Carotid Artery Intima-Media Thickness and Lacunar Versus Nonlacunar Infarcts

L.M. Cupini, MD; P. Pasqualetti, PhD; M. Diomedi, MD; F. Vernieri, MD; M. Silvestrini, MD; B. Rizzato, MD; F. Ferrante, MD; G. Bernardi, MD

Background and Purpose—Increases in the thickness of the intima and media of the carotid artery have been associated with an increased risk of myocardial infarction and stroke in subjects without a history of cardiovascular disease. Lacunar infarcts, one of the most common subtype of ischemic stroke, show unique pathological and clinicoradiological characteristics. The present study examines the relationship between vascular risk factors, including carotid artery intima-media thickness (IMT), and lacunar versus nonlacunar infarcts.

Methods—We collected data from patients with acute ischemic stroke admitted to hospital. Patients and 129 control subjects underwent B-mode ultrasonographic measurements of IMT of the common carotid artery. We examined the association of lacunar and nonlacunar infarcts with age, sex, and potential vascular risk factors.

Results—Of 292 adult patients with an acute first-ever ischemic stroke, 96 were considered lacunar and 196 were considered nonlacunar strokes. We did not find a significantly different percentage of diabetes, smoking, hypertension, dyslipidemia, myocardial infarction, and previous transient ischemic attack between the 2 groups of patients. The multinomial logistic regression procedure selected carotid artery IMT and atrial fibrillation as the only independent factors able to discriminate between lacunar and nonlacunar patients. IMT values were significantly higher in patients with nonlacunar stroke versus both those with lacunar stroke and control subjects.

Conclusions—The present results indicate the usefulness of noninvasive measurement of IMT with ultrasonic techniques as a diagnostic tool that may help to identify different subtypes of ischemic stroke patients. The noninvasive measurements may have predictive power with respect to lacunar versus nonlacunar infarcts. (Stroke. 2002;33:689-694.)

Key Words: lacunar infarction ■ risk factors ■ ultrasonography

High-resolution B-mode ultrasonography provides a noninvasive method of quantifying subclinical arterial wall thickening and atherosclerotic progression. This technique permits us to obtain measures of intima-media thickness (IMT), an increase in which is generally considered an early marker of atherosclerosis. Measurement of carotid artery IMT is regarded as a valid index of the involvement of other arterial beds with atherosclerosis. In addition, carotid artery IMT has been found to be strongly associated with cardiovascular risk factors. Several studies have shown an association between carotid artery IMT and incidence of myocardial infarction and stroke.

Measurements at different sites of the carotid artery have been performed by different groups. It has been shown that common carotid artery (CCA) IMT is a good predictor of stroke incidence, whereas internal carotid artery (ICA) IMT measurement has a greater power of prediction for myocardial infarction. Similarly, CCA IMT has been shown to be strongly associated with risk factors for stroke and prevalent stroke, whereas IMT bifurcation and plaque were more directly related to ischemic heart disease and its risk factors.

There is no standardized method to measure IMT by ultrasound. Because it has been suggested that measurement of IMT at the CCA alone is a reasonable alternative to more detailed and theoretically difficult measurements at other sites and because of the relatively common occurrence of plaques at the origin of the ICA, we confined measurements of IMT to the CCA. 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.

Lacunar infarction, one of the most common causes of ischemic stroke, is presumed to result from the occlusion of...
single perforating arteries. Small-artery disease (from lipohyalinosis and fibrinoid degeneration), 16–20 large-artery atherosclerosis, 21–23 and embolism 24–28 have been implicated as potential causes of lacunar infarcts. However, some authors consider cardiac and carotid embolism unlikely causes of lacunar infarction.17,29,30 Recently, a relationship has been shown to be disease free were entered in the present study. Subjects complaining of symptoms like tension-type headache, dizziness, and hypoacusia and who were subsequently turned to the left or right. Longitudinal images of the left and right CCAs, bifurcation, and ICAs. Carotid artery disease was assessed and defined by continuous-wave Doppler and color-flow Doppler ultrasound examination according to validated criteria.35 Twelve patients underwent conventional angiography, and 45 patients underwent MR angiography to optimize treatment and to exclude severe intracranial atherosclerotic disease. The results of Duplex ultrasound examination and MR angiography were always concordant.

Patients and 129 control subjects underwent B-mode ultrasonographic measurements of CCA IMT. Control subjects were recruited among individuals who consecutively underwent ultrasound examination at the same institution for any reason other than cerebrovascular disease. Subjects complaining of symptoms like tension-type headache, dizziness, and hypoaacusia and who were subsequently shown to be disease free were entered in the present study.

The subjects were examined in the supine position with the head turned ~45° to the left or right. Longitudinal images of the left and right CCAs were acquired. The near and far walls of the carotid artery were displayed as 2 bright white lines separated by a hypoechoic space. Two frozen images of IMT from the far wall on both the right and left CCAs were acquired. IMT of the far wall was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface. The measurement of IMT in the CCA was made 1 cm proximal to the carotid bulb. The number of measurements ranged from 3 to 5 for each frozen image. The actual measurement of the IMT was performed offline and was calculated as the average of the maximal IMT measured at the far wall of each CCA. Subjects were examined by the same 2 sonographers. Both sonographers were neurologists with experience in ultrasound examination of the carotid artery. The study began after a 3-month training program in IMT measurements. The reproducibility of IMT measurements between and within sonographers had previously been checked.

### Subjects and Methods

We prospectively collected data from 420 consecutive patients with acute ischemic stroke admitted to our neurology ward from January 1998 to September 2000 and from control subjects recruited during the same period. A stroke was defined as rapidly developing signs of focal or global disturbance of cerebral function lasting >24 hours with no apparent cause other than vascular. Exclusion criteria were age <45 years, isolated transient ischemic attacks (TIAs), and history of previous stroke. Neurological status was assessed by the National Institutes of Health Stroke Scale. All patients underwent a CT scan on admission as part of standard stroke patient care. MRI (or CT when MRI was unperformable because of the presence of a metal implant or if the patient refused or was claustrophobic) was performed within 1 week from the onset of symptoms. Axial T1-, T2-, and proton density-weighted images were obtained with a 1.5-T MRI (Gyroscan ACS, NT Philips Medical Systems). Images were evaluated at a central reading center by neuroradiologists. To check

### Group Statistics and Multiple Regression Results for Demographic and Vascular Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Lacunar (n=96)</th>
<th>Nonlacunar (n=196)</th>
<th>Control Subjects (n=129)</th>
<th>Likelihood Ratio Test</th>
<th>Simple Multinomial Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, y (SD)</strong></td>
<td>68.4 (10.5)</td>
<td>70.3 (10.8)</td>
<td>66.6 (8.8)</td>
<td>10.64</td>
<td><strong>0.98 (0.96–1.01)</strong></td>
</tr>
<tr>
<td><strong>Mean IMT, mm (SD)</strong></td>
<td>0.91 (0.16)</td>
<td>1.04 (0.25)</td>
<td>0.91 (0.24)</td>
<td>30.48</td>
<td><strong>&lt;0.001 1.01 (0.88–1.15)</strong></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>57.3</td>
<td>66.3</td>
<td>55.8</td>
<td>4.37</td>
<td><strong>0.94 (0.55–1.61)</strong></td>
</tr>
<tr>
<td>Smoking, %</td>
<td>35.4</td>
<td>33.2</td>
<td>24.0</td>
<td>4.35</td>
<td><strong>0.114 0.58 (0.32–1.03)</strong></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>17.7</td>
<td>21.4</td>
<td>14.7</td>
<td>2.40</td>
<td><strong>0.301 0.80 (0.39–1.64)</strong></td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>37.5</td>
<td>37.8</td>
<td>22.5</td>
<td>9.73</td>
<td><strong>0.008 0.48 (0.27–0.88)</strong></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>61.5</td>
<td>67.9</td>
<td>44.2</td>
<td>18.23</td>
<td><strong>&lt;0.001 0.50 (0.29–0.85)</strong></td>
</tr>
<tr>
<td>AF, %</td>
<td>4.2</td>
<td>23.5</td>
<td>0.0</td>
<td>60.02</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>11.5</td>
<td>15.8</td>
<td>5.4</td>
<td>8.93</td>
<td><strong>0.011 0.44 (0.17–1.19)</strong></td>
</tr>
<tr>
<td>Previous transient ischemic attack, %</td>
<td>11.5</td>
<td>6.6</td>
<td>0.0</td>
<td>20.09</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Carotid stenosis, %</td>
<td>16.7</td>
<td>24.5</td>
<td>8.5</td>
<td>35.03</td>
<td>0.001 0.47 (0.21–1.06)</td>
</tr>
</tbody>
</table>

*RRR for each decimillimeter.
†Not evaluable (0% in control subjects).

the reliability of the radiological definition, 2 observers (1 neuroradiologist and 1 neurologist who were unaware of patients’ vascular risk factors) reexamined the images for this study. The carotid arteries were evaluated with a high-resolution ultrasound (AU5 Harmonic, Esaote Biomedica) equipped with a linear transducer with 7.5 MHz in B mode. The carotid arteries were evaluated for the presence of atherosclerotic lesions (plaques), defined as focal widening relative to adjacent segments, with protrusion into the lumen of only calcified deposits or a combination of calcification and noncalcified material. This measurement was performed for the left and right CCAs, bifurcation, and ICAs. Carotid artery disease was assessed and defined by continuous-wave Doppler and color-flow B-mode Doppler ultrasound examination according to validated criteria.15 Twelve patients underwent conventional angiography, and 45 patients underwent MR angiography to optimize treatment and to exclude severe intracranial atherosclerotic disease. The results of Duplex ultrasound examination and MR angiography were always concordant.
The sonographers were unaware of clinical and radiological information about the participants. Information on demographic characteristics, previous diseases, habits, and cardiovascular risk factors was collected from both patients and control subjects with a structured medical history.

Traditional risk factors for cerebrovascular disease were evaluated. Height and weight were measured. Age, sex, diabetes, history of smoking (current smokers), heavy alcohol consumption (≥300 g/wk), history of hypertension (previously diagnosed and treated or systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg persistently observed during admission and after the acute phase), low-density and high-density lipoprotein cholesterol levels, presence or absence of atrial fibrillation (AF; history of AF confirmed by previous ECG examination or AF diagnosed at the time of admission and/or during the hospital stay), cardiovascular diseases, carotid stenosis (≥50%), and history of previous TIA were recorded.

Referring to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, ischemic strokes were classified into the following categories: infarction resulting from extracranial or intracranial atherosclerosis, embolism from a commonly accepted cardiac source, lacunar infarction, infarction of other determined origin, and infarction of undetermined origin. Brain imaging was classified as lacunar or nonlacunar infarcts (border-zone, cortical, or large subcortical infarcts). Lacunar infarcts were defined by a combination of cerebral infarcts. Lacunar infarcts were defined by a combination of:

- Round or oval in shape; (2) measure ≥1.5 cm in diameter; (3) be located in the typical territory supplied by deep or superficial small perforating arteries; (4) not be in cortical territories; and (5) not have the morphological and topographical distribution consistent with partial internal border-zone infarcts. Patients with a clinical presentation consistent with a lacunar syndrome and neuroimaging confirmation of ≥1 lacunar lesions located in the appropriate area of the brain to explain the symptoms were classified as having lacunar infarcts.

Patients were subdivided into 2 groups, lacunar and nonlacunar infarctions, for further statistical analysis. The association of the IMT with lacunar and nonlacunar infarcts was examined before and after control for the potential risk factors.

### Statistical Analysis

The main objective of this cross-sectional study was to assess the discriminating role of the CCA IMT among patients with lacunar infarcts and nonlacunar infarcts and control subjects, taking into account eventual differences in terms of demographic characteristics and presence of cerebrovascular risk factors. For such a purpose, the multinomial logistic regression, able to handle >2 outcomes, was applied. To better understand the effect of each variable alone, several multinomial simple logistic regressions were performed first. Thereafter, the multiple multinomial logistic regression analysis allowed us to determine which variables could be considered independent factors. To perform only independent contrasts (always k-1, where k is the number of considered groups) and because we wanted to focus on discriminating lacunar infarcts from nonlacunar infarcts and from control subjects, the relative risk ratios (RRRs) and 95% confidence intervals were computed with the lacunar infarct group as reference. Finally, a binary logistic regression was applied to the 2 groups of patients to obtain the model-predicted probabilities and to evaluate the eventual interaction between the significant discriminating factors. Statistical analysis was performed with SPSS 10.0 (SPSS Inc).

### Results

Among 420 adult patients consecutively recruited during the study period, 42 subjects were excluded because they had had ≥1 previous stroke, 29 because they were <45 years of age, and 57 because they were diagnosed as having had isolated TIA. Therefore, the studied population consisted of 292 adult, first-ever ischemic stroke patients 45 to 90 years of age (mean, 69.7±10.7 years) and 129 control subjects.

Among the patients who entered the present study, 96 were considered to have had lacunar and 196 to have had nonlacunar strokes. The 5 classic lacunar syndromes accounted for 96.9% of the lacunar infarctions; other lacunar syndromes accounted for only 3.1%. Among the cases of nonlacunar infarcts, atherosclerotic stroke accounted for 24% of cases, cardiac embolism for 28%, undetermined origin for 45%, and stroke of other determined origin for 3%. The average of left and right IMTs was considered for statistical analysis as a parameter of atherosclerosis.

The Table summarizes the descriptive statistics of the 3 groups, as well as the simple and multiple regression findings for the demographic and vascular risk factor characteristics. The overall tests indicated that age, IMT, dyslipidemia, hypertension, AF, myocardial infarction, previous TIA, and carotid stenosis were able to discriminate between the 3 groups.

When all variables were considered together in a multiple regression model, slight changes occurred. Age, able to discriminate only patients with nonlacunar stroke from control subjects in the simple analysis, was no more significant. The presence of dyslipidemia or hypertension reduced by ≈50% the probability of being a control subject compared with having lacunar stroke. The RRRs for AF and previous TIA were not computable because of the absence of such risk factors in the control group. The nonlacunar infarct group

### Table

<table>
<thead>
<tr>
<th>Likelihood Ratio Test</th>
<th>Relative Risk Ratios (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Control Subjects vs Lacunar</td>
<td>Nonlacunar vs Lacunar</td>
</tr>
<tr>
<td>χ² (df=2)</td>
<td>P</td>
</tr>
<tr>
<td>12.96 0.002</td>
<td>1.12 (0.97–1.29)</td>
</tr>
<tr>
<td>2.98 0.226</td>
<td>0.97 (0.54–1.75)</td>
</tr>
<tr>
<td>4.76 0.093</td>
<td>0.52 (0.28–0.98)</td>
</tr>
<tr>
<td>0.77 0.680</td>
<td>0.83 (0.39–1.78)</td>
</tr>
<tr>
<td>7.53 0.023</td>
<td>0.53 (0.28–0.98)</td>
</tr>
<tr>
<td>7.69 0.021</td>
<td>0.54 (0.30–0.98)</td>
</tr>
<tr>
<td>59.80 &lt;0.001</td>
<td>†</td>
</tr>
<tr>
<td>3.90 0.142</td>
<td>0.52 (0.18–1.47)</td>
</tr>
<tr>
<td>17.19 &lt;0.001</td>
<td>†</td>
</tr>
<tr>
<td>0.55 0.062</td>
<td>0.58 (0.23–1.43)</td>
</tr>
</tbody>
</table>
Probabilities of nonlacunar vs lacunar stroke as predicted by the logistic regression model. Both significant factors are represented: IMT (on the x axis) and AF (square when absent and circle when present). According to this model, a patient with an IMT value of 0.6 mm has a risk of ~40% to have a nonlacunar vs lacunar stroke, but the risk increases to 80% in the presence of a concomitant AF. Without AF, the same 80% level could be reached by a patient with an IMT >1.2 mm. The 2 modeled lines also indicate the smaller effect of AF in patients with an IMT value >1.5 mm and the less relevant role of IMT in the presence of AF. The significance of the interaction term AF×IMT confirmed this observation.

Discussion

In the present study, we observed that CCA IMT and AF are the only 2 independent factors able to discriminate between lacunar and nonlacunar ischemic strokes. Lacunar infarcts, one of the most common subtypes of ischemic stroke, show unique clinical, pathophysiological, and radiological characteristics. When a stroke occurs, the ultimate outcome differs with the subtype of stroke and is influenced by patient comorbidities. Patients with lacunar stroke have the best short- and long-term prognoses and the highest survival rate. In addition, lacunar patients have the lowest risk for early and late recurrence.

Lacunes are considered to account for between 12% and 30% of all cases of ischemic stroke. The higher proportion of patients with lacunar infarct in our population (33%) could be due to selection factors inherent in the referral of patients to our neurological department. In fact, stroke patients who present large hemispheric strokes and thus require an intensive care unit are admitted to a special department; for this reason, they could not have been entered in the present study. Moreover, because we excluded stroke patients <45 years of age, a group of mostly nonlacunar strokes did not enter the present study.

According to the lacunar hypothesis, small-vessel disease (from lipohyalinosis and fibrinoid degeneration) is the most important cause of lacunar infarction, whereas atherosclerosis and embolism are less important. Nevertheless, both cardiac embolism and large-artery atherosclerosis have been increasingly recognized and described as potential causes of lacunar stroke.

Increases in CCA IMT thickness have been associated with involvement of other arterial beds with atherosclerosis and an increased risk of stroke in adults. However, there is only a little knowledge concerning the relationship between CCA IMT and subtypes of brain infarction. Recently, it has been observed that an increased CCA IMT was associated with brain infarctions both overall and in the main subtypes. Authors have concluded that an increased IMT may help in the selection of patients at high risk for brain infarction. In our study, lacunar and nonlacunar infarcts differed in terms of CCA IMT. In addition, we did not find a significant difference in IMT between control subjects and patients with lacunar infarcts, whereas Touboul et al observed a slight but significantly higher IMT even in lacunar infarcts compared with control subjects. Different criteria in the selection of patients could account for these different results. In fact, because an increase in IMT has been described as an independent risk factor for stroke in older subjects, we excluded stroke patients <45 years of age. In addition, we included only first-ever stroke patients. For these reasons, we believe that our data provide a different perspective on the capability of CCA IMT to discriminate lacunar and nonlacunar infarcts.

There is a long-standing debate as to whether lacunar infarcts have a different risk profile compared with other forms of ischemic stroke. Case-control studies reported an association between diabetes, hypertension, smoking habit, and lacunar infarcts. On the other hand, studies comparing lacunar and nonlacunar stroke patients failed to find important differences in diabetes and hypertension and in smoking, previous TIA, and hypercholesterolemia between the 2 groups of patients. Similarly, a recent population-based study reported that hypertension and diabetes are not more common among patients with lacunar infarcts. We observed that the 2 groups did not differ significantly in prevalence of hypertension, diabetes, smoking, dyslipidemia, myocardial infarction, and previous TIA.
The significance difference between the 2 groups in terms of presence of AF confirms previous findings, 17-29,30 and our data support the hypothesis that AF may represent a coincidental finding in lacunar infarct. In our population, although quite similar percentages of carotid stenosis were found, a strong, significant probability value documented an increased IMT in the nonlacunar compared with the lacunar group. The finding that the 2 groups of patients significantly differed in terms of increased CCA IMT suggests that IMT does not reflect vascular changes that are etiologically related to lacunar disease.

After adjustment for conventional risk factors, increases in CCA IMT and AF were the variables most strongly associated with the risk of nonlacunar infarcts. This finding indicates that noninvasive measurements of IMT with ultrasonic techniques may help to identify different subtypes of ischemic stroke patients (see the logistic regression model in the Figure). Our study suggests that using a model of investigation that includes analysis of clinical syndromes, results of diagnostic imaging, and analysis of the most common stroke risk factors, including CCA IMT measurement, allows us to reliably predict the occurrence of lacunar infarcts compared with other infarct subtypes.

In conclusion, IMT measurements may add data to the predictive power, represented by a constellation of findings, with respect to lacunar versus nonlacunar infarcts.

References


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