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Coronary Artery Calcification and Myocardial Perfusion in Asymptomatic Adults

The MESA (Multi-Ethnic Study of Atherosclerosis)

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OBJECTIVES	This study assessed the cross-sectional association between coronary artery calcification (CAC) and myocardial perfusion in an asymptomatic population.
BACKGROUND	Clinical studies showed that the prevalence of stress-induced ischemia increased with CAC burden among patients with coronary heart disease (CHD). Whether an association between CAC and myocardial perfusion exists in subjects without a history of CHD remains largely unknown.
METHODS	A total of 222 men and women, ages 45 to 84 years old and free of CHD diagnosis, in the Minnesota field center of the MESA (Multi-Ethnic Study of Atherosclerosis) were studied. Myocardial blood flow (MBF) was measured using magnetic resonance imaging during rest and adenosine-induced hyperemia. Perfusion reserve was calculated as the ratio of hyperemic to resting MBF. Agatston CAC score was determined from chest multidetector computed tomography.
RESULTS	Mean values of hyperemic MBF and perfusion reserve, but not resting MBF, were monotonically lower across increasing CAC levels. After adjusting for age and gender, odds ratios (95% confidence intervals) of reduced perfusion reserve (<2.5) for subjects with CAC scores of 0, 0.1 to 99.9, 100 to 399, and ≥ 400 were 1.00 (reference), 2.16 (0.96 to 4.84), 2.81 (1.04 to 7.58), and 4.99 (1.73 to 14.4), respectively. Further adjustment for other coronary risk factors did not substantially modify the association. However, the inverse association between perfusion reserve and CAC attenuated with advancing age (p for interaction < 0.05).
CONCLUSIONS	Coronary vasodilatory response was associated inversely with the presence and severity of CAC in asymptomatic adults. Myocardial perfusion could be impaired by or manifest the progression to subclinical coronary atherosclerosis in the absence of clinical CHD. (J Am Coll Cardiol 2006;48:1018–26) © 2006 by the American College of Cardiology Foundation

The identification of subclinical coronary heart disease (CHD) before the occurrence of critical events is important for prevention. Use of multiple risk factors to assess CHD risk has limited predictive value in a given individual. Further noninvasive methods, such as coronary artery

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calcium scanning, have been developed to detect subclinical atherosclerosis. Both pathological (1–3) and angiographic (4–6) data have documented that the coronary calcium burden closely correlates with the extent and severity of total coronary atherosclerosis.

Impairment of coronary vascular reactivity caused by atherosclerosis can be detected using noninvasive imaging of myocardial blood flow (MBF) and MBF response to vasoactive stimuli. Myocardial perfusion imaging during exercise or vasodilator-induced vasodilation was found to be valuable for predicting future coronary events, even in patients known to be at relatively low risk (7). Current knowledge about coronary artery calcification (CAC), a structural marker, and myocardial perfusion, a functional parameter, suggest that they could be complementary tests, whose relation may nevertheless vary by age, gender, risk profile, and clinical history of CHD. In clinical settings, the prevalence of stress-induced ischemia has been seen to increase with CAC burden among patients suspected to have CHD (8,9).

Vasoreactivity may be impaired early in the coronary atherosclerosis process, even in the absence of clinical CHD and ischemic symptoms (10–12). Whether an association between myocardial perfusion and CAC exists in the general population of asymptomatic subjects remains largely unknown. Furthermore, the relationship between MBF and CAC among free-living individuals without symptoms or history of CHD, if any, may differ in younger versus older

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Abbreviations and Acronyms

AV	= atrial-ventricular
CAC	= coronary artery calcification
CHD	= coronary heart disease
CI	= confidence interval
CMR	= cardiac magnetic resonance
CT	= computed tomography
MBF	= myocardial blood flow
MESA	= Multi-Ethnic Study of Atherosclerosis
SI	= signal intensity
SPECT	= single-photon emission computed tomography

people and in men versus women. To address these questions, this study assessed the cross-sectional relationship between CAC and MBF at rest and during hyperemia, in middle-age and older asymptomatic adults who participated in a large population-based study. We hypothesized that vasodilator-induced MBF response was inversely associated with CAC.

METHODS

Study subjects. Subjects were recruited from participants in the Minnesota field center of the MESA (Multi-Ethnic Study of Atherosclerosis), a population-based prospective cohort study of subclinical cardiovascular disease and its progression. Study design and participant characteristics of the MESA have been described in detail elsewhere (13). In brief, 6,814 men and women from four ethnic origins (Caucasian, African American, Hispanic, and Chinese), aged 45 to 84 years at baseline, were enrolled from 6 U.S. field centers (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California). Individuals with known clinically diagnosed cardiovascular disease were not recruited, and eligibility was determined from self-reported information. The baseline examinations for the entire MESA cohort took place between July 2000 and September 2002, including chest computed tomography (CT) to measure CAC. Each cohort member at the MESA Minnesota Field Center ($n = 1,066$) was contacted for participating in a perfusion study, either immediately after the baseline clinic examination or later by mail. Of these, 234 agreed to participate. The MESA participants who declined seemed to be primarily concerned about possible adverse effects of adenosine and the need for intravenous access to administer contrast. The MBF was measured 0.5 to 33 months (mean 9 months) after the baseline examination. This subcohort was 45 to 84 years of age, comprised 57% men and 57% Caucasian subjects (remaining subjects were Hispanic). Subjects who participated in the perfusion study were comparable with those who did not on CAC levels and characteristics of most standard coronary risk factors, but had a smaller body mass index (28.9 vs. 29.6 kg/m²) and a lower prevalence of hypertension (27% vs.

36%). The perfusion study was approved by the Institutional Review Board at the University of Minnesota. All study subjects provided informed consent.

CT scanning and assessment of CAC. Chest CT was performed using a four-detector-row CT (14) (Volume Zoom, Siemens, Erlangen, Germany), with 361-ms exposure and 35-cm field of view, at 140 kVp, 139 mA, 0.361-s scan, 4×2.5 -mm collimation, sequential axial scans with prospective cardiac gating, and standard filter reconstruction. During a single breath-hold, prospectively electrocardiogram-triggered scans were acquired at 50% of each RR interval, covering four simultaneous 2.5-mm slices for each cardiac cycle. To increase reliability of CAC measures and for quality control, each subject was scanned twice consecutively and over a phantom with known calcium content. Scans were read centrally at the Harbor-UCLA Research and Education Institute in Torrance, California, to identify and quantify CAC, calibrated to the calcium phantom. Agatston calcification score (15) was calculated as a product of the area of calcified plaque multiplied by a coefficient rated 1 through 4 on the basis of the peak calcium density in the identified deposit. Total calcification score was the sum of the scores of individual lesions. The agreement for presence of CAC on the consecutive CT scans for the same participant was high (kappa statistic = 0.92). The intraclass correlation coefficients for readings of CAC amount performed by the same or by different readers were >0.99 . The average of two CAC scores was used for analysis. The CAC was also assessed regionally for specific coronary artery segments.

Magnetic resonance imaging and quantification of MBF. Cardiac magnetic resonance (CMR) imaging was performed with a 1.5-T clinical MR scanner (Sonata, Siemens Medical Systems, Iselin, New Jersey). Participants were asked to abstain from caffeine intake for 12 h before their MR examination. During the examination, each participant was positioned supine, and a needle was inserted into an antecubital vein for injection of MR contrast and infusion of adenosine. A flexible four-element phased-array coil was placed over the participant's heart, with two elements of a spine array coil serving as posterior antennae. Blood pressure, heart rate, and the electrocardiogram were monitored and recorded during the CMR examination. Rate-pressure product, at rest and hyperemia, was calculated as the product of heart rate (in beats/min) multiplied by systolic blood pressure (in mm Hg) measured during the examination, and divided by 10,000.

To track the passage of injected contrast agent through the right ventricle, left ventricle, and left ventricle myocardium, T1-weighted images of two to three slices in a short-axis orientation (slice thickness, 8 mm) were acquired during each heartbeat with a fast electrocardiogram-triggered gradient echo sequence, for a total of 50 heartbeats. An example is shown in Figure 1. Starting at the third or fourth heartbeat, a gadolinium complex of diethylenetriamine pentaacetic acid (Gd-DTPA) bolus (Magnevist, Berlex, Wayne, New Jersey) of 0.04 mmol/kg body weight

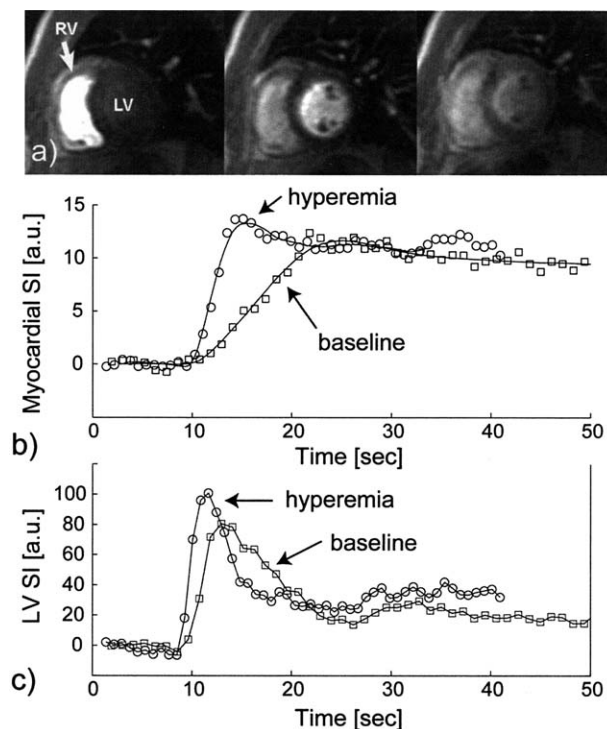


Figure 1. (a) The first pass of an intravenous contrast agent bolus of gadolinium complex of diethylenetriamine pentaacetic acid (Gd-DTPA) through the right ventricle (RV) and left ventricle (LV) is shown in a short-axis view on 3 frames, out of a total of 50 for each slice, acquired by T1-weighted fast magnetic resonance imaging with a temporal resolution of 1 frame per heartbeat at each of 3 slice levels. (b) The myocardial signal enhancement in 1 of 8 myocardial sectors, located in the inferior wall, for baseline and hyperemia is analyzed by model-independent deconvolution with the respective arterial inputs, shown in c. The solid line in b represents the myocardial response calculated from the estimated tissue impulse response by convolution with the measured arterial input. SI = signal intensity.

was administered with a power injector through an antecubital vein, at a rate of 7 ml/s, followed by a saline flush of 15 ml at the same injection rate. A first perfusion scan was performed during rest, followed by a second scan during maximal vasodilation about 15 min later. Vasodilation was induced by intravenous infusion of adenosine: 0.14 mg/kg/min for 3 min before start of the scan, blocked for approximately 3 s during MR contrast injection, and then continuing until acquisition of the first 10 to 15 images. Brief atrial-ventricular (AV) blocks (duration <5 s) were observed after the initial 3-min contrast bolus injection in 43 cases, all of which resolved after the adenosine infusion was immediately stopped. The perfusion scan was still completed and hyperemic MBF was determined in cases where adenosine infusion was prematurely terminated. All subjects had normal global left ventricular systolic function.

The observers who analyzed MR images were blinded to participants' characteristics and CAC measurements. Endocardial and epicardial contours were manually traced. Signal intensity (SI) curves were generated with the MASS cardiac MRI image analysis software (Laboratory for Clinical and Experimental Image Processing, Leiden University, the

Netherlands) for eight transmural myocardial sectors of equal circumferential extent along the myocardial centerline. The SI curves represent the change of mean SI in each myocardial sector as a function of time, with mean SI before appearance of the contrast agent in the left ventricle subtracted for baseline correction. The SI curves were also corrected for coil-sensitivity variations, based on the baseline signal. In accordance with the central volume principle (16), MBF was estimated from the initial amplitude of the myocardial impulse response by deconvolution-analysis of the myocardial SI curves. Custom-written software was used to perform a model-independent deconvolution of the SI curves, with an arterial input measured in the center of the left ventricular cavity. As described and validated previously (17–19), MBF estimated by the method used in this study had an excellent linear correlation ($R^2 = 0.995$; slope, 0.96; intercept, 0.06) with the measurements from radioisotope-labeled microspheres, which is regarded as the reference method for quantification of MBF. Perfusion reserve was calculated as the ratio of MBF during hyperemia to rest. The MBF measurements are reported in the present study as global averages over the 8 myocardial segments and 2 to 3 slices, unless stated otherwise.

Measurement of coronary risk factors. Coronary risk factors were measured at the MESA clinic using standardized methods. All participants reported no previous history of CHD. “Ever smoking” was defined as lifetime consumption of more than 100 cigarettes. “Current smoking” was defined as smoking cigarettes within the past 30 days. Resting seated blood pressure was measured three times using an automated oscillometric sphygmomanometer (Dinamap Pro 100, Critikon, Tampa, Florida), and the average of last two measurements was used for analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-reported history of hypertension, or current use of antihypertensive medications. Blood samples were obtained from participants after 8 h of fasting and analyzed at a central laboratory (University of Vermont) for glucose, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dl, self-reported history of diabetes, or taking diabetes medications.

Statistical analysis. Statistical analysis was performed using SAS software version 8 (SAS Institute, Cary, North Carolina). Participants were excluded from statistical analysis if they had missing values on any 1 of the major perfusion measurements (resting MBF, hyperemic MBF, or perfusion reserve; $n = 5$), or if they took caffeine within 12 h before CMR scanning ($n = 7$). A total of 222 subjects remained after the exclusions. The CAC scores were divided into 0, >0 to 99.9, 100 to 399, and ≥ 400 . The demographic characteristics and perfusion measurements were compared across levels of CAC score using analysis of variance. The Spearman correlation coefficient was assessed between continuous CAC score and MBF or perfusion

reserve. Logistic regression was performed to estimate the odds ratios and 95% confidence interval (CI) of reduced perfusion reserve, defined as <2.5 (20), in association with levels of CAC score. Model 1 only adjusted for age and gender. Model 2 further adjusted for coronary risk factor burden estimated overall using the Framingham risk scoring method (21). Because of concerns about the statistical properties of ratios such as perfusion reserve (22,23), we also modeled low hyperemic MBF as the response variable, with resting MBF adjusted in the model as independent covariate. Linear trend across increasing levels of CAC score was tested using the median value of each score category as an ordinal variable. The region-specific association was also studied between CAC in specific coronary arteries and global perfusion as well as regional perfusion in the corresponding artery territories. Modification of the associations by age and gender was tested. Because neither CAC scores nor perfusion measurements differed by ethnicity, analyses were not separated for Caucasian and Hispanic subjects. Analyses were repeated using the percentiles of CAC scores distribution, instead of absolute values, as cutoff points for categorization. Analyses were also repeated after excluding participants who experienced brief AV block during adenosine infusion. All of these sensitivity analyses yielded similar results and therefore are not presented. A value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

The 222 participants had a mean \pm SD global resting MBF of 1.01 ± 0.23 ml/g/min (range 0.54 to 1.82 ml/g/min). During hyperemia, MBF increased significantly to 3.02 ± 0.84 ml/g/min (range 0.98 to 5.63 ml/g/min). Calculated as the ratio of hyperemic MBF divided by resting MBF, perfusion reserve averaged 3.05 ± 0.84 (range 1.18 to 5.24). The correlation between MBF and rate-pressure product was

stronger at rest (Pearson $r = 0.57$) than during hyperemia (Pearson $r = 0.28$). Mean resting MBF, hyperemic MBF, and perfusion reserve were all significantly lower in men (0.93 ml/min/g, 2.66 ml/min/g, and 2.94 , respectively) than in women (1.12 ml/min/g, 3.48 ml/min/g, and 3.20 , respectively). Hyperemic MBF and perfusion reserve were also significantly lower in older subjects age 65 to 84 years (2.78 ml/min/g and 2.76 , respectively) than in middle-age subjects age 45 to 64 years (3.14 ml/min/g and 3.20 , respectively). None of the major perfusion measurements differed by ethnicity. The predicted 10-year CHD risk, estimated by risk factors using Framingham prediction equations, correlated inversely with hyperemic MBF (Pearson $r = -0.46$, $p < 0.0001$) and perfusion reserve (Pearson $r = -0.33$, $p < 0.0001$).

The CAC scores in these asymptomatic participants ranged from 0 to 6,063. Of 222 subjects, 103 subjects (46%) had a CAC score of 0, 59 (27%) had a CAC score of 0.1 to 99.9, 33 (15%) had a CAC score of 100 to 399, and 27 (12%) had a CAC score ≥ 400 . The median of CAC scores for those with a score >0 was 102. Compared with those subjects with no evidence of CAC, those with CAC were significantly older and were more likely to be male (Table 1). The CAC score was also associated positively with most major CHD risk factors (data not shown) and the predicted 10-year CHD risk (Spearman $r = 0.14$, $p = 0.04$). The proportion of Hispanic subjects was similar across different CAC scores.

Mean resting MBF did not differ across CAC levels (Table 1). In contrast, mean hyperemic MBF (3.31 , 2.95 , 2.65 , and 2.53 ml/min/g) and perfusion reserve (3.34 , 2.88 , 2.82 , and 2.60) were progressively lower across increasing CAC levels. The Spearman correlations of resting MBF, hyperemic MBF, and perfusion reserve with CAC scores were -0.03 ($p = 0.70$), -0.38 ($p < 0.0001$), and -0.35 ($p < 0.0001$), respectively. Consistent with the responses of

Table 1. Demographic Characteristics and Myocardial Perfusion Measures Across Levels of Coronary Artery Calcification in Subjects With No Clinical Coronary Heart Disease (CHD) From the Multi-Ethnic Study of Atherosclerosis

	Coronary Artery Calcium Score					p for Trend
	Total (N = 222)	0 (n = 103)	0.01–99.9 (n = 59)	100–399.9 (n = 33)	≥ 400 (n = 27)	
Age (yrs)	59.8	54.5	61.2	67.5	67.5	<0.0001
Gender (% men)	56.3	42.7	61.0	72.7	77.8	0.0025
Ethnicity (% Hispanic)	43.2	47.6	45.8	24.2	44.4	0.63
Predicted 10-yr CHD risk (%)*	10.8	7.5	12.0	16.2	14.8	0.0002
Measurements from perfusion study						
myocardial blood flow†						
Resting (ml/min/g)	1.01 ± 0.23	1.01 ± 0.22	1.05 ± 0.26	0.97 ± 0.23	0.99 ± 0.18	0.41
Hyperemic (ml/min/g)	3.02 ± 0.84	3.31 ± 0.77	2.95 ± 0.83	2.65 ± 0.77	2.53 ± 0.75	<0.0001
Perfusion reserve	3.05 ± 0.84	3.34 ± 0.79	2.88 ± 0.77	2.82 ± 0.89	2.60 ± 0.79	0.0004
Measurements from perfusion study,						
rate-pressure product†						
Resting (mm Hg \times beat/min)	0.91 ± 0.21	0.86 ± 0.20	0.95 ± 0.23	0.93 ± 0.20	0.97 ± 0.14	0.08
Hyperemic (mm Hg \times beat/min)	1.09 ± 0.27	1.09 ± 0.29	1.12 ± 0.27	1.07 ± 0.23	1.05 ± 0.21	0.35
Ratio change	1.22 ± 0.22	1.29 ± 0.24	1.18 ± 0.18	1.16 ± 0.19	1.09 ± 0.20	0.0002

*Predicted CHD risk was estimated using Framingham prediction equations with total cholesterol categories. †Mean \pm standard deviation.

Table 2. Mean Myocardial Perfusion Measures Across Levels of Coronary Artery Calcification in Subjects With No Clinical Coronary Heart Disease, Stratified By Age and Gender From the Multi-Ethnic Study of Atherosclerosis

	Coronary Artery Calcium Score				p for Trend
	0	0.01-99.9	100-399.9	≥400	
Age 45-64 yrs					
n	89	37	13	9	
Hyperemic blood flow (ml/min/g)*	3.33	2.99	2.88	2.25	<0.0001
Perfusion reserve†	3.43	2.98	2.85	2.31	0.0002
Age 65-84 yrs					
n	14	22	20	18	
Hyperemic blood flow (ml/min/g)*	3.17	2.88	2.51	2.68	0.29
Perfusion reserve†	2.80	2.71	2.81	2.74	0.95
Men					
n	44	36	24	21	
Hyperemic blood flow (ml/min/g)‡	2.96	2.56	2.53	2.37	0.02
Perfusion reserve§	3.33	2.79	2.81	2.51	0.007
Women					
n	59	23	9	6	
Hyperemic blood flow (ml/min/g)‡	3.57	3.55	2.96	3.09	0.06
Perfusion reserve§	3.35	3.01	2.87	2.91	0.18

*p for interaction by age = 0.03. †p for interaction by age = 0.004. ‡p for interaction by gender = 0.62. §p for interaction by gender = 0.69.

MBF to the infusion of adenosine, the corresponding systemic hemodynamic responses, presented as the ratio of rate-pressure product at hyperemia to rest, was blunted in participants with elevated CAC scores. The inverse associations of hyperemic MBF and perfusion reserve with CAC score were similar in men and in women (p for interaction = 0.62 for hyperemic MBF, 0.69 for perfusion reserve), but were stronger in middle-age subjects than in older subjects (p for interaction = 0.03 for hyperemic MBF, 0.0004 for perfusion reserve) (Table 2). In the middle-age subjects, mean perfusion reserve was significantly lower in those with high CAC scores compared with those with no CAC.

Correspondingly, the prevalence of reduced perfusion reserve (<2.5) was substantially higher across increasing levels of CAC score among middle-age participants (Fig. 2). A perfusion reserve lower than 2.5 was observed in only 12% of middle-age subjects with a CAC score of 0 but in nearly 80% of middle-age subjects with CAC score ≥400. By contrast, the prevalence of reduced perfusion reserve was only slightly higher among older subjects with a CAC score ≥100, compared with those with no CAC or a CAC score <100. Although presented as middle-age subjects compared with older subjects, attenuation of the inverse associations with advancing age was statistically significant

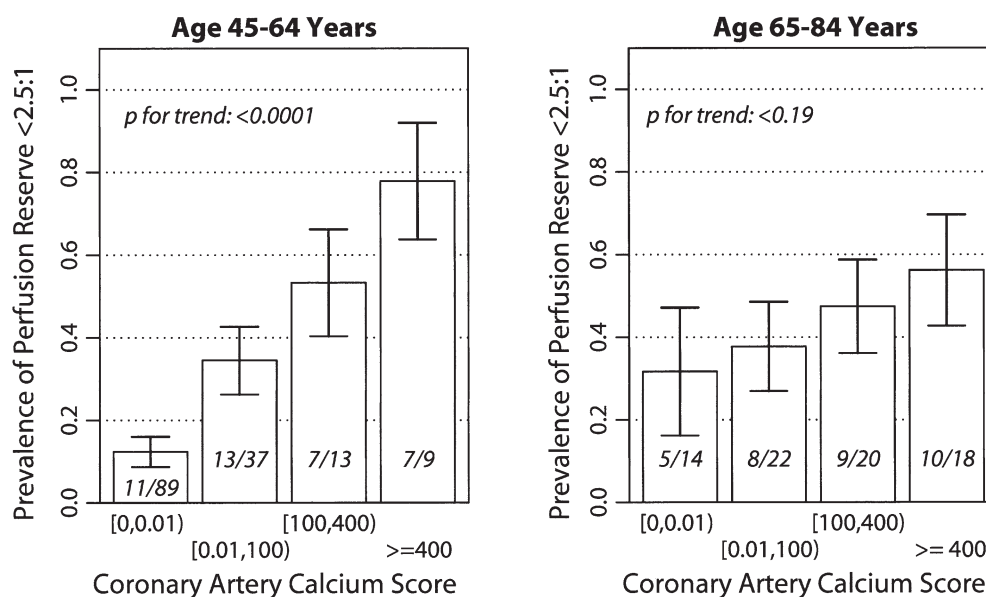


Figure 2. Prevalence of reduced perfusion reserve (<2.5) across levels of coronary artery calcification in subjects with no clinical coronary heart disease, stratified by age group. Numbers in bars are the number of subjects with reduced perfusion reserve/total n of subjects in the respective coronary artery calcium score category. Error bars show the standard error for prevalence obtained by a bootstrap estimate.

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Reduced Perfusion Reserve (<2.5) Across Levels of Coronary Artery Calcification in Subjects With No Clinical Coronary Heart Disease From the Multi-Ethnic Study of Atherosclerosis

	Coronary Artery Calcium Score			
	0	0.01–99.9	100–399	≥400
Overall sample				
n (proportion) of perfusion reserve <2.5	16 (15.5%)	21 (35.6%)	16 (48.5%)	17 (63.0%)
Age- and gender-adjusted OR* (95% CI)	1.00 (Reference)	2.16 (0.96–4.84)	2.81 (1.04–7.58)	4.99 (1.73–14.4)
Additional risk factor burden† adjusted OR (95% CI)	1.00 (Reference)	2.16 (0.96–4.86)	2.76 (1.02–7.50)	4.83 (1.66–14.0)
Subjects aged 45–64 years				
n (proportion) of perfusion reserve <2.5	11 (12.4%)	13 (35.1%)	7 (53.8%)	7 (77.8%)
Age- and gender-adjusted OR* (95% CI)	1.00 (Reference)	2.92 (1.11–7.68)	4.68 (1.19–18.5)	13.3 (2.24–79.0)
Additional risk factor burden† adjusted OR (95% CI)	1.00 (Reference)	2.99 (1.14–7.90)	4.80 (1.20–19.2)	12.6 (2.11–74.9)
Subjects aged 65–84 years				
n (proportion) of perfusion reserve <2.5	5 (35.7%)	8 (36.4%)	9 (45.0%)	10 (55.6%)
Age- and gender-adjusted OR* (95% CI)	1.00 (Reference)	0.68 (0.15–3.09)	0.82 (0.17–3.90)	1.40 (0.29–6.77)
Additional risk factor burden† adjusted OR (95% CI)	1.00 (Reference)	0.62 (0.13–2.90)	0.75 (0.16–3.64)	1.29 (0.26–6.39)

*Age was modeled as a continuous variable. †Additional risk factor burden was estimated as relative coronary heart disease risk over the baseline risk conferred by age and gender alone, using Framingham prediction equations (21).

throughout the age range of our study sample when age was modeled as a continuous variable.

A high CAC score remained significantly associated with a higher likelihood of reduced perfusion reserve after adjusting for age and gender (Table 3). Compared with subjects with a CAC score of 0, the age- and gender-adjusted odds ratios of reduced perfusion reserve were 2.16 (95% CI 0.96 to 4.84), 2.81 (95% CI 1.04 to 7.58), and 4.99 (95% CI 1.73 to 14.4) for those with a CAC score of 0.1 to 99.9, 100 to 399, and ≥400, respectively. Further adjustment for overall coronary risk factor burden, estimated using Framingham prediction equations, did not materially attenuate the association. The association between CAC scores and odds of reduced perfusion reserve was stronger in middle-age subjects than in older subjects (*p* for interaction = 0.03). Similar to that observed in a linear regression model, the attenuation of association with advancing age was also statistically significant when age was modeled as a continuous variable. Using low hyperemic MBF (<2.53 ml/min/g, which is the 40th percentile) alternatively as the response variable, with adjustment for resting MBF as an independent covariate, yielded somewhat weaker results (data not shown).

The CAC scores were calculated for specific coronary arteries—left main, left anterior descending, left circumflex, and right coronary artery—in 207 subjects; 31 (14%) subjects had CAC in 1 artery, 32 (15%) in 2 arteries, 33 (15%) in 3 arteries, and 10 (5%) in all 4 major arteries. Global hyperemic MBF and perfusion reserve were lower, with more arteries containing calcium (Table 4). The inverse association between perfusion reserve and number of arteries with calcium was similar in men and women (*p* for interaction = 0.81), but stronger in middle-age subjects than in older subjects (*p* for interaction = 0.008). The regional hyperemic MBF and perfusion reserve in the anterior segment of left ventricle myocardium, which is supplied by the left anterior descending artery, were inversely associated with CAC score in the left anterior descending artery (data not shown), similar to the inverse

relationship observed between global MBF and total CAC scores. Region-specific associations could not be investigated in other artery territories because information about the left/right dominance of the coronary artery system was unavailable for MESA participants.

DISCUSSION

In the current study, we found that among asymptomatic adults, the coronary vasodilatory response, assessed by hyperemic MBF and perfusion reserve, correlated inversely with the presence and severity of CAC, a marker of atherosclerosis. The inverse association was strong and independent of cardiovascular risk factor burden. However, the data showed that these associations significantly attenuated with advancing age, although some caution is due, given the sample size and some inconsistency across the age strata. To our knowledge, this is the first population-based study on the relationship between CAC burden and myocardial perfusion among individuals with no clinical CHD.

The volume of CAC is an excellent marker of overall atherosclerotic burden (1–6). Calcium deposition occurs only when atherosclerosis is present, and more severe plaques tend to have a greater amount of calcium (24,25). Therefore, higher CAC scores are associated with a higher likelihood of significant coronary stenosis, whereas the absence of CAC is associated with a very low likelihood of obstructive CHD. In our population-based study, 54% (119 of 222) of asymptomatic adults had some evidence of CAC, whereas 12% (27 of 222) had a CAC score ≥400. Complementary to CAC measurements, assessment of myocardial perfusion was originally designed to provide physiologic information about the hemodynamic severity of coronary stenosis. Recent research further suggests that myocardial perfusion could also be affected in the absence of significant stenosis in epicardial arteries, which may be attributable to impaired smooth muscle relaxation, endothelial dysfunction (26,37), or both at the microcirculation level. In the present

Table 4. Mean Myocardial Perfusion Measures Across Number of Coronary Arteries Containing Calcium (Coronary Artery Calcium Score >0 in the Respective Artery) in Subjects With No Clinical Coronary Heart Disease From The Multi-Ethnic Study of Atherosclerosis

	Calcified Coronary Artery Count				p for Trend
	0	1	2	≥3	
Overall sample					
n	111	31	32	43	
Hyperemic blood flow (ml/min/g)	3.27	2.98	2.79	2.57	<0.0001
Perfusion reserve	3.30	2.75	2.86	2.72	<0.0001
Age 45–64 yrs					
n	94	21	17	14	
Hyperemic blood flow (ml/min/g)*	3.31	2.88	3.05	2.42	<0.0001
Perfusion reserve†	3.39	2.80	2.98	2.63	0.0002
Age 65–84 yrs					
n	17	10	15	29	
Hyperemic blood flow (ml/min/g)*	3.03	3.21	2.49	2.64	0.06
Perfusion reserve†	2.80	2.66	2.73	2.76	0.95
Men					
n	50	15	22	35	
Hyperemic blood flow (ml/min/g)‡	2.91	2.44	2.60	2.44	0.004
Perfusion reserve§	3.26	2.57	2.77	2.66	0.001
Women					
n	61	16	10	8	
Hyperemic blood flow (ml/min/g)‡	3.56	3.49	3.20	3.10	0.04
Perfusion reserve§	3.33	2.96	3.06	2.98	0.08

*p for interaction by age = 0.33. †p for interaction by age = 0.008. ‡p for interaction by gender = 0.69. §p for interaction by gender = 0.81.

study, we found that among individuals without clinical CHD, coronary vasoreactivity was inversely associated with the coronary calcium burden. Hyperemic MBF and perfusion reserve decreased with increasing levels of total CAC scores as well as a greater number of arteries with CAC. These findings support the hypothesis that impairments in coronary vasoreactivity could appear before clinical manifestations of CHD because of the underlying pathologic lesion, and thereafter may serve as an early marker of subclinical atherosclerosis. The inverse association remained significant after the traditional CHD risk factors were accounted for, indicating that other atherosclerosis-related factors, many of which may not be known yet, could explain the correlations between the two measurements, and the two tests could both provide additional information on subclinical CHD beyond the known risk factors.

Another noteworthy finding of our study is that the inverse association between CAC and perfusion reserve significantly attenuated with age. In our analyses, we arbitrarily divided the study sample into two age groups to show a stronger association in middle-age subjects than in older subjects, although the interaction stayed significant with continuous age. An increased prevalence of cardiovascular risk factors and an admixture of factors that reduce coronary vasoreactivity with aging may explain the reduced power of coronary calcium alone to predict a reduced perfusion reserve in older subjects. In addition, although the mean hyperemic MBF and perfusion reserve were significantly higher in middle-age than in older participants, in the category of CAC scores ≥400, the difference across age strata was nonsignificantly reversed ($p = 0.17$ for hyperemic

MBF, 0.19 for perfusion reserve). It is reasonable to hypothesize that elevated CAC score may have a higher predictive value of hemodynamically significant lesions in younger than in older subjects, possibly related to the stronger effects of risk factors on the development of atherosclerosis in a younger population. However, because coronary angiography was not performed in our study, this hypothesis cannot be tested. With a relatively small sample and the observations somewhat different from expected, we could not fully rule out the possibility that this age interaction is attributable to chance.

Our findings are consistent with those of earlier reports from clinical studies, with the distinction that this study showed an inverse association between CAC burden and perfusion reserve in a population-based sample of asymptomatic subjects, and a significant attenuation of the association with advancing age. The first published study on the relationship of myocardial perfusion with CAC (9) investigated 411 generally asymptomatic patients at a single imaging center, using single-photon emission computed tomography (SPECT) for perfusion imaging and electron beam CT for CAC measurements. No patient with a CAC score <10 had stress-induced myocardial ischemia by SPECT compared with 3% of those with a CAC score 11 to 100, 11% of those with CAC score 101 to 399, and 46% of those with CAC score ≥400 ($p < 0.0001$). A CAC score was the best univariate predictor of an abnormal SPECT. The predictive value of CAC ≥400 versus <400 for an abnormal SPECT did not differ when the cohort was split into two categories ages ≤50 and >50 years. A more recent study (8) of 1,195 patients without known CHD, 51%

asymptomatic, showed similarly that the frequency of stress-induced myocardial ischemia on SPECT increased progressively with CAC. Absolute CAC score was the most potent predictor of SPECT ischemia by multivariable analysis. Quantitative measurements of MBF and perfusion reserve, and their relationship to CAC, was reported in one previous study of 21 asymptomatic subjects with a family history of premature CHD (28). Using positron emission tomography to determine coronary vascular reactivity, Pirich et al. (28) found no cases of reduced global perfusion reserve (<2.5) among subjects with a CAC score <100, but 38% of those with a CAC score >100 had reduced perfusion reserve. Although in their study, subjects with CAC tended to have lower quantitative stress MBF and perfusion reserve than those with no CAC, there was no close correlation between CAC score and resting or stress MBF or perfusion reserve ($r = 0.17, 0.18, \text{ and } 0.10$, respectively, $p = \text{NS}$), possibly because of the small sample size.

Study limitations. The first limitation of this study is its cross-sectional design. Therefore, the temporal sequence of events, and any cause-effect relationship, could not be established. The presence of calcified plaque could damage vessel reactivity, and it may also be possible that reduced vascular function and reduced wall shear stress contribute to formation or calcification of plaques in epicardial arteries. There was a mean of 9 months of time lag between CAC measurements and perfusion measurements. We do not think atherosclerosis would substantially progress within such a time period, so we still consider our analysis as cross-sectional. Second, because these asymptomatic participants did not undergo coronary angiography, it remained unknown whether or not the subjects with CAC had obstructive atherosclerotic lesions. The presence of undetected obstructive stenoses may weaken the implication of our finding, i.e., a close correlation between pathological changes and functional changes underlying the coronary arteries in the absence of established CHD. However, among population-based study subjects who had no clinical evidence of CHD and had on average a low risk profile, the probability of significant coronary stenoses should be small. A small proportion of subjects in this sample having very high CAC scores supported this hypothesis. Finally, we cannot rule out the possibility that the hyperemic MBF response was blunted in cases in which adenosine was prematurely terminated because of AV block. Previous studies with intracoronary administration of adenosine report that after stopping the adenosine infusion, coronary blood flow will stay close to its peak for a plateau phase (29,30), which is sufficiently long for the initial myocardial contrast enhancement and thereafter valid hyperemic MBF estimation (18). In addition, analyses excluding subjects with AV block yielded similar results.

Conclusions. Our study showed that independent of CHD risk factors, myocardial perfusion reserve was inversely correlated with the presence and severity of CAC in asymptomatic adults. This finding implies that a substantial

number of adults without clinical evidence of CHD could have reduced coronary vasoreactivity, possibly caused by subclinical coronary atherosclerosis. Future studies with follow-up data are expected to assess the predictive value of myocardial perfusion measurements on CHD event risk and its relative importance compared with other subclinical measurements in risk prediction on a population basis (27).

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Coronary Artery Calcification and Myocardial Perfusion in Asymptomatic Adults: The MESA (Multi-Ethnic Study of Atherosclerosis)

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