Mitral Annular Calcification, Aortic Valve Sclerosis, and Incident Stroke in Adults Free of Clinical Cardiovascular Disease
The Strong Heart Study

Jorge R. Kizer, MD, MSc; David O. Wiebers, MD; Jack P. Whisnant, MD; James M. Galloway, MD; Thomas K. Welty, MD; Elisa T. Lee, PhD; Lyle G. Best, MD; Helaine E. Resnick, PhD, MPH; Mary J. Roman, MD; Richard B. Devereux, MD

Background and Purpose—Mitral annular calcification (MAC) and aortic valve (AV) sclerosis have each been linked to cardiovascular disease. Whether MAC and AV sclerosis are risk factors for stroke independent of other echocardiographic or laboratory predictors has not been established. We evaluated the relationship between MAC, AV sclerosis, and first stroke events in a population-based cohort.

Methods—Our study cohort consisted of 2723 American Indians participating in the Strong Heart Study who were free of prevalent cardiovascular disease. Participants underwent standardized clinical, echocardiographic, and laboratory evaluation, and incident stroke was ascertained using validated methods.

Results—During a median follow-up of 7 years, 86 strokes occurred. Age- and sex-adjusted incidence rates of stroke were significantly increased for MAC (rate ratio [RR], 3.12; 95% CI, 1.77 to 5.25) but not for AV sclerosis (RR, 1.15; 95% CI, 0.45 to 2.49). MAC was also associated with a reduced time to first stroke events after adjustment for clinical variables and the inflammatory markers C-reactive protein and fibrinogen (hazard ratio [HR], 2.42; 95% CI, 1.39 to 4.21) or the echocardiographic covariates left ventricular hypertrophy and left atrial enlargement (HR, 1.89; 95% CI, 1.04 to 3.41). Individuals with and without AV sclerosis showed no significant difference in stroke-free survival in unadjusted analyses (P=0.698). Crossing of the survival curves precluded multivariable analysis using Cox models.

Conclusions—In this cohort of American Indians without clinical cardiovascular disease, the presence of MAC, but not AV sclerosis, proved to be a strong risk factor for incident stroke after extensive adjustment for other predictors. Individuals exhibiting MAC may benefit from aggressive risk factor modification, but this will require further investigation. (Stroke. 2005;36:2533-2537.)

Key Words: calcium ─ echocardiography ─ heart valves ─ stroke

Mitral annular calcification (MAC) is characterized by calcium and lipid deposition in the annular fibrosa of the mitral valve, whereas aortic valve (AV) sclerosis results from similar accumulation involving the AV leaflets.1 Clinical precursors of atherosclerosis are also risk factors for MAC and AV sclerosis,2,3 and the 2 conditions often exist concurrently.2 Each, in turn, has been documented to be an independent predictor of cardiovascular events.4,5 Several,6,7 although not all,8,9 studies have detailed a similar relationship between MAC and stroke, but an independent association between AV calcification and cerebral infarction has only been demonstrated in the presence of AV stenosis.5,10,11 MAC and AV sclerosis are associated with atherosclerosis risk factors that can promote left ventricular (LV) hypertrophy and left atrial (LA) enlargement, each of which has been reported to predict cerebrovascular events.12,13 However, available studies linking valvular calcification with cerebral ischemia have adjusted only partly, if at all, for these concurrent echocardiographic predictors.6,7,11 Whether valvular calcification has prognostic value independently of these...
abnormalities in cardiac chamber structure is uncertain. Furthermore, inflammatory markers are also correlated with valvular calcification and have emerged as risk factors in their own right for the occurrence of stroke. Yet the degree to which MAC and AV sclerosis provide additive information to that afforded by these easily obtained measures of inflammation is unknown. We addressed these questions in a population-based cohort free of clinical cardiovascular disease.

Methods

Participants

The Strong Heart Study is a population-based survey of risk factors for cardiovascular disease in 13 American Indian communities. Tribe members 45 to 74 years of age were recruited for an initial examination (July 1989 to January 1992), which included collection of fasting blood samples. The second examination (July 1993 to December 1995) involved the addition of echocardiography, performed in 97% of 3501 returning individuals. The present analyses are limited to 2723 participants in the second examination free of clinical or echocardiographic cardiovascular disease. Clinical cardiovascular disease included a history of stroke, transient ischemic attack, coronary heart disease (CHD), congestive heart failure (CHF), or atrial fibrillation (AF). AF was also excluded by digitized ECG, available for 100% in the initial examination, but only for the base of the mitral leaflets on M-mode or 2D imaging in 97% of the study cohort in the second examination because of a catastrophic disk crash; and by echocardiography, based on the presence of a documented A wave on the transmitral Doppler profile. Echocardiographic disease included >1 mitral or aortic regurgitation or stenosis of any severity, LV ejection fraction <0.50, or segmental wall motion abnormalities.

Echocardiographic Methods and Measurements

Cardiac sonography was performed with phased-array echocardiographs following a standardized protocol. A computerized review station equipped with digitizing tablet and monitor screen overlay was used for measurement. Assessment of LV internal dimensions and wall thicknesses and of LA dimension has been described. MAC was identified by the presence of bright echoes at the base of the mitral leaflets on M-mode or 2D imaging in the parasternal or apical windows. Determination of AV sclerosis relied on visualization of bright echoes on the AV leaflets, irrespective of ECG, available for 100% in the initial examination, but only for segmental wall motion abnormalities.

Calculation of Derived Variables

End-diastolic LV dimensions were used to calculate LV mass as described previously. LV hypertrophy was defined by previously derived partition values of LV mass indexed by height. Prevalence of LV hypertrophy and the continuous inflammatory markers CRP (logarithmically transformed serum creatinine, and binary sex, hypertension, diabetes, and current smoking. Also considered were the categorical echocardiographic variables LA enlargement and LV hypertrophy and the continuous inflammatory markers CRP (logarithmically transformed) and fibrinogen. Covariates exhibiting univariable relationships to stroke-free survival in Cox models at a significance of P<0.20 were included in multivariable analyses. Fulfillment of proportional hazards assumption was tested by use of log-log plots.

Results

The characteristics of the study cohort are presented in Table 1, with generally greater prevalences or values for cardiovascular risk factors among individuals with MAC or AV sclerosis.

During a median follow-up of 7 years, there were 86 strokes, 55 (64.0%) of which were definite and 10 (11.6%) were fatal. Available information prevented classification of stroke in 16 cases. Sixty-eight patients had documented computed tomography or MRI of the brain. Neurovascular imaging was documented in 46 cases. Sixty-two strokes were ischemic, comprising 7 (11.5%) cardioembolic, 6 (9.7%) atherothrombotic, 19 (30.6%) lacunar, and 30 (48.4%) other, unknown infarctions. Eight events were intraparenchymal hemorrhages.

There were 19 incident strokes in individuals with MAC and 7 in participants with AV sclerosis. Age- and sex-adjusted incidence rates for individuals with and without MAC were 12.6 and 4.1 per 1000 person years (incidence rate ratio [IRR], 3.12; 95% CI, 1.77 to 5.25), and for participants with and without AV sclerosis, 5.4 and 4.7 per 1000 person years (IRR, 1.15; 95% CI, 0.45 to 2.49). Kaplan–Meier curves (Figure) illustrate a significantly shorter stroke-free time for individuals with MAC but not with AV sclerosis. For MAC, the corresponding unadjusted hazard ratio (HR) for stroke is shown in Table 2. This increased risk was diminished after adjustment for clinical risk factors, indicative of confounding. Further confounding was uncovered after adjustment for echocardiographic predictors, chiefly LA enlargement. This attenuated the association further, but the latter remained statistically significant (HR, 1.89; 95% CI, 1.04 to 3.41). Separate adjustment for...
inflammatory markers did not meaningfully alter the association observed after controlling for clinical predictors. The relationship was virtually unchanged after exclusion of interim cases of myocardial infarction, CHF, or AF.

In contrast to MAC, for which the proportional hazards assumption was satisfied, the hazards associated with AV sclerosis were not proportional. This precluded use of multivariable Cox models to assess the relationship between AV sclerosis and incident stroke. It also prevented adjustment for this variable in models assessing the relationship between MAC and stroke. Nevertheless, when evaluation was limited to the subset of participants without AV sclerosis, the relationship between MAC and stroke did not change appreciably.

**Discussion**

This study shows MAC, but not AV sclerosis, to be an independent predictor of stroke events in American Indians without clinical cardiovascular disease. To our knowledge, this is the first time that MAC has been determined to confer prognostic information after comprehensive adjustment for clinical confounders and echocardiographic or inflammatory covariates.

Previous studies have reported conflicting findings with respect to MAC and stroke. A prospective evaluation of older adults documented a significant relationship after adjustment for selected clinical and echocardiographic covariates, but this was not confirmed by another prospective study of older subjects. Like these studies, the strengths of the present investigation lie in its population-based design and its systematic ascertainment of baseline risk factors and incident events. However, the focus of our study is on a younger, ethnically distinct cohort with a high prevalence of atherosclerosis risk factors. Although there are no data regarding different ethnic predispositions to MAC, the consistent association of the latter with atherosclerosis risk factors across populations makes an ethnic susceptibility independent of these factors unlikely. Regardless, our results in this ethnically distinct population after extensive adjustment for clinical covariates...
TABLE 2. Mitral Annular Calcification and Stroke

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>3.19 (1.92–5.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>2.67 (1.65–4.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable-adjusted, clinical risk factors*</td>
<td>2.34 (1.35–4.06)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable-adjusted, clinical risk factors*+CRP</td>
<td>2.47 (1.42–4.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariable-adjusted, clinical risk factors*+CRP+fibrinogen</td>
<td>2.42 (1.39–4.21)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable-adjusted, clinical risk factors*+LV hypertrophy</td>
<td>2.26 (1.28–3.99)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multivariable-adjusted, clinical risk factors*+LV hypertrophy+LA enlargement</td>
<td>1.89 (1.04–3.41)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Age, hypertension, diabetes, total/high-density lipoprotein cholesterol, body mass index, and serum creatinine.

Emboli. Various reports attest to this possibility by documenting mobile calcific or thrombotic debris, often in the setting of frank ulceration of annular calcium, in patients with cerebral embolism, and even demonstrating calcific or bland emboli in the infarct-related artery at autopsy. In addition, MAC may predispose to infective endocarditis and embolization of vegetative material. MAC has also been reported to be a risk factor for incident AF, although the present analyses accounted in large measure for this risk.

The absence of a relationship between AV sclerosis and stroke is unexpected. It is no less well documented that AV calcification is related to atherosclerosis risk factors, aortic and carotid atheroma, and CHD than it is for MAC. But the failure to detect an AV sclerosis–stroke relationship in this study could be attributable not to a difference in kind, but of degree. By eliminating all but the least severe cases, the exclusion of patients with AV stenosis from analysis may have left a population with such mild AV calcification as to dampen its potential predictive power. This is suggested by the fact that the only study to date to demonstrate a predictive role for AV calcification for incident stroke has done so in the setting of established AV stenosis. Because the degree of AV calcification (or MAC) was not assessed, even on a semiquantitative scale, this possibility cannot be addressed directly in the present study. Irrespectivey, our findings suggest that in patients without AV stenosis, which imposes a hemodynamic stimulus to LV hypertrophy and LA enlargement, MAC may be a stronger biomarker for stroke risk than nonstenotic AV calcification.

This study has several limitations. Classification of stroke events was based on the documented diagnostic evaluations conducted in medical facilities serving these communities. Consequently, a proportion of strokes could not be categorized, and the number of ischemic stroke subtypes was too small to permit meaningful analysis of MAC-related stroke mechanisms. Furthermore, the loss of digitized ECGs from the second examination allowed only partial use of this modality to exclude baseline AF in our cohort. Nevertheless, our findings persisted in separate analyses of the subgroup for which such data were available. Together with the use of complete ECG data from the initial examination, and of clinical history and transmitral Doppler echocardiography to exclude prevalent AF, this makes it unlikely that our results would be attributable to unrecognized AF among individuals with MAC.

In conclusion, these findings show that MAC, but not AV sclerosis, is a powerful independent predictor of incident stroke in American Indians free of clinical cardiovascular disease. These results build on early autopsy observations, echocardiographic case reports, and previous longitudinal studies by confirming the prognostic value of MAC and, more importantly, by showing independence of the latter from an extensive set of covariates in a distinct population. The detection of MAC by transthoracic echocardiography in similar patients may warrant more aggressive risk factor modification, but the efficacy of specific approaches requires further investigation.

Acknowledgments

This work was supported by grants U01-HL41642, U01-HL41652, and U01-HL41654 from the National Heart, Lung, and Blood Institute, Bethesda, Md, and M10RR0047 (G.C.R.C.) from the National Institutes of Health, Bethesda, Md. J.R.K. was supported in part by career development award K23-HL070854 from the National Heart, Lung, and Blood Institute.

References


Mitral Annular Calcification, Aortic Valve Sclerosis, and Incident Stroke in Adults Free of Clinical Cardiovascular Disease: The Strong Heart Study


Stroke. 2005;36:2533-2537; originally published online October 27, 2005; doi: 10.1161/01.STR.0000190005.09442.ad

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/12/2533

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/