Are Hypertension or Cardiac Embolism Likely Causes of Lacunar Infarction?

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We tested the hypothesis that hypertension is more common and cardiac embolism less common in patients with lacunar infarction than in patients with other types of cerebral infarction. We studied risk factor profiles in a series of 102 consecutive patients with a lacunar infarct and 202 consecutive patients with a carotid artery-distribution infarct involving the cortex registered in the Oxfordshire Community Stroke Project, a community-based study of first-ever stroke. The two groups did not differ in the prevalence of prestroke hypertension (defined in a number of ways) or in the prevalence of markers of sustained hypertension. The presence of atrial fibrillation and a history of myocardial infarction, particularly during the 6 weeks before the stroke, were significantly more common in the group with carotid-distribution infarcts involving the cortex. There was no significant difference in the prevalence of other accepted risk factors for ischemic stroke, including previous transient ischemic attack, cervical bruit, diabetes mellitus, peripheral vascular disease, or cigarette smoking. Our results suggest that hypertension is no more important in the development of lacunar infarction than it is in the development of other types of ischemic stroke that are presumed to be due to atherosclerotic thromboembolism in a major cerebral artery. Our data support the autopsy evidence that cardioembolic occlusion is an unusual cause of lacunar infarction. (Stroke 1990;21:375-381)

Lacunar infarcts are thought to result from the occlusion of a single perforating artery and may be manifested clinically as a few specific lacunar syndromes.¹,² This clinicopathologic concept was substantiated in a recent community-based natural history study.³ Almost 25% of all first-ever ischemic strokes in that study were due to lacunar infarction, and similar proportions have been reported from other studies.¹⁻⁶ From his studies on its pathogenesis, Fisher originally suggested that lacunar infarction was caused almost exclusively by small-vessel disease related to hypertension,¹ although he could not exclude embolism as a possible cause in a few cases.⁷ However, the role of hypertension in the genesis of lacunar infarction has been questioned recently.⁸ Both cardiac and carotid emboli have been suggested as possible causes of lacunar infarcts, because hypertension appeared not to be present in a substantial number of cases.

Distinguishing the types of cerebral infarction on the basis of the underlying pathogenesis is important in the planning of stroke treatment trials.⁹,¹⁰ Although additional unselected pathologic studies would be of great value, they are difficult to perform because of the low early case-fatality rate and consequently the low autopsy rate for persons with lacunar infarction.³ Therefore, one needs to use other methods of examining whether the underlying vascular pathology of lacunar infarction is qualitatively different from that of infarction involving the cortical distribution of the major cerebral arteries, in which thromboembolism is thought to be the most likely pathologic process. Comparing the distributions of vascular risk factors could add to our understanding of the pathogenesis of lacunar infarction. We report the results of such a comparison among patients registered with the Oxfordshire Community Stroke Project, a community-based stroke registry.

Subjects and Methods

The detailed methodology of the Oxfordshire Community Stroke Project has been described.¹¹ In brief, it is a prospective, community-based registry of...
all first-ever strokes and transient ischemic attacks (TIAs) occurring in a population of approximately 105,000. Patients were assessed by a study neurologist soon after the event, whether or not they were admitted to a hospital. When taking the history, particular note was made of symptoms of cardiac disease, previous TIA, the diagnosis of diabetes mellitus, intermittent claudication of the lower limbs, and whether the patient was currently taking antihypertensive medication. The patients were questioned about their smoking habits. During a standard physical examination, special note was made of blood pressure, signs of cardiac disease, presence of cerebral bruises, or evidence of lower limb ischemia. We attempted to obtain a computed tomogram (CT scan) or autopsy on all patients to determine accurately the pathologic type of stroke. An electrocardiogram (ECG) was recorded at the time of assessment to document cardiac rhythm abnormalities and as an indirect assessment of left ventricular hypertrophy. On a standard chest roentgenogram cardiomegaly was defined as a cardiothoracic ratio of >50%.

One major advantage of the British National Health Service is that >98% of the population is registered with a general practitioner who provides primary health care and arranges for specialist advice or hospital admission. A unique set of health records that comprises all correspondence with hospital specialists and details of consultations with the general practitioner (e.g., blood pressure recordings) is held by each patient’s general practitioner. If the patient moves to another area, then these health records are transferred to the next general practitioner, thereby creating a lifelong health record. We reviewed the general practitioner’s and hospital notes of all patients with a stroke or TIA registered in the Oxfordshire Community Stroke Project and recorded the details of prestroke blood pressure measurements and checked the details of any significant previous medical events. A diagnosis of myocardial infarction (MI) was accepted only if an episode of typical chest pain was supported by either the development of pathologic Q waves on a standard twelve-lead ECG or characteristic enzyme changes at the time of the event. Since some patients were likely to have more than one manifestation of ischemic heart disease, a number of features (nonrheumatic atrial fibrillation [AF], definite MI, angina, or typical ECG changes of myocardial ischemia) were considered to indicate any ischemic heart disease, even if there were no clinical symptoms.

Stroke was classified as being due to definite cerebral infarction if a CT scan performed ≤28 days after the onset of symptoms showed either a low-density area in a region compatible with the clinical symptoms and signs or no specific abnormality or if an autopsy showed an appropriate infarct. If adequate CT or autopsy data were not available, the Guy’s Hospital Diagnostic Score, a CT-validated score that predicts the probability of a stroke being due to infarction or hemorrhage using a number of clinical features, was applied. This is the most accurate clinical method of making such a differentiation and has been tested on data sets other than the one from which it was derived. Patients who had a score of <4 (i.e., a >90% probability that their stroke was due to cerebral infarction) were classified as having probable cerebral infarction. For the purposes of this report, cases of definite and probable cerebral infarction were combined.

Lacunar infarction was defined as a cerebral infarction in a patient with clinical symptoms and signs compatible with a lacunar syndrome (pure motor stroke, pure sensory stroke, sensorimotor stroke, or ataxic hemiparesis) as defined previously. Where available, CT or autopsy in such patients showed either infarcts in an appropriate area supplied by a single artery or no specific abnormality.

Carotid artery–distribution infarction involving the cortex was defined as a cerebral infarction in a patient with one of the following clinical patterns at presentation: 1) any unilateral motor and/or sensory disturbance if accompanied by acute ipsilateral higher cortical dysfunction (e.g., dysphasia) and/or an ipsilateral homonymous hemianopsia; 2) an isolated motor or sensory disturbance restricted to the face, arm, or leg (for distinction from lacunar syndromes); or 3) isolated acute higher cortical dysfunction. These clinical features are usually considered to arise from infarcts in areas supplied by cortical branches of the anterior or middle cerebral arteries. Where available, CT or autopsy in such patients showed either infarcts in an appropriate area or no specific abnormality.

Patients with cerebral infarction presumed to be within the distribution of the vertebrobasilar system were excluded from the present study for two reasons. First, there is some pathologic evidence that such infarcts are more likely to be due to in situ thrombosis than are carotid-distribution infarcts, and second, there continues to be debate as to whether lacunes can cause some of the classic brainstorm syndromes.

Differences between the two groups were analyzed using odds ratios with 95% confidence intervals for discrete variables and using analysis of covariance for continuous variables. The χ² test was performed using Yates’ correction.

Results

Between November 1, 1981, and October 31, 1984, 515 patients with a first-ever stroke were registered with the Oxfordshire Community Stroke Project; 102 had a lacunar infarct and 202 a carotid-distribution infarct involving the cortex. A CT scan ≤28 days after onset or an autopsy was performed in 87 (85%) and 171 (85%) of the patients in the two groups, respectively; 29 (28%) and 103 (51%) of the patients showed infarcts in an appropriate area, respectively. The former group comprised 42 men and 60 women with a mean±SD age of 71.8±11.9 years, while the latter group comprised 108 men and 94 women with

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[Reference citations and further details are omitted for brevity.]
a mean±SD age of 73.2±10.9 years. The odds ratio of the sex difference was 0.61 (95% confidence interval 0.38–0.99, \( \chi^2 = 3.62 \); difference not significant). The age and sex distributions of the two groups is shown in Figure 1.

Table 1 summarizes the prevalence of hypertension defined in a number of ways as discrete variables. Table 2 shows the mean in each group for maximum blood pressure ever recorded, last blood pressure recorded in the general practitioner’s notes before the stroke, and blood pressure recorded at the time of poststroke assessment for registration in the Oxfordshire Community Stroke Project. Blood pressure was recorded at some time before the stroke in 91 of the 102 patients (89%) with lacunar infarcts and in 184 of the 202 patients (91%) with cortical infarcts, of which 88 and 179, respectively, were in the general practitioner’s notes. There were no significant differences between groups for the prevalence of any marker of sustained hypertension or for either measurement of prestroke blood pressure.

Point estimates of the odds ratios and 95% confidence intervals for the prevalence of potential cardiac sources of emboli and other accepted risk factors for ischemic stroke are detailed in Table 3. The presence of AF and MI before the stroke were significantly more common among the patients with carotid-distribution infarcts involving the cortex.

### Discussion

The lacunar hypothesis has two distinct components, first, that a few specific clinical syndromes are usually caused by small deep infarcts or lacunes and second, that lacunes are usually the result of a distinct small-vessel arteriopathy that occludes a single perforating artery at the base of the brain. The lacunar hypothesis was generated from a few meticulously performed autopsy studies. The clinicalopathologic correlation has been tested and substantiated in our prospective, community-based study, in which among 108 patients with carefully defined lacunar syndromes, only three had a primary intracerebral hemorrhage and only three had CT or autopsy findings not compatible with occlusion of a single perforating artery. However, the second part of the lacunar hypothesis (i.e., that these strokes are due to a qualitatively distinct small-vessel arteriopathy [not atheroma]) has proven more difficult to test. In view of the low case-fatality rate of lacunar infarction, few pathologic studies on unselected patients are likely to be performed and current radiologic techniques are of little help. Therefore, we turned to epidemiology and asked the question "Is there a difference in the prevalence of vascular risk factors between patients with lacunar infarcts and those who might reasonably be considered to have infarcts due to thromboembolism?"

### Table 1. Prevalence of Hypertension as Discrete Variables in Patients With Lacunar Infarction and Those With Carotid Artery-Distribution Infarction Involving the Cortex

<table>
<thead>
<tr>
<th>Hypertension defined as</th>
<th>Patients with Lacunar Infarction (n=102)</th>
<th>Patients with Cortical Infarction (n=202)</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestroke blood pressure of &gt;160/90 mm Hg at least twice</td>
<td>45 (44%)</td>
<td>95 (47%)</td>
<td>0.89</td>
<td>0.55–1.43</td>
</tr>
<tr>
<td>On antihypertensive medication</td>
<td>28 (27%)</td>
<td>58 (29%)</td>
<td>0.94</td>
<td>0.55–1.60</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on electrocardiogram*</td>
<td>15 (15%)</td>
<td>23 (12%)</td>
<td>1.34</td>
<td>0.67–2.70</td>
</tr>
<tr>
<td>Cardiomegaly on chest roentgenogram†</td>
<td>32 (33%)</td>
<td>80 (44%)</td>
<td>0.70</td>
<td>0.42–1.15</td>
</tr>
</tbody>
</table>

Odds ratio of <1.0, less prevalent in group with lacunar infarcts.

*\( n=100 \) for lacunar infarction and \( n=197 \) for cortical infarction.

†\( n=97 \) for lacunar infarction and \( n=181 \) for cortical infarction.
The methodologic details of the Oxfordshire Community Stroke Project have been reported in detail and should have avoided any selection bias. We have shown that patients with impairment of consciousness (not a feature of lacunar infarction) are more likely than those with normal consciousness to be admitted to a hospital, and therefore it is important that any study of risk factor prevalence among clinically distinct types of stroke be community-based and obtain complete case ascertainment. Our study was restricted to cases of first-ever stroke since one might expect certain pathologic processes to be more likely to cause recurrent stroke than others; in particular, one might expect that recurrent embolism could result from a carotid or cardiac lesion, whereas further symptoms related to occlusion of a single perforating artery are unlikely. There is also considerable difficulty in assessing whether patients have a lacunar syndrome if there are residual physical signs due to a previous stroke. The data on clinical features and risk factors of patients registered with the Oxfordshire Community Stroke Project were collected prospectively and independently of each other.

The definition of lacunar infarction has been discussed in detail. We confined our comparison to two groups of patients with combinations of symptoms and signs expected to result from lesions involving the cerebral cortex and conventionally thought of as being referable to the distribution of the cortical branches of the carotid artery. We excluded patients with symptoms and signs of brainstem or occipital lobe disturbance. Since it is unusual to see CT abnormalities in >40% of patients with lacunar syndromes, we considered that distinguishing the groups by their clinical features was the method least likely to lead to bias. Recent work using magnetic

### Table 2. Blood Pressure Recordings in Patients With Lacunar Infarction and Those With Carotid Artery-Distribution Infarction Involving the Cortex

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patients with Lacunar Infarction (n=102)</th>
<th>Patients with Cortical Infarction (n=202)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum BP before stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>91</td>
<td>179.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>91</td>
<td>97.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last BP recorded by GP before stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>88</td>
<td>158.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>88</td>
<td>88.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP at OCSP assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>102</td>
<td>165.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>102</td>
<td>89.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure; OCSP, Oxfordshire Community Stroke Project; GP, general practitioner; NS, not significant.

### Table 3. Prevalence of Cardiac Sources of Emboli and Other Accepted Risk Factors for Ischemic Stroke in Patients With Lacunar Infarction and Those With Carotid Artery-Distribution Infarction Involving the Cortex

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Patients with Lacunar Infarction (n=102)</th>
<th>Patients with Cortical Infarction (n=202)</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation on electrocardiogram</td>
<td></td>
<td></td>
<td>0.39</td>
<td>0.19–0.81</td>
</tr>
<tr>
<td>Myocardial infarction ≤6 weeks before stroke</td>
<td></td>
<td></td>
<td>0.22</td>
<td>0.05–0.96</td>
</tr>
<tr>
<td>At any time before stroke</td>
<td></td>
<td></td>
<td>0.50</td>
<td>0.26–0.94</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
<td>1.05</td>
<td>0.58–1.92</td>
</tr>
<tr>
<td>Any ischemic heart disease</td>
<td></td>
<td></td>
<td>0.65</td>
<td>0.40–1.05</td>
</tr>
<tr>
<td>Cardiac valve disease</td>
<td></td>
<td></td>
<td>0.79</td>
<td>0.35–1.79</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.51–1.78</td>
</tr>
<tr>
<td>Cervical bruits</td>
<td></td>
<td></td>
<td>1.03</td>
<td>0.51–2.07</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td>1.41</td>
<td>0.66–2.98</td>
</tr>
<tr>
<td>Lower limb claudication</td>
<td></td>
<td></td>
<td>0.75</td>
<td>0.36–1.58</td>
</tr>
<tr>
<td>Ever smoked cigarettes</td>
<td></td>
<td></td>
<td>0.94</td>
<td>0.57–1.58</td>
</tr>
</tbody>
</table>

Odds ratio of <1.0, less prevalent in group with lacunar infarcts.
resonance imaging supports the view that lacunar syndromes are usually caused by small deep infarcts even if no lesion is visible on CT.28 The absence of any significant difference in the age distributions between the groups allowed direct comparisons even for variables the prevalence of which are known to be age-dependent.

For many years it has been accepted that lacunes are caused by hypertensive small-vessel disease; indeed, some authors have insisted on the presence of hypertension as a diagnostic feature of lacunar infarcts. However, recent reports have noted that such lesions can occur in patients who have no evidence of hypertension. Kappelle and van Gijn29 reviewed 14 recent studies of lacunar stroke and found that 43–83% of cases were "hypertensive." The association between hypertension and the presence of lacunes at autopsy was recognized by Fisher,1 although in his study 80% of the lacunes occurred in a single patient with the clinical features of the lacunar state rather than with discrete strokes presenting as lacunar syndromes. However, these pathologic findings cannot necessarily be regarded as one extreme of a disease spectrum in which patients with single lacunes presenting as lacunar strokes are at the other end and all have similar risk factors. No previous study has compared the prevalence of hypertension between patients with lacunar and other types of ischemic stroke in a population unbiased by hospital admission, yet this is important since hypertension is recognized as the most important risk factor (after age) for all types of stroke.30 Additional problems include the facts that "hypertension" has not been uniformly defined in the literature and most studies have relied on poststroke blood pressure measurements, which do not reliably reflect prestroke levels.31

It is clear that the most detailed way of assessing the impact of prestroke blood pressure is in a cohort of patients free of stroke at entry into the study. The main problem lies in the fact that huge numbers of people need to be followed over many years for there to be a sufficient number of stroke events to allow meaningful statistical analysis. We assessed prestroke blood pressure in a number of ways, and it is noteworthy that 90% of patients had had their blood pressure recorded by their general practitioner at some time before their stroke. We also analyzed our data using a conventional definition of hypertension (blood pressure of >160/90 mm Hg on two or more occasions). We also compared indirect markers of sustained hypertension. No significant or substantial difference was found in the prevalence of any of these factors between the groups. The significantly lower mean systolic blood pressure in the group with carotid-distribution infarcts involving the cortex at the time of the stroke probably reflects the higher prevalence of acute cardiac disease in this group. Therefore, we could not find any evidence to support the view that patients with hypertension are more likely to develop lacunar infarction than other types of cerebral infarction, nor did hypertension (however defined) appear to be a prerequisite for developing lacunar infarction. Therefore, other causes of a small-vessel arteriopathy need to be considered.

Could some lacunar infarcts be caused by cardioembolic emboli? Fisher6 suggested that embolism might have caused lacunar infarcts in two patients who at autopsy had no obstruction of the artery supplying the infarcted territory. However, in view of the acute angle at which the perforating arteries arise from the parent artery and the flow characteristics of particulate matter in the blood, one might speculate that embolic occlusion of an individual perforating artery is unlikely. Moreover, cardioembolic emboli are presumed to be large and more likely to lodge at a major arterial branch.32 Bladin and Berkovic33 reported that embolism could cause large striatocapsular infarcts, but these lesions were usually caused by occlusion of more than one perforating artery, the embolus lodging in the proximal segment of the middle cerebral artery. Patients with this type of lesion do not usually present with a classic lacunar syndrome. Although the cases reported by Santamaria et al34 were likely to be due to cardioembolic emboli, the authors noted that few presented with classic lacunar syndromes.

The fashion for diagnosing cardioembolic stroke waxed and waned, and no diagnostic tests have changed the fact that the majority of such diagnoses are made by inference when a stroke and a cardiac lesion coexist.35 Of the factors recorded in our study, both AF and MI, especially MI ≤6 weeks before the stroke, would be accepted as potential sources of cardioembolic emboli, although they may also be markers of generalized atherosclerosis. The prevalence of AF was significantly lower in the group with lacunar infarcts, and this finding is similar to that of a hospital-based study.36 A recent case–control study reported that patients with lacunar infarcts had the same prevalence of AF as controls without stroke.37 Only two of our patients with lacunar infaracts had sustained a recent MI, which meant that the confidence interval was wide; even so, conventional statistical significance was almost attained.

While potential sources of cardioembolic emboli are less prevalent in patients with lacunar infarcts, it is not certain whether embolism was actually the pathologic mechanism for the infarction since there was a trend for cardiac disease in general to be less prevalent among such patients. Therefore, our results support the view that cardioembolic embolism is unlikely to be a common cause of lacunar infarction.

We did not directly assess disease at the carotid bifurcation, although the prevalence of cervical bruits was similar in the two groups. However, a previous review has suggested that significant lesions are much less frequent in patients with lacunar infarction than in patients with other types of cerebral infarction.39,40,41 This again supports the view that artery-to-artery embolism is not a frequent cause of lacunar infarction. It is well recognized that patients with no
abnormalities of the carotid artery can have TIAs and that TIAs can occur in patients who subsequently have a lacunar stroke. Therefore, one cannot necessarily accept that distal artery-to-artery embolism is the cause of all TIAs. The prevalence of previous TIAs was similar in our two groups.

Diabetes mellitus is associated with small-vessel disease in other parts of the body as well as with atheroma, but there was no significant difference in the prevalence of this condition between the groups. Similarly, intermittent claudication (a marker of generalized atherosclerosis) was equally prevalent in the two groups. Although our data did not permit a detailed analysis of the duration of smoking, we have no reason to think that this differed between the groups.

In conclusion, hypertension is not a prerequisite for the development of lacunar infarction and is no more prevalent in patients with lacunar infarcts than in those with cerebral infarcts due to occlusion of one or more major cortical branches of a carotid artery. Further research should be directed toward determining why some patients develop small-vessel disease within the brain and subsequently lacunar strokes while others with similar risk factors develop atheromatous large-vessel disease and then large infarcts involving the cortex. The possibility that some patients have both types of arterial pathology, with one type simply becoming symptomatic first, needs to be examined. Cardiogenic embolism seems less likely to be a cause of lacunar infarction than cortical infarction in the carotid artery territory. This supports the idea that lacunar infarcts may be due to a specific small-vessel arteriopathy, which may require different treatment than large-vessel atherosclerosis. Although we cannot comment on the possibility of artery-to-artery embolism, other work suggests that this is also less likely to cause lacunar than cortical infarction.

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