Silent Infarcts in Patients With Ischemic Stroke Are Related to Age and Size of the Left Atrium

F. Mounier-Vehier, MD; D. Leys, MD; Ph. Rondepierre, MD; O. Godefroy, MD; J.P. Pruvo, MD

Background and Purpose: Possible specific risk factors for silent infarcts remain unknown. The aim of this study was to investigate whether risk factors for silent infarcts differ from those for symptomatic infarcts in stroke patients.

Methods: Silent infarcts were defined as asymptomatic infarcts detected on computed tomographic scan in patients free of history of stroke and unrelated to the symptoms and signs of the index stroke. Of 595 consecutive patients with stroke or transient ischemic attacks, 116 (19%) had at least one silent infarct on the first computed tomographic scan performed within 24 hours after onset. They were compared with the 479 remaining patients for cerebrovascular risk factors and for presumed mechanism of stroke by means of the odds ratio method. A discriminant analysis was then performed in the subgroup of 216 patients with ischemic stroke who underwent an exhaustive cardiac and vascular workup.

Results: One hundred forty-one silent infarcts (99% confidence interval [CI], 29% to 41%) and 265 symptomatic infarcts (99% CI, 59% to 71%) were subcortical infarcts smaller than 15 mm. Univariate analysis showed that patients with silent infarcts were more likely to be older than 65 years (odds ratio [99% CI], 1.11 to 3.49) and to have left atrial enlargement on echocardiogram (odds ratio [99% CI], 1.02 to 26.70) and leukoaraiosis (odds ratio [99% CI], 1.39 to 4.21). Discriminant analysis found only two independent risk factors for silent infarcts: left atrial enlargement (P=.007) and age older than 65 years (P=.03); leukoaraiosis was not found to be an independent risk factor (P=.86).

Conclusions: Age and left atrial enlargement are the main risk factors for silent infarcts in patients with ischemic stroke or transient ischemic attacks. (Stroke. 1993;24:1347-1351.)

Key Words • aging • cerebral infarction • cerebrovascular disorders • risk factors

In patients with a first acute stroke, computed tomographic (CT) scans sometimes reveal early hypodensities not appropriate for the clinical deficits and suggestive of a previous brain infarction.1-3 To our knowledge there are only three studies dealing with such "silent" infarcts in consecutive patients with an acute stroke.4-6 These studies suggested that silent infarct might be related to age,1,3 arterial hypertension,1 smoking,3 and diabetes mellitus.2 However, their results can hardly be compared since these studies differed in their inclusion criteria. Moreover, two of the studies included their first patients more than 12 years ago and used different methods to determine the presumed cause of stroke.1,2 In other studies,4-6 patients were not always representative of all stroke patients because these studies were performed in selected populations: patients with transient ischemic attacks (TIA) or minor strokes and free of atrial fibrillation;2 patients with nonvalvular atrial fibrillation;4-6 and patients with carotid stenosis.7-10 These studies revealed that atrial fibrillation4-6 and carotid stenosis were predisposing factors for silent infarct.7-10 To our knowledge, systemic echocardiography in consecutive patients who were not selected on the basis of a potential cause of stroke has never been used in studies on silent infarct.1,10

The aim of our study was to determine, among consecutive patients with stroke or TIA, whether the presence of silent infarct is related to the various vascular risk factors for the presumed mechanism of stroke. Magnetic resonance imaging frequently detects silent lesions,11 but some are of nonvascular origin12; for this reason we performed this study by means of CT scan.

Subjects and Methods

We defined silent infaracts as asymptomatic infarcts detected on CT scan in patients free of any history of stroke and unrelated to the symptoms and signs of the index stroke.

We conducted this study over a 32-month period (October 1, 1989, through May 31, 1992) in 595 consecutive patients admitted as emergency cases for a stroke or TIA after exclusion of patients with previous neurosurgery or severe head trauma, cerebral arterial or arteriovenous malformation, and dementia. All patients were examined at admission by a resident in neurology and within 24 hours by a senior neurologist. These patients consisted of 299 men and 296 women with a mean age of 65.3 years (range, 15 to 100 years). One hundred ten patients had TIA, defined as episodes of focal cerebral dysfunction, presumably ischemic in ori-

Received January 14, 1993; revision received April 20, 1993; accepted April 22, 1993.

From the Departments of Neurology (F.M.-V., D.L., Ph.R., O.G.) and Neuroradiology (J.P.P.), University Hospital, Lille, France.

Correspondence to F. Mounier-Vehier, MD, Service de Neurologie B, Hôpital B, F-59037 Lille, France.
gin, lasting less than 24 hours and followed by return to normality, and 485 had a stroke, defined as clinical signs of focal disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin. The 485 stroke patients consisted of 383 patients with ischemic stroke and 102 with intracerebral hemorrhages. All patients had standard blood and urine tests, electrocardiography, chest radiography, and CT scan within 24 hours. When there was no hemorrhage on the first CT scan, a second scan was performed between day 8 and day 15. Doppler ultrasonography and B-mode echotomography, echocardiogram, and 24-hour electrocardiography were performed only in patients with ischemic strokes. Cerebral angiography was performed in selected cases. We prospectively collected the following data: age; sex; presence of hypertension, defined as systolic blood pressure higher than 140 mm Hg or diastolic blood pressure higher than 80 mm Hg or current treatment with antihypertensive drugs; diabetes mellitus, defined as serum glucose level higher than 1.05 g/L or current use of antidiabetic drugs; and previous TIA or stroke.

Computed tomographic scans were performed without contrast on a Siemens Somatom II machine (Siemens, Germany) with 5-mm contiguous slice thickness in a plane 12° negative to the canthomeathal plane. Scan time was 9.6 seconds per slice. In a conference, one neuroradiologist and one neurologist, blinded to the clinical data, determined the types of focal lesions on the first CT scan. In seven cases a consensus was not obtained between the two observers, and the final diagnosis was that of an independent neuroradiologist.

The interobserver and intraobserver reliability of this method of assessment of CT data has been previously evaluated as excellent. The observers determined whether the following lesions were present: cortical infarcts (any infarct involving the cortical surface and cerebellar infarcts); small subcortical infarcts (any infarct smaller than 15 mm involving the basal ganglia, thalamus, internal capsule, or white matter and sparing the cortical surface); border zone infarcts (any infarct located between two arterial territories); cortical hemorrhage (any hemorrhage involving the cortical surface); subcortical hemorrhage (any hemorrhage involving the basal ganglia, thalamus, or internal capsule and sparing the cortical surface); and hyperdense middle cerebral artery sign according to previous criteria. Hemorrhagic changes within an infarct were categorized as infarcts. For the purpose of this study, pure laterostriate infarcts larger than 15 mm were grouped together with cortical infarcts because they are attributed to large-vessel disease. Leukoaraiosis was defined using the criteria of Inzitari et al and scored by means of the 0- to 3-point rating scale of Blennow et al. Cerebral atrophy was assessed by means of the semiquantitative 0- to 3-point rating scale of Leys et al. Leukoaraiosis and cerebral atrophy were assessed for the hemisphere opposite to a unilateral focal vascular lesion and for the right hemisphere in the remaining patients.

For the first step of statistical analysis we divided the 595 patients into two groups: those with one or more silent infarcts and those without silent infarct. We compared the two groups according to the characteristics listed in Table 1 and the presumed cause of the

| TABLE 1. Comparison of Patients With One or More Silent Infarcts and Patients Without Silent Infarct |
|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|
| Patients without SI | Patients with SI | OR (99% CI) | P* |
| No. of subjects | 479 | 116 | 0.83 (0.49-1.42) | .37 |
| Male sex | 246 | 54 | 1.97 (1.11-3.49)† | .0019† |
| Age >65 years | 254 | 80 | 1.22 (0.7-2.11) | .34 |
| Hypertension | 264 | 70 | 1.37 (0.72-2.63) | .20 |
| Diabetes mellitus | 84 | 27 | 0.53 (0.27-2.51) | .65 |
| Left ventricular hypertrophy on ECG | 35 | 7 | 0.63 (0.63-2.91) | .29 |
| Atrial fibrillation on ECG | 58 | 18 | 1.09 (0.37-3.16) | .84 |
| Anterior myocardial infarction on ECG | 31 | 8 | 1.89 (0.56-6.32) | .16 |
| Left bundle branch block on ECG | 16 | 7 | 1.22 (0.37-4.09) | .66 |
| Left ventricular hypertrophy on echo | 23 | 7 | 5.23 (1.02-26.70)† | .003† |
| Left atrial enlargement on echo | 5 | 6 | 1.34 (0.06-26.93) | .81 |
| Left atrial thrombosis on echo | 3 | 1 | 0.87 (0.16-4.99) | .87 |
| Left ventricular akinesia on echo | 13 | 3 | 0.36 (0.29-6.49) | .6 |
| Mitral calcification on echo | 12 | 4 | 6.34 (0.57-70.23) | .02 |
| Aortic stenosis on echo | 2 | 3 | 8.09 (0.33-198.76) | .04 |
| Dilated cardiomyopathy on echo | 1 | 2 | 5.0 (0.07-3.69) | .36 |
| Atrial septal aneurysm on echo | 15 | 2 | 1.05 (0.56-2) | .82 |
| Previous transient ischemic attack or stroke | 105 | 27 | 0.08 (0.41-1.89) | .67 |
| Hyperdense middle cerebral artery | 75 | 17 | 2.42 (1.39-4.21)† | <.001† |
| Leukoaraiosis | 164 | 66 | 0.79 (0.36-1.73) | .47 |

Values of odds ratios (OR) >1 mean that the factor is more frequent in patients with SI (silent infarct). CI, confidence interval; ECG, electrocardiogram; echo, echocardiogram.

*By χ² test.
†Shown to be related to the presence of SI by univariate analysis.
TABLE 2. Criteria for Presumed Cause of Stroke

Embolic from heart
Patient fulfilled the 2 following criteria:
1. No evidence of primary hemorrhagic stroke on CT
2. Evidence of ≥1 of the following diseases (by clinical examination, electrocardiogram, or echocardiogram): acute phase of myocardial infarction, ventricular aneurysm, cardiomyopathy, congenital heart disease, rheumatic heart disease, endocarditis, atrial fibrillation, atrial myxoma, sick sinus syndrome, or atrial septal defect with evidence of a deep venous thrombosis and lung embolism

Large-vessel disease
Patient fulfilled the 3 following criteria:
1. No evidence of primary hemorrhagic stroke on CT
2. No evidence that >1 cerebral vessel had been involved
3. Evidence of a stenosis of the internal carotid (or vertebral) artery leading to a stenosis >50% relevant to the clinical deficits, or evidence of an internal carotid (or vertebral) artery dissection

Small-vessel disease
Patient fulfilled 1 of the 2 following criteria:
1. Evidence of a nonhemorrhagic stroke on CT and clinical presentation as a pure motor hemiplegia, or pure sensory stroke, or sensorimotor stroke, or ataxic hemiplegia syndrome, and history of arterial hypertension
2. Deep primary intracerebral hemorrhage associated with history of arterial hypertension

Undetermined cause
Patients fulfilled criteria for at least 2 of the 3 previous causes

Unknown cause
Patient did not fulfill criteria for any of the 3 previous causes

CT, computed tomography.

index stroke as defined in Table 2, by means of the odds ratio (OR) method<sup>19</sup> with 99% confidence intervals (CI). All variables were classified as absent (0) or present (1).

The second step of statistical assessment consisted of a discriminant analysis performed with the SAS package<sup>20</sup> with the presence of silent infarct as dependent variable and the 24 independent variables used for univariate analysis. All variables were classified as 0 when absent and 1 when present. The discriminant analysis was performed in the 216 patients (120 men, 96 women; mean age, 59.9 years) who underwent an exhaustive vascular and cardiac checkup, ie, all stroke patients except those who did not require echocardiogram (patients with dissection of the cervical arteries or intracerebral hemorrhage) and those who could not have an echocardiogram during hospitalization because of early death.

Results

Of the 595 patients included in this study, 116 (19%; 99% CI, 15% to 24%) had a total of 179 silent infarcts. The univariate analysis revealed that four factors were related to the presence of silent infarct: age older than 65 years, left atrial enlargement on echocardiogram, leukoaraiosis score greater than 0 (Table 1), and the qualifying event being a small subcortical infarct (Table 3). No statistical relation was found with other vascular risk factors or with the presumed cause of stroke (Table 4). The discriminant analysis found only two independent variables related to the presence of silent infarct: left atrial enlargement on echocardiogram (<span>P</span> = .007) and age older than 65 years (<span>P</span> = .03); leukoaraiosis score greater than 0 was not found to be significantly related (<span>P</span> = .86).

Discussion

Our study found silent infarcts in 19% (99% CI, 15% to 24%) of patients with stroke or TIA and showed that most silent infarcts are small and subcortical and mainly depend on two factors: age and left atrium enlargement. We classified as silent infarcts all asymptomatic, well-demarcated CT areas of low density detected on CT scan in patients free of any history of stroke and

<table>
<thead>
<tr>
<th>Table 3. Topography of Infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic infarcts</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Cortical or large</td>
</tr>
<tr>
<td>subcortical</td>
</tr>
<tr>
<td>Small subcortical</td>
</tr>
<tr>
<td>Border zone</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
*By Mann-Whitney <span>U</span> test.
unrelated to the symptoms and signs of the index stroke. However, small hemorrhagic lesions may become hypodense after a few weeks. Some of our so-called silent infarcts might therefore be sequelae of hemorrhages, as in previous studies.

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Stroke Data Bank found a prevalence of 11% in 1805 patients. This study included only patients without history of stroke or with symptomatic lesions unrelated to the current deficits but excluded patients with TIA. The Framingham study group found silent infarcts in 10% of a small group of 124 patients with criteria close to those of the NINCDS. Both studies were conducted in the early 1980s; ours was conducted from 1989 to 1992. During this period the quality of CT scans has improved, and this may explain the higher prevalence of silent infarcts in our study. The difference in prevalence of silent infarcts between the Dutch study (13%) and ours can be explained by their criteria of inclusion (TIA or minor strokes) and exclusion (atrial fibrillation). Our study has been performed in hospital patients with stroke or TIA; therefore, our results cannot be generalized to silent infarcts detected in “true” asymptomatic subjects. Silent infarcts were more likely to be subcortical, as previously suggested by the Dutch TIA Trial Study Group. However, the NINCDS and Framingham studies found fewer subcortical infarcts in silent infarcts. This difference may also be explained by the improvement of the quality of the CT scans, which now allows an easier detection of small subcortical infarcts. We found more silent infarcts in patients older than 65 years, and this was an independent variable on the discriminant analysis. The NINCDS and the Dutch TIA Trial Study Group found similar results. The latter study also found a significant relation of silent infarct with arterial hypertension and current cigarette smoking. Tobacco was not included in our variables because this item could not be collected in aphasic or comatose patients, contrary to the Dutch group in which only patients with TIA or minor residual deficits were included. We did not find a significant relation with arterial hypertension, which may result from the smaller numbers in our study. In the Framingham study, silent infarcts occurred more frequently in patients with diabetes mellitus; we could not confirm this in our study.

We found that left atrial enlargement at echocardiogram was an independent risk factor for silent infarct. In patients with nonvalvular atrial fibrillation, age and increased left atrial diameter were associated with additional risk for silent stroke. The same findings have been found by Caplan et al in symptomatic patients with stroke and atrial fibrillation, but not in the Boston Area Anticoagulation Trial for Atrial Fibrillation primary prevention trial. Our study was the first to explore in consecutive patients with stroke of any type the role of the size of the left atrium at echocardiogram on the occurrence of silent infarct. Other studies on silent infarct in atrial fibrillation are difficult to interpret because the definition of brain infarction was different, and information on other cerebrovascular risk factors was not always detailed. Although our study found a strong relation between left atrial enlargement and silent infarct, we did not find any relation between silent infarct and atrial fibrillation or other sources of embolism in the heart as potential causes of the index stroke. Thus, the mechanism of silent infarct remains uncertain in patients with left atrial enlargement.

We cannot exclude the possibility that silent infarct and left atrial enlargement might both be secondary to a common factor that was not included in our study. It might be incorrect to perform the discriminant analysis in a subgroup of patients smaller than half of the original group. However, no specific investigation has been performed for this study, and we did not perform echocardiography in patients with intracerebral hemorrhages or dissection of the cervical arteries. Discriminant analysis was performed only in patients with ischemic stroke or TIA who survived long enough to have echocardiography. Thus, our conclusions are valid only for the subgroup of patients with TIA or ischemic stroke who survived a few days. Silent infarcts are frequent in patients with carotid stenosis. In patients with asymptomatic carotid stenosis greater than 70%, the presence of silent infarct might be an argument for endarterectomy, although the advantages have not been proved to outweigh the risk of operation. Studies on silent infarct in carotid stenosis have so far provided little information about associated cerebrovascular risk factors, so that it is difficult to determine the exact role of large-artery disease in the pathogenesis of silent infarct. The predominance of small subcortical infarcts in our study would argue against a major role.

In the univariate analysis there was a significant relation between leukoaraiosis and presence of silent infarct that was not confirmed in the multivariate analysis. Most silent infarcts are subcortical infarcts smaller than 15 mm, and leukoaraiosis is more likely to be present in patients with such infarcts. Because leukoaraiosis increases with age, the higher prevalence of

### Table 4. Comparison of Patients With One or More Silent Infarcts and Patients Without Silent Infarct According to Presumed Cause of Stroke

<table>
<thead>
<tr>
<th>Presumed cause of stroke</th>
<th>Patients without SI</th>
<th>Patients with SI</th>
<th>OR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-vessel disease</td>
<td>74</td>
<td>11</td>
<td>0.57 (0.24-1.39)</td>
<td>.09</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>108</td>
<td>28</td>
<td>1.09 (0.58-2.05)</td>
<td>.71</td>
</tr>
<tr>
<td>Heart disease</td>
<td>60</td>
<td>18</td>
<td>1.28 (0.60-2.73)</td>
<td>.39</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>217</td>
<td>53</td>
<td>1.02 (0.59-1.74)</td>
<td>.94</td>
</tr>
<tr>
<td>Undetermined cause</td>
<td>20</td>
<td>6</td>
<td>1.25 (0.36-4.31)</td>
<td>.63</td>
</tr>
</tbody>
</table>

*Values of odds ratios (OR) >1 mean that the factor is more frequent in patients with SI (silent infarct). CI, confidence interval.
*By χ² test.

5*By χ² test.
silent infarct in patients with leukoaraiosis might be just an effect of age.

Longitudinal studies are necessary to assess the exact role of left atrial enlargement in the pathogenesis of silent brain infarction.

Acknowledgments

This study was supported in part by a grant from the Direction de la Recherche et des Etudes Doctorales. We are grateful to D. Guerouaou, MD, X. Leclerc, MD, L. Guillard, MD, and E. Chamas, MD, for their help in recording clinical, radiological, and cardiological data. A. Duhamel, PhD, is acknowledged for expert statistical assistance. M. Marchau, Jr, and G.L. Leys reviewed the final version of the manuscript. Yasmine Kucharski and Maryse Moulin provided expert secretarial assistance.

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Silent infarcts in patients with ischemic stroke are related to age and size of the left atrium.
F Mounier-Vehier, D Leys, P Rondepierre, O Godefroy and J P Pruvo

*Stroke*. 1993;24:1347-1351
doi: 10.1161/01.STR.24.9.1347

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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