Stroke by Cause
Some Common, Some Exotic, Some Controversial

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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.

Nineteenth-century cardiology, exemplified by the work of William Osler, established that cerebrovascular events were the result of either cardiac or aortic causes. The condition of the aorta and its branches was always a major clinical concern. The increasing sophistication of modern imaging made it possible to define 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 and stroke. Of interest was the absence of correlation between NVAF 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 with the use of anticoagulants. Apart from rhythm monitoring and echocardiography, extensive cardiac investigation is not required. NVAF is a disease to which the elderly are predisposed, and it is predicted that by 2050 50% of individuals ≥80 years of age will be afflicted. Long-term warfarin has become the proven therapy for patients with persisting NVAF who are without contraindications to anticoagulation. Aspirin alone has muted benefit and should be used when anticoagulants are contraindicated.

Akin to the disagreements in the early days of the observations about NVAF, controversy has characterized the acceptance of claims about many of the newer examples of cardiac causes of stroke. Additional clinical and pathological studies are bringing some of these putative claims into proper perspective. For example, the causal association of stroke and patent foramen ovale (PFO) is now widely accepted. French investigators have been at the forefront in the studies of PFO as a cause of stroke, and Mas has done a recent review of this topic.

The condition is common and identified in 50% of subjects less than 45 years. Most of the openings are small, and most remain asymptomatic, needing no therapy. Nevertheless, patients with PFO will experience ischemic symptoms. Before accepting it as unequivocally causal, other possible vascular and cardiac conditions must be excluded. Then, the alternatives for therapy are anticoagulants, aspirin, or endovascular closure. The WARRS investigators extracted from their database the group who had “uncertain stroke cause” including the PFO patients. Recurrences were not different whether on aspirin or warfarin. This post-hoc study may not be definitive but the reaction to an ischemic event would be to prescribe aspirin first. Should events continue and if the foraminal opening is large, it would then be reasonable to consider the promising albeit unproven technology of endovascular closure.

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 embolicogenic 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 (pictures of both lesions are illustrated in the 2 references cited). 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.

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Stroke is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000194560.65809.47

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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 cardioembolic 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. 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.” A large majority of afflicted individuals are asymptomatic and will remain 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. 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. 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. As with MAC, coincidental stroke causes, including PFO and atheroma, must be eliminated. The recent statement by Ricci that “uncomplicated mitral valve prolapse should not be considered a cause of stroke” is incorrect and misleading. 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. 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. 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. As with MAC, coincidental stroke causes, including PFO and atheroma, must be eliminated. The recent statement by Ricci that “uncomplicated mitral valve prolapse should not be considered a cause of stroke” is incorrect and misleading. 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 spare 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. 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 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 recurrence rate was high (27%) during the Olmstead follow-up period of a decade. Published photos of myxomatous 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 just as they were indebted to Avierinos et al in June of 2003.

References


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Stroke. 2005;36:2523-2525; originally published online November 17, 2005;
doi: 10.1161/01.STR.0000194560.65809.47
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
http://stroke.ahajournals.org/content/36/12/2523

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