Silent Brain Infarctions in Patients With First-Ever Stroke
A Community-Based Study in Umbria, Italy

Stefano Ricci, MD; Maria Grazia Celani, MD; Francesco La Rosa, SD; Enrico Righetti, MD; Emilio Duca, MD; and Nevia Caputo, MD

Background and Purpose: The relative frequency of computed tomographic evidence of old cerebral infarctions without prior history of stroke, and their effect on short- and long-term outcome of patients with first-ever ischemic stroke, are currently unknown. Silent infarctions may relate to specific risk factors and may influence the rate of survival free of handicap.

Methods: We studied the prevalence of such lesions in patients registered with SEPIVAC, a community-based survey of stroke incidence and outcome in the Sixth Local Health Unit of Umbria, Italy. Of 375 first-ever strokes, 209 patients with cerebral infarction (computed tomogram done within 30 days after the stroke) were included in this study. Computed tomograms were reviewed blindly, and cases were classified as having a single lesion or multiple lesions; in the latter case, it was assumed that at least one silent brain infarction was present. The two groups were compared in terms of risk factors and outcome. To avoid a selection bias, these patients were also compared with 68 patients who were not submitted to computed tomography but were judged on clinical grounds to have a >90% probability of having suffered a cerebral infarction.

Results: Risk factors and outcome did not differ between patients without and with a computed tomogram. In the latter group, 80 patients (38.3%; 95% confidence interval, 31.7%–44.9%) had silent brain infarction. Male sex (odds ratio, 1.84; 95% confidence interval, 1–3.4), ischemic changes on an electrocardiogram (odds ratio, 2.5; 95% confidence interval, 1.3–4.9), and—in the multivariate analysis—hypertension (odds ratio, 1.46; 95% confidence interval, 1.1–2) were significantly more frequent in these patients. Outcome at 1, 6, and 12 months was not influenced by the presence of silent infarctions.

Conclusions: This community-based study shows that silent brain infarctions in patients with first-ever stroke are not significantly related to risk factors commonly described in hospital-based series (atrial fibrillation, transient ischemic attack, etc.); rather, silent infarctions seem to be a marker of widespread vascular disease. (Stroke 1993;24:647–651)

Key Words • cerebral infarction • Italy • risk factors • stroke outcome

It is not unusual to find computed tomographic (CT) evidence of previous asymptomatic brain infarction(s) in patients who present with a first-ever-in-a-lifetime stroke. Interest in these lesions is growing because of suggestions of a worse prognosis, perhaps related to the development of multi-infarct dementia. However, very few studies have addressed the topic in terms of the frequency and characteristics of these silent lesions in the whole population of stroke patients. The National Institute of Neurological and Communicative Disorders and Stroke Stroke Data Bank (SDB)1 was a hospital-based study. Although this allowed a careful and detailed study of each patient, it introduced a bias2 because both very mild and very severe cases might have been overlooked. The Framingham Study3 was population based, but the cohort was selected by age at entry and not all the possible stroke cases in a given period were included in the retrospective review. Therefore, data from community-based, prospective studies on stroke incidence should be examined for a more exact estimate of the prevalence of silent brain infarctions and their relation with risk factors and outcome. We present our results from Studio Epidemiologico sull’Incidenza delle Vascolopatie Acute Cerebrali (SEPIVAC) or Epidemiological Study on the Incidence of Cerebrovascular Diseases.

Subjects and Methods

SEPIVAC is a community-based survey of the incidence and outcome of cerebrovascular diseases in the Sixth Local Health Unit of Umbria, central Italy; the methodology of SEPIVAC has been described elsewhere.4,5 In brief, from September 1, 1986, to August 31, 1989, all possible cases of first-ever-in-a-lifetime stroke (hereafter referred to as first stroke) in a population of
49,218 were registered. There were 375 cases of first stroke during the study period; of those, 218 (58.13%) were definite cerebral infarctions according to the Oxfordshire Community Stroke Project classification6 (clinical diagnosis was confirmed by a CT scan performed within 30 days after the stroke). Two CT machines (CRG ND 8000 and GE CT 9800) were used. We also considered 68 patients registered in SEPIVAC as having suffered a probable infarction; they were not submitted to a CT examination within 30 days after the stroke but were judged to have a >90% probability of having suffered a cerebral infarction.2 Patients were followed up at 1, 6, and 12 months, and survivors were assessed for stroke recurrences and residual handicap: the Rankin Scale7 was used to measure handicap before and after the stroke, and patients with a score of >2 were considered handicapped. For each case, clinical data (including the clinical subtype of infarction8), risk factors, and outcome were recorded. At the end of the study period all the available CT scans were collected and one of us, blinded to the clinical details of each case, reexamined the scans, describing the site, size, and number of every hypodense lesion. A lacunar infarct was defined as a hypodensity in the region of the basal ganglia, corona radiata, or brain stem with a maximum diameter of <1 cm; all other lesions were defined as nonlacunar. Thereafter we compared these reports with the clinical picture. Cases with no evidence of focal lesions on a CT scan or showing a hypodensity in a region compatible with the clinical symptoms and signs were considered as having a single lesion. When the above-mentioned conditions were not fulfilled, cases were classified as having multiple lesions. When a CT scan was included in the multiple lesions group, the patient was considered to have suffered at least one silent brain infarction. Patients with and without silent infarctions were compared in terms of age, sex, clinical presentation (available in 208 cases), vascular territory, and risk factors.9 The following risk factors were considered: hypertension, history of myocardial infarction and/or angina, atrial fibrillation (AF), smoking habit (current smoker, ever smoker), diabetes, claudication, carotid bruit, Doppler sonographic findings (available in 118 cases), and electrocardiographic (ECG) findings (available in 206 cases). (See the appendix for definitions of risk factors.) The influence of silent infarction on outcome was then analyzed. The t test, Mann-Whitney U test, χ2 test, Fisher test, and odds ratio (OR) with 95% confidence interval (CI) were used for the univariate analysis (EPINFO software), the χ2 test for goodness of fit was used to compare expected and observed frequencies (STATGRAPHICS), and the Mantel-Haenszel procedure (EPINFO) and multiple logistic regression (SPSS, backward procedure) were used for the multivariate analysis.

Results

Compared with the 68 patients without a CT scan, the 218 patients with definite cerebral infarction were younger (mean ages 71 and 78 years, p < 0.000006), less likely to have a prestroke handicap (OR, 0.10; 95% CI, 0.04–0.24; p < 0.00001), less likely to be at home during the acute phase of the stroke (OR, 0.36; 95% CI, 0.17–0.77; p < 0.007), and less likely to be smokers (OR, 0.46; 95% CI, 0.24–0.85; p < 0.01). No other risk factor differed significantly between these two groups. Poststroke handicap at 1, 6, and 12 months did not differ either (p = 0.18, 0.09, and 0.58, respectively).

Of 218 CT scans done during the study, four were no longer available, having been done privately, four were missing from the archive, and in one case, because the camera was out of order, the neuroradiologist wrote the report from the monitor. Of the 209 CT scans reviewed, 129 (61.7%; 95% CI, 55.1%–68.3%) were classified as showing a single lesion and 80 (38.3%; 95% CI, 31.7%–44.9%) as showing multiple lesions. In the single lesion group, the CT scan was normal in 79 cases and showed a single hypodensity in the remaining 50 cases. In the multiple lesions group the CT scan showed more than one hypodensity in 70 cases (including 23 with a lesion compatible with the clinical presentation), whereas in 10 cases the CT scan showed only one hypodensity that was considered not compatible with the clinical presentation. Reasons for this decision included infratentorial stroke and “old” (that is, no mass effect or edema, and sharp boundaries) cortical hypodensity (four cases), cortical stroke and infratentorial hypodensity (one case), “old” small hypodense lesion in patients with severe stroke and CT scan done within 12 hours (three cases), and site of the lesion not compatible with the symptoms (two cases). The median interval between stroke onset and CT examination was 7 days for the single lesion group and 6 days for the multiple lesions group (p = 0.36). A symptomatic infarction was detected in 38.8% of patients with a single lesion and in 28.8% of those with multiple lesions (p = 0.18).

The two groups did not differ in mean age (single lesion group, 71.1 years; multiple lesions group, 72.4 years; p = 0.86), vascular territory of the stroke (p = 0.85), or clinical presentation (p = 0.77). Seventeen of 80 patients with multiple lesions and 29 of 128 with a single lesion presented with a lacunar syndrome (p = 0.91). As far as the CT appearance of the multiple lesions is concerned, lacunar infarcts were equally distributed in the right and left hemispheres: there were 13 right-hemisphere, 16 left-hemisphere, and 13 bilateral multiple lesions. Right-hemisphere nonlacunar infarcts were slightly more frequent than left-hemisphere ones (23 and 15, plus two bilateral multiple lesions and 11 lesions in the posterior circulation), although the difference was not significant (χ2 for goodness of fit, p = 0.41).

Results of the univariate analysis on risk factors are shown in Table 1. Only male sex and the presence of ECG changes (judged by the consultant cardiologist as due to ischemia) were significantly related to the presence of a silent infarction. However, smoking habit and hypertension showed an interesting trend, with the lower limit of the 95% CI of the OR greater than 0.9. Interestingly, a history of previous transient ischemic attacks (TIAs) did not appear to be significantly related to the presence of a silent infarction; furthermore, in three of 14 patients with TIAs in the multiple lesions group no lesion was possibly related to the TIA. Multivariate analysis (multiple logistic regression) was performed, including in the model all the risk factors but one; due to the small number of patients who had a Doppler examination, this variable was not included. Results are shown in Table 2. In addition to male sex and ischemic ECG changes, hypertension was also
TABLE 1. Risk Factors for Silent Brain Infarction—Univariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Multiple lesions</th>
<th>Single lesion</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>51/80</td>
<td>63/129</td>
<td>1.84*</td>
<td>1–3.4</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14/80</td>
<td>20/129</td>
<td>1.16</td>
<td>0.51–2.59</td>
</tr>
<tr>
<td>Smoker</td>
<td>19/80</td>
<td>21/129</td>
<td>1.60</td>
<td>0.76–3.39</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>23/80</td>
<td>30/129</td>
<td>1.33</td>
<td>0.67–2.63</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>42/80</td>
<td>51/129</td>
<td>1.69</td>
<td>0.93–3.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17/80</td>
<td>21/129</td>
<td>1.39</td>
<td>0.64–2.99</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44/80</td>
<td>54/129</td>
<td>1.70</td>
<td>0.93–3.10</td>
</tr>
<tr>
<td>Ischemic heart disease (infarction and/or angina)</td>
<td>8/80</td>
<td>7/129</td>
<td>1.94</td>
<td>0.61–6.24</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>14/80</td>
<td>12/129</td>
<td>2.07</td>
<td>0.84–5.11</td>
</tr>
<tr>
<td>Claudication</td>
<td>5/80</td>
<td>3/129</td>
<td>2.80</td>
<td>0.53–18.5</td>
</tr>
<tr>
<td>Carotid bruit</td>
<td>4/80</td>
<td>8/129</td>
<td>0.80</td>
<td>0.19–3.05</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>21/48</td>
<td>27/70</td>
<td>1.24</td>
<td>0.55–2.80</td>
</tr>
<tr>
<td>Ischemic changes on electrocardiogram</td>
<td>30/79</td>
<td>25/127</td>
<td>2.5*</td>
<td>1.27–4.93</td>
</tr>
</tbody>
</table>

*p < 0.05.

significantly related to the presence of a silent brain infarction.

The presence of a silent brain infarction did not affect the outcome at 1, 6, and 12 months. In fact, the number of patients who were dead or dependent at the three follow-up periods were 51, 49, and 48, respectively, in the multiple lesions group and 80, 74, and 69, respectively, in the single lesion group; ORs were 1.1 (95% CI, 0.6–2), 1.2 (95% CI, 0.6–2.2), and 1.3 (95% CI, 0.7–2.4), respectively. Even when considering death alone as an end point, no significant difference between the groups was observed: ORs were 0.26 (95% CI, 0.01–2.21) at 1 month, 0.96 (95% CI, 0.37–2.5) at 6 months, and 1.28 (95% CI, 0.54–2.99) at 12 months. Logistic regression confirmed these results.

Discussion

We have shown that up to 38% of patients with a first ischemic stroke have unrelated ischemic lesions documented when submitted to a CT examination within 30 days. Despite the minimization of possible selection biases by such a community-based study, some pitfalls may be recognized. First, 4% of definite cerebral infarctions were not included due to unavailability of CT recordings. Second, the patients with first stroke who received a CT examination were not a random sample, the decision for examination being based on several practical and clinical points (i.e., age, neurological status, availability of the machine, etc.); had we been able to examine all the patients with CT the proportion of silent lesions might have been different. However, the comparison with patients without a CT scan did not show important differences in terms of risk factors and outcome. Therefore, our results might not be too far from the real proportion of silent lesions in all patients with first stroke.

Silent infarctions were more common in this study than in the Framingham Study and the SDB.\cite{1,3} We did not use the same definition of silent brain infarction as the two American studies; yet, even if we consider the 10 cases with only one hypodense area as having a single lesion, the percentage of silent infarctions is still higher (33%) than that found in the Framingham Study and the SDB.

Results of CT scans in cerebral ischemia can vary according to the interval from the stroke to the CT examination; differing intervals might explain differing results. A silent infarction occurring shortly before a symptomatic one would be hidden by the "fogging effect" in an early CT scan but visible in a scan performed a few weeks later. However, a comparison cannot be made because the median intervals were not reported in the American studies.

The type of CT machine can also play a role, more modern devices being more sensitive. Had we used magnetic resonance imaging (MRI), silent infarction would probably have been even more frequent. The only MRI study of silent infarction was performed in 246 normal adults, 13% of whom had silent "lacunar" lesions.\cite{10}

A large hypodense lesion involving the whole territory of the middle cerebral artery caused by a clinically detectable stroke can mask an old, small, silent infarction. If the admission of more severe cases, and thus the percentage of large lesions, is higher in some studies, comparisons in terms of silent lesions might be biased. Because the frequency of such large lesions in the other studies cannot be analyzed, we examined the percentage of normal CT scans, which is similar in the Framingham Study (32%; 95% CI, 24–41%), the SDB (37%; 95% CI, 34–39%), and SEPIVAC (38%; 95% CI, 29–48%).

TABLE 2. Risk Factors for Silent Brain Infarction—Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.086</td>
<td>1.52</td>
<td>1.11–2.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.017</td>
<td>1.46</td>
<td>1.07–1.98</td>
</tr>
<tr>
<td>Ischemic changes on electrocardiogram</td>
<td>0.006</td>
<td>1.59</td>
<td>1.15–2.20</td>
</tr>
</tbody>
</table>
31%–44%), leading to the assumption that the number of large lesions does not differ greatly.

Organizational differences (including centralized review of CT scans) may explain the varying results between our study and the two American studies. However, recent data suggest a frequency of silent infarction of 35% in patients with first stroke admitted to a single hospital10; hence, we cannot advocate the study design (community-based versus hospital-based) as the only reason for the difference in results.

Different risk factors may contribute to the variation of silent infarction prevalence in different studies. Our patients were older than those in the SDB; we found no age difference between the single lesion and multiple lesions groups, but, like others,10 we found a higher prevalence of silent infarction in men. The presence of ischemic changes on an ECG was a strong predictor of silent brain infarction in both univariate and multivariate analyses; this fact can be easily explained by the consideration that coronary atherosclerosis is closely related to both extracranial and intracranial artery disease. Hypertension became significantly related to the presence of silent infarction only in the multivariate analysis; in the Framingham Study hypertension was not considered significant, yet there was an excess of 3.7% of hypertension in patients with silent infarction. Interestingly, TIA's are consistently unrelated to the presence of silent infarction.

Hospital-based series12–14 have suggested a higher prevalence of silent brain infarction in patients with AF than in patients in sinus rhythm. We could not confirm the role of AF, nor could another community-based study in Denmark.15 We therefore suggest that a selection bias is probably present in hospital-based series (i.e., age, severity of stroke, more men).

We could perform a Doppler study in only 56% of our patients, not chosen at random; more severe cases, older patients, and those who were treated at home were less likely to have the test. Therefore, we cannot draw any firm conclusions on the role of carotid artery disease in determining silent brain infarction, as suggested by several papers.16–19

We found no influence of silent infarction on short- and long-term outcome. This is in agreement with data from the SDB1 and a community-based TIA study,20 but not with data from a hospital-based series.21 Cognitive evaluation was not performed, yet handicap at 12 months reveals no evidence of a higher frequency of very severe, disabling, multi-infarct dementia in the multiple lesions group; however, a 1-year follow-up is probably too short to study this problem.22

Appendix

Definitions of Risk Factors

**Hypertension.** One of the following: 1) current treatment with antihypertensive drugs, and 2) diastolic blood pressure of >95 mm Hg and/or systolic blood pressure of >180 mm Hg in two different recordings either before the stroke or at least 1 week after the stroke.

**History of myocardial infarction and/or angina.** Myocardial infarction: a clinical event diagnosed as a myocardial infarct confirmed by hospital records and appropriate ECG and/or enzymes. Angina: diagnosis based on the standard Rose Questionnaire.

**Atrial fibrillation.** Evidence on ECG recording soon after the stroke or on ECG recording within the previous 2 weeks (when the poststroke ECG is in sinus rhythm).

**Claudication.** A very clear history of claudication or vascular surgery.

**Diabetes.** One of the following: 1) therapy with specific drugs, or 2) two or more abnormal results of glucose concentration (>120 mg fasting) in the past before the stroke and/or 1 week after the stroke.

**Ischemic changes on electrocardiogram.** ECG alterations judged to be due to ischemia by the local consultant cardiologist.

**Doppler findings.** A carotid stenosis diagnosed either by echotomography (direct measure) or by spectral analysis (systolic shift of >5,000 Hz with a 4-MHz probe).

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**References**


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