Mitral Annular Calcium, Inducible Myocardial Ischemia, and Cardiovascular Events in Outpatients With Coronary Heart Disease (from the Heart and Soul Study)

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We sought to determine whether mitral annular calcium (MAC) is associated with inducible myocardial ischemia and adverse cardiovascular outcomes in ambulatory patients with coronary artery disease (CAD). MAC is associated with cardiovascular disease (CVD) in the general population, but its association with CVD outcomes in patients with CAD has not been evaluated. We examined the association of MAC with inducible ischemia and subsequent cardiovascular events in 1,020 ambulatory patients with CAD who were enrolled in the Heart and Soul Study. We used logistic regression to determine the association of MAC with inducible ischemia and Cox proportional hazards models to determine the association with CVD events (myocardial infarction, heart failure, stroke, transient ischemic attack or death). Models were adjusted for age, gender, race, smoking, history of heart failure, blood pressure, high-density lipoprotein, and estimated glomerular filtration rate. Of the 1,020 participants 192 (19%) had MAC. Participants with MAC were more likely than those without MAC to have inducible ischemia (adjusted odds ratio 2.06, 95% confidence interval 1.41 to 3.01, p = 0.0002). During an average of 6.26 ± 2.11 years of follow-up, there were 310 deaths, 161 hospitalizations for heart failure, 118 myocardial infarctions, and 55 cerebrovascular events. MAC was associated with an increased rate of cardiovascular events (adjusted hazard ratio 1.39, 95% confidence interval 1.08 to 1.79, p = 0.01). In conclusion, we found that MAC was associated with inducible ischemia and subsequent CVD events in ambulatory patients with CAD. MAC may indicate a high atherosclerotic burden and identify patients at increased risk for adverse cardiovascular outcomes. Published by Elsevier Inc. (Am J Cardiol 2012;109:1092–1096)

Prospective studies of community-living populations without known coronary artery disease (CAD) such as the Northern Manhattan Study, the Cardiovascular Health Study, and the Framingham Heart Study, have demonstrated that mitral annular calcium (MAC) is associated with incident cardiovascular disease (CVD) events, CVD mortality, and all-cause mortality independent of traditional atherosclerotic risk factors.[1–5] However, no study has evaluated the association between MAC and inducible myocardial ischemia or CVD events in patients with established CAD. MAC is easy to visualize and readily detectable on noninvasive imaging with echocardiography. Therefore, MAC could be used to identify patients at increased risk for adverse CVD outcomes. In a prospective cohort study of 1,020 patients with CAD, we hypothesized that MAC predicts inducible ischemia and adverse CVD outcomes.

Methods

The Heart and Soul Study is a prospective cohort study of outpatients with stable CAD. The enrollment process for the Heart and Soul Study has been previously described.[6] We used administrative databases to identify outpatients with documented CAD at 2 departments of Veterans Affairs (San Francisco and Palo Alto, California), the University of California, San Francisco, and 9 public health clinics from the Community Health Network of San Francisco. Participants were eligible to participate if they met 1 of the following: (1) history of myocardial infarction, (2) angiographic evidence of ≥50% stenosis by area in ≥1 coronary vessel, (3) evidence of exercise-induced ischemia by treadmill electrocardiogram (ECG) or stress nuclear perfusion imaging, (4) history of coronary revascularization, or (5) a previous diagnosis of CAD by an internist or cardiologist. Individuals were excluded if they had a myocardial infarction within the previous 6 months, deemed themselves unable to walk 1 block, or were planning to move out of the local area within 3 years.

From September 2000 through December 2002, 1,024 study participants provided informed consent and completed baseline echocardiographic and laboratory testing. This included 549 (54%) with a history of myocardial in-

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Table 1
Characteristics of 1,020 participants with coronary artery disease by presence or absence of mitral annular calcium

Variable	MAC		p Value
	Absent (n = 828)	Present (n = 192)	
Age (years)	66 ± 11	72 ± 9	<0.0001
Men	691 (83%)	147 (77%)	0.02
White race	486 (59%)	126 (66%)	0.08
Current smoker	174 (21%)	27 (14%)	0.03
Smoking history (pack-years)	19 ± 20	19 ± 20	0.69
Angina pectoris (weekly or more)	161 (19%)	29 (15%)	0.16
Pre-existing heart failure	132 (16%)	46 (24%)	0.0009
Previous cerebrovascular accident	107 (13%)	40 (21%)	0.005
Hypertension	583 (71%)	137 (71%)	0.85
Previous myocardial infarction	436 (53%)	110 (57%)	0.29
Diabetes mellitus	208 (25%)	56 (29%)	0.26
Atrial fibrillation on baseline electrocardiogram	30 (4%)	11 (6%)	0.18
Body mass index (kg/m^2)	28.4 ± 5.3	28.5 ± 5.4	0.70
Systolic blood pressure (mm Hg)	132.1 ± 20.4	136.3 ± 22.6	0.01
Diastolic blood pressure (mm Hg)	75.0 ± 11.4	73.0 ± 10.9	0.03
Calcium (mg/dl)	9.51 ± 0.52	9.55 ± 0.49	0.37
Phosphorus (mg/dl)	3.68 ± 0.61	3.71 ± 0.54	0.47
Log C-reactive protein (mg/dl)	0.69 ± 1.29	0.81 ± 1.40	0.24
Low-density lipoprotein (mg/dl)	104.6 ± 33.1	103.3 ± 36.4	0.63
High-density lipoprotein (mg/dl)	45.3 ± 13.6	48.1 ± 15.8	0.01
Creatinine (mg/dl)	1.13 ± 0.60	1.22 ± 0.91	0.11
Estimated glomerular filtration rate (ml/min)*	77.3 ± 23.2	71.7 ± 23.2	0.003
Medications			
Aspirin	648 (78%)	144 (75%)	0.33
β Blocker	485 (59%)	107 (56%)	0.47
Statin	528 (64%)	126 (66%)	0.63
Renin–angiotensin system blocker	418 (50%)	104 (54%)	0.36
Warfarin (coumadin)	61 (7%)	14 (7%)	0.97
Echocardiographic parameters			
Aortic sclerosis†	305 (37%)	122 (64%)	<0.0001
Mitral regurgitation	143 (17%)	53 (28%)	0.001
End-systolic left atrial volume (ml)	63 ± 23	70 ± 27	0.0002
Left ventricular ejection fraction (%)	61.7 ± 9.8	61.2 ± 9.6	0.47
Left ventricular mass index (g/m^2)	99.5 ± 35.7	101.0 ± 25.5	0.59

Data are presented as mean ± SD.
* Calculated using the Modification of Diet in Renal Disease equation.
† Defined as focal areas of aortic valve leaflet thickening and/or increased echogenicity with preserved leaflet mobility and a peak Doppler velocity across the valve >2.0.

farction, 237 (23%) with a history of revascularization but not myocardial infarction, and 238 (23%) with a diagnosis of CAD that was documented by their physician (based on a positive angiogram or treadmill test in 98% of cases). The

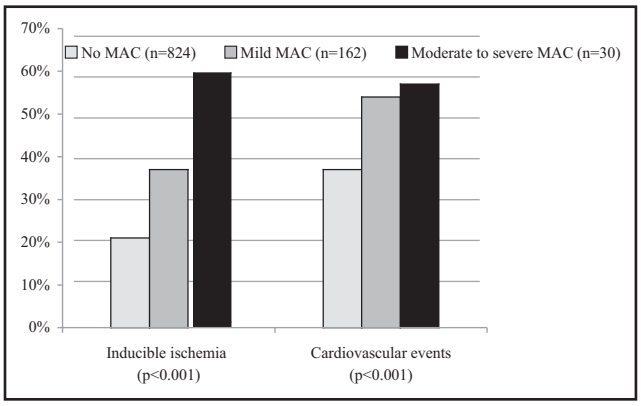

Figure 1. Proportion with inducible myocardial ischemia and cardiovascular events by presence of mitral annual calcium on echocardiogram.

institutional review board at each enrolling center approved the study protocol, and all participants provided written informed consent. All participants completed a baseline examination that included an interview, fasting blood draw, questionnaire, echocardiogram at rest, exercise treadmill test with stress echocardiogram, and ECG. Of the 1,024 participants who completed the baseline examination, 933 completed stress echocardiography and 227 participants were found to have inducible ischemia present. Four participants (<1%) were lost to follow-up, leaving 1,020 for longitudinal analysis.

A complete 2-dimensional echocardiogram at rest was obtained in all patients using an Acuson Sequoia ultrasound system with harmonic imaging and a 3.5-MHz transducer (Siemens Medical Solutions, Mountain View, California). All standard views were obtained during quiet respiration. Two highly experienced sonographers made all sonographic measurements and a single cardiologist reader (N.B.S.) blinded to clinical and laboratory information evaluated, confirmed, and, when needed, corrected each measurement. MAC was defined as a highly reflective area with acoustic shadowing located at the junction of the atrioventricular groove and the posterior mitral leaflet on the parasternal long-axis, apical 4-chamber, or parasternal short-axis view.[7] Severity of MAC was reported qualitatively as mild, moderate, or severe based on degree of calcification. MAC was defined as "mild" when limited to the posteromedial terminus of the posterior annulus, "moderate" when involving the posteromedial and anterolateral termini of the posterior annulus but not continuously, and "severe" as continuous calcification extending from the lateral to medial termini of the posterior annulus at the level of the medial commissure.

Left ventricular end-systolic and end-diastolic volumes were obtained by planimetry using the biplane method of discs.[8] Left ventricular ejection fraction was calculated as (end-diastolic volume minus end-systolic volume)/end-diastolic volume. Left ventricular mass was calculated with a truncated ellipsoid equation and indexed to body surface area.[8,9] Left atrial volume was obtained at end-ventricular systole by manual planimetry with the biplane method of discs for the left atrium and single plane method of discs for the right atrium.[10] All chamber volumes were subsequently indexed to body surface area. Severity of mitral regurgitation was determined according to American Society of

Table 2
Association of mitral annular calcium with inducible myocardial ischemia (odds ratio) and subsequent cardiovascular events (hazard ratio)

Variable	Number of Events	Model 1		Model 2		Model 3	
		OR/HR (95% CI)	p Value	OR/HR (95% CI)	p Value	OR/HR (95% CI)	p Value
Inducible myocardial ischemia	227	2.10 (1.46–3.03)	<0.0001	2.06 (1.41–3.01)	0.0002	NA	NA
Myocardial infarction	118	1.29 (0.84–1.99)	0.25	1.23 (0.79–1.92)	0.36	1.32 (0.81–2.14)	0.26
Heart failure hospitalization	161	1.83 (1.30–2.57)	0.0005	1.62 (1.14–2.29)	0.007	1.54 (1.05–2.26)	0.03
Cerebrovascular accident or transient ischemic attack	55	1.82 (1.01–3.30)	0.05	1.63 (0.89–3.00)	0.11	1.84 (0.97–3.52)	0.06
All-cause mortality	310	1.39 (1.07–1.80)	0.01	1.41 (1.08–1.84)	0.01	1.30 (0.98–1.74)	0.07
All cardiovascular events*	408	1.46 (1.16–1.83)	0.001	1.49 (1.18–1.88)	0.0009	1.39 (1.08–1.79)	0.01

Model 1 was adjusted for age. Model 2 was adjusted for age, male gender, white race, smoking, history of heart failure, systolic blood pressure, diastolic blood pressure, high-density lipoprotein, and estimated glomerular filtration rate. Model 3 was adjusted for age, male gender, white race, smoking, history of heart failure, systolic blood pressure, diastolic blood pressure, high-density lipoprotein, estimated glomerular filtration rate, and inducible myocardial ischemia.

* Includes myocardial infarction, heart failure hospitalization, cerebrovascular accident/transient ischemic attack, and/or death.

NA = Not applicable.

Echocardiography guidelines.[11] We defined aortic sclerosis as focal areas of aortic valve leaflet thickening and/or increased echogenicity with preserved leaflet mobility and a peak Doppler velocity across the valve >2.0 m/s.

We evaluated inducible myocardial ischemia using exercise treadmill testing with stress echocardiography.[12] Participants were instructed to fast for ≥4 hours before exercise except for taking their usual medications as prescribed. We performed a symptom-limited graded exercise treadmill test according to a standard Bruce protocol. Participants were asked to walk on a treadmill beginning at a workload of 20 to 30 W and increasing by 20 to 30 W every 3 minutes until reaching dyspnea, symptom-limited fatigue, or chest discomfort or showing electrocardiographic changes suggestive of ischemia. To achieve maximum heart rate participants who were unable to continue the standard Bruce protocol (for orthopedic or other reasons) were switched to slower settings on the treadmill and encouraged to exercise for as long as possible. Immediately before exercise and again at peak exercise, parasternal long-axis and short-axis and apical 2-chamber and 4-chamber views were used to detect the development of left ventricular wall motion abnormalities. Inducible ischemia was defined as the presence of new wall motion abnormalities at peak exercise that were not present at rest.

After the baseline examination we conducted annual telephone follow-up interviews asking about hospitalization for "heart trouble." For any reported event, medical records, ECGs, death certificates, and coroner's reports were retrieved and reviewed by 2 independent blinded adjudicators. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator as necessary. Outcome events were heart failure, myocardial infarction, stroke, transient ischemic attack, or death. Heart failure was defined as hospitalization for a clinical syndrome with a minimum 1-night hospital stay and involving ≥2 of the following: paroxysmal nocturnal dyspnea, orthopnea, increased jugular venous pressure, pulmonary rales, cardiomegaly on chest x-ray, or pulmonary edema on chest x-ray. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and must have been accompanied by failing cardiac output as determined by peripheral hypoperfusion (in the absence of other causes such as sepsis or dehydration) or peripheral or pulmonary edema treated with intravenous diuretics, inotropes, or vasodilators.[13]

Nonfatal myocardial infarction was defined using standard criteria.[14] Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other cause. Transient ischemic attack was defined as a focal neurologic deficit (in the absence of head trauma) lasting >30 seconds and ≤24 hours, with rapid evolution of symptoms to the maximal level of deficit in <5 minutes and with subsequent complete resolution. Death certificates and coroners' reports determined death.

Age, gender, race, medical history, smoking, and alcohol use were determined by self-report. ECG at rest was obtained for assessment of atrial fibrillation. Study personnel measured height, weight, and blood pressure. Subjects brought all their medication bottles to the baseline examination. We recorded all medications and categorized them according to Epocrates Rx (San Mateo, California). Calcium, phosphorus, creatinine, C-reactive protein, low-density lipoprotein, and high-density lipoprotein cholesterol were measured from fasting blood samples. Estimated glomerular filtration rate was calculated using the Modified Diet in Renal Disease equation.

Differences in participant characteristics stratified by MAC were determined using analysis of variance for continuous variables and chi-square tests for dichotomous variables. We used logistic regression to evaluate the independent association between MAC and inducible ischemia. For these analyses we report odds ratios (ORs) with 95% confidence intervals (CIs). To evaluate the association between MAC and CVD events, we performed multivariate analysis using Cox proportional hazard models. Candidate covariates for adjustment were determined based on their association with MAC in univariate analyses. To evaluate potential mediators of the association between MAC and CVD events, we also adjusted for presence of atrial fibrillation, mitral regurgitation, aortic sclerosis, and left atrial volume. Proportional hazards assumptions were verified for all models. For these analyses we report hazard ratios (HRs) with 95% CIs. Analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Of the 1,020 participants with CAD, 19% had MAC. Those with MAC were older, less frequently men, and less likely to currently smoke (Table 1). Participants with MAC were more likely to have pre-existing heart failure, previous stroke, higher systolic blood pressure, lower diastolic blood pressure, higher high-density lipoprotein, and lower estimated glomerular filtration rate. Patients with MAC had a higher prevalence of aortic sclerosis, mitral regurgitation, and larger left atrial volumes.

In total 227 participants had inducible ischemia. Prevalences of inducible ischemia were 21% (159/765) in patients without MAC, 37% (54/145) in patients with mild MAC, and 61% (14/23) in patients with moderate to severe MAC (Figure 1). Because of the small number of participants with moderate to severe MAC, patients with mild, moderate, or severe MAC were combined for further analyses. Compared to patients without MAC, those with MAC had a twofold increased odds of inducible ischemia (OR 2.10, 95% CI 1.46 to 3.03, $p < 0.001$). After multivariable adjustment MAC remained independently associated with inducible ischemia (OR 2.06, 95% CI 1.41 to 3.01, $p = 0.0002$; Table 2).

During an average of 6.26 ± 2.11 years of follow-up, 118 participants had a myocardial infarction, 161 were hospitalized for heart failure, 55 had cerebrovascular accidents, and 310 died. Proportions of patients with cardiovascular events were 37% (304/824) in patients without MAC, 54% (87/162) in patients with mild MAC, and 57% (17/30) in patients with moderate to severe MAC (Figure 1). After multivariable adjustment including inducible ischemia, MAC remained independently associated with an increased rate of CVD events (HR 1.39, 95% CI 1.08 to 1.79, $p = 0.01$; Table 2).

To evaluate potential mediators of the association between MAC and CVD events, we sequentially added left atrial volume, mitral regurgitation, atrial fibrillation, and aortic sclerosis to multivariable models that were simultaneously adjusted for age, gender, race, smoking, history of heart failure, blood pressure, high-density lipoprotein, and estimated glomerular filtration rate. MAC remained independently predictive of future CVD events after adjustment for these potential mediators (HR 1.38, 95% CI 1.08 to 1.75, $p = 0.009$). Although the association between MAC and CVD events was attenuated after further adjustment for inducible ischemia, it still remained statistically significant (HR 1.29, 95% CI 1.00 to 1.67, $p = 0.05$).

Discussion

In 1,020 ambulatory participants with CAD who were followed for >6 years, MAC was present in 19% and independently associated with inducible ischemia and subsequent CVD events. Compared to participants who did not have MAC, those with MAC had a twofold increased odds of inducible ischemia and an almost 50% increased risk of subsequent CVD events after adjustment for traditional atherosclerotic risk factors. Participants with MAC were at greater risk for CVD events even after adjustment for left atrial volume, mitral regurgitation, aortic sclerosis, and presence of atrial fibrillation. These findings suggest that MAC may be a marker of atherosclerotic burden in patients with CAD and may identify patients at increased risk for CVD events.

MAC has previously been associated with adverse CV outcomes including myocardial infarction, heart failure, and all-cause mortality in otherwise healthy populations.[1,3,4,15,16] One recent study demonstrated that a calcification score index, expressed as the sum of aortic root sclerosis, aortic valve sclerosis, and MAC, assessed by transthoracic echocardiography was associated with the Framingham risk score, Duke score, and left ventricular mass index in a population without known CAD.[17] Our study adds to this body of evidence by demonstrating that MAC independently predicts CVD events in a population of patients with known CAD.

We also found that MAC was associated with inducible ischemia. This finding adds an important phenotype to the accumulating literature linking MAC with heavier atherosclerotic burden. MAC has previously been associated with CAD as detected by radionuclide myocardial perfusion imaging,[18] coronary computed tomography,[19] and invasive coronary angiography.[20,21] MAC is also an independent predictor of coronary artery stenosis[18,22] and significant 3-vessel disease.[21] The increased risk of inducible ischemia that we observed in patients with MAC shows that these anatomic findings have functional significance. Furthermore, we found that the increased risk of CVD events associated with MAC was partly attenuated after adjustment for inducible ischemia. This suggests that the atherosclerotic burden associated with MAC may play a significant role in its correlation with adverse CVD outcomes. However, MAC did not have an association with myocardial infarction, underscoring the fact that acute plaque rupture and thrombus formation cannot always be predicted by atherosclerotic burden and traditional risk factors.

Another explanation for the association of MAC with inducible ischemia and CVD events is that MAC may function as a surrogate marker for longitudinal exposure to traditional CVD risk factors. MAC has been linked with many traditional CVD risk factors such as age, female gender, obesity, smoking, diabetes mellitus, hypertension, dyslipidemia, and increased calcium–phosphorus product.[2,23–25] Factors such as inflammation and metabolic risk factors may also predispose patients to MAC and CVD events. We previously found that fetuin-A (an inhibitor of calcification) concentrations are inversely associated with MAC, suggesting that other dystrophic valvular calcification mechanisms may play a role.[26] Genetic factors may influence the development of MAC because its early presence has been reported in patients with Marfan syndrome and systemic lupus erythematosus.[27,28]

To our knowledge this is the first study to examine the association of MAC with CVD events in a large prospective cohort of patients with known CAD. Our study is unique because of the combination of CVD outcome data and stress echocardiographic data revealing the potential relation of MAC with CVD outcomes and inducible ischemia. Our study is strengthened by its relatively large sample and measurement of a wide spectrum of potential confounding variables. However, our study also has important limitations. First, the Heart and Soul Study consists of mostly

older men from Northern California and almost 1/2 were recruited from Veterans Affairs medical centers. Therefore, our results may not generalize to other populations such as women and younger populations with CAD. Second, we used qualitative 2-dimensional echocardiography rather than M-mode, which some previous studies have used to quantify calcification depth.[3,29] However, 2-dimensional evaluation of MAC is the clinical standard of care and offers improved sensitivity and spatial distribution than is possible with M-mode echocardiography.

In conclusion, we found that MAC was associated with inducible ischemia and subsequent CVD events in ambulatory patients with CAD. MAC may indicate a high atherosclerotic burden and identify patients at increased risk for adverse CV outcomes.

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