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 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 lacunar hypothesis is purely anecdotal!

References