Does a Relationship Exist Between Carotid Stenosis and Lacunar Infarction?

J. Tejada, MD, PhD; E. Díez-Tejedor, MD, PhD; L. Hernández-Echebarría, MD; O. Balboa, MD

Background and Purpose—The presence of carotid stenosis (CS) in a patient with lacunar stroke is usually considered an indication of atherosclerosis and not directly related to the development of this infarction subtype. This study was designed to determine the relationship between CS and lacunar infarction (LI) and to assess the differences between single and multiple LIs.

Methods—We classified 330 patients with a first-ever cerebral infarction in the carotid territory into LI and non-LI (NLI) groups. In the LI group, patients with a single LI and those with multiple LIs were identified. In this last subgroup, 2 patterns were identified: 1 subtype with lacunar lesions distributed in both cerebral hemispheres, and another with lesions predominantly in 1 hemisphere.

Results—In the LI group, isolated CS was significantly more frequent on the homolateral side than on the contralateral side (odds ratio [OR], 5.5; 95% CI, 1.2 to 23; \( P = 0.03 \)). A significant relationship between the pattern of distribution of the infarctions in only 1 hemisphere and homolateral CS was observed (OR, 4.4; 95% CI, 0.9 to 19; \( P = 0.03 \)). In a multivariate analysis, the following variables were found to predict unilateral multiple LI: left ventricular hypertrophy (OR, 9.1; 95% CI, 2.5 to 33.6) and homolateral CS (OR, 75%; 95% CI, 2.0 to 99.6).

Conclusions—The significant incidence of isolated ipsilateral CS in patients with LI located in the carotid territory and the relationship of CS to ipsilateral multiple LI suggest that CS has a very important role in the development of LI. (Stroke. 2003;34:1404-1411.)

Key Words: carotid stenosis ■ lacunar infarction

Lacunar infarctions (LIs) represent 25% of ischemic strokes.1–3 Unlike other types of ischemia such as cortical infarctions or infarctions in watershed territory in which the relationship with atherosclerotic extracranial lesions is well established, the question of whether the occlusion of a perforating artery by mechanisms related to atherosclerotic extracranial lesions can result in an LI is controversial.4 Even Fisher,5 the creator of the “lacunar hypothesis,” observed in some postmortem examinations that it was not possible to explain all LIs as secondary to specific disease of the perforating vessel and assumed that the cases in which no histological abnormality was identified in the perforating artery could indicate that the occlusion depended on embolic mechanisms. Animal models have been achieved that can demonstrate that embolic material originating from an artificially created source may enter the perforating arteries and occlude them, producing an LI.6,7

Clinical studies aimed at the evaluation of the relationship between carotid stenosis (CS) and LI can be divided into those carried out on symptomatic LI,8–19 those carried out on asymptomatic or silent LI,20–24 and those carried out on lacunar-size deep infarctions that are expressed as nonlacunar syndromes.9,10,25–30 It has been observed that the incidence of CS in patients with symptomatic LI is much lower than that found in non-LIs (NLIs). However, the pathogenic value of CS is questionable because its appearance in patients with LI has been associated with stenosis in the contralateral carotid artery in more than half of the cases.12,31 These findings suggest that carotid lesions should be considered within the context of generalized arteriosclerosis rather than as a potential factor for the development of this type of subcortical ischemia. On the other hand, asymptomatic LI has been related to carotid obstructive lesions,23,24 although this association has not been confirmed by other authors.20

Despite the fact that the pathogenic relationship between LI and CS is still not well defined, the trials carried out to demonstrate the efficiency of carotid endarterectomy included patients with minor stroke infarctions located in the perforating artery territory.32–35

The aim of this study was to evaluate the role of CS in LI through the use of selected patients with clinical or radiological criteria for ischemia in the carotid territory and to evaluate the causes of single LI and multiple LIs separately.
Subjects and Methods

From November 1992 to December 1997, data were prospectively collected from patients with a first-ever cerebral infarction in the carotid territory and no evidence of a cardiac source of embolism who were admitted to the neurological ward of our hospital. All patients underwent a CT scan on admission and a second CT after 72 hours (Philips CX Tomoscan or Elscint Twin Flash). Four-millimeter-thick slices were scanned in the examination of posterior fossa up to the chiasmatic cistern, and 8-mm slices were used above that level. Complete ultrasound examination of the carotid arteries with continuous-wave Doppler sonography and color-coded duplex sonography was performed on a Philips SD-800 system with a 7.5-MHz linear-array transducer with 5-MHz Doppler frequency. Doppler sonography parameters were used to determine the degree of stenosis according to the established criteria. In the narrowest part of the stenosis, the cross-sectional area ratio (minimal residual area to total area) was measured for stenosis quantification. Final stenosis grading of the carotid artery stenosis used velocimetric criteria, measuring pulsed peak velocities in the stenosis. Cerebral angiography (digital angiography, Phillips Integris) or MR angiography (Magnetom SP1 Tesla System, Siemens AG) was performed in selected patients and in those with CS >50%. CS was evaluated with the North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) method. Electrocardiography and echocardiography were performed to evaluate cardiac abnormalities with embolic risk.

The risk factors considered were age, sex, tobacco consumption (10 cigarettes a day in the 6 months before ischemic stroke and ex-smokers who had a similar consumption for periods of 6 months on a regular basis), alcohol consumption (>80 g/d), diabetes (fasting glucose levels >140 mg/mL or the use of medication to control glucose), hypertension (HT; known or in treatment with antihypertensives, arterial blood pressure >150/90 mm Hg before the cerebral ischemic stroke or a week afterward, or presence of hypertensive heart disease on ECG or echography), left ventricular hypertrophy (LVH) defined by ECG or echocardiogram, ischemic heart disease (typical angina, myocardial infarction, or ischemia-type signs on ECG), previous carotid transient ischemic attack (TIA), peripheral vascular disease (intermittent claudication or vascular surgery), lipid profile (total cholesterol, triglycerides, and high-density lipoprotein [HDL] cholesterol), hematocrit, and fibrinogen. The presence of leukoaraiosis, defined as an alteration in the white matter with appearance of areas of attenuated density in the periventricular regions and centrum ovalis detected on CT, was also evaluated.

Classification of Patients

Patients were classified according to clinical and radiological features into the LI and NLI groups. Within the LI group, patients with a single LI and those with multiple LIs were distinguished. In this last subgroup, 2 CT scan patterns were identified: a subtype with lacunar lesions distributed in both hemispheres and another subtype with a CT showing lesions located predominantly in 1 hemisphere. We compared the following 3 groups: patients with NLI, patients with a single LI, and those with multiple LIs (unilateral and bilateral lesions).

LI Groups With Carotid Distribution

In this group, patients demonstrated 1 of the known clinical lacunar syndromes (pure motor syndrome, sensitive-motor syndrome, ataxic hemiparesis, and dysarthria clumsy hand), as well as hypodensity on the CT scan, with a diameter of 1.5 cm, not visible in 2 adjacent cuts, with an appropriate anatomic localization of the deficit in dependent areas of the perforating arteries of the carotid network. Patients with a pure sensitive syndrome were excluded because this is usually caused by a thalamic lesion in dependent territories of posterior circulation. These criteria were used to achieve a greater reliability of clinical syndrome and radiological image association and adapt it to the concept of probable LI located in an area supplied by the carotid network.

In this group, cerebral CT allowed differentiation of patients with 1 isolated lesion (isolated LI) or with >1 LIs (multiple LI).

Those patients with a first event of lacunar syndrome, in which the small deep infarct responsible for the deficit and >1 infarct with lacunar-type radiological characteristics were detected on CT, were defined as multiple LIs. Two subgroups were defined. The first was a predominance of lesions with lacunar-type radiological characteristics in 1 hemisphere. The predominance was established by evaluating the number of lesions in both hemispheres, and subjects were included in this subgroup when there existed ≥1 isolated lesions in 1 hemisphere and ≥2 lesions in the contralateral hemisphere, all situated in anterior circulation areas. The second was homogenous distribution of the lesions. This group consisted of patients with multiple LIs in both hemispheres who had a CT showing symmetric distribution.

NLI Group

Patients with cortical and subcortical infarctions (territorial) with a hypodense area >1.5 cm in the carotid territory and an appropriate neurological deficit were included in this category.

Statistical Analysis

The SPSS program for Windows was used for the analyses. Comparisons between groups were performed by the t test (or the Mann-Whitney test for abnormally distributed variables), and the χ² test was used to compare noncontinuous data. Logistic regression was used to determine which risk factors were independently related to the presence or absence of LI or multiple LIs. The level of significance was set at P < 0.05.

Results

Of a total of 922 patients, 330 fulfilled the criteria of localization of infarction in dependent areas of carotid circulation and absence of major embolic heart disease. Of these, 125 corresponded to NLI and 205 to LI (135 isolated, 70 multiple LIs).

The comparative study of the vascular risk factors showed that the isolated LI and NLI groups had similar characteristics with regard to their presence and distribution except for previous history of TIA, which was more frequent in the NLI group (odds ratio [OR], 0.4; 95% CI, 0.2 to 0.8; Table 1).

A total of 114 angiographic procedures were performed (31 of the invasive type and 22 by MR angiography in the LI group; 49 by digital angiography and 12 by MR in the NLI group). In the isolated LI group, the incidence of CS >50% was 22% for the artery ipsilateral to the symptomatic hemisphere and 8% for the contralateral side. For stenosis >75%, incidences of 14% (ipsilateral) and 8% (contralateral) were observed. Four cases of ipsilateral carotid occlusion were detected in this group. In the comparative analysis with the NLI group, the frequencies (both CS ≥50% and ≥75%) were significantly lower in the LI group for both the symptomatic and contralateral arteries (Table 2).

The presence of isolated homolateral or contralateral CS is distributed in similar proportions in both groups of infarctions (isolated LI and NLI). In the LI group, isolated CS was significantly more frequent on the homolateral side than on the contralateral side (22 of 30 versus 4 of 12; OR, 5.5; 95% CI, 1.2 to 23; P = 0.03). As for the contralateral artery, it could be observed that most patients with contralateral CS showed associated CS in the symptomatic artery (8 of 12 in the LI group and 20 of 36 in the NLI group). In the logistic regression analysis in the isolated LI group using the presence
The relationship of LI with hemodynamically significant carotid or potentially embolic lesions is a controversial question. Nevertheless, the high incidence of this type of ischemia and the circumstances, which are very well recognized and cannot be exclusively associated with LI with a pathological pattern of the perforating artery dependent on HT or diabetes, require the evaluation of other disease mechanisms. In this study, we tried to determine with great accuracy the pathogenic role of carotid atheromatosis in LI. The selection of patients with isolated LI was made by the use of criteria designed to include those whose responsible lesion could be directly observed, omitting patients with potentially embolic heart disease and those with a deficit in which the carotid topography was not clearly defined. These considerations have not usually been taken into account in studies aimed at the same objectives that included patients with negative image examinations, although the inclusion of LI in a vertebrobasilar localization or lacunar syndromes related to cortical ischemia may lead to significant errors.

The comparative analysis of the risk factors in the 2 groups (isolated LI and NLI) revealed differences only in history of TIA. The other variables presented similar frequencies, even those that have been specifically related to LI (HT or diabetes). The presence of CS >50% was significantly higher in patients with NLI for both the artery ipsilateral and the artery contralateral to the ischemia. This result is similar to those obtained by other authors. In these studies, the technique used to evaluate the grade of CS was arteriography, Doppler, or both. In 3 of the studies in which CS >70% has been reported, the incidence of this parameter was >14%. Ghika et al identified a hemodynamically significant carotid lesion in 32 cases of a series of 102 (31%), and the European Carotid Surgery Trial (ESCT) trialists reported a percentage of 28% (stenosis criteria, including ulcerated plaques). Horowitz et al identified a hemodynamically significant carotid lesion in 32 cases of a series of 102 (31%), and the European Carotid Surgery Trial (ESCT) trialists reported a percentage of 19% in the cohort studied (Table 5). Regarding CS in the contralateral artery, our study revealed a higher percentage of cases with CS >70% in the NLI group compared with the LI group, indicating that this marker of atheromatosis does not occur more frequently in the latter group. This finding is in contrast to other studies in which similar percentages for severe CS in the contralateral artery in both groups have been reported. Another finding of interest is the observation in the LI group of patients with occlusions of the extracranial carotid internal artery (4 of 35 in the homolateral artery). This has not been specifically reported in previous studies, and in those studies in which it was referred to, no patients with carotid occlusion were detected in the LI group. Nevertheless, the association of carotid occlusions and lacunar syndrome with LI has been confirmed in particular cases in clinical series. Lindgren et al found 6% of the cases (3 of 49) with stenosis in the group of patients with LI.

Taking these previous findings into account and comparing them with those obtained in this study, we can affirm that, although the incidence of significant CS was significantly lower in the LI than the NLI group, this parameter cannot be ignored in the LI group because, when the selection proce-
The role of CS in the presence of LI has been recently evaluated in the patients enrolled in NASCET. In this study, 12.2% of the patients with 70% to 99% stenosis had a hemispheric stroke classified as probable lacunar stroke (lacunar syndrome and an appropriate lacunar lesion). In addition, carotid endarterectomy reduced the risk of stroke by 35% in this type of cerebral ischemia.

The ischemic lesions identified on CT as clinically asymptomatic or silent can be of 3 types, depending on their localization and morphology: small deep infarctions, infarctions in the territory of a main brain artery, or infarctions in marginal territories of the 2 main arteries. It is not infrequent that asymptomatic lacunar-size infarctions are detected by imaging studies in patients showing a first ischemic episode (lacunar syndrome). It is also clear from clinical experience that, on numerous occasions, the hypodense lesions observed on CT clearly predominate in 1 hemisphere.

Within the risk factors, the presence of peripheral arterial disease seemed to be a significant variable for the prediction of CS in the isolated LI group. This observation is of great clinical importance because it allows the selection of LI patients with a higher probability of developing carotid lesion.

Data related to the presence of significant isolated CS (CS not associated with contralateral stenosis) are also interesting. Previous studies showed a low incidence of isolated CS and a majority of patients with contralateral CS. Thus, these findings suggest that CS was a clinical marker for atherosclerosis rather than a potential disease factor. In the series presented here, 73% of the ipsilateral CS was isolated, whereas for contralateral CS, the percentage of isolated CS was smaller than that of multiple CS. Therefore, and according to those observations, although significant CS was observed at lower levels in LI, its pathogenic value should be taken into account because, when detected on the symptomatic side, it is not only a marker of atheromatosis but also a process potentially linked to LI.

### TABLE 3. Baseline Characteristics of the Single LI and Multiple LI Patients

<table>
<thead>
<tr>
<th>Baseline Characteristics/Risk Factors</th>
<th>Single LI (n=135)</th>
<th>Multiple LI (n=70)</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.5±8.7</td>
<td>67.3±8.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>100 (74)</td>
<td>51 (73)</td>
<td>1.1</td>
<td>0.8–2.5</td>
<td>NS</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>75 (56)</td>
<td>50 (71)</td>
<td>2.0</td>
<td>1.08–3.7</td>
<td>0.027</td>
</tr>
<tr>
<td>LVH, n (%)</td>
<td>43 (32)</td>
<td>34 (49)</td>
<td>2.0</td>
<td>1.1–3.7</td>
<td>0.0019</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>30 (22)</td>
<td>17 (24)</td>
<td>0.8</td>
<td>0.4–1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>52 (38)</td>
<td>29 (41)</td>
<td>1.1</td>
<td>0.6–2.0</td>
<td>NS</td>
</tr>
<tr>
<td>HDL &lt;35 mg/dL, n (%)</td>
<td>35 (26)</td>
<td>21 (30)</td>
<td>1.2</td>
<td>0.6–2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertriglyceridemia, n (%)</td>
<td>27 (20)</td>
<td>13 (19)</td>
<td>0.9</td>
<td>0.4–1.9</td>
<td>NS</td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>15 (11)</td>
<td>10 (14)</td>
<td>1.3</td>
<td>0.5–3.1</td>
<td>NS</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>16 (12)</td>
<td>9 (13)</td>
<td>1.1</td>
<td>0.4–2.6</td>
<td>NS</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>17 (13)</td>
<td>12 (17)</td>
<td>1.4</td>
<td>0.6–3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>36 (27)</td>
<td>17 (24)</td>
<td>0.9</td>
<td>0.4–2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>71 (53)</td>
<td>26 (37)</td>
<td>0.5</td>
<td>0.2–0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Hematocrit &gt;45%, n (%)</td>
<td>48 (36)</td>
<td>35 (50)</td>
<td>1.8</td>
<td>1.0–3.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Fibrinogen &gt;450 mg/dL, n (%)</td>
<td>30 (28)</td>
<td>29 (41)</td>
<td>2.4</td>
<td>1.3–4.6</td>
<td>0.039</td>
</tr>
<tr>
<td>Leukoaraiosis, n (%)</td>
<td>9 (7)</td>
<td>31 (44)</td>
<td>11.1</td>
<td>4.8–25.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

### TABLE 4. CS in Multiple LI: Unilateral and Bilateral Patterns

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unilateral Pattern (n=25), n (%)</th>
<th>Bilateral Pattern (n=45), n (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral carotid stenosis &gt;50%</td>
<td>9 (36)</td>
<td>8 (18)</td>
<td>0.08</td>
<td>2.6</td>
</tr>
<tr>
<td>Contralateral carotid stenosis &gt;50%</td>
<td>8 (32)</td>
<td>10 (22)</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Ipsilateral carotid stenosis &gt;75%</td>
<td>6 (24)</td>
<td>3 (7)</td>
<td>0.03</td>
<td>4.4</td>
</tr>
<tr>
<td>Contralateral carotid stenosis &gt;75%</td>
<td>0 (0)</td>
<td>3 (7)</td>
<td>0.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>
hemisphere. These findings suggest that the carotid lesions could intervene in the development of LI situated in dependent areas of the perforating arteries because of a hemodynamic or microembolic mechanism. The radiological pattern of multiple LI distributed in both hemispheres is more often associated with leukoaraisis, and as suggested, common microangiopathic mechanisms could intervene in both processes.\(^4\,^8\,^9\)

The relationship of silent infarction and carotid disease has not been adequately established, probably because it is an aspect of cerebrovascular disease in which application of the appropriate methodology (patient selection, obtaining of samples from outpatients, definition of the comparative groups) is not easy. In cases of significant carotid obstruction, studies of brain blood flow showed the possibility of the development of asymptomatic small deep infarctions by a hemodynamic mechanism.\(^19\) In an initial study on this subject, a relationship was found between the grade of CS and the incidence of ipsilateral silent infarctions at the stenosis location,\(^23\) and this association was more evident between silent lesions >1 cm and high-grade carotid lesions or ulcerated stenosis.\(^22\) Results of the Asymptomatic Carotid Stenosis Study (ACAS) did not show any relationship between CS and silent infarction.\(^21\) Boon et al,\(^20\) in their analysis of silent infarctions in 755 patients with a first supratentorial ischemic episode, observed that small silent deep infarctions are preferably associated with small symptomatic infarctions and that the other 2 types of silent infarctions (territorial and watershed) appeared more frequently related to symptomatic NLI.s and to emboli of cardiac or arterial origin.\(^21\)

Only patients with LI were included in our study, and the radiological pattern of unilateral distribution was associated with the presence of ipsilateral CS. The methodological differences between the studies cited above and the present study are noteworthy. In ACAS,\(^21\) the authors studied individuals with diagnosed CS but without previous history of cerebrovascular disease. In the study of Hougaku et al,\(^24\) patients examined with MR and ultrasonography who had at least 1 vascular risk factor and no history of stroke were included. The present series included inpatients with symptomatic cerebrovascular disease (multiple LI) in whom the presence of CS was evaluated as part of the complementary examinations. Nevertheless, it can be argued that the number of patients included here is insufficient to obtain consistent results and that studies including a higher number of individuals are desirable.

In summary, our data show that moderate CS appears in appreciable proportions of LI, depending on the carotid circulation, and that significant CS is related to ipsilateral multiple LIs. For these reasons, we conclude that CS plays a pathogenic role in ipsilateral LI and is not merely an outside factor in the development of LI. Thus, its presence in patients with this type of cerebral ischemia should be considered when therapeutic decisions are made.

### References


### TABLE 5. Clinical Studies Comparing the Incidence of CS in LI and NLI

<table>
<thead>
<tr>
<th>Study</th>
<th>LI, n (%)</th>
<th>NLI, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ipsilateral Carotid</td>
<td>Contralateral Carotid</td>
<td>Patients,</td>
</tr>
<tr>
<td>Kappelle et al(^{12})</td>
<td>45</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>Ghika et al(^{10})</td>
<td>100</td>
<td>28 (28)</td>
<td></td>
</tr>
<tr>
<td>Horowitz et al(^{11})</td>
<td>102</td>
<td>32 (31)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Norving and Crongvist(^{15})</td>
<td>61/58*</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Tegeler et al(^{18})</td>
<td>55</td>
<td>17 (13)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Boiten and Lodder(^{6})</td>
<td>86†</td>
<td>11 (13)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Landi et al(^{13})</td>
<td>88</td>
<td>16 (18)</td>
<td></td>
</tr>
<tr>
<td>ECST(^{23})</td>
<td>222</td>
<td>43 (19)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Present study</td>
<td>135</td>
<td>30 (22)</td>
<td>12 (9)</td>
</tr>
</tbody>
</table>

*Number of patients with carotid stenosis determined.
†Total number of patients: 103 lacunar and 144 nonlacunar strokes. Number of patients with a procedure for carotid stenosis performed.
The Fall and Rise of Lacunar Infarction With Carotid Stenosis

Lacunar infarction (LI) is one of the most common subtypes of ischemic stroke.⁴ Introduced by Fisher,⁵ the term lacunar infarction is now established in the literature. However, the concept of LI remains a subject of debate,⁶ since lacunar syndromes were not found to be exclusively pathognomonic of small-artery disease.

In this issue of Stroke, Tejada et al⁷ address the potential relationship between LI and the presence of an internal carotid artery stenosis (ICAS). Whether this finding is causative or coincidental is debatable. Previous studies⁸–¹⁴ have already investigated the question with opposite opinions. In the ECST study, patients with LI had less severe ICAS, leading to the hypothesis that severe ICAS in patients with LI may just be coincidental. Recently, studies using carotid and transcranial ultrasound have revisited this question. In the

Editorial Comment

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study of Cupini et al,15 the intima-media thickness (IMT) of carotids as measured by ultrasound was significantly higher in patients with nonlacunar infarction (NLI) versus both those with LI and controls. The IMT, considered as an early marker of atherosclerosis when increased, may have a predictive value to separate LI versus NLI. However, another study17 also using the IMT did not find a difference between LI and NLI. Mead et al16 studied patients with recent LI and compared the results of carotid and middle cerebral artery (MCA) ultrasound. The authors16 could not find a difference between patients with LI and those with NLI for either carotid or MCA disease. They concluded that ICA stenosis in patients with LI may be coincidental.

In this debate, the article by Tejada et al4 investigates the relationship between LI and ICAS in a large prospective study of 330 patients, including 205 with LI and 125 with NLI. The authors draw 4 interesting conclusions: First, even if the presence of significant (>50%) ICAS is lower in LI compared with NLI, the probability of carotid disease increases when LI is present in the ipsilateral carotid territory. Second, ICAS without contralateral ICAS was reported in 73% of the cases, suggesting that ICAS is indeed a marker of ipsilateral LI. Third, logistic regression analysis in “pure” LI associated with ICAS >50% showed that peripheral artery disease was the only significant factor associated with stroke. Fourth, the combined presence of a left ventricular hypertrophy (LVH) with ICAS >70% determined predominance of LI in 1 hemisphere, suggesting a role of ICAS. Multivariate analysis showed that only 2 factors predicted unilateral LI:LVH and ICAS >75%. Tejada et al4 conclude that moderate ICAS may appear in an appreciable percentage of LI in the ipsilateral territory and that severe ICAS is related to multiple LI.

The main message of the report is the identification of the need to search for large-artery disease as the cause of LI. The question raised is whether the etiological association between ICAS and LI should be accepted as a final evidence. The study of Tejada et al4 presents some limitations: First, authors used only clinical examination and CT scan (not MRI) to diagnose LI. Cortical small infarcts may mimic LI and inversely,18 so that MRI with DWI is currently the “gold standard” to investigate an isolated and “active” lacune. Second, because of possible differences between the 2 centers for grading the degree of ICAS, it is reasonable to assume that some ipsilateral or contralateral ICA stenoses were overestimated. Indeed, only 34.5% of cases had radiological examination (DSA or MRA) to confirm ultrasound. In this series, 73% of ipsilateral ICAS were not associated with contralateral ICAS, which is very high. The problem is that criteria to grade ICAS and the technique used, either DSA or ultrasound or MRA, limit the comparisons with other studies. Third, as seen in the article’s Tables 1 and 3, there are no precise data on potential cardiac sources of embolism and the type of echocardiography used. Moreover, as the neuroimaging used to diagnose LI was CT scan, some LI located in the brainstem may have been considered as hemispheric LI ipsilateral to ICAS.

Nevertheless, the study of Tejada et al4 is a new cornerstone illustrating the controversy about LI. For instance, we19 have demonstrated that atrial fibrillation is not always coincidental in patients with subcortical infarcts and a lacunar stroke. We also suggested that some clinical and radiological characteristics were different between patients with subcortical infarcts and cardioembolism versus patients with subcortical infarcts due to small-artery disease. New neuroimaging has shown DWI to be a highly sensitive and specific diagnostic tool for acute small-vessel infarction. These studies7,20–22 accepted the concept that LI may occasionally be associated with ICAS. In addition, an animal model of stroke23 has demonstrated lacunes in the brain of normotensive rats after nonocclusive thrombus in the carotid. DWI-MRI performed in acute lacunar syndrome24 showed that there may be a variety of brain lesions and locations. Another DWI study25 reported that almost 1 in every 6 patients presenting with a classical lacunar syndrome had multiple infarcts, including cortical lesions. A recent study26 showed that MCA stenosis should also be found in patients with LI. DWI combined to PWI27 altered the final diagnosis of infarct pathogenesis from small-vessel disease to large-artery embolism in 13 of 19 patients with LI.

The study of Tejada et al4 suggests that lacunar syndromes are not indicative of a single underlying mechanism of stroke. However, further studies using a large number of patients and modern diagnostic tools (DWI and PWI MRI) are needed before altering the current management28 of lacunar infarction.

G. Devuyst, MD, Guest Editor
J. Bogousslavsky, MD, Guest Editor
Department of Neurology
Lausanne CH
Lausanne, Switzerland

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Editorial Comment: The Fall and Rise of Lacunar Infarction With Carotid Stenosis
G. Devuyst and J. Bogousslavsky

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