Common Carotid Artery Intima-Media Thickness and Brain Infarction

The Étude du Profil Génétique de l’Infarctus Cérébral (GÉNIC) Case-Control Study

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Background—The use of intima-media thickness (IMT) as an outcome measure in observational studies and intervention trials relies on the view that it reflects early stages of atherosclerosis and cardiovascular risk. There is little knowledge concerning the relation between IMT and brain infarction (BI).

Methods and Results—We investigated the relation of IMT with BI and its subtypes in 470 cases and 463 controls. Cases with BI proven by MRI were consecutively recruited and classified into subtypes by cause of BI. Controls were recruited among individuals hospitalized at the same institutions and matched for age, sex, and center. IMT was measured at the far wall of both common carotid arteries (CCA) using an automatic detection system. Adventitia-to-adventitia diameters and CCA-IMT were measured on transverse views; lumen diameter was computed using these measures. Mean (±SEM) CCA-IMT was higher in cases (0.797±0.006 mm) than in controls (0.735±0.006 mm; P<0.0001). This difference remained after adjustment for lumen diameter and when analyses were restricted to subjects free of previous cardiovascular or cerebrovascular history. The difference in CCA-IMT between cases and controls was significant in the main subtypes. The risk of BI increased continuously with increasing CCA-IMT. The odds ratio per SD increase (0.150 mm) was 1.82 (95% confidence interval, 1.54 to 2.15); adjustment for cardiovascular risk factors slightly attenuated this relation (odds ratio, 1.73; 95% confidence interval, 1.45 to 2.07).

Conclusions—An increased CCA-IMT was associated with BI, both overall and in the main subtypes. An increased IMT may help select patients at high risk for BI. (Circulation. 2000;102:313-318.)

Key Words: stroke ■ epidemiology ■ risk factors

Carotid ultrasonographic methods capable of visualizing the arterial wall have been used to obtain measures of intima-media thickness (IMT). Increased IMT is generally considered an early marker of atherosclerosis. Cross-sectional associations have been reported between IMT and cardiovascular risk factors, prevalent cardiovascular disease, and peripheral atherosclerosis. Recently, prospective studies showed that an increased carotid IMT was associated with an increased risk of incident myocardial infarction. Two studies also showed that an increased carotid IMT was associated with an increased risk of stroke. However, none of these studies distinguished brain infarction (BI) from hemorrhages, nor did any take into account the different BI subtypes.

Data on the relation between BI and IMT are therefore lacking, and our objective was to study their association. IMT evaluation is purported to detect early stages of atherosclerosis. Therefore, we confined measurements of IMT to the common carotid artery (CCA) because of the relatively common occurrence of plaques at the origin of the internal carotid artery (ICA). In addition, we used a computerized and automatic measurement method that increases the accuracy of the measurements. Using these methods, we compared the CCA-IMT in cases with BI and in controls. Because it has been suggested that IMT may, in part, reflect an adaptive response to changes in tensile and shear stress, we also studied IMT in association with CCA lumen diameter.

Methods

Cases

Patients (n=510) were consecutively recruited in 12 French neurological centers if they fulfilled the following criteria: (1) clinical...
symptoms suggestive of stroke, (2) no brain hemorrhage on CT scan, (3) infarct proven by MRI, (4) 18 to 85 years old, and (5) both parents of Caucasian origin. Cases were included in the study in the week after the event. Patients reporting a previous cardiovascular or cerebrovascular history were eligible.

**Controls**

Controls were recruited among individuals hospitalized at the same institutions for any reason other than neurological disease (orthopedic, 46%; ophthalmologic, 12%; rheumatologic, 11%; surgical, 6%; other, 25%). One control was matched by sex, age (±5 years), and center to each case. History of stroke or other cardiovascular disease was assessed by the investigator. Individuals reporting a positive history of stroke were not eligible, whereas those reporting a positive cardiovascular history other than stroke were eligible. The parents of the controls also had to be of Caucasian origin. Because IMT variations have been reported in relation to ethnicity,16 cases and controls should be comparable with respect to ethnicity.

**Data Collection and Risk Factor Definition**

Information on demographic characteristics and risk factors was collected using a structured questionnaire. Hypertension was defined by a history of treated hypertension. Smoking history was coded as never, previous, and current smoker. Subjects were classified as diabetics when treated for insulin-dependent or non-insulin-dependent diabetes. Use of lipid-lowering drugs was assessed. History of myocardial infarction, angioplasty, coronary artery bypass surgery, or lower-limb arterial disease was recorded; a positive cardiovascular history was defined by the presence of any of these diseases. History of stroke or transient ischemic attacks was obtained in cases.

**Carotid Ultrasonography Studies**

All subjects underwent a carotid ultrasound examination to evaluate the presence and site of plaques and to quantify the degree of stenosis. The protocol involved scanning the CCAs, the carotid bifurcations, and the origins (first 2 cm) of the ICAs. The near and far wall of these arterial segments were scanned longitudinally and transversally to assess the presence of plaques (localized echostuctures that encroached into the vessel >1 mm beyond the interface between lumen and intima).

All subjects had an IMT measurement at the far wall of both CCAs, with video recording for off-line review (C.K., P.-J.T.). Ultrasonographers were trained at each center and were asked to send a minimum of 3 examinations recorded on videotape to be validated by the central reading committee before the study began. They had to follow a standard protocol that included acquiring images of both CCAs in longitudinal and cross-sectional views to allow the visualization of ≥10 mm of the IMT complex on the far wall (Figure). These 10 mm could be seen continuously or be the sum of 2 segments of variable length (summing to 10 mm). These 10 mm had to be free of plaques. The IMT measurement was not obtained at a standard portion of the cardiac cycle. The median time between BI and IMT evaluation was 8 days (range, 0 to 78 days) for cases, and the median time between hospitalization and IMT evaluation was 7 days (range, 0 to 80 days) for controls (Wilcoxon’s test, P<0.02).

All examinations were reviewed at a central reading center (P.-J.T., C.K.) for automatic IMT measurement using software developed for that purpose.13 The reader froze the best images of both CCAs and selected the region of interest, within 10 mm of which edge detection and IMT measurement were automatically performed (Figure). A total of 100 measurements were automatically performed on the right and left far walls, yielding 2 average measures on each side. If the 10 mm was seen continuously, each average measure was the mean of 50 measures; if the 10 mm was seen as 2 segments, each average measure was the mean of a number of measures proportional to the length of the corresponding segment. Adventitia-to-adventitia diameters and CCA-IMT (one measurement on each side) were measured on transverse views at the level of longitudinal measurements. Intra- and interobserver reproducibility have been reported in other studies using the same method for IMT evaluation.13,17,18

**Other Investigations**

Blood was drawn in the morning from fasting subjects for DNA extraction and lipid profile determination in one centralized laboratory. Other investigations in cases included an ECG (100%), 2D echocardiography (91%), transesophageal echocardiography (70%), and cerebral angiogram (42%).

**Stroke Etiology Classification**

Patients were classified into etiologic subtypes by 2 neurologists (P.A., F.C.) according to prespecified criteria as follows:

- Atherosclerotic stroke: patients who had (1) an ipsilateral internal carotid stenosis >30%, (2) an ipsilateral stenosis >50% in another intra- or extracranial artery, or (3) plaques >4 mm in the aortic arch with a mobile component.
- Cardioembolic stroke: patients who had mitral stenosis, myocardial infarction within the prior 3 weeks, mural thrombus in left cavities, left ventricular aneurysm, atrial fibrillation (with or without spontaneous echocontrast or left atrial thrombus), endocarditis, or an intracardiac mass.
- Lacunar stroke: patients who had a small, deep infarct measuring <15 mm in size on an MRI in the territory corresponding to symptoms and who presented with a clinical syndrome compatible with the diagnosis of lacune, without any finding in favor of an atherothrombotic or cardioembolic stroke.
- Arterial dissection: patients with typical clinical-angiographic patterns of carotid/vertebral arterial dissection.
- Rare causes: patients who had rare causes of stroke, such as polycythemia vera, thrombocythemia, and lupus erythematosus.
- Undetermined cause: patients who had ≥2 possible, coexisting etiologies.
- Unknown cause: patients who did not meet criteria for the groups defined above. These patients may have had incidental findings, such as isolated elevation of antiphospholipid antibodies, patent foramen ovale, atrial septal aneurysm, valvular strands, mitral valve prolapse, mitral annulus calcifications, or plaques in the aortic arch without a mobile component.

**Data Analysis**

A good-quality IMT recording was obtained for 470 of the 510 cases (92%) and 463 of the 510 controls (91%). Among them, 4 average measures were available for 418 cases and 416 controls, 3 average measures were available for 5 cases and 5 controls, and 2
average measures were available for 47 cases and 42 controls (these were on the same side for 87 of the 89 individuals). When we compared individuals for whom 4 measures were available with other individuals, we found that the latter more frequently reported a history of hypertension ($P=0.03$) or diabetes ($P=0.05$) and had a higher body mass index ($P=0.004$). Not all cases had a matched control and vice versa, but we decided to include these subjects in the analysis using appropriate methods.

When 1 or 2 measures were missing, missing values were imputed using the available IMT measures, age, sex, and center as the independent variables in a multiple regression linear model (procedure impute, STATA). Using this method, 4 measures (2 on each side) were finally (ie, after the imputation procedure) available for 470 cases and 463 controls. Mean CCA-IMT was computed as the mean of the 4 average measures. Lumen diameter was computed as the interadventitial diameter minus 2×CCA-IMT (measured on transversal views).

We used ANCOVA to compare the mean CCA-IMT between cases and controls. Our first analyses concerned the entire study group. Further analyses were stratified according to subtypes; in each strata, cases were compared with their matched controls. All analyses were adjusted for the matching variables (age, sex, and center). Multiplicative terms were introduced in the models to test whether the relation between IMT and BI was modified by sex, age, or cardiovascular history. Primary analyses were conducted with and without adjustment for cardiovascular history; they were repeated after the exclusion of cases who reported a positive cardiovascular or cerebrovascular history. ANCOVA was also used to compare mean CCA-IMT between cases belonging to different subtypes; Tukey’s method was used to adjust for multiple comparisons. Analyses concerning strokes of undetermined cause are not reported because this is, by definition, a highly heterogeneous group of patients.

The linearity of the relation between the logit BI and CCA-IMT was tested using logistic regression while adjusting for age, sex, and center. After categorization of CCA-IMT according to quartiles, the relative risk of BI for the upper 3 quartiles relative to the lowest quartile was estimated through the calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Because we found that ORs for BI increased regularly with increasing CCA-IMT, we also computed the OR associated with an increase of 1 SD in CCA-IMT. The homogeneity of the association between IMT and BI across the main strata was tested using the Breslow-Day heterogeneity test.

Further analyses were stratified according to subtypes; in each strata, cases were compared with their matched controls. All analyses were adjusted for the matching variables (age, sex, and center). Logistic regression and ANCOVA (both adjusted for age, sex, and center) were used to compare proportions and continuous variables, respectively; unadjusted means are reported.

Adjusted for age, sex, center, lipid-lowering treatment, and blood sample delay. The median delay was 5 days (range, 0 to 61 days) in cases and 6 days (0 to 79 days) in controls (Wilcoxon test: $P=0.003$).

Statistical testing was done at the 2-tailed $\alpha$ level of 0.05. Data were analyzed using the SAS package.

### Results

Table 1 describes the general characteristics of 470 cases and 463 controls. Cases had a higher prevalence of cardiovascular risk factors and reported a previous cardiovascular history more frequently than controls. Distribution of BI subtypes in cases and their basic characteristics are shown in Table 2.

Table 3 shows the adjusted mean CCA-IMT values in cases and controls, both overall and according to subtypes. There were no significant differences in CCA-IMT among controls according to the main hospitalization departments (data not shown). Overall, mean CCA-IMT was higher in cases than in controls. The relation between BI and IMT was not modified by age ($P=0.8$), sex ($P=0.9$), or cardiovascular history ($P=0.5$). In all subtypes, the difference in mean CCA-IMT between cases and controls was significant. Adjustment for cardiovascular history did not modify these results overall or among subtypes. When analyses were restricted to individuals free of previous cardiovascular or cerebrovascular history (295 cases and 410 controls), the mean (±SEM) CCA-IMT was 0.782±0.008 in cases and 0.723±0.007 in controls ($P<0.0001$). The difference in mean CCA-IMT remained significant in all subtypes except cardioembolic strokes ($P=0.12$), although this is probably related to a loss of power because this group included the lowest number of subjects and the OR remained unchanged (see below). After adjust-

<table>
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<th>TABLE 2. Distribution of BI Subtypes</th>
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<td>Lacunar</td>
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<td>Strokes of undetermined cause</td>
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<td>Other causes (dissections, rare causes)</td>
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$P^*$<0.001 <0.001† 0.15 <0.001

$^*\chi^2$ analysis was used for comparison of proportions across subtypes; †Kruskal-Wallis test.
ment for lumen diameter, the association remained significant, both overall ($P<0.0001$) and among subtypes, except in cardioembolic strokes ($P=0.08$).

When analyses were restricted to cases, we found a significant difference in CCA-IMT across subtypes (adjustment for age, sex, and center: $P=0.01$; further adjustment for history of hypertension or diabetes, current smoking, and cholesterol level: $P=0.05$); cases with a BI of unknown cause had a lower IMT than cases with atherothrombotic or lacunar strokes (Tukey’s method, $P<0.05$ using both adjustments).

After categorization of CCA-IMT into quartiles, the risk of BI increased gradually with increasing CCA-IMT (Table 4). Therefore, we computed ORs per 1 SD increase in CCA-IMT (Table 3); adjustment for cardiovascular history did not modify our findings (overall: OR, 1.79; 95% CI, 1.51 to 2.11). ORs were not significantly different ($P=0.4$) in men (OR, 1.76; 95% CI, 1.44 to 2.17) and women (OR, 2.10; 95% CI, 1.53 to 2.90). ORs were significantly greater than 1.00 in all subtypes, and there was no heterogeneity in the relation between BI and IMT according to main subtypes ($P=0.4$).

When subjects with previous cardiovascular or cerebrovascular history were excluded, similar results were observed overall (OR, 1.80; 95% CI, 1.48 to 2.19) and among subtypes (atherothrombotic: OR, 2.65; 95% CI, 1.69 to 2.16; lacunar: OR, 1.75; 95% CI, 1.20 to 2.55; cardioembolic: OR, 1.60; 95% CI, 0.91 to 2.83; unknown: OR, 2.10; 95% CI, 1.38 to 3.43). Again, the association was not significantly different ($P=0.6$) in men (OR, 1.76; 95% CI, 1.37 to 2.30) and women (OR, 2.13; 95% CI, 1.47 to 3.09).

The association of CCA-IMT with several risk factors was investigated separately in cases and controls (data not shown). We found a significant association of CCA-IMT with male sex, age, history of hypertension or diabetes, body mass index, smoking, and evidence of plaque in both cases and controls. The relation between CCA-IMT and BI was investigated after adjustment for these variables (Table 3); the relation between CCA-IMT and BI was slightly attenuated but remained significant.

**Discussion**

We found an association between BI and far wall CCA-IMT; this association was present in the main BI subtypes. The risk of BI increased continuously with increasing CCA-IMT. This association remained after adjustment for cardiovascular risk factors. Adjustment for CCA lumen diameter did not modify these findings significantly.

The main limitation of this study is that neither case nor control selection was population-based. However, in Western countries, BI leads to hospitalization in the majority of cases. Patients were included consecutively in the week after the event; because early case fatality rates in BI are rather low, we do not believe that survival bias is likely to have occurred. Our findings were confirmed when analyses were restricted to cases with first events. Controls were selected in a variety of departments, and we did not find a significant relation between IMT and main hospitalization department; a bias related to control selection is, therefore, unlikely.

Three other studies investigated the relation between stroke and IMT. In the Atherosclerosis Risk in Communities study, the prevalence of cerebrovascular disease was cross-sectionally associated with an increased IMT in whites; cerebrovascular disease was defined using an algorithm based on self-reported symptoms. In a further report, the relation between cerebrovascular disease and IMT was not linear, with a significant association only present for the highest IMT values. IMT was measured at the CCA far wall, the carotid bifurcation, and the ICA origin.

In a case-control study nested in the Rotterdam study, an increased IMT was associated with an increased risk of stroke. Stroke diagnosis was made by a neurologist according to information transmitted by general practitioners or by reviewing hospital records. IMT was measured at the far and near wall of the CCA.

In the Cardiovascular Health Study, 4476 participants (≥65 years) were followed for a median duration of 6 years; 284 strokes were ascertained. An association between increased IMT and the risk of incident stroke was observed. The relative risk increased in a linear fashion with increasing IMT, and it was of the same magnitude as the relative risk for
myocardial infarction. Detection of cases was based on self-reported symptoms and hospital records. IMT was measured at the near and far wall of the CCA and ICA, and the maximal rather than the mean IMT was used for the analyses. A composite measure that combined CCA and ICA IMTs was a better statistical predictor of events than either measure taken separately.

None of these studies distinguished BI from hemorrhage, nor did any study distinguish between BI subtypes. In this study, BI was confirmed in all patients by a neuroradiological investigation. All patients were recruited in neurological centers with expertise in stroke diagnosis and management, and the medical records of all cases were reviewed by 2 neurologists. Moreover, an extensive set of investigations was used to classify patients into subtypes by cause of BI. This approach is likely to have increased the reliability of BI diagnosis compared with the case-finding methods used in the aforementioned studies.

There is no standardized method to measure IMT by ultrasound. Some studies obtained measures at the near and far walls, whereas others obtained them at the far wall only. Because far wall measurements are considered more valid than near wall measurements, we focused on far wall IMT. Some studies measured CCA- and ICA-IMT, and others focused on CCA-IMT. We confined measurements of IMT to the CCA because of the relatively common occurrence of plaques at the origin of the ICA. IMT evaluation is purported to detect early stages of atherosclerosis; because ICA-IMT measures are at risk of including plaques, they are at risk of measuring later stages of atherosclerosis. In addition, because plaques are associated with BI, they could lead to an overestimation of the association between BI and ICA-IMT. Therefore, we measured CCA-IMT at a site free from plaque. Moreover, we used an automatic detection system that averaged a large number of measures to increase the accuracy of each measure, and we used mean rather than maximal IMT.

We found a highly significant association between BI and CCA-IMT in the atherothrombotic group. In this subtype, the arterial occlusion is due to a ruptured plaque of an extra- or intracranial artery. Plaques were very strongly associated with this subtype (P<0.001); moreover, they were more frequent in atherothrombotic strokes than in other subtypes. A relation between plaques and CCA-IMT has previously been reported. Therefore, the strong relation found in this subtype was not unexpected. Although the OR point estimate in the atherothrombotic group was the highest, we failed to demonstrate heterogeneity in the relation between IMT and BI according to subtypes. However, in interpreting these findings, we should take sample size and power considerations into account.

An association between CCA-IMT and BI was also present in other subtypes; the relation between BI and CCA-IMT was less significant in the cardioembolic group than in other subtypes, but this group included the lowest number of patients. Several studies have shown that an increased IMT is associated with several cardiovascular risk factors, and in our study, most of them were associated with BI in all subtypes. Therefore, the association that we found may be viewed, at least in part, as the marker of exposure to cardiovascular risk factors. The reasons why some individuals develop a more severe carotid atherosclerosis than others while exposed to similar risk factors remain to be elucidated. Other factors (ie, anatomical/hemodynamic factors and genetic susceptibility) may play a role.

The relation between CCA-IMT and BI remained after adjustment for main cardiovascular risk factors. However, we did not measure all risk factors that may be associated with an increased IMT (eg, hemostatic factors, hyperinsulinemia, and hyperhomocysteinemia), and some risk factors were defined as binary variables, although duration and severity are important. In addition, other risk factors for increased IMT have probably not yet been identified. Nevertheless, if IMT reflects exposure to cardiovascular risk factors, it can be considered an intermediate phenotype, and it is not clear whether analyses aiming to evaluate the risk of BI related to an increased IMT should be adjusted for cardiovascular risk factors. BI occurs at a mean older age than myocardial infarction and often in individuals with several risk factors. Risk profiles identify individuals at a high risk for stroke; however, they do not take into account more recently determined risk factors or the borderline elevation of risk factors that is common in the elderly. Thus, IMT measurements may be a more global and actual way to identify subjects at a high risk of BI.

Finally, because it has been suggested that an increased IMT reflects an adaptive response to changes in shear and tensile stress, we studied the relation between BI and CCA-IMT after adjustment for lumen diameter; the relation between BI and CCA-IMT remained basically unchanged. It is likely that an adjustment for lumen diameter is insufficient to adjust for wall stress; other measures (ie, tensile stress and CCA end-diastolic lumen diameter) may be more meaningful.

In conclusion, we showed that an increased CCA-IMT was associated with BI, both overall and in its main subtypes. Use of IMT as an outcome measure in observational studies and intervention trials relies on the view that IMT is a marker of atherosclerosis and reflects cardiovascular risk. As far as BI is concerned, this hypothesis is supported by the present study.

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