Lacunar Infarction  
Embolism is the Key  
Nancy Futrell, MD

Lacunes are small deep infarcts which cavitate, producing “lacunes” (French for lake).1 “Lacunar infarcts” have been thought of as strokes caused by intrinsic disease of small vessels called lipohyalinosis, resulting from hypertension2 and diabetes.3 Contrary to this established dogma, the literature demonstrates that emboli are the cause of lacunes.

Almost all of the histopathological evaluation of blood vessels associated with lacunes has been done by C. Miller Fisher. In 11 patients with lacunes there was only a single case of lipohyalinosis compared with 2 cases of cerebral emboli.2 Although not commonly cited this way, Fisher’s own writing demonstrates emboli are more common than lipohyalinosis in patients with lacunes.

Fisher was also responsible for the hypothesis of hypertension as a cause of lacunes, based on his report of hypertension in 111/114 of his patients with lacunes. This has not been documented by subsequent studies, which showed hypertension in 24% to 73% of patients with lacunes, similar to that found in stroke patients in general.4 Fisher’s inflated report of hypertension may be in part because transient reactive hypertension was misinterpreted as hypertension. In addition, 13 of these patients were assumed to have hypertension based on heart weight >400 g, in the absence of any documented elevated blood pressure recording!5 It is surprising that a nonreproducible result such as this has remained highly quoted, rather than actively refuted.

Animal models of both hypertension and diabetes exist. The pathology in the spontaneously hypertensive rats includes glial scars and focal cortical atrophy,6 not lacunes. There is also no report of lipohyalinosis in these animals. If lipohyalinosis were “a hypertensive cerebral vasculopathy” as claimed by Fisher,7 one would expect to see this pathological finding in the brains of hypertensive animals.

A literature search using PubMed access to the NIH database was done. “Stroke” plus “spontaneously hypertensive rats” produced 231 references, but there was not a single reference to these rats in combination with “lacunes.” Similarly, “stroke” plus “rat” plus “diabetes” had 63 references, but there was not a single reference using keywords “lacune” plus “rat” plus “diabetes.” The lack of lacunes in animals with hypertension and diabetes does NOT support the hypothesis that hypertension or diabetes causes lacunes.

There was only one reference with “lacune” in any animal model, and this is a model of cerebral embolism which produces lacunes.8 Embolism has indeed been proven to cause lacunes. There is no animal data to support the standard lacune hypothesis.

After cerebral infarction, macrophages remove dead tissue, and less severely damaged tissue undergoes neuronal degeneration and reactive gliosis. Production of a lacune would logically require tissue damage severe enough to cause removal of tissue. The location would need to be relatively deep in the brain, as superficial infarcts result in focal cortical atrophy and periventricular infarcts often produce dilatation of the neighboring ventricle. Severity of tissue damage depends on the primary ischemic insult and the availability or lack of availability of collateral flow to that tissue. In patients with diabetes and hypertension there is reduced microvascular perfusion and impaired autoregulation, which certainly could result in decreased collateral flow and more severe ischemia following an embolic (or any other type) of occlusion to a penetrating blood vessel in the brain. Thus, the diabetes or hypertension could be responsible for an increased tendency for a small deep infarct to cavitate, but would not necessarily be responsible for the production of the initial infarct.

The exercise of a debate, taking a firm position that emboli are the key to lacunes, and trying to prove this point through the literature makes it clear that this position is more defensible than the “lacune hypothesis.” In reality my position is more moderate and is similar to that of other investigators.9 It is simply that lacune is a type of stroke, caused by focal ischemia in the brain, and is much more complicated in terms of potential etiology than has been suggested by the “lacune hypothesis.”10 Focal ischemic infarct is most often caused by thrombi or emboli composed of platelets or fibrin (often with incorporated red blood cells) or both. Any patient with focal cerebral ischemia is entitled to a
complete neurovascular, cardiovascular and chemical evaluation to determine whether platelet inhibition, anticoagulation, statins, and ACE inhibitors (any or all of these agents) are appropriate to prevent stroke and progression of atherosclerotic vascular disease.

The “lacune hypothesis” has done a disservice to neurovascular medicine. The position has been extreme, leading to poor patient evaluation and preventive care. There has been a tendency to oversimplify and to persist in a dogmatic approach despite the lack of evidence. Furthermore, there has been a major inconsistency of thinking as many proponents of the lacune hypothesis are also the champions of evidence-based medicine. Certainly these individuals must recognize there have been no controlled trials related to lacunes, and the lacune hypothesis is purely anecdotal!

References

Lacunar Infarction
Emboli is the Key: Against

Bo Norrving, MD, PhD

No stroke syndrome is specific to cause, but several are suggestive. According to a recent classification, lacunar infarcts are small subcortical infarcts that result from occlusion of a single perforating artery.1 When symptomatic, lacunar infarcts present with lacunar syndromes, 5 of which are well documented: pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria (ie, clumsy hand).

I am aware of no clinical stroke syndrome that is absolutely specific with respect to pathophysiology. The lacunar syndromes are no exception. In 5% to 10% a small hemorrhage is the underlying cause. A lacunar syndrome may also result from restricted striatocapsular infarct, anterior choroidal artery territory infarct, cortical infarct, and infarcts simultaneously affecting penetrator and cortical artery territories. However, several studies using diffusion-weighted MRI (dw-MRI) show that a small subcortical ischemic area corresponding to the territory of a penetrating artery is the most common finding, being present in 84% to 94% of patients with a lacunar syndrome. Simultaneous involvement of penetrator territory and cortical artery territories was demonstrated in 16% in a recent series.2 Such lesion patterns are obviously important to recognize, but they constitute a minority.

Mechanisms of Occlusion in Patients With a Lacunar Syndrome Caused by a Single Ischemic Lesion Confined to Penetrating Artery Territory

Although subject to some limitations, the original neuropathological studies should not be forgotten because they proved that occlusion due to in situ disease of the penetrating artery was by far the most common finding in this setting.3–4 Findings suggesting previous embolism were seen in few cases only.

Several clinical studies have analyzed the association between verified small deep infarcts presenting with a lacunar syndrome and presence of cardioembolic or large artery disease. The methodologically and most carefully conducted studies show that small-vessel occlusion is the most likely mechanism in ≈three fourths of cases.5 Are associated findings of large artery atherosclerosis or a cardioembolic source coincidental, or are they causative? Probably they are a mix of both. In a recent study,6 there was a 7% absolute excess of ipsilateral, compared with contralateral, carotid stenosis >75%, and another study showed that atrial fibrillation is not always coincidental.7 However, on best estimate, atherosclerosis, cardioembolism, cryptogenetic, and unusual causes add up only to about a quarter of cases.

The early recurrence rate in lacunar infarcts is low compared to infarcts due to cardioembolism and large artery disease. A recent dw-MRI study showed that clinical recr-
rence substantially underestimates the true incidence of early recurrent ischemic lesions. New ischemic areas consistent with active embolism or fragmentation of an embolus was seen in \( \approx \) half of patients with large-artery atherosclerosis or cardioembolism, but in none of the patients classified as small-vessel occlusion. A transcranial Doppler study has also shown that asymptomatic circulating emboli in the middle cerebral artery are rare in the lacunar infarct subtype.

Animal stroke models are instrumental to study the molecular basis and salvage of ischemic brain tissue, but they are not suitable to explore the risk factors and underlying causes of human stroke. White matter constitutes half of the brain volume in humans compared to 14% in rodents, and vascular topographies differ. The finding that a small embolus can lodge in a penetrating artery, or in any artery, in an experimental stroke model cannot be extrapolated to assess the quantitative importance of embolic mechanisms in lacunar infarcts in humans.

**Most Lacunar Infarcts Do Not Present With Stroke**

Unrecognized (“silent”) lacunar infarcts are at least 5 times more common than symptomatic infarcts: both types are part of a broader spectrum of cerebral small-vessel disease which also includes vascular white matter disease. Small-vessel disease is an important determinant for the development of vascular cognitive impairment and dementia. There is at present no evidence to suggest that embolism plays any important role in these disorders.

**“Lacunar Infarct” Remains a Clinically Useful Term**

In my view, the best available data show that in situ penetrating artery disease is the most common cause of lacunar infarcts. Embolism from cardiac and large artery sources is undoubtedly clinically relevant, but account for a quarter or less of symptomatic lacunar infarcts. In clinical practice, patients with presumed lacunar infarcts should, of course, be investigated with respect to embolic sources along the same principles as patients with ischemic stroke in general, and findings might well change therapy. Nevertheless, such findings are only present in a minority of patients. To state that embolism is the key in lacunar infarction would be to ignore the key findings in several reports that belong to the classics in stroke research.

**References**


**Why Lacunar Syndromes Are Different and Important**

Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP

The lacunar hypothesis has been one of the hallmarks of the modern understanding of the clinical categorization of the pathogenesis of stroke. Stated simply, the hypothesis implies that classical lacunar syndromes are caused by small deep brain infarcts, due to occlusion of a single penetrating artery. The underlying pathology has been documented to be either in situ microatheroma or lipohyalinosis, rather than embolism. The controversy arises because many clinicians remain less than convinced that embolism is not a frequent cause of lacunar infarcts and hence would not warrant a different investigative strategy from other ischemic stroke syndromes. As we see it, the established facts are as follows:

1. There is no animal model of lacunar infarction due to in situ small-vessel disease, in contrast to the embolic model quoted by Futrell.
2. The proportion of embolic sources in patients with lacunar syndromes is substantially lower than for other hemispheric ischemic strokes, as stated by Norrving.
3. MRI studies have demonstrated that variable proportions of patients presenting with classical lacunar syndromes have sometimes shown multiple concurrent infarcts or more widespread perfusion abnormalities suggesting embolism.2

4. Other evidence for a possible embolic source in some cases includes a benefit to the subset of patients with lacunar syndromes and ipsilateral high-grade carotid stenosis in the NASCET trial.3 Further, aortic arch atheroma has been shown to be a risk factor for lacunar stroke.4

While recognizing that there is some heterogeneity of mechanism within the lacunar syndromes, we believe that the concept is clinically useful, and that the evidence favors the view that the majority are due to in situ, small-vessel disease. Hence, their recognition enables clinicians to be less aggressive in the search for an embolic source, although we would suggest that exclusion of large-vessel disease and cardiac screening is appropriate. Further, there are compelling clinical and epidemiological reasons to separate lacunar from nonlacunar ischemic strokes. For example, their outcome is substantially more favorable and their location in deep white matter may have implications for therapy. Intriguingly, in the recently reported IMAGES trial, a planned subanalysis showed an unexpected benefit for lacunar syndromes.5 We encourage further trials of therapy within this group such as the current SPS3 trial of combined antiplatelet and blood pressure lowering therapy.6 It may well be that the therapeutic response in lacunar infarcts may be somewhat different than in predominantly gray matter infarcts, given the well-known differences in ischemic neurochemical cascades.7

Given the importance of small-vessel disease, particularly in Asian countries, and its relationship to both clinical stroke and cognitive decline, we strongly believe that this disease entity deserves specific recognition to focus future research initiatives. While embolism is the likely cause of a minority of lacunar infarcts, we do not see it as the key, but perhaps a small component of a combination lock.

References

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