Mitrval Annular Calcification Predicts Cardiovascular Morbidity and Mortality

The Framingham Heart Study

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Background—Mitrval annular calcification (MAC) has been associated with stroke in longitudinal, community-based cohorts and cardiovascular disease (CVD) outcomes in many small retrospective studies. Prospective data are limited on the relation of MAC with CVD morbidity and mortality.

Methods and Results—We examined the association between MAC assessed by M-mode echocardiography and the incidence of CVD, CVD death, and all-cause death over 16 years of follow-up in the Framingham Heart Study subjects who attended a routine examination between 1979 and 1981. Cox proportional hazards models were used to estimate hazard ratios (HRs) associated with the presence of MAC for each outcome. Of 1197 (445 male, 752 female) subjects who had adequate echocardiographic assessment, 14% had MAC. There were 307 incident CVD events and 621 deaths. In multivariable adjusted analyses, MAC was associated with an increased risk of incident CVD (HR, 1.5; 95% CI, 1.1, 2.0), CVD death (HR, 1.6; 95% CI, 1.1, 2.3), and all-cause death (HR, 1.3; 95% CI, 1.04, 1.6). For each 1-mm increase in MAC, the risk of incident CVD, CVD death, and all-cause death increased by ∼10%.

Conclusions—The independent association of MAC with incident CVD and CVD death underscores that cardiac calcification is a marker of increased CVD risk. (Circulation. 2003;107:1492-1496.)

Key Words: calcium ▪ echocardiography ▪ cardiovascular diseases ▪ mortality
a Hoffrel 201 ultrasound machine with an Aerotech 2.25-MHz transducer and a Jason thermographic printer. Echocardiographers reinterpreted M-mode echocardiograms, blinded to all clinical information about the subjects, to determine the presence and severity of MAC as defined previously. Briefly, the disorder was considered present if an echodense band was visualized throughout systole and diastole, was distinguishable from the posterior mitral valve leaflet, and was located anterior and parallel to the posterior left ventricular wall. MAC was measured in millimeters by a cardiologist from the leading anterior to the trailing posterior edge at its greatest width during the cycle on at least 3 cardiac cycles.

Risk factors were characterized at the index Framingham Heart Study clinic examination. Details about the methods of risk factor measurement and laboratory analysis have been described. Diabetes was defined as a fasting glucose level ≥140 mg/dL, a random nonfasting glucose level ≥200 mg/dL, or use of insulin or oral hypoglycemic agents. Because only M-mode echocardiography was available at the index examination, baseline valvular disease was defined as any diastolic murmur, or a systolic murmur >2/6 on the physical examination performed by the Heart Study physician. Covariates were obtained at the index examination except for smoking, HDL cholesterol, and serum creatinine, which were ascertained at the prior examination.

Subjects were followed for up to 16 years for CVD events. A panel of 3 experienced investigators reviewed all CVD events, blinded to MAC status. Incident CVD events included myocardial infarction, coronary insufficiency, congestive heart failure, and nonhemorrhagic stroke; fatal CVD additionally included sudden cardiac death defined by previously reported criteria.

Statistical Analyses
For principal analyses, MAC was dichotomized (present/absent); in secondary analyses, MAC was examined as a continuous variable. Differences in baseline risk factors in subjects with and without MAC were tested by ANOVA or logistic regression after adjustment for age and sex. All incidence rates were age and sex adjusted and presented as events per 10 000 person-years of follow-up. Cox proportional hazards regression models were used to estimate the association of MAC with the risks of myocardial infarction, congestive heart failure, incident CVD events, CVD death, and all-cause death. Because the interaction between MAC and sex was not significant, all analyses were performed for pooled sexes, with further adjustment for interim myocardial infarction and congestive heart failure (HR, 1.5; 95% CI, 1.1, 2.2). After multivariable adjustment, subjects with MAC were 50% more likely to have CVD in follow-up (HR, 1.5; 95% CI, 1.1, 2.0).

Overall, there were 621 deaths; 213 were attributed to CVD. The CVD mortality rate was 428 per 10 000 compared with 162 in 10 000 in subjects with and without MAC (Table 2). The Figure shows the age- and sex-adjusted cumulative incidence of CVD; the corresponding hazard ratio (HR) was 1.7 (Table 3). After multivariable adjustment, subjects with MAC were 50% more likely to have CVD in follow-up (HR, 1.5; 95% CI, 1.1, 2.0).

The all-cause mortality rate among subjects with MAC was 847 per 10 000 person-years, compared with 443 per 10 000 person-years in subjects without MAC; the Cox proportional hazards data are presented in the Figure. In age- and sex-adjusted analyses, the HR was 1.5. After multivariable

Results
Of 1197 subjects with adequate ECG assessment, 14% (n=169) had MAC. At the baseline examination, subjects with MAC were older; more likely to be female; and more likely to have higher systolic blood pressure, higher BMI, diabetes, ECG left ventricular hypertrophy, and clinical valve disease (Table 1). Subjects with MAC were also more likely to have prevalent atrial fibrillation, CVD, and congestive heart failure.

Overall, there were 307 cases of incident CVD, with an age- and sex-adjusted incidence rate of 554 per 10 000 person-years in subjects with MAC compared with 268 in

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of Participants With and Without MAC*</th>
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<tr>
<td>Age, y</td>
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<tr>
<td>Female sex, %</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<td>Hypertension treatment, %</td>
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<td>Total cholesterol/HDL, ratio</td>
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<td>BMI, kg/m²</td>
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<td>ECG left ventricular hypertrophy, %</td>
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<td>Myocardial infarction, %</td>
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<td>Congestive heart failure, %</td>
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<td>Prevalent CVD, %</td>
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Values are means±SD for continuous variables. *P value for baseline characteristics other than age and sex in subjects with and without MAC obtained from ANOVA or logistic regression after adjustment for age and sex. †P<0.05; ‡P<0.01; §P<0.001.

<table>
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<tr>
<th>TABLE 2. Incidence Rates per 10 000 Person-Years (Number of Events) Over 16 Years of Follow-Up in Participants With and Without MAC, Age- and Sex-Adjusted</th>
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<td>All-cause death</td>
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adjustment, the increased risk of all-cause death remained statistically significant (HR, 1.3). In an exploratory analysis adjusting for interim myocardial infarction or congestive heart failure, these results were essentially unchanged (HR, 1.3; 95% CI, 1.03, 1.6; Table 3).

In secondary analyses, MAC was analyzed as a continuous variable. For each 1-mm increase in MAC, the risk of incident CVD, CVD death, and all-cause death adjusted for relevant baseline risk factors increased by 9% (P<0.007), 12% (P<0.004) and 9% (P<0.001), respectively.

There were 138 cases of myocardial infarction and 191 cases of congestive heart failure in follow-up. In age- and sex-adjusted models, MAC was significantly related to incident myocardial infarction (HR, 1.7; P<0.01) and heart failure (HR, 1.9; P<0.001). After further adjustment for baseline covariates, MAC was not an independent risk factor for myocardial infarction (HR, 1.4; 95% CI, 0.8, 2.2) or heart failure (HR, 1.3; 95% CI, 0.9, 1.8). Given the small number of cases for these outcomes, we only had power of 30% and 12%, respectively, to detect HRs of 1.4 and 1.3 at an \( P \) level of 0.05 in fully adjusted dichotomous models. Of interest, when we analyzed MAC as a continuous variable in fully adjusted models, MAC was not associated with myocardial infarction but was associated with a significantly increased risk of heart failure. For each 1-mm increase in MAC, the HR for heart failure was 1.1 (95% CI, 1.03, 1.2; \( P<0.01 \)). Thus, our lack of significant association between the presence or absence of MAC and myocardial infarction and congestive heart failure should be interpreted with caution.

**Discussion**

In summary, the presence of mitral annular calcification predicts incident CVD events, CVD death, and all-cause death. We have shown that this increase in risk occurs in a dose-responsive manner. We believe that the association between MAC and incident CVD and death is consistent with the hypothesis that MAC is a marker of subclinical CVD.

**Possible Mechanisms**

Increasingly, it is recognized that vascular calcification, assessed by multiple modalities, including electron beam CT,\textsuperscript{29,30} echocardiography,\textsuperscript{21,25} and aortic arch calcification,\textsuperscript{32} is associated with CVD risk factors. Recent data also suggest an association between vascular calcification and incident...
CVD events.\textsuperscript{32–34} The pathophysiology of cardiac calcification is not known but may stem from metabolic causes. For example, it is known that coronary artery calcification is common in patients with end-stage kidney disease undergoing dialysis,\textsuperscript{35} and it has also been observed that MAC is common in patients with end-stage kidney disease.\textsuperscript{36} Thus, derangements in calcium-phosphorus metabolism may contribute to MAC.

The association between vascular calcification, specifically MAC, and increased cardiovascular risk may also be due to the burden of shared risk factors, including age, hypertension, hyperlipidemia, diabetes, and obesity.\textsuperscript{22–25} Furthermore, MAC may function as a bioassay for longitudinal exposure to risk factors. For example, MAC may more accurately “measure” the impact of longitudinal blood pressure elevation than a blood pressure reading at one examination. MAC may also be a marker for atherosclerotic disease burden; the association between MAC and aortic plaque\textsuperscript{37,38} and coronary calcification\textsuperscript{6} has been previously noted. It is also possible to speculate that other unmeasured factors such as metabolic, inflammatory, and hemostatic risk factors might be associated and may account for relations of MAC with CVD end points.

Study Limitations and Strengths

Some limitations of our study warrant attention. The Framingham Heart Study sample is neither ethnically diverse nor nationally representative. However, the coronary heart disease risk factor relations from Framingham have recently been validated in 6 ethnically and geographically diverse cohorts and were found to be applicable in other populations.\textsuperscript{39} Second, our sample was elderly, and our findings may not be generalizable to younger individuals. In addition, to have sufficient numbers of events longitudinally to provide adequate statistical power for analyses, we relied on the echocardiographic technology available at the baseline examination, M-mode, which is less sensitive for the detection of MAC. Finally, as noted above, our study lacked sufficient power to adequately examine the relation of MAC to many clinically important CVD outcomes such as endocarditis and heart failure.

There are several strengths of our study. Many prior studies of cardiovascular outcomes with MAC have been limited by sample sizes as small as 38 subjects,\textsuperscript{7,10–12} retrospective\textsuperscript{12} or cross-sectional designs,\textsuperscript{5,7,25} nonuniform ascertainment of echocardiography,\textsuperscript{5,7,40} lack of recruitment of an appropriate control group,\textsuperscript{10–12} and lack of routine ascertainment of covariate data and multivariable analyses.\textsuperscript{5,25,40}

The present study is among the first large-scale community-based cohort studies to examine the prospective association between MAC and incident cardiovascular events and death. Our study is the first to show a graded relation between MAC severity and clinical outcome. To our knowledge, the only prior longitudinal cohort study to examine the relation of MAC to CVD outcomes was the Cardiovascular Health Study,\textsuperscript{9} which examined multiple echocardiographic variables including left ventricular mass, dimensions, and wall thickness and left atrial dimensions, in addition to MAC (dichotomously analyzed). The investigators observed that the presence of MAC was associated with an unadjusted increased hazard for incident stroke, heart failure, coronary heart disease, and all-cause death. However, after adjustment for CVD risk factors, MAC only remained predictive of incident coronary heart disease. Possible reasons for the disparate findings between the two studies may include the older mean age (73 years), the shorter duration of follow-up (7 years), and the utilization of 2-dimensional MAC assessment in the Cardiovascular Health Study. Conceivably, our reliance on the less-sensitive M-mode technology may have led to the detection of more severe degrees of MAC, with a greater risk of incident events.

Implications

In conclusion, MAC was independently associated with incident CVD, cardiovascular death, and all-cause death after adjusting for traditional CVD risk factors, suggesting that MAC is a marker of increased cardiovascular risk. We have shown that this increased risk occurs in a graded fashion by MAC severity. The mechanisms of increased risk are undoubtedly multifactorial and include mechanical characteristics of MAC, shared risk factors between MAC and cardiovascular outcomes, and valvular calcification as an overall marker of atherosclerotic burden. The association of calcification of the mitral annulus with increased CVD risk parallels the previously reported elevated cardiovascular risk observed with the presence of echocardiographic aortic sclerosis. The prognostic importance of the calcification phenotype in multiple cardiac locations underscores the importance of understanding the genetic and environmental determinants of cardiac calcification.

Acknowledgments

This work was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (N01-HC-25195 and SR01-NH-17950). Dr. Vasan is the recipient of a research career award (1K24HL043344) from the National Heart, Lung, and Blood Institute/ National Institutes of Health.

References


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Circulation. 2003;107:1492-1496; originally published online March 10, 2003; doi: 10.1161/01.CIR.0000058168.26163.BC
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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