MITRAL ANNULAR CALCIFICATION AND THE RISK OF STROKE IN AN ELDERLY COHORT

EMELIA J. BENJAMIN, M.D., M.SC., JONATHAN F. PLEHN, M.D., RALPH B. D'AGOSTINO, PH.D., ALBERT J. BELANGER, M.A., KATHY COMAI, M.A., R.D.C.S., DEBORAH L. FULLER, R.D.C.S., PHILIP A. WOLF, M.D., AND DANIEL LEVY, M.D.

Abstract *Background.* Previous clinical studies have suggested that there is an association between mitral annular calcification and the risk of stroke, but it is unclear whether this association is independent of the traditional risk factors for stroke. We examined the relation between mitral annular calcification and the incidence of stroke in a population-based study.

Methods. Subjects in the Framingham Study receiving a routine examination underwent M-mode echocardiography to determine the presence and severity (thickness in millimeters) of mitral annular calcification. The incidence of stroke during eight years of follow-up was analyzed with a proportional-hazards model adjusting for the calcification, age, sex, systolic blood pressure, diabetes mellitus, cigarette smoking, atrial fibrillation, and coronary heart disease or congestive heart failure.

Results. Among 1159 subjects whose echocardiograms could be assessed for mitral annular calcification and who had no history or current evidence of stroke at the index examination (51 percent of all subjects), the prevalence of mitral annular calcification was 10.3 percent in the men and 15.8 percent in the women. Multivariate analysis demonstrated that the presence of mitral annular calcification was associated with a relative risk of stroke of 2.10 (95 percent confidence interval, 1.24 to 3.57; $P = 0.006$). There was a continuous relation between the incidence of stroke and the severity of mitral annular calcification; each millimeter of thickening as shown on the echocardiogram represented a relative risk of stroke of 1.24 (95 percent confidence interval, 1.12 to 1.37; $P<0.001$). Furthermore, even when subjects with coronary heart disease or congestive heart failure were excluded from the analysis, subjects with mitral annular calcification still had twice the risk of stroke.

Conclusions. In an elderly, longitudinally followed population-based cohort, mitral annular calcification was associated with a doubled risk of stroke, independently of traditional risk factors for stroke. Whether such calcification contributes causally to the risk of stroke or is merely a marker of increased risk because of its association with other precursors of stroke remains unknown. (N Engl J Med 1992;327:374-9.)

CALCIFICATION of the mitral annulus is a noninflammatory chronic degenerative process of the fibrous support structure of the mitral valve.[1-4] Mitral annular calcification (MAC) occurs more commonly in women and the elderly.[5] It has also been reported to be associated with elevated systolic blood pressure, obesity, and atrial fibrillation.[5] The putative sequelae of MAC include mitral stenosis,[3] mitral regurgitation,[3,4,6] infective endocarditis,[4,7] atrial arrhythmias,[3,8] heart block,[4,6] congestive heart failure,[4,6,8] and stroke.

Since the account of a stroke in a patient with MAC by Rytand and Lipsitch in 1946,[6] numerous hospital-based case reports,[9-11] case series,[3,4,7,12-19] case–control studies,[20-22] and cohort studies[8,23] have suggested an association between this disorder and stroke. Nair and colleagues followed a cohort of 107 patients with MAC and 107 patients without MAC who were matched for age and sex, for a mean of 4.4 years. Among the 200 subjects not lost to follow-up, cerebrovascular events occurred in 10 percent of patients with MAC and 2 percent of those without it ($P<0.01$).[8] Recently, two randomized, controlled studies of subjects with atrial fibrillation have reached opposite conclusions; the Boston Area Anticoagulation Trial for Atrial Fibrillation suggested that MAC was associated with an increased risk of stroke,[23] whereas the Stroke Prevention in Atrial Fibrillation trial failed to find an association.[24] It remains unresolved whether MAC is independently associated with stroke or merely related to stroke by virtue of its correlation with many known risk factors for stroke. The purpose of our investigation was to examine the relation between MAC and the risk of stroke in a longitudinal study of subjects initially free from stroke who were evaluated by echocardiography for the presence and severity of MAC.

From the Framingham Heart Study, Framingham, Mass. (E.J.B., J.F.P., K.C., D.L.F., P.A.W., D.L.); the Cardiology Department, Boston City Hospital, Boston (E.J.B.); the Cardiology Section, Dartmouth–Hitchcock Medical Center, Lebanon, N.H. (J.F.P.); the Department of Mathematics, Boston University, Boston (R.B.D., A.J.B.); the Departments of Neurology (P.A.W.) and Preventive Medicine (E.J.B., P.A.W., D.L.), Boston University School of Medicine, Boston; the Divisions of Cardiology and Clinical Epidemiology, Beth Israel Hospital, Boston (D.L.); and the National Heart, Lung, and Blood Institute, Bethesda, Md. (D.L.). Address reprint requests to Dr. Benjamin at the Framingham Heart Study, 5 Thurber St., Framingham, MA 01701.

The Framingham Study is supported in part under a contract (N01-HC-38038) with the National Heart, Lung, and Blood Institute and by a grant (2-R01-NS-17950-09 [to Drs. Wolf and Benjamin]) from the National Institute of Neurological Disorders and Stroke. The research was also supported in part by a grant to the Training Program in Clinical Effectiveness (Dr. Benjamin) from the W.K. Kellogg Foundation.

Presented in part at the 62nd Scientific Sessions of the American Heart Association, New Orleans, November 1989.

METHODS

In 1948, 5209 residents of Framingham, Massachusetts, between the ages of 30 and 62 were selected to undergo biennial examinations (that is, every two years) in a prospective epidemiologic study. The details of population selection and the study design have been described previously.[25,26] The Framingham Study examination was approved by the investigational review board of Boston University Medical Center; informed written consent was obtained from each subject before the clinic examination began. In the present study, the index examination was biennial examination 16, performed between 1979 and 1981, at which M-mode echocardiograms were obtained for all surviving participants.

A history of subsequent symptoms or signs of a stroke during the eight years after this examination, whether noted during a biennial examination or during daily surveillance of admissions to the only hospital in Framingham, prompted an evaluation by a study neurologist. The criteria for stroke were applied by a panel of three investigators, including a neurologist, who were unaware of wheth-

er the subjects had MAC. Determinations about the occurrence of strokes were made after a review of all available hospital and physicians' records, reports on noninvasive examinations of the carotid artery, CT scans of the head, data from cerebral angiography, autopsy data, and death certificates.[27,28] CT scans of the head were obtained in 86 percent of all patients who had strokes, and cerebral angiograms in 5 percent. The eight-year incidence of stroke after the index examination (biennial examination 16) was analyzed. Completed strokes were classified as due to ischemia or hemorrhage and further categorized according to the criteria of the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke.[29] Hemorrhagic strokes included those due to subarachnoid hemorrhage (none occurred during follow-up) and those due to intraparenchymal hemorrhage. The diagnosis of intraparenchymal hemorrhage required a focal neurologic deficit associated with an altered level of consciousness, and was often accompanied by headache; in all seven patients with such hemorrhage, an area of increased attenuation consistent with blood was found on CT scanning. Ischemic strokes were subdivided into atherothrombotic strokes (those due to lacunar infarcts, large-artery atherothrombotic infarcts, or infarcts of undetermined cause) and embolic strokes. The diagnosis of cerebral embolism required that a cardiac source of embolus be identified, such as atrial fibrillation, the presence of a prosthetic valve, mitral stenosis, a recent myocardial infarction, or a ventricular thrombus. MAC was not considered a cause of embolism. In an additional analysis, isolated transient ischemic attacks were included among the cerebrovascular events.

Systolic blood pressure was measured by the examining physician while the subject was seated. Diabetes was considered present if the subject had a random, nonfasting blood glucose level of at least 200 mg per deciliter (11 mmol per liter) or was taking insulin or an oral hypoglycemic agent. The concentration of total cholesterol and data on cigarette smoking were obtained from biennial examination 15. Prevalent cardiac disease was defined as a history of congestive heart failure or coronary heart disease (angina pectoris, coronary insufficiency, or myocardial infarction) at or before the index examination (biennial examination 16). Whether the subjects had congestive heart failure and events related to coronary heart disease was determined by a panel of three physicians after they had reviewed all available medical and clinic records, using previously described criteria.[27] Prevalent atrial fibrillation was considered present if this rhythm was documented at any biennial examination up to and including the index examination or by an electrocardiogram obtained during any previous hospitalization. Interim atrial fibrillation was defined as a documented episode of atrial fibrillation occurring after examination 16 but before a stroke. If atrial fibrillation was found on the initial electrocardiogram during hospitalization for stroke, the arrhythmia was assumed to have begun before the stroke. All electrocardiograms demonstrating atrial fibrillation were verified by a cardiologist.

From 1979 to 1981, M-mode echocardiograms were obtained in the 2291 surviving members of the cohort undergoing their 16th biennial examination. Echocardiography was performed with two-dimensional guidance, through a parasternal window. M-mode recordings were made with a Hoffrel 201 ultrasound machine with an Aerotech 2.25-MHz transducer and a Jason thermographic printer. In the previous investigation of MAC at examination 16 of the Framingham Study, MAC was recorded as a dichotomous variable, either present or absent.[5] In the present study, the M-mode echocardiograms were reinterpreted by echocardiographers blinded to all clinical information about the subjects, to determine both the presence and severity of MAC. This disorder was considered present if an echo-dense band was visualized throughout systole and diastole, was distinguishable from the posterior mitral-valve leaflet, and was located behind the posterior mitral-valve leaflet and anterior and parallel to the posterior left ventricular wall (Fig. 1). The

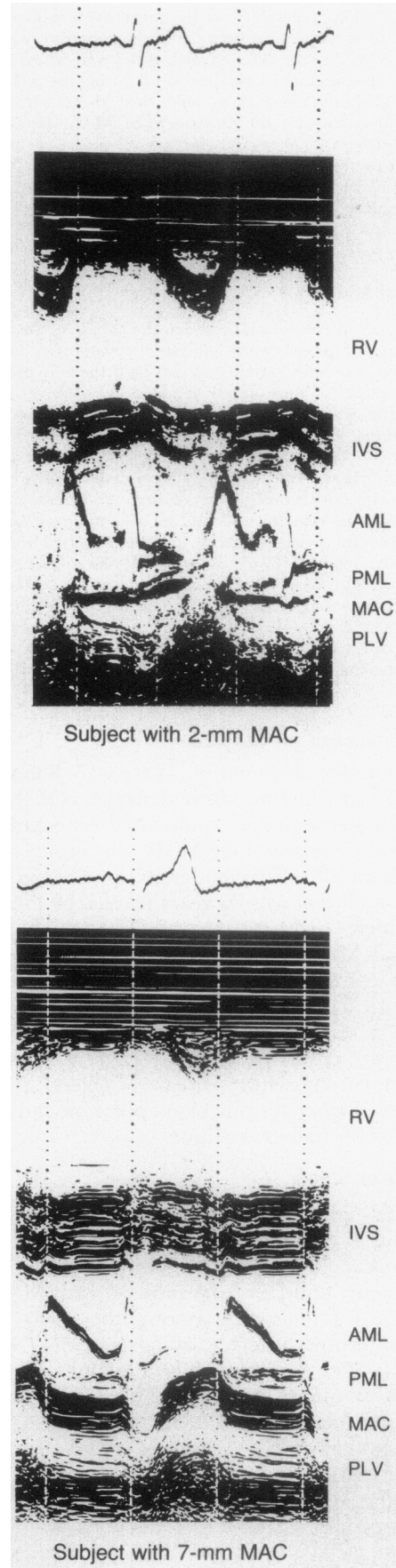

Figure 1. M-Mode Echocardiograms of Two Subjects with MAC.
RV denotes right ventricle, IVS interventricular septum, AML anterior mitral-valve leaflet, PML posterior mitral-valve leaflet, and PLV posterior left ventricular wall.

severity of MAC (expressed as its thickness in millimeters) was measured by a cardiologist from the leading anterior to the trailing posterior edge. At least three cardiac cycles were assessed, and the MAC was measured at its greatest width during the cycle. Subjects were excluded from the investigation if their M-mode tracing was of suboptimal quality for the assessment of MAC. Because of the stringent criteria for measurability, the advanced age of the subjects, and the reliance on the M-mode technique, the tracings of 48.6 percent of the subjects could not be interpreted with respect to MAC. Subjects were also excluded for the following indications: mitral stenosis, a mitral-valve prosthesis, or prevalent stroke (at or before the index examination).

Statistical Analysis

Differences in risk factors between the subjects with MAC and those without it were tested by analysis of covariance,[30] with control for age and sex. Multivariate analyses used the Cox proportional-hazards model.[31] Unless otherwise stated, the multivariate models included the variables age, sex, MAC, systolic blood pressure, diabetes mellitus, cigarette smoking, prevalent atrial fibrillation, and prevalent coronary heart disease or congestive heart failure. The model was first analyzed with MAC as a dichotomous variable, to assess the effect of its presence or absence. Analyses were also performed with the severity of MAC as a continuous variable. An estimated cumulative incidence of stroke was plotted from the multivariate Cox model.[32] Two curves were produced that represented the subjects with MAC and those without it; for both curves, all other covariates were held constant at the mean values for the entire study population. A chi-square test was performed to examine the influence of interim atrial fibrillation on the risk of stroke, according to status for MAC. Two-sided tests were used for all P values.

Results

Characteristics of the Subjects

At the index examination, there were 888 men and 1367 women who had not had strokes. Of these subjects, 426 men and 733 women had echocardiograms that could be assessed for MAC; this group served as the basis for all subsequent analyses. The average age of the population was 70 years (range, 59 to 90). Forty-four men (10.3 percent) and 116 women (15.8 percent) had MAC, with severity ranging from 1 to 11 mm. As compared with the subjects without MAC, those with MAC were older, were more likely to be women, and more frequently had prevalent atrial fibrillation, prevalent congestive heart failure, and prevalent coronary heart disease (Table 1); they tended to have higher systolic blood pressure and a higher frequency of diabetes mellitus.

Table 1. Characteristics of the Study Subjects, According to Whether or Not They Had MAC.

Characteristic	No MAC (N = 999)	MAC (N = 160)	P Value*
Age (yr)	69	73	<0.001
Sex (% male)	38.2	27.5	0.03
Systolic blood pressure (mm Hg)	140	147	0.05
Diabetes mellitus (%)	9.8	16.3	0.06
Atrial fibrillation (%)	4.6	11.3	0.009
Cholesterol (mg/dl)†	231	234	0.49
Cigarette smoking (%)	21.1	12.5	0.21
Congestive heart failure (%)	2.3	8.1	<0.001
Coronary heart disease (%)	17.4	28.8	0.006

*The comparison of the ages of the groups was adjusted for sex, and the comparison of sex was adjusted for age; the comparisons of the other variables were adjusted for both age and sex.
†To convert to millimoles per liter, multiply by 0.02586.

Incidence of Stroke

During eight years of follow-up, 30 men (7.0 percent) and 43 women (5.9 percent) sustained strokes. Stroke occurred in 51 of the subjects without MAC (5.1 percent) and 22 of the subjects with MAC (13.8 percent). Its incidence among the 1096 subjects with uninterpretable echocardiograms was 7.4 percent (n = 81); after adjustment for age and sex, this rate was not significantly different from the incidence among the subjects without MAC.

MAC was associated with a relative risk of stroke of 2.10 (95 percent confidence interval, 1.24 to 3.57; P = 0.006) after adjustment for age, sex, systolic blood pressure, diabetes mellitus, cigarette smoking, prevalent atrial fibrillation, and prevalent coronary heart disease or congestive heart failure. The predicted cumulative incidence of stroke among subjects with and without MAC, adjusted for all these variables, is shown in Figure 2. The relation between MAC and stroke was continuous; on multivariate analysis, each millimeter of calcification increased the relative risk of stroke by 1.24 (95 percent confidence interval, 1.12 to 1.37; P<0.001). The results were similar when the data were analyzed according to sex. The multivariate relative risk of stroke per millimeter of calcification was 1.27 for men (95 percent confidence interval, 1.06 to 1.52; P = 0.009) and 1.19 for women (95 percent confidence interval, 1.06 to 1.34; P = 0.003). During eight years of follow-up of 999 subjects without MAC, there were 51 strokes: 27 were atherothrombotic infarcts, 21 were embolic infarcts, and 3 were intracerebral hemorrhages. Of the 22 strokes among the 160 subjects with MAC, 14 were due to emboli, 4 to intracerebral hemorrhages, and 4 to atherothrombosis. During follow-up there were no subarachnoid hemorrhages and no strokes in the presence of endocarditis.

The preponderance of embolic strokes in the subjects with MAC prompted an investigation of the role of atrial fibrillation. When the risk of stroke was classified according to whether the subjects had prevalent atrial fibrillation and MAC, the risk was doubled if either MAC or prevalent atrial fibrillation was present, and was increased approximately fivefold if both factors were present (Fig. 3). Furthermore, when all subjects with prevalent atrial fibrillation were excluded, the presence of MAC still significantly increased the relative risk of stroke (multivariate relative risk, 1.96; 95 percent confidence interval, 1.09 to 3.52; P = 0.02).

A further analysis explored the contribution to the risk of stroke of interim atrial fibrillation (fibrillation after the index examination but before the stroke). In an analysis restricted to subjects free of prevalent atrial fibrillation, 19 percent of new strokes in subjects without MAC (9 of 47) were associated with the development of interim atrial fibrillation; among

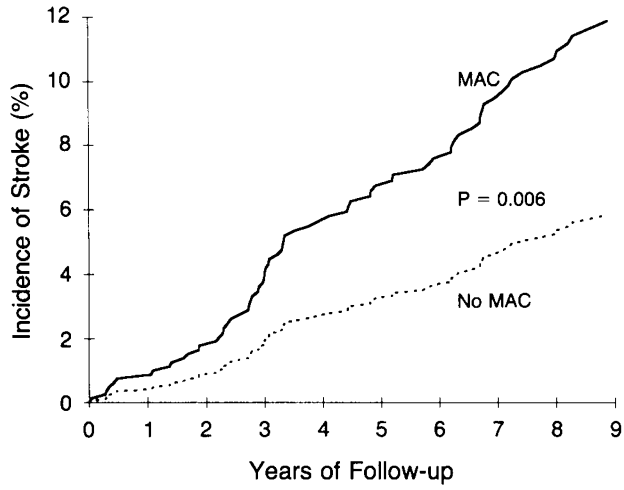

Figure 2. Cumulative Incidence of Stroke, According to the Presence or Absence of MAC.

The incidence rates were adjusted for age, sex, systolic blood pressure, diabetes mellitus, prevalent atrial fibrillation, and prevalent coronary heart disease or congestive heart failure. The Kaplan–Meier curves were significantly different.

subjects with MAC who had strokes, 41 percent (7 of 17) had interim atrial fibrillation before the stroke (P = 0.07).

Atrial fibrillation (prevalent or interim) was involved in 12 of 22 strokes occurring in the presence of MAC. However, even after the multivariate analysis was adjusted for a history of atrial fibrillation at any time before the stroke (i.e., prevalent or interim atrial fibrillation), MAC remained associated with stroke (relative risk, 1.91; 95 percent confidence interval, 1.12 to 3.25; P = 0.02).

Additional Analyses

Cardiac Disease

MAC was associated with prevalent coronary heart disease and congestive heart failure (Table 1), which in turn are known to be important risk factors for stroke.[33] To examine the role of cardiac disease further, the multivariate model was reanalyzed after subjects with prevalent congestive heart failure or coronary heart disease were excluded. The doubling of the risk of stroke in the presence of MAC persisted (relative risk of stroke with MAC, 2.15; 95 percent confidence interval, 1.13 to 4.09; P = 0.02).

Stroke End Points

Eliminating cerebral hemorrhages from the stroke-related outcomes did not eliminate the excess risk of stroke in the subjects with MAC. After adjustment for age, sex, systolic blood pressure, diabetes mellitus, cigarette smoking, prevalent atrial fibrillation, and prevalent coronary heart disease or congestive heart failure, the relative risk of ischemic stroke in the presence of MAC was 1.78 (95 percent confidence interval, 1.00 to 3.16; P = 0.05).

In addition, when transient ischemic attacks were included in the multivariate model (attacks occurred in 3 subjects with MAC and in 21 without MAC), the relative risk of stroke or transient ischemic attack with MAC was 1.93 (95 percent confidence interval, 1.18 to 3.16; P = 0.009).

Left Atrial Size

After adjustment for left atrial size (in addition to the other risk factors described above), MAC remained significantly associated with the incidence of stroke (relative risk, 1.81; 95 percent confidence interval, 1.03 to 3.18; P = 0.04).

Discussion

In our study, the presence of MAC was predictive of a doubling in the risk of stroke after adjustment for multiple risk factors, including age, sex, systolic blood pressure, diabetes mellitus, and cigarette smoking. The association between MAC and stroke was also observed irrespective of the presence or absence of atrial fibrillation. Furthermore, limiting the analysis to subjects free of prevalent congestive heart failure or coronary heart disease did not change the doubled risk of stroke in the presence of MAC.

The causes of stroke in patients with MAC are uncertain, but most speculation has centered on an embolic pathogenesis. The present study supports this hypothesis, in that approximately two thirds of the strokes in subjects with MAC fulfilled criteria for a cerebral embolism. The mechanisms of embolism in patients with MAC remain undetermined. Autopsy reports have documented calcific emboli to the brain and other organs in a few patients with MAC.[9,10,13]

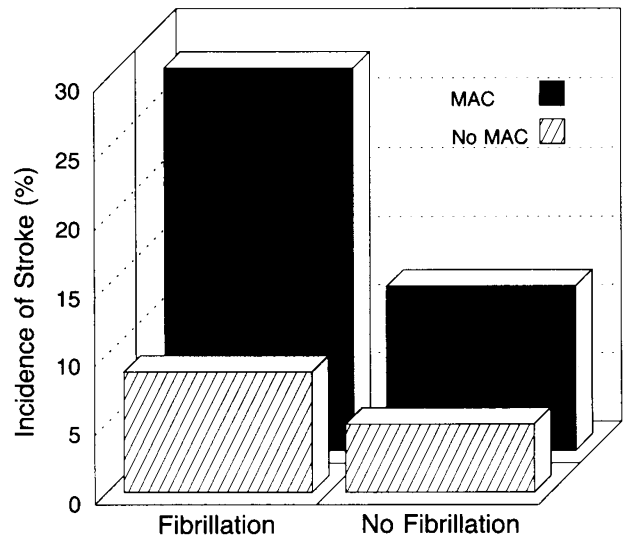

Figure 3. Incidence of Stroke during Eight Years of Follow-up, According to Presence or Absence of MAC and the Presence or Absence of Prevalent Atrial Fibrillation at or before the Index Examination.

Some authors have also suggested that MAC serves as a nidus for thrombus formation[34] or endocarditis.[7]

Perhaps the most important cause of embolic stroke is atrial fibrillation, which occurs more commonly in subjects with MAC.[5,8] The risk of stroke in such subjects remained increased after multivariate adjustment for prevalent or interim atrial fibrillation.

Because one third of the strokes in the subjects with MAC were considered to be nonembolic (atherothrombotic or hemorrhagic), other mechanisms of the relation between MAC and stroke must be considered. The current observations of an association between MAC and risk factors for stroke are consistent with earlier reports linking MAC with advancing age,[35] elevated systolic blood pressure,[3,4] and diabetes mellitus.[36] Furthermore, MAC is associated with several cardiac conditions that are known to predispose patients to stroke,[33] including congestive heart failure[8,37] and atherosclerosis.[38] Consequently, MAC may be predictive of stroke because of the clustering of risk factors for stroke in subjects with MAC. For example, high blood pressure may predispose patients to MAC and to stroke; MAC may serve as a marker for severe chronic hypertension and a concomitant risk of stroke. Furthermore, MAC may be associated with an increased risk of stroke by serving as a surrogate for other unknown or unmeasured risk factors. Although every effort was made to adjust for potential confounding variables, the current analyses cannot determine whether MAC is a causal risk factor or merely a marker of an increased risk of stroke.

Many echocardiograms could not be interpreted with respect to MAC. As noted above, subjects with uninterpretable echocardiograms had a stroke rate that was not significantly different from the rate among subjects without MAC, suggesting that the application of stringent criteria for assessing the acceptability of M-mode tracings did not introduce a systematic bias. The number of uninterpretable echocardiograms is not surprising, because the investigation was based on M-mode echocardiography and involved elderly subjects. The frequency of technically inadequate studies is greater among elderly subjects.[39] However, we do not know whether the detection of MAC in younger subjects or by two-dimensional echocardiography (with its greater spatial resolution) will portend the same increased risk of stroke.

Misclassification among categories of strokes may have occurred. The investigators of the Framingham Study classified a stroke as embolic only if it had a potential cardiac source of embolus other than MAC. Other investigators have had difficulty in determining types of stroke, including workers from a multihospital registry, who found that the causes of 40 percent of strokes were undetermined.[29] Because precise classification according to the type of stroke is currently unattainable, the multivariate analyses emphasized the association of MAC with all stroke-related events rather than with individual categories of strokes.

We believe that our study has advantages over previous studies. Such investigations have been limited by selection biases inherent in autopsy studies,[3,7,9-11,13,14] retrospective analyses,[3,4,6,7,9,10,13,18,19] and analyses without control groups.[3,4,6,7,12-19] Case–control studies conducted previously have been limited by difficulties in forming appropriate control groups and by a lack of multivariate analyses to adjust for other factors that increase the risk of stroke.[20-22] The first cohort study in which subjects with MAC were followed was limited to subjects less than 61 years of age, enrolled subjects referred for echocardiography as controls, and was unable to carry out multivariate analyses adjusting for traditional risk factors for stroke.[8] The other two cohort-based studies that examined a relation between MAC and stroke were hospital-based, were limited to subjects with atrial fibrillation, and reached conflicting conclusions.[23,24]

In this population-based study of an elderly cohort, both the presence and the severity of MAC were predictive of the risk of stroke. The association between MAC and stroke was observed both in subjects without prevalent atrial fibrillation and in subjects without clinically apparent prevalent coronary heart disease or congestive heart failure. Our findings suggest that the detection of MAC contributes prognostic information beyond that provided by the detection of traditional risk factors for stroke, facilitating the identification of persons at an increased risk of stroke.

We are indebted to David M. Pollak for editorial assistance, to John Orav, Ph.D., for statistical insights from preliminary analyses, and to Deborah Dumphy for programming assistance.

References

1. Bönniger M. Bluttransfusionen bei perniziöser Anämie. Dtsch Med Wochenschr 1908;34:2292-3.
2. *Idem.* Zwei Fälle von Herzblock. Dtsch Med Wochenschr 1908;34:2293.
3. Korn D, DeSanctis RW, Sell S. Massive calcification of the mitral annulus: a clinicopathological study of fourteen cases. N Engl J Med 1962;267:900-9.
4. Fulkerson PK, Beaver BM, Auseon JC, Graber HL. Calcification of the mitral annulus: etiology, clinical associations, complications and therapy. Am J Med 1979;66:967-77.
5. Savage DD, Garrison RJ, Castelli WP, et al. Prevalence of submitral (anular) calcium and its correlates in a general population-based sample (the Framingham Study). Am J Cardiol 1983;51:1375-8.
6. Rytand DA, Lipsitch LS. Clinical aspects of calcification of the mitral annulus fibrosus. Arch Intern Med 1946;78:544-64.
7. Burnside JW, DeSanctis RW. Bacterial endocarditis on calcification of the mitral anulus fibrosus. Ann Intern Med 1972;76:615-8.
8. Nair CK, Thomson W, Ryschon K, Cook C, Hee TT, Sketch MH. Long-term follow-up of patients with echocardiographically detected mitral anular calcium and comparison with age- and sex-matched control subjects. Am J Cardiol 1989;63:465-70.
9. Zak FG, Elias K. Embolization with material from atheromata. Am J Med Sci 1949;218:510-5.
10. Ridolfi RL, Hutchins GM. Spontaneous calcific emboli from calcific mitral annulus fibrosus. Arch Pathol Lab Med 1976;100:117-20.
11. Guthrie J, Fairgrieve J. Aortic embolism due to myxoid tumour associated with myocardial calcification. Br Heart J 1963;25:137-40.
12. Furlan AJ, Craciun AR, Salcedo EE, Mellino M. Risk of stroke in patients with mitral annulus calcification. Stroke 1984;15:801-3.
13. Lin CS, Schwartz IS, Chapman I. Calicification of the mitral annulus fibrosus with systemic embolization: a clinicopathologic study of 16 cases. Arch Pathol Lab Med 1987;111:411-4.
14. Kirk RS, Russell JGB. Subvalvular calcification of mitral valve. Br Heart J 1969;31:684-92.
15. Greenland P, Knopman DS, Mikell FL, Asinger RW, Anderson DC, Good DC. Echocardiography in diagnostic assessment of stroke. Ann Intern Med 1981;95:51-3.

16. Good DC, Frank S, Verhulst S, Sharma B. Cardiac abnormalities in stroke patients with negative arteriograms. Stroke 1986;17:6-11.
17. Todnem K, Vik-Mo H. Cerebral ischemic attacks as a complication of heart disease: the value of echocardiography. Acta Neurol Scand 1986;74:323-7.
18. Rem JA, Hachinski VC, Boughner DR, Barnett HJM. Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 1985;16:950-6.
19. Bogousslavsky J, Hachinski VC, Boughner DR, Fox AJ, Vineula F, Barnett HJM. Cardiac and arterial lesions in carotid transient ischemic attacks. Arch Neurol 1986;43:223-8.
20. de Bono DP, Warlow CP. Mitral-annulus calcification and cerebral or retinal ischaemia. Lancet 1979;2:383-5.
21. Jespersen CM, Egeblad H. Mitral annulus calcification and embolism. Acta Med Scand 1987;222:37-41.
22. Nishide M, Irino T, Gotoh M, Naka M, Tsuji K. Cardiac abnormalities in ischemic cerebrovascular disease studied by two-dimensional echocardiography. Stroke 1983;14:541-5.
23. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323:1505-11.
24. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. II. Echocardiographic features of patients at risk. Ann Intern Med 1992;116:6-12.
25. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham study. Am J Public Health 1951;41:279-86.
26. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. Ann N Y Acad Sci 1963;107:539-56.
27. Shurtleff D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 18 year follow-up. In: Kannel WB, Gordon T, eds. The Framingham Study: an epidemiological investigation of cardiovascular disease. Section 30. Washington, D.C.: Government Printing Office, 1974. (DHEW publication no. (NIH) 74-599.)
28. Cupples LA, D'Agostino RB. Survival following initial cardiovascular events: 30 year follow-up. In: Kannel WB, Wolf PA, Garrison RJ, eds. The Framingham Study: an epidemiological investigation of cardiovascular disease. Section 35. Bethesda, Md.: Department of Health and Human Services, 1988. (NIH publication no. 88-2969.)
29. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. Ann Neurol 1989;25:382-90.
30. Analysis of covariance and other methods for adjusting continuous data. In: Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. 2nd ed. Boston: PWS-Kent Publishing, 1988: 297-313.
31. Lawless JF. Statistical models and methods for lifetime data. New York: John Wiley, 1982:359-63.
32. The proportional hazards model. In: Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley, 1980:70-118.
33. Kannel WB, Wolf PA, Verter J. Manifestations of coronary disease predisposing to stroke: the Framingham Study. JAMA 1983;250:2942-6.
34. Barnett HJM. Heart in ischemic stroke — a changing emphasis. Neurol Clin 1983;1:291-315.
35. Pomerance A. Pathological and clinical study of calcification of the mitral valve ring. J Clin Pathol 1970;23:354-61.
36. Nair CK, Sudhakaran C, Aronow WS, Thomson W, Woodruff MP, Sketch MH. Clinical characteristics of patients younger than 60 years with mitral anular calcium: comparison with age- and sex-matched control subjects. Am J Cardiol 1984;54:1286-7.
37. Mellino M, Salcedo EE, Lever HM, Vasudevan G, Kramer JR. Echographic-quantified severity of mitral anulus calcification: prognostic correlation to related hemodynamic, valvular, rhythm, and conduction abnormalities. Am Heart J 1982;103:222-5.
38. Roberts WC, Perloff JK. Mitral valvular disease: a clinicopathologic survey of the conditions causing the mitral valve to function abnormally. Ann Intern Med 1972;77:939-75.
39. Savage DD, Garrison RJ, Kannel WB, Anderson SJ, Feinleib M, Castelli WP. Considerations in the use of echocardiography in epidemiology: the Framingham Study. Hypertension 1987;9:Suppl II:II-40–II-44.