in France \((P<0.05)\); and (4) older age \((P<0.05)\) and higher manual worker frequency \((P=0.01)\) in Sweden. In the high-risk group, the Framingham index and risk factors did not differ between countries, except lower age and blood glucose \((P<0.001)\) in Sweden and higher total to HDL cholesterol ratio \((P<0.01)\) in France. In the low-risk group, lower values of age \((P<0.001)\), manual worker frequency \((P<0.01)\), body mass index \((P<0.001)\), systolic pressure \((P<0.01)\), blood glucose \((P<0.001)\), smoking frequency \((P<0.01)\) and Framingham index \((P<0.01)\) were found in Sweden as compared with France.

Table 2 shows carotid artery parameters by risk and geographic status after adjustment for age, type of work, and body mass index. As compared with low-risk status, high-risk status was associated with higher carotid IMT \((P<0.001)\), higher lumen diameter \((P<0.01)\), and higher CSA-IMT \((P<0.001)\) in France and with higher CSA-IMT \((P<0.05)\) in Sweden. IMT, lumen diameter, and CSA-IMT were higher in Sweden than in France in the low-risk group \((P<0.001)\) and in the high-risk group \((P<0.01, P<0.001, P<0.001)\).

Table 3 shows that in the multivariate analysis of the whole study population, (1) IMT was independently associated with age \((P<0.05)\), body mass index \((P<0.05)\), risk status \((P<0.01)\), and geographic status \((P<0.001)\); (2) lumen diameter was independently associated with body mass index \((P<0.001)\), risk status \((P<0.01)\), and geographic status \((P<0.001)\); (3) CSA-IMT was independently associated with age \((P<0.05)\), body mass index \((P<0.001)\), risk status \((P<0.001)\), and geographic status \((P<0.001)\).

### Discussion

The two main findings are that the carotid artery structure is influenced independently by (1) the burden of traditional cardiovascular risk factors, as estimated with the Framingham index and (2) the geographic status of the subject, which thereby may be considered as a potential risk marker independent of the Framingham risk factors.

Before these findings can be interpreted, some methodologic aspects need to be considered. First, the objective to show a geographic difference needs to control as far as possible for ethnic and genetic factors. We have tried to control for ethnicity by restricting our study to Caucasian subjects, so excluding immigrants from other ethnic origin who are frequent among auto workers. However, the usual method consisting in looking at immigrant populations within the same population to assess the effects of geography would have answered the geography question to a greater degree than the approach in the present work. A second problem is that our subject samples are not representative of the general population in both countries. However, our selection processes were well characterized and so have provided individuals at high and low risk for cardiovascular disease. We have also minimized influences of age and sex by studying men with a narrow range of age from 45 to 50 years. We have taken into account potential bias regarding socioeconomic status assessed by defined the type of work in a dichotomous

### Table 2: Carotid Artery Parameters by Risk and Geographic Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT, mm</td>
<td>0.54 (0.01)</td>
<td>0.60 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
<td>5.76 (0.06)</td>
<td>6.27 (0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSA-IMT, mm²</td>
<td>10.72 (0.26)</td>
<td>12.96 (0.30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 3: Multivariate Analysis of Carotid Artery Parameters on Demographic Risk and Geographic Status in the Whole Study Population

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>IMT</th>
<th>Lumen Diameter</th>
<th>CSA-IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>0.0074 (0.0030)*</td>
<td>0.0224 (0.0189)</td>
<td>0.212 (0.089)*</td>
</tr>
<tr>
<td>Type of work (0, manual; 1, clerical)</td>
<td>0.0021 (0.0047)</td>
<td>−0.0047 (0.0297)</td>
<td>0.022 (0.139)</td>
</tr>
<tr>
<td>Body mass index (continuous)</td>
<td>0.0037 (0.0014)*</td>
<td>0.0430 (0.0093)</td>
<td>0.165 (0.043)†</td>
</tr>
<tr>
<td>Risk status (0, high; 1, low)</td>
<td>0.0156 (0.0049)†</td>
<td>0.0931 (0.0310)†</td>
<td>0.552 (0.144)‡</td>
</tr>
<tr>
<td>Geographic status (0, Sweden; 1, France)</td>
<td>0.0255 (0.0050)‡</td>
<td>0.2280 (0.0316)‡</td>
<td>1.024 (0.148)‡</td>
</tr>
</tbody>
</table>

### Values are slopes (SE).

*†‡Mean \(P<0.05\), \(P<0.01\), \(P<0.001\).

Multivariate linear regression models were used (see Methods).

Distributions of IMT, diameter, and CSA-IMT were not skewed (see Methods).
way (manual or clerical worker). As the percentage of these two categories of workers differed between certain groups, we have performed 2 by 2 comparison of groups by adjusting for type of work. We have also introduced the type of work as an independent variable in the multivariate analyses of carotid artery parameters in the whole population. Unfortunately, we did not have additional information on the socioeconomic status, such as family income, about which questioning of subjects was not possible because of the problem of confidentiality. A third issue is the physiological meaning of the changes measured in the structure of the distal common carotid artery free from atherosclerosis. These changes are not measures of atherosclerotic plaque and represent rather adaptive changes of the arterial wall to shear and/or tensile stresses. Moreover, previous studies have shown that IMT is a picture of integrated effects of traditional risk factors such as hypertension but is not necessarily related to embolic disease. Therefore, the relation of IMT to clinical complications such as stroke is not clear, although several prospective studies have shown that increased carotid IMT was a powerful predictor of subsequent clinical events including myocardial infarction and stroke. A last methodologic aspect is the reliability of our arterial measurements. The reliability was enhanced by the fact that ultrasound images obtained by sonographers were sent after storage on optical disk to a blinded central reader who performed off-line measurements. However, one limitation may be that the reproducibility between sonographers was not tested. Therefore this source of measurement error could not be evaluated, but sonographers in both countries were extensively trained in a common protocol before the beginning of the study. Moreover, on the basis of the work of Riley et al, it has been shown that the standardized ultrasonic technique yields highly reproducible measures of carotid IMT. In addition, our IMT measurement was completely automated, thanks to a computerized edge-tracking program allowing optimal precision and reproducibility rates to be obtained.

The finding that high-risk status was associated with increased carotid IMT, increased lumen diameter, and increased CSA-IMT is not surprising. Previous studies have shown that IMT correlated positively with all risk factors used in the Framingham risk estimation, supporting the view that IMT is a comprehensive picture of the integrated effects of traditional risk factors. The association between carotid artery lumen diameter and high-risk status is newer and more in line with a previous study in middle-aged subjects showing that the common carotid artery diameter was correlated with risk factors for cardiovascular disease. The mechanisms of the carotid artery dilation found in high-risk subjects may be related to early compensatory enlargement to preserve lumen area. However, the influence of high-risk status on carotid artery IMT and lumen diameter was more marked in the French than in the Swedish subjects, suggesting that effects of traditional risk factors on carotid artery structure is blunt in the latter, perhaps by other nontraditional risk factors exclusive of geographic difference. Such factors may be new or emerging risk factors, of environmental and/or genetic nature, not analyzed in the present work. The strong and independent influence of the geographic status on carotid artery IMT, diameter, and CSA-IMT constitutes the main finding of our work. As compared with French subjects, Swedish subjects have hypertrophy of the carotid wall as shown by CSA-IMT, which is an estimation of the arterial mass and a dilation of the carotid lumen. This Swedish-French difference in carotid artery structure exists in subjects at low risk and at high risk. It is therefore independent of the level of cardiovascular risk of the subjects, as confirmed by the multivariate analysis of arterial parameters on the geographic status in the whole population. The multivariate analysis shows also that the association of geographic status with carotid artery structure is independent of the two determinant factors of IMT and lumen diameter, namely, age and body mass index. However, the mechanism relating the geographic status to the carotid artery structure has not been elucidated and may be caused by factors unmeasured in the present work.

In conclusion, this study shows for the first time, to our knowledge, an independent association between the geographic status (ie, Swedish or French status) of white middle-aged men and a well-recognized marker of early arterial wall change as carotid IMT. Because increased carotid IMT predicts the occurrence of a subsequent cardiovascular event, its geographic dependence should be used in further investigations for more in-depth analysis of the factors contributing to the cardiovascular mortality and morbidity gradient between Northern and Southern Europe. However, the small number of subjects of our study reduces its statistical power, and larger studies are needed to confirm our findings.

Appendix

The Renault Volvo Coeur Projet Group

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References


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