Lacunar Infarcts
Pathogenesis and Validity of the Clinical Syndromes

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Background and Purpose: In this study, we investigated the lacunar hypothesis to answer three questions: 1) Is the lacunar syndrome valid for diagnosing lacunar infarction? 2) What is the frequency of potential cardiac versus carotid sources of embolism in patients with lacunar versus cortical infarct? 3) What is the frequency of vascular risk factors in these two groups of patients?

Methods: The study was performed in a well-defined prospective series of 103 patients with a first-ever lacunar infarct and 144 other patients with a first-ever infarct involving the cortex.

Results: Sensitivity and specificity of the lacunar syndromes in diagnosing lacunar infarction were 95% and 93%, respectively. Positive and negative predictive values of diagnosing lacunar infarction in patients with lacunar syndromes were 90% and 97%, respectively. Risk factor analysis showed no differences for either group of cerebral infarction. A cardiac source of embolism was significantly less frequent in patients with lacunar infarction (odds ratio=0.32, 95% confidence interval=0.17–0.61, p<0.001). Significant carotid stenosis (diameter reduction ≥50%) was also less frequent in patients with lacunar infarction (odds ratio=0.35, 95% confidence interval=0.16–0.76, p<0.001).

Conclusions: These findings show that the lacunar syndrome is an excellent clinical test for diagnosing lacunar infarction and that cardiac and carotid embolism are unlikely causes of lacunar infarction, supporting the hypothesis that lacunar infarcts are usually caused by small vessel disease. (Stroke 1991;22:1374–1378)

Lacunar infarcts constitute up to 25% of all ischemic strokes, forming a numerically important subgroup.1–6 It is important to define their pathogenesis because they may warrant treatment different from infarcts involving the cerebral cortex.7,8 The lacunar hypothesis suggests that symptomatic lacunar infarcts usually present with specific lacunar syndromes and usually are caused by a distinct vasculopathy of the small perforating arteries.9 A prospective community-based study partly substantiated the first half of this hypothesis by determining the positive predictive value of lacunar syndromes.4 Some researchers still question the clinical value of the lacunar syndrome because case reports have associated it with a range of pathologies on computed tomography (CT), with hemorrhage, and with nonvascular causes.5,10–13 To our knowledge, no single study has attempted to determine the overall validity (sensitivity, specificity, and predictive values) of lacunar syndromes in diagnosing symptomatic lacunar infarction.

The second part of the lacunar hypothesis is more difficult to investigate. There are few pathological studies because of the low early case fatality rate.14,15 We therefore have to turn to clinical studies to elucidate the pathogenesis indirectly by establishing the frequency of potential cardiac and carotid sources of embolism that would yield more insight into the importance of small vessel disease as the cause of lacunar infarction. Some authors suggest the possibility of cardiac embolism in patients with lacunar infarction,16,17 but more recently it was shown that lacunar infarcts are very unlikely to be caused by this mechanism.18 Some researchers proposed that lacunar infarction could be caused by artery-to-artery embolism from the carotid artery,11,16,19 thus arguing against the second part of the lacunar hypothesis. Others did not find carotid embolism to be a usual cause of lacunar infarction,20–22 but these studies either used selected patients11,16,19–21 or the criteria for patient selection were not specified.22 The possibility of carotid embolism should be studied in a prospective series of all lacunar infarct patients without patient selection. If lacunar infarction is usually caused by small vessel disease, the frequency of cardiac and carotid sources of embolism would be significantly lower in patients with lacunar infarcts compared to patients with cortical infarcts.
In the present study, we established the overall validity of the lacunar syndrome in diagnosing lacunar infarction and compared the frequency of cardiac and carotid sources of embolism, as well as vascular risk factors, in patients with lacunar versus cortical infarct.

**Subjects and Methods**

Two hundred fifty-two patients with a first brain infarct of >24 hours' duration were entered into a prospective registry between July 1987 and August 1989 at the University Hospital of Maastricht. The University Hospital serves as the only hospital in Maastricht for 180,000 people. All patients were examined soon after admittance.

Brain infarction was defined as the rapid onset of clinical signs of focal disturbance of cerebral function, lasting longer than 24 hours or leading to death, and with no apparent cause other than of vascular origin. In many patients, CT showed an area of low attenuation compatible with the clinical signs and symptoms; in some, CT showed no specific lesion. At autopsy, an infarct with clinical signs and symptoms confirmed the diagnosis. When neither CT nor autopsy was available, we used the Guy's Hospital Stroke Diagnostic Score (Allen score) to predict the probability that the stroke was due to infarction. Probable infarction was diagnosed when the score was less than 4, with a 90% probability that the stroke was due to infarction.

After clinical examination, patients were classified as either a lacunar or cortical syndrome. Lacunar infarct and cortical infarction were defined as described below, but before knowledge of CT results. A definite diagnosis of lacunar or cortical infarction was made only after CT or autopsy. This procedure allowed assessment of the reliability of diagnosis by the lacunar syndrome. Computed tomography or autopsy was ultimately decisive in the decision as to whether a patient had lacunar or cortical infarction.

We distinguished four lacunar syndromes: pure motor stroke, sensorimotor stroke, pure sensory stroke, and ataxic hemiparesis including dysarthria-clumsy hand cases. Lacunar infarction was defined as a case of a lacunar syndrome in which CT findings were suggestive of infarction due to occlusion of one single perforating artery, that is, a subcortical, sharply margined hypodense lesion with a diameter <2 cm. In some cases, no lesion was demonstrated.

A cortical infarct was defined as a case of a cortical syndrome (unilateral motor or sensory deficit, combined with signs of cortical dysfunction such as aphasia, visual field deficit, apraxia, neglect, and agnosia) in which CT findings were suggestive of infarction involving the cortex or showed a large (diameter >2 cm) subcortical, nonlacunar lesion.

We were able to calculate the sensitivity and specificity of the lacunar syndromes in predicting lacunar infarction by establishing how often patients with lacunar infarction actually had a lacunar syndrome and how often those without lacunar infarction indeed had no lacunar syndrome. We also calculated the positive predictive value (the proportion of patients with a lacunar syndrome who actually had lacunar infarction) and negative predictive value (the proportion of patients without a lacunar syndrome who truly did not have lacunar infarction).

We divided cortical infarcts into three groups by presumed cause: cardioembolic, atherothrombotic, and rare etiologies. Cardioembolic infarction was defined as an infarct involving the cortex in the presence of one of the following cardiac sources of embolism: atrial fibrillation (chronic, paroxysmal), recent myocardial infarction (≤6 weeks), prosthetic aortic or mitral valve, endocarditis, cardiomyopathy, mitral stenosis, left ventricular aneurysm, and intraventricular thrombus. Atherothrombotic infarction was defined as an infarct involving the cortex, with no other apparent cause than large vessel disease, that is, atherothrombosis or artery-to-artery embolism. The last group contained cases with rare etiologies, such as vasculitis, arterial dissection, fibromuscular dysplasia, and hematologic disorders.

Routine investigations included standard blood and urine tests, electrocardiography, chest radiography, noninvasive carotid studies, and CT. Echocardiography, 24-hour electrocardiographic (Holter) monitoring, and cerebral angiography were performed in selected cases. Overall, 82% of all patients had noninvasive carotid study, of which 86% had either multigated pulsed Doppler or duplex scanning and 14% had continuous-wave Doppler. Noninvasive carotid studies were not performed in 18% of the patients because they were too ill to cooperate adequately.

We recorded the following risk factors: hypertension (known hypertension treated with antihypertensive medication; two or more blood pressure recordings of >160/90 mm Hg before stroke or at least 1 week after stroke), diabetes mellitus (known diabetes treated with diet, medication, or both; fasting serum glucose level >6 mmol/l measured on at least two occasions), and history of ischemic heart disease.

After definitive diagnosis was made, we compared the frequency of potential cardioembolic sources between the lacunar and cortical infarct groups. The frequency of significant stenosis of the ipsilateral internal carotid artery (diameter reduction ≥50%) as a potential carotid embolic source and the frequency of vascular risk factors were compared between the lacunar and atherothrombotic infarct group; the cardioembolic infarction group was excluded from this comparison.

Computed tomographic scans were independently reviewed by two physicians without knowledge of the clinical syndrome. In case of disagreement as to the presence of an infarct, the CT was regarded as negative. There was no disagreement on the distinction of lacunar and nonlacunar infarcts. Proportions are given with 95% confidence intervals (CIs). Dichotomous variables were analyzed using odds ratios (ORs) with 95% CI and
Among the 149 patients with infarction involving the cortex, 50 had probable cardioembolic infarction and 49 had atherothrombotic infarction. The remaining risk factors did not differ between patients with lacunar and atherothrombotic cortical infarction (Table 3).

A cortical syndrome affected 143 patients. Seven of these (5%) had neither CT nor autopsy but an Allen score of less than 4. Five patients had no cortical infarct but ipsilateral lacunar infarction on CT, which might have caused the symptoms, and therefore were included in the lacunar infarction group for further analysis. In total, there were 103 cases of lacunar infarction (41%; 95% CI=35–47%; mean age 67.2±10.3 years [±SD]) and 149 cases of infarction involving the cortex (mean age 71.2±12.4 years). Among the 149 patients with infarction involving the cortex, 50 had probable cardioembolic infarction and 94 had atherothrombotic infarction. The remaining five patients with miscellaneous causes were not included in further analysis.

Ninety-five percent of the patients with lacunar infarction had presented with a lacunar syndrome, which means that the sensitivity of the lacunar syndrome in diagnosing lacunar infarction was 95% (Table 1). Ninety-three percent of the patients without lacunar infarction did not present with a lacunar syndrome, which means that the specificity of the lacunar syndrome as a clinical test was 93%. Ninety percent of the patients who presented with a lacunar syndrome actually had lacunar infarction, which means that the positive predictive value of diagnosing lacunar infarction in patients with a lacunar syndrome was 90%. Ninety-seven percent of the patients that did not present with a lacunar syndrome truly had no lacunar infarction, meaning a negative predictive value of 97%.

A cardiac source of embolism was approximately three times less frequent in lacunar than in cortical infarction (OR=0.32, 95% CI=0.17–0.61, p<0.001) (Table 2). This difference was caused by a three times higher frequency of nonrheumatic atrial fibrillation in the cortical infarction group (OR=0.25, 95% CI=0.12–0.53, p<0.001). The numbers of other cardiac sources were too small to allow conclusions on separate causes.

Ipsilateral internal carotid artery stenosis of ≥50% was significantly more frequent in patients with atherothrombotic cortical infarction compared with the lacunar stroke patients (OR=0.35, 95% CI=0.16–0.76, p<0.001) (Table 3). Stenosis of ≥50% of the contralateral internal carotid artery was found in six patients (7.0%) with lacunar infarction and in 10 patients (13.3%) with atherothrombotic cortical infarction. Prevalence of remaining risk factors did not differ between patients with lacunar and atherothrombotic cortical infarction (Table 3).

### Discussion

Lacunar syndromes are clinical syndromes usually caused by symptomatic lacunar infarcts that usually result from small vessel disease occluding one small perforating artery. This clinicopathological correlation was tested and in part substantiated in a prospective community-based study. Only six of 108 patients in that study presenting with a lacunar syndrome had a lesion on CT not compatible with occlusion of one single perforating artery. However, the overall validity of the lacunar syndromes in diagnosing lacunar infarction could not be assessed. Pathological heterogeneity in patients with lacunar syndromes was reported, but this mainly concerned single cases, whereas the syndromes in these patients had a lesion on CT not compatible with occlusion of one single perforating artery.
studies often were not carefully defined. We found positive and negative predictive values of 90% and 97%, showing that the lacunar syndromes are a good or even excellent clinical test for diagnosing lacunar infarction.

Forty-one percent (95% CI = 35-47%) of all registered patients with a first supratentorial brain infarct had a lacunar infarct. In other hospital-based studies, the percentage of lacunar infarcts among all cases of cerebral infarction varied between 13% and 22%. In two population-based studies, approximately 25% of all registered patients with cerebral infarction had a lacunar infarct. However, we only registered supratentorial brain infarcts, whereas lacunar infarcts can also occur in the brain stem. Percentage of lacunar infarcts among all types of cerebral infarction, including in the brain stem, would subsequently then be lower. The proportion of lacunar stroke in our series is therefore quite similar to that in the community-based Oxfordshire Community Stroke Project, suggesting no major referral bias in our study.

Fisher found in most cases of lacunar infarction a small vessel vasculopathy at autopsy, which he associated with hypertension. However, hypertension is the most important risk factor for all types of ischemic stroke, and many patients with lacunar infarction do not have hypertension. Many studies used blood pressure recordings shortly after stroke, which do not always reflect prestroke levels reliably. However, prestroke measurements are sometimes missing. In those cases, we used blood pressure measurements at least 1 week after stroke, when blood pressure had leveled off to prestroke values. Our data agree with those from the Oxfordshire Community Stroke Project, in which no difference in hypertension was found between patients with lacunar infarction and carotid artery distribution infarction involving the cortex. Obviously, hypertension is an important but rather nonspecific and not unique risk factor in lacunar infarction. We, as others, did not find a difference in the frequency of diabetes mellitus between both groups.

Some previous studies reported a potential cardioembolic source in up to 17% of patients with lacunar infarction. However, most of these studies selected patients by abnormal CT, whereas in one study, the number of patients was too low for firm conclusions to be reached. The frequency of the most prevalent potential cardioembolic source, namely, nonrheumatic atrial fibrillation, did not differ between patients with lacunar infarction and hospital control subjects or patients with primary intracerebral hemorrhage. We found a potential cardiac source of embolism approximately three times more frequently in the cortical than in the lacunar infarct group, indicating that a cardioembolic source should be considered as an unlikely cause of lacunar infarction, or even as a coincidental finding. Therefore, it is doubtful whether these patients should undergo extensive cardiac investigations or should be anticoagulated in the presence of one of these cardioembolic sources.

We found that significant carotid stenosis was three times more prevalent in patients with cortical infarction as compared to patients with lacunar infarction, supporting the view that carotid lesions should be considered as an unlikely cause of lacunar infarction and probably only as a coincidental marker of generalized atherosclerosis.

Further risk factor analysis showed no differences between both groups, indicating that the same known risk factors for ischemic stroke are equally important in the pathogenesis of both lacunar and atherothrombotic cortical infarction, with the exception of potential cardiac and carotid sources of embolism. This supports the hypothesis that pathogenesis underlying lacunar infarction differs from that in infarcts involving the cortex, namely, that usually a small vessel disease underlies lacunar infarctions. What determines whether mainly small or mainly large vessels, or both, will become affected in the presence of the remaining risk factors and whether small vessel disease is qualitatively different from large vessel disease remains unclarified. We also showed that the lacunar syndromes constitute a good or even excellent clinical test for diagnosing lacunar infarction. Therefore, contrary to others, we think the concept of the lacunar hypothesis is clinically valid and useful.

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References


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