Is Investigating for Carotid Artery Disease Warranted in Non-Cortical Lacunar Infarction?

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Abstract—Carotid intervention in severe carotid stenosis after an anterior circulation ischemic event reduces the risk of further infarcts if the surgery is performed soon after the incident event. At present, there is no recommendation to differentiate among subtypes of anterior circulation infarcts or transient ischemic events. However, evidence is mounting that demonstrates a difference in pathophysiology of lacunar and nonlacunar (large artery) infarcts. The natural history of lacunar strokes is different from large artery infarcts for recurrence and mortality. Stroke is a heterogenous disease and consideration needs to be directed to manage different stroke subtypes differently. Lacunar infarcts mostly do not arise from large artery atheromatous disease or by cardioembolic phenomena, and there is a negative predictive value for severe carotid stenosis in lacunar strokes. Thus, current evidence suggests that lacunar strokes may not warrant investigation for carotid stenosis. (Stroke. 2011;42:217-220.)

Key Words: carotid artery disease ▪ lacunar infarct ▪ stroke

Lacunar infarcts, which are small deep infarcts ranging from 2 to 20 mm in size (the size varies in different studies) resulting from occlusion of a penetrating artery, account for approximately 25% of ischemic strokes.1,2 The term “lacune” has been used to describe small holes in the deep cerebral tissue for almost 150 years; Fisher,3 in 1968, demonstrated that such lacunes are a result of occlusion of a single perforating artery. The “lacunar hypothesis” suggests that particular clinical syndromes are caused by small infarcts of the brain owing to single perforating artery occlusion, the result of local microatheroma and thrombosis of that single vessel.4,5 Differentiation must be made among “lacunes,” “lacunar stroke,” and “lacunar infarct.”6 Lacunes are cerebrospinal fluid-filled cavities, usually located in the basal ganglia and white matter. Although a lacune is only a radiological appearance, lacunar stroke describes a clinical stroke syndrome with the typical symptoms and signs referable to a small subcortical or brain stem lesion.1,7 When the underlying lesion causing such a clinical stroke is radiologically demonstrated to be an infarct, it is named a lacunar infarct.

There is controversy as to the relationship between radiological “lacunes” and lacunar infarcts. Lacunes are commonly seen in asymptomatic patients, especially the elderly. Whether these represent previous lacunar infarcts is not clearly known. Considerable clinicoradiological overlap occurs between lacunar and nonlacunar clinical syndromes with approximately 16% of clinical lacunar syndromes arising as a result of cortical infarcts and nearly one fourth of cortical syndromes caused by lacunar infarcts.8 Over the years, there has been mounting evidence that lacunar strokes are distinct from nonlacunar strokes in terms of pathophysiology, etiology, and outcome. Despite this, current stroke guidelines9 do not differentiate between lacunar and nonlacunar strokes with regard to treatment or risk factor modification. Similarly, many of the major secondary stroke prevention trials have not distinguished between the different types of stroke, which is an important shortcoming of these studies because different antplatelet drugs may have differential influence on stroke prevention depending on incidental stroke subtypes.10 In this article, we review the evidence base that suggests that lacunar strokes are a separate entity and suggest that investigation for risk factors for large artery strokes, in particular carotid Doppler, may be inappropriate in patients with lacunar strokes and not justifiable from a health economics standpoint.

Pathophysiology of Lacunar Strokes

It has often been postulated that the arterial lesions that result in lacunar strokes are different from those that result in nonlacunar stroke. Direct pathological evidence of this is however somewhat limited, because tracing the vascular supply to the subcortical regions is technically difficult. Additionally, lacunar infarcts have a low early poststroke mortality rate2 and fatalities occur long after the stroke, making autopsy material scant and difficult to study. Much of the clinicopathological evidence on the vascular basis of lacunar infarcts is from the work reported in Fisher’s3,11 studies, in which he performed postmortem dissection of the vascular supply of 68 lacunar infarcts in 18 brains. Fisher reported that most symptomatic lacunar infarcts were a result of occlusion of perforating arteries by atheromatous plaques.
and thrombus formation. However, these pathological studies were mostly performed months or years after the infarcts had occurred, and in any case, the numbers were small; hence, it is difficult to draw firm conclusions on the histopathology of lacunar infarcts from this study. A carefully conducted clinicopathological study showed that lacunar infarcts occurred due to occlusion of small vessels through a mechanism distinct from cardioembolism in three fourths of cases.12

The exact pathophysiology of lacunar infarcts remains unresolved. Several abnormalities of the perforating small vessels have been suggested, including microatheroma formation, vasospasm, changes in the vasculature, poor cerebral blood flow, and vascular leakage. Large vessel atheroma does not appear to be associated with lacunar infarction,13,14 although this does not preclude the possibility of microatheroma formation in small vessels being responsible for lacunar infarcts. Changes in retinal vessels (which are thought to reflect changes in cerebral small vessels15), in particular widening of venules, focal arterial narrowing, arteriovenous nipping, and reduction in arteriovenous ratios, are more commonly seen in lacunar infarcts than nonlacunar infarcts.16,17 Vasospasm resulting in fibrinoid necrosis is associated with severe hypertension; however, severe hypertension has not been shown to be significantly associated with lacunar over nonlacunar strokes.13 It has been suggested that endothelial failure occurring in small cerebral vessels could be one of the events that causes lacunar infarcts. This endothelial failure may result in breaking down of the blood–brain barrier with extravasation of blood components into the vessel wall and consequently leading to vessel wall, perivascular neuronal, and glial cell damage, ultimately causing lacunar infarction.18–20 In contrast, although failure of the blood–brain barrier occurs in large artery cortical infarction, this is secondary to damage resulting from the arterial occlusion that caused the cortical infarct in the first place. Patients with lacunar strokes have elevated systemic plasma markers of endothelial activation such as plasma intercellular adhesion molecule-1, thrombomodulin, and tissue factor pathway inhibitor compared with age-matched normal control subjects, although these levels have not been compared with nonlacunar strokes.21 Cerebral microbleeds have been shown to be twice as common in clinicoradiologically defined lacunar strokes compared with cortical strokes, suggesting a similar microvascular abnormality in lacunar infarction and cerebral microbleeds.22 Certain polymorphisms of the endothelial nitric oxide gene have been shown to be associated with a reduced risk of cerebral small vessel disease.23 Hyperhomocysteinemia has been also shown to be an independent risk factor for cerebral small vessel disease.24 Overall, considerable evidence is present to suggest that lacunar infarcts arise, at least in the majority of cases, due to a distinct arteriopathy of the cerebral small vessels.

Do Lacunar Infarcts Behave Differently?

Lacunar infarcts behave differently from nonlacunar infarcts. The risk of recurrent stroke and death in short- and long-term follow-up studies is lower in lacunar infarcts compared with nonlacunar infarcts.25,26 Lacunar infarcts also tend to breed true (ie, further lacunar infarcts are more likely after lacunar than nonlacunar infarcts; OR, 6.5; 95% CI, 2.4 to 17.5).27

Are Risk Factors for Lacunar Infarcts Different?

Gan et al12 suggested that three fourths of patients with radiologically confirmed lacunar infarction had a lacunar mechanism of infarction, that is, infarction was due to disease of cerebral small vessels, atherosclerosis (9%), cardioembolism (5%), cryptogenic (9%), and other unusual causes (2%) accounted for the remainder. The risk of myocardial infarction is lower in patients with lacunar infarcts compared with nonlacunar infarcts.27 Atrial fibrillation and carotid stenosis were associated more commonly with nonlacunar than lacunar infarction.13 Moreover, anticoagulation does not seem to prevent recurrent lacunar infarcts after an initial lacunar infarct to a higher degree as compared with aspirin alone, whereas anticoagulation remains superior to aspirin for prevention of cardioembolic infarcts, thus suggesting a different pathophysiology of the 2 subtypes of infarcts.28 Although it is difficult to compare the effects of treatment modalities in lacunar and nonlacunar infarcts, because most stroke trials have not differentiated between the 2 types, there is, however, some suggestion that different antiplatelet drugs may have a differential influence on secondary prevention in lacunar and nonlacunar infarcts:29 clopidogrel might be more effective than aspirin plus dipyridamole to prevent recurrent events after large artery infarcts, but the 2 regimens seem to have similar efficacy after lacunar infarcts. Although there is no clearcut evidence that hypertension is more likely to be associated with lacunar stroke, hypertension and diabetes mellitus are well-known risk factors for recurrent lacunar stroke.29,30

Carotid Artery Disease and Lacunar Infarcts

Determining the link between carotid artery disease and lacunar infarcts is fraught with methodological difficulties. Much of the available evidence is from studies that investigate the proportion of patients with carotid artery disease, demonstrated either by Doppler ultrasound or angiographic methods, in patients with acute stroke. In most of these studies, carotid artery disease was found to be significantly less frequent in patients with lacunar strokes compared with nonlacunar strokes.31–36 The frequency of carotid disease in lacunar strokes has been considerably variable in different studies, ranging from 3% to 39%,31–41 although it must be noted that the methodology used to both classify lacunar infarcts as well as to detect carotid disease also varied widely. A study of 726 patients with anterior circulation transient ischemic events or infarcts, excluding total anterior circulation infarcts, revealed a negative association of severe carotid stenosis with lacunar events.42 There was a significant positive association of ipsilateral carotid bruit, previous transient ischemic disease, and diabetes with severe carotid stenosis. Given the fact that carotid disease clearly appears to be less commonly found in patients with lacunar infarcts, the question is whether such carotid disease is causally related to the lacunar infarcts given the fact that many risk factors for both lacunar and nonlacunar infarcts coexist. Mead et al43 studied 259 patients with recent lacunar strokes without prior other
stroke and found that there was no difference between the severity of ipsilateral and contralateral internal carotid artery disease; it was therefore suggested that carotid stenosis in lacunar infarcts may be an incidental finding. An observational study of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) data showed that with 70% to 99% carotid arterial stenosis, lacunar infarcts comprised just 21.6% of the total number of infarcts, whereas the proportion of infarcts of cardioembolic origin was 43.5%.43

Homburg et al44 recently published the first study to actually look at the relationship between atherosclerotic carotid plaque rupture and stroke subtypes. In this study, 750 patients with anterior circulation stroke symptoms were evaluated for the prevalence of atherosclerotic plaque rupture in the symptomatic carotid artery using multidetector CT angiography. Plaque ulcerations were found to be independently associated with nonlacunar stroke compared with lacunar stroke.

Overall, the bulk of the evidence fails to demonstrate a causal relationship between carotid disease and lacunar stroke, although carotid disease is clearly associated with nonlacunar stroke. It is important to note that the impact of carotid endarterectomy on lacunar stroke is unknown, because the large carotid endarterectomy trials (European Carotid Surgery Trial [ECST]45 and NASCET46) did not differentiate between the stroke subtypes.

Conclusion
Clinical noncortical lacunar strokes and proven lacunar infarcts are etiologically and pathophysiologically distinct from large artery infarcts and are caused by cerebral small vessel disease. The link between lacunar strokes and carotid disease needs further elucidation, but current evidence suggests that (1) carotid disease is less common in lacunar infarcts compared with nonlacunar infarcts; and (2) carotid stenosis, even when present, may not be causally related to lacunar infarcts. Hence, routinely evaluating for carotid artery disease is probably not required in patients presenting with radiologically confirmed lacunar infarcts without other evidence of large vessel atherosclerotic disease (ie, confirmed ischemic heart disease or peripheral vascular disease). Furthermore, because the association between lacunar infarcts and carotid disease is not clearly established, is carotid surgery warranted if severe carotid stenosis is discovered after a lacunar infarct? In other words, should carotid stenosis discovered after routine investigation after a lacunar infarct be considered to be “symptomatic” carotid stenosis, thus needing endarterectomy as per current guidelines,9 or should it be considered equivalent to “asymptomatic” carotid stenosis? For instance, the recent guidelines for stroke by the Royal College of Physicians of London recommend carotid Doppler examination in patients with nondisabling anterior circulation transient ischemic events or strokes aiming for carotid surgery if a significant stenosis is diagnosed.9 By virtue of their mild and nondisabling nature, this recommendation would lead to a higher proportion of patients being investigated after a lacunar ischemic event. Because there is a negative prediction of carotid stenosis with lacunar disease, a large proportion of patients thus investigated would not be diagnosed to have significant stenosis. This would thus not be an economical use of scarce resources. Moreover, lacunar strokes may be diagnosed with coexistent carotid disease, which is not the cause of the infarct.

Recommendation
Given the high risk of complications of carotid endarterectomy, in light of this evidence, it would seem highly questionable to perform carotid endarterectomy in patients with pure lacunar ischemic events.

Admittedly, this would emphasize the need for a clear differential diagnosis of noncortical lacunar stroke syndromes from cortical strokes. In the United Kingdom, CT scanning is the standard recommended investigation for stroke and is used primarily to distinguish infarction from primary intracerebral hemorrhage.37 However, evidence of cerebral infarction on CT scanning would be prevalent only in 61%,48 and CT scanning has an even lower sensitivity for detecting lacunar infarction.40 Although MRI is more sensitive at detecting lacunar infarcts, the use of MRI to differentiate lacunar from nonlacunar stroke would be substantially more expensive. On the other hand, the lack of radiological evidence of a cortical infarct on CT scan in a patient with clinical features of a lacunar stroke syndrome should be pragmatically sufficient to confirm the event to be a noncortical lacunar stroke.

Because patients with a total anterior circulation infarct have significant and disabling neurological deficit, they are not candidates for carotid surgery and have not been investigated in some of the studies on the subject.42 Patients with partial anterior circulation strokes are ideal for urgent investigation because the majority of them have relatively less severe disability and would be suitable for urgent carotid intervention. It would thus appear that there is a need to review and revise the guidelines so as to preferentially investigate patients at a higher risk of carotid stenosis, that is, patients with nondisabling partial anterior circulation syndromes (strokes and transient ischemic attacks alike) and/or radiologically confirmed cortical infarcts through an urgent pathway for carotid investigation. The presence of additional factors such as diabetes and ischemic heart disease may further increase the urgency of investigation of this group of patients.

On the other hand, patients with clinical lacunar stroke syndromes in whom neuroimaging (either CT scan or, when indicated, MRI scan) does not reveal a cortical infarct do not routinely require investigation and surgery as explained previously.

Disclosures
None.

References
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