In this exciting era of stroke prevention and treatment, the stroke neurologist is privileged and obliged to determine with reasonable certainty the cause of every cerebral or ocular vascular event. Investigation must seek evidence for either cardiac, large-artery, penetrating artery (lacunar) or, in their absence, for a growing miscellany of “other” causes. Thanks to the increasing accuracy of cardiac, aortic, arterial, and brain imaging, precise evidence about the cause but also the site, size, and type (hemorrhagic or bland) of the lesion will be available. In conjunction with a careful history of the mode of onset of present symptoms and of past events, the modern imaging data will allow for specific and particular short and long-term treatment programs for most patients. Decisions about the use of anticoagulants, platelet inhibitors, or recommendations for surgical procedures directed to the heart or the great vessels depend on the accurate accumulation of data about stroke-by-cause.

When rheumatic heart disease virtually disappeared and as the population aged, nonvalvular atrial fibrillation (NVAF) became increasingly prevalent. Scepticism greeted the hypothesis that there was a causal relationship between AF without valve disease and stroke. These doubts were reduced when observational studies reported an increasing incidence of stroke with NVAF.

Dispute ceased when clinical trials proved without equivocation that the occurrence of stroke in these individuals was significantly and substantially reduced when anticoagulants are contraindicated. Aspirin alone has muted benefit and should be used when NVAF who are without contraindications to anticoagulation.

First, mitral annulus calcification, (MAC). Second, mitral valve lesions loom as possibly exclusive causes of stroke:

- Caseous necrosis
- Adherent fresh red thrombus attached to the rough edge of an affected valve
- Red thrombus attached to the rough edge of an affected valve

In patients with stroke of “unknown cause,” 2 mitral valve lesions loom as possibly exclusive causes of stroke: First, mitral annulus calcification, (MAC). Second, mitral valve prolapse (MVP). Both are common and both will occur with other coexisting conditions capable of causing stroke. Pomerance, a British cardiac pathologist, examined the hearts of a series of consecutive nonagenarians and described calcification of the mitral ring in 27 of the 100 subjects. Age-related increase of other potential causes of stroke, including carotid stenosis and other aortic and cardiac embolic lesions, makes it difficult to assign precisely a causal stroke relationship to MAC.

Pathological findings have seriously raised the probability of embolic stroke when either of these lesions may exist: caseous necrosis of the valve margin and adherent fresh red thrombus attached to the rough edge of an affected valve. Additionally, a few case reports provided evidence of calcific embolic material in patients with MAC.

Several case-matched series were tantalizing, suggestive of a causal role for MAC by virtue of its more frequent existence in the stroke group than in the comparative age-matched controls. The most convincing correlation is presented in this issue of Stroke. The Strong Heart Study surveyed 2723 subjects in a population-based cohort from which they excluded all subjects with existing evidence of cardiovascular disease. With follow-up out to 7 years, MAC proved to be an independent and strong risk factor for stroke. Of interest was the absence of correlation with stroke and aortic calcific valve stenosis.
Having confirmed the independent importance of MAC as a risk and probable cause of stroke in the elderly, the enigma persists about optimum therapy for the individual patient. The most important first step in management when MAC presents with cerebral or ocular ischemia is the exclusion of other cardiac or operable carotid lesions. Then, knowing that the cardiological material may be from either calcific debris or from thrombi adherent to the valve, strict risk factor control appears to be the most important regimen in therapy. If antithrombotic therapy is given when ischemic events develop, this author would favor a short period on warfarin followed by aspirin, knowing that this plan is based on speculation without supporting clinical trial data. Furthermore, it will be recognized that neither treatments are likely to diminish the likelihood of calcific debris emboli. Persistence of events despite antithrombotics may lead to consideration of valve replacement.

The introduction of echocardiography and the observations made by cardiologists and cardiac pathologists lead to the recognition of the prolapsing mitral valve resulting from a myxomatous change in the valve. 12,13 It is not a rare finding. In a series of 1984 consecutive routine hospital autopsies, 90 patients were described as having "significant prolapse of the mitral valve." 14 A large majority of afflicted individuals are asymptomatic and will remain so. 15 Nevertheless, the condition has an uncommon association with atrial fibrillation, heart failure related to the gradual or sudden (from rupture of degenerate chordae tendineae) development of mitral regurgitation, and instances of sudden death and of superimposed bacterial endocarditis. The last complication to be described was the occurrence of transient ischemic attack and cardioembolic stroke. 16 Initial case control series dating back to the 1970s depended on the use of an imperfect mode of echocardiography. Early conclusions about its incidence as a stroke cause may have been distorted by overreading and possibly by some referral bias. Other case series were less impressive and have been summarized. 17 A good review of modern diagnostic methodology and of the complications of the disorder concluded that the incidence of transient ischemic attack or stroke in MVP subjects as perceived from a large cardiac unit is below 1% per year. 18 As with MAC, coincidental stroke causes, including PFO and atheroma, must be eliminated. The recent statement by Ricci that "uncomplicated mitral valve prolapse should no longer be considered a cause of embolism from the heart to the brain" is incorrect and misleading. 19 It may be less so. Nevertheless, the condition has an uncommon association with atrial fibrillation, heart failure related to the gradual or sudden (from rupture of degenerate chordae tendineae) development of mitral regurgitation, and instances of sudden death and of superimposed bacterial endocarditis. The last complication to be described was the occurrence of transient ischemic attack and cardioembolic stroke. 16 Initial case control series dating back to the 1970s depended on the use of an imperfect mode of echocardiography. Early conclusions about its incidence as a stroke cause may have been distorted by overreading and possibly by some referral bias. Other case series were less impressive and have been summarized. 17 A good review of modern diagnostic methodology and of the complications of the disorder concluded that the incidence of transient ischemic attack or stroke in MVP subjects as perceived from a large cardiac unit is below 1% per year. 18 As with MAC, coincidental stroke causes, including PFO and atheroma, must be eliminated. The recent statement by Ricci that "uncomplicated mitral valve prolapse should no longer be considered a cause of embolism from the heart to the brain" is incorrect and misleading. 19 It may be less common than earlier reports suggested, but it still must remain on the list of uncommon but “other” causes of stroke. Skeptics about MVP as a cause of stroke will want to contemplate the accumulated ophthalmoscopic images, the reports of surgical specimens, and even the sparse postmortem evidence that has appeared. More importantly, they will be interested in the recent Olmstead County 10-year follow-up evaluation of 777 subjects diagnosed (1989–1998) with MVP by Doppler echocardiography. 20 A lifetime excess rate of ischemic neurological events (RR of 2.2) compared with the expected rates in the large Olmstead County database was reported. The risk was increased for patients >50 years old, with onset of atrial fibrillation, with increase in mitral thickening, and when surgery was needed because of development of mitral regurgitation. In the Critique accompanying this Olmstead County report, Oppenheimer 21 remarked that “recommendations for treatment are complex”. In the lower-risk group it is doubtful that there is need for anything other than observation. In patients over 50, atrial fibrillation or mitral regurgitation should be anticipated, and in time some will require valve replacement. Once symptoms have developed, careful longterm observation must be given. The occurrence rate was high (27%) during the Olmstead follow-up period of a decade. Published photos of myxomatously degenerate valves illustrate cracks and fissures. On some of these may be seen adherent platelet-fibrin debris. When cerebral or ocular symptoms develop, aspirin may be the treatment of first choice. Trial data are nonexistent.

The gap between the certainty of diagnosis and speculation as to cause of stroke is narrowing. Good imaging coupled with an understanding of the risks for stroke and the pathological processes that cause it will determine any treatment program. Nothing less than exact diagnosis should be accorded to any patient at risk of stroke. Nor should any clinical trial of therapy be given credence if all trial subjects are not submitted to the most scrupulous investigation by experts in the field. “Ischemic Stroke” is a very generic condition, and all therapeutic strategies require specific definition. In the search for the importance of 2 heart-valve lesions that cause stroke, the readers of this Journal are indebted to Kizer et al in this issue of Stroke 11 just as they were indebted to Avierinos et al in June of 2003. 20

References


Stroke by Cause: Some Common, Some Exotic, Some Controversial
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