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Association of Mitral Annulus Calcification, Aortic Valve Sclerosis and Aortic Root Calcification With Abnormal Myocardial Perfusion Single Photon Emission Tomography in Subjects Age ≤65 Years Old

Doo-Soo Jeon, MD, Shaul Atar, MD, Andrea V. Brasch, MD, Huai Luo, MD, James Mirocha, MS, Tasneem Z. Naqvi, MD, FACC, Robert Kraus, MD, FACC, Daniel S. Berman, MD, FACC, Robert J. Siegel, MD, FACC

Los Angeles, California

OBJECTIVES We examined the hypothesis that mitral annulus calcification (MAC), aortic valve sclerosis (AVS) and aortic root calcification (ARC) are associated with coronary artery disease (CAD) in subjects age ≤65 years.

BACKGROUND Mitral annulus calcification, AVS and ARC frequently coexist and are associated with coronary risk factors and CAD in the elderly.

METHODS We studied 338 subjects age ≤65 years who underwent evaluation of chest pain with myocardial perfusion single photon emission computed tomography (SPECT) and a two-dimensional transthoracic echocardiogram for other indications. The association of MAC, AVS and ARC with abnormal SPECT was evaluated by using chi-square analyses and logistic regression analyses.

RESULTS Compared with no or one calcium deposit and no or one coronary risk factor other than diabetes, multiple (≥2) calcium (or sclerosis) deposits with diabetes or multiple (≥2) coronary risk factors were significantly associated with abnormal SPECT in women age ≤55 years old (odds ratio [OR], 20.00), in women age >55 years old (OR, 10.00) and in men age ≤55 years old (OR, 5.55). Multivariate analyses identified multiple calcium deposits as a significant predictor for an abnormal SPECT in women ($p < 0.001$), younger subjects age ≤55 years ($p < 0.05$) and the total group of subjects ($p < 0.01$).

CONCLUSIONS When coronary risk factors are also taken into consideration, the presence of multiple calcium deposits in the mitral annulus, aortic valve or aortic root appears to be a marker of CAD in men ≤55 years old and women. (J Am Coll Cardiol 2001;38:1988–93) © 2001 by the American College of Cardiology

Mitral annulus calcification (MAC) and aortic valve sclerosis (AVS) represent a degenerative process that progresses with advancing age (1–4). These calcifications are associated with coronary risk factors (3–7). Thus, they are also considered as a manifestation of generalized atherosclerosis in elderly populations (3,8,9). However, the clinical significance of these calcifications in a younger population has not been previously determined. Therefore, we hypothesized that in subjects age ≤65 years, MAC, AVS and aortic root calcification (ARC) would be associated with a higher prevalence of an abnormal myocardial perfusion single photon emission computed tomography (SPECT), a marker of angiographically significant coronary artery disease (CAD), and that the presence of multiple sites with calcium deposits (or sclerosis) would infer a greater risk of CAD.

METHODS

Study subjects. The study is based on analysis of patients age ≤65 years who underwent both a two-dimensional transthoracic echocardiogram (TTE) and a rest/stress myocardial perfusion SPECT at Cedars-Sinai Medical Center in Los Angeles, California, between 1992 and 1998. Patients with normal SPECT who had received percutaneous transluminal angioplasty or coronary bypass graft surgery were excluded. Of these 338 consecutive patients, there were 198 men and 140 women (18 to 65 years old, mean age of 55.3 ± 9.0 years). One hundred thirty-six patients were age ≤55 years and 202 patients were age >55 years. The indication for the TTE was for the assessment of ventricular or valvular function whereas the SPECT was performed because of chest pain. The coronary risk factors evaluated at the time of the SPECT study were diabetes mellitus, systemic hypertension, hypercholesterolemia, cigarette

From the Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California. This work was supported in part by Catholic University Medical College, Seoul, Korea; Western Cardiac Research Fund; the Lee E. Siegel, MD, Memorial Fund; and Save a Heart Foundation.

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Abbreviations and Acronyms

ARC = aortic root calcification
AVS = aortic valve sclerosis
CAD = coronary artery disease
CI = confidence interval
MAC = mitral annulus calcification
OR = odds ratio
SPECT = single photon emission computed tomography
SSS = summed stress score
TTE = transthoracic echocardiogram

smoking and male gender. Patients with ≥2 coronary risk factors were defined to have multiple risk factors. Diabetes was defined as hyperglycemia requiring previous or ongoing pharmacologic therapy. Hypertension was defined as either systolic or diastolic elevation of blood pressure (>140/90 mm Hg) or ongoing antihypertensive pharmacologic therapy. Hypercholesterolemia was defined as either a known treated hypercholesterolemia or a total cholesterol level of ≥200 mg/dl. Current cigarette smoking was defined as active smoking within the past 12 months.

SPECT and TTE imaging. Rest thallium-201/stress technetium-99m sestamibi myocardial perfusion SPECT was performed as previously described (10,11), using symptom-limited exercise by the Bruce protocol and adenosine stress. Standard reconstruction of SPECT images was employed with no attenuation correction (12). All stress imaging employed a combination of supine and prone imaging to minimize false positive studies (13). Semiquantitative visual interpretation of SPECT images was performed with short-axis and vertical long-axis tomograms divided into 20 segments for each study (10). Each segment was scored by consensus of two expert observers using a 5-point scoring system (0 = normal; 1 = equivocal; 2 = moderate; 3 = severe reduction of radioisotope uptake; 4 = absence of detectable radiotracer in a segment) without knowledge of the TTE results. Summed stress score (SSS) was obtained by means of adding the scores for the 20 segments of the stress sestamibi images. Patients with SSS ≥4 were considered to have abnormal SPECT (11,14). Complete TTE studies were performed in all patients with a commercially available system (Acuson XP/128 and Sequoia C256 [Mountain View, California], ATL HDI 5000 [Bothell, Washington], Hewlett-Packard SONOS 1000 or 5500 [Andover, Massachusetts]). The TTE studies were read by four echocardiologists without knowledge of the SPECT results. Patients with rheumatic valvular disease, prosthetic valves or bicuspid aortic valves were excluded from this study. The TTE criteria for MAC included an intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral valve leaflet on the parasternal long axis, apical four-chamber or parasternal short-axis views and was similar to that of Adler et al. (15). We defined ARC as a focal area of increased echogenecity and thickening in the aortic root on the parasternal long-axis view and AVS as a focal area of increased echogenecity and thickening of the aortic valve leaflets using the criteria of Stewart et al. (4) and Otto et al. (16) (Fig. 1). Calcification was graded from 0 to a maximum of 3 according to the number of anatomic sites involved, namely at the mitral annulus, the aortic valve and/or the aortic root. Patients with calcific deposits at two or more of three locations were defined to have multiple calcium deposits.

Statistics. Numeric values are given as mean ± SD or as a proportion of the sample size. Student's *t* test was used to compare the baseline interval level data of subjects according to presence or absence of MAC, AVS or ARC. Chi-square analysis was used to compare the baseline percent of gender, risk factors and abnormal SPECT according to the presence or absence of MAC, AVS or ARC. Mantel-Haenszel tests were used to assess linear trends with the number of sites with calcium deposits. Logistic regression analysis was used to assess the association of abnormal SPECT with multiple calcium deposits and with coronary risk factors. Data analysis was performed using the SAS statistical package (version 6.12).

RESULTS

Baseline characteristics. Factors associated with the presence of MAC, AVS and ARC based on bivariate analyses are shown in Table 1. Of the risk factors studied, hypertension ($p < 0.05$) and diabetes mellitus ($p < 0.05$) were significantly associated with the TTE detected MAC.

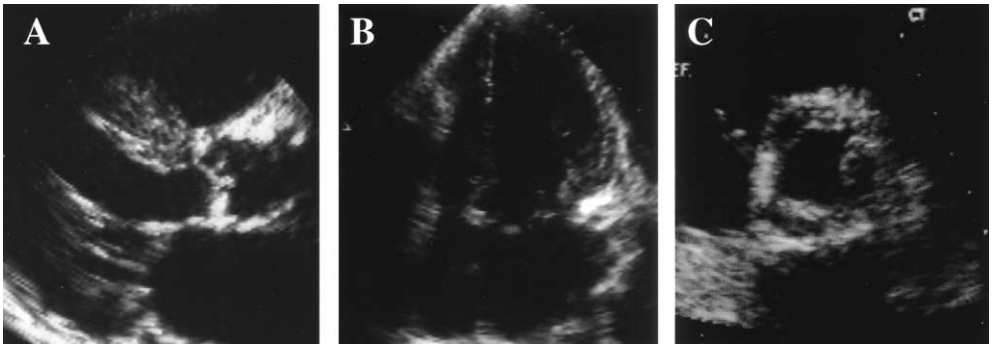

Figure 1. Transthoracic echocardiogram showing aortic root calcification **(A)**, mitral annulus calcification **(B)** and aortic valve sclerosis **(C)**.

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Table 1. Baseline Characteristics

	MAC (n = 176)	No MAC (n = 162)	AVS (n = 157)	No AVS (n = 176)	ARC (n = 206)	No ARC (n = 130)
Age, yr (mean ± SD)	56.6 ± 7.8	53.9 ± 9.8†	57.7 ± 7.6	53.0 ± 9.6‡	57.3 ± 7.6	52.2 ± 10.1‡
Male	55.7%	61.7%	61.8%	55.7%	59.7%	56.9%
Hypertension	63.1%	49.4%*	65.0%	48.3%†	61.7%	48.5%*
Hypercholesterolemia	48.3%	52.5%	49.0%	51.7%	51.5%	49.2%
Diabetes	34.9%	21.0%‡	33.8%	22.3%*	27.8%	28.5%
Current smoking	18.2%	21.6%	26.1%	14.8%*	22.8%	15.4%
SSS ≥4	59.1%	39.5%‡	56.7%	43.2%*	54.9%	41.5%*

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$.
ARC = aortic root calcification; AVS = aortic valve sclerosis; MAC = mitral annulus calcification; SD = standard deviation; SSS = summed stress score.

Hypertension ($p < 0.01$), diabetes mellitus ($p < 0.05$) and a current smoking history ($p < 0.05$) were significantly more prevalent in the subjects with AVS than those without AVS. Hypertension was significantly more frequent in subjects with ARC ($p < 0.05$) (Table 1). Compared with subjects without calcium deposits, those with MAC (59.1% vs. 39.5%, $p < 0.001$), AVS (56.7% vs. 43.2%, $p < 0.05$) and ARC (54.9% vs. 41.5%, $p < 0.05$) had a significantly higher prevalence of abnormal SPECT. As demonstrated in Table 2, there was a progressive increase in age ($p < 0.001$), prevalence of hypertension ($p < 0.001$) and diabetes ($p < 0.05$) with an increasing number of sites with calcium deposits. The time interval between TTE and SPECT was 276.1 ± 398.2 days.

The number of sites with calcium deposits and abnormal SPECT. For the entire cohort of subjects, compared with patients with no calcium deposits, those with calcium deposits in two sites had twice the odds of SSS ≥4 (odds ratio [OR] = 2.12; 95% confidence interval [CI], 1.18 to 3.78; $p < 0.05$) and those with calcium deposits in three sites had nearly three times the odds of SSS ≥4 (OR = 2.99; 95% CI, 1.58 to 5.68; $p < 0.005$). In female subjects with calcium deposits in three sites, the odds of SSS ≥4 were more than five times that of female subjects with no calcium deposits (OR = 5.14; 95% CI, 1.76 to 15.03; $p < 0.005$). The odds of SSS ≥4 were nearly four times that of subjects with no calcium deposits in subjects age ≤55 years with calcium deposits in three sites (OR = 3.94; 95% CI, 1.37 to 11.24; $p < 0.005$). As demonstrated in Table 3, in male patients as well as in the group age >55 years there was no significant difference in identifying patients with abnormal SPECT regardless of the number of sites with calcium deposits.

Subjects were classified according to the presence of multiple calcium deposits and the presence of diabetes or multiple coronary risk factors other than diabetes mellitus. For the entire group of subjects, compared with no or one calcium deposit and no or one coronary risk factor other than diabetes, multiple calcium deposits with diabetes or multiple coronary risk factors were significantly associated with abnormal SPECT (OR = 4.28; 95% CI, 2.30 to 7.98). In the subgroup analyses, multiple calcium deposits with diabetes or multiple coronary risk factors were significantly associated with abnormal SPECT in men age ≤55 years (OR = 5.55; 95% CI, 1.59 to 19.38), in women age ≤55 years (OR = 20.00; 95% CI, 2.16 to 184.87) and in women >55 years (OR = 10.00; 95% CI, 1.93 to 51.77) (Table 4).

Multiple logistic analyses. As shown in Table 5, multiple logistic regression analyses were performed for the entire group of subjects, male subjects, female subjects, subjects age ≤55 years and subjects age >55 years. The following variables were entered into the model: age, gender, diabetes mellitus, hypertension, hypercholesterolemia, current smoking and multiple calcium deposits. The analyses identified the multiple calcium deposits (OR = 2.08; 95% CI, 1.27 to 3.41; $p < 0.01$), age (OR = 1.03; 95% CI, 1.01 to 1.06; $p < 0.05$), male gender (OR = 2.85; 95% CI, 1.73 to 4.72; $p < 0.001$), diabetes mellitus (OR = 2.60; 95% CI, 1.50 to 4.49; $p < 0.001$) and hypercholesterolemia (OR = 1.66; 95% CI, 1.03 to 2.67; $p < 0.05$) as significant predictors for the presence of abnormal SPECT in the total group of subjects. The multiple calcium deposits (OR = 4.88; 95% CI, 1.92 to 12.37; $p < 0.001$) and diabetes mellitus (OR = 6.16; 95% CI, 2.59 to 14.70; $p < 0.001$) were significant predictors in female subjects. In subjects aged ≤55 years, the multiple calcium deposits (OR = 2.41; 95% CI, 1.08 to 5.38; $p <$

Table 2. Baseline Characteristics According to the Number of Sites With Calcium Deposits (or Sclerosis)

	No. of Sites With Calcium Deposits				
	0 (n = 80)	1 (n = 58)	2 (n = 119)	3 (n = 81)	p Value for Trend
Age, yr (mean ± SD)	49.5 ± 10.7	56.7 ± 6.7	57.2 ± 7.3	57.3 ± 8.3	< 0.001
Male	57.5%	62.1%	55.5%	61.7%	NS
Hypertension	42.5%	48.3%	63.0%	66.7%	<0.001
Hypercholesterolemia	55.0%	44.8%	48.7%	51.9%	NS
Diabetes	20.0%	25.9%	30.5%	34.6%	< 0.05
Current smoking	16.3%	17.2%	18.5%	27.2%	NS

NS = not significant.

Table 3. Coronary Artery Disease (or Summed Stress Score ≥4) According to the Number of Sites With Calcium Deposits (or Sclerosis)

Group	No. of Sites With Calcium Deposits			
	0	1	2	3
Total	1*	1.16 (0.58–2.31)	2.12 (1.18–3.78)†	2.99 (1.58–5.68)‡
Male	1*	1.49 (0.62–3.58)	2.22 (0.98–4.81)	2.12 (0.93–4.80)
Female	1*	0.51 (0.12–2.19)	2.31 (0.88–6.03)	5.14 (1.76–15.03)‡
Younger (age ≤55 yrs)	1*	1.13 (0.38–3.32)	2.36 (1.01–5.53)†	3.94 (1.37–11.24)†
Older (age >55 yrs)	1*	0.88 (0.33–2.36)	1.49 (0.63–3.55)	1.94 (0.78–4.4)

*Reference category. †$p < 0.05$. ‡$p < 0.005$. Data are expressed odds ratio (95% confidence interval).

0.05), diabetes mellitus (OR = 3.15; 95% CI, 1.30 to 7.59; $p < 0.05$) and male gender (OR = 2.31; 95% CI, 1.03 to 5.18; $p < 0.05$) were statistically significant predictors of abnormal SPECT.

DISCUSSION

Although previous studies have shown that MAC, AVS or ARC are associated with CAD in the elderly (1–4,17), the significance of cardiac calcification has not been evaluated in younger subjects. To our knowledge, our study is the first to demonstrate that: 1) calcium deposits at multiple sites in the mitral annulus, aortic valve or aortic root are a marker of CAD in subjects age ≤65 years, and 2) patients with multiple calcium deposits and diabetes or multiple coronary risk factors have about 6 times the odds of abnormal SPECT in men ≤55 years old, 20 times in women ≤55 years old and 10 times in women >55 years old, compared with those with no or one calcium deposit site and no or one coronary risk factor other than diabetes. Thus, the presence of multiple calcium deposits has a significant discriminative power in identifying CAD when associated with multiple coronary risk factor or diabetes mellitus.

Coronary risk factors and cardiac calcifications. Mitral annulus calcification and AVS represent a degenerative process that occurs mainly in the elderly (1–4). Although the prevalence of these calcifications increases with age, several studies suggest that these calcifications are not a simple degenerative process (3–7). In humans, during adolescence, and the second as well as the third decade of life, focal yellow deposits that consist of foam cells are observed in the epicardial coronary arteries as well as on the ventricular surface of the posterior mitral leaflets (8). The disease process in the aortic valve leaflets of patients with aortic sclerosis or stenosis has some similarities to that of atherosclerosis, which include the process of lipid deposition, macrophage and T-cell infiltration, and basement membrane disruption (18). Boon et al. (3) suggested that age, female gender, systemic hypertension, diabetes mellitus and hypercholesterolemia predispose to MAC. Adler et al. (6) found that diabetes mellitus and female gender were frequently detected in patients with MAC. The Helsinki Aging Study showed that hypertension, age and a low body mass index were independent predictors of AVS; however, cholesterol, smoking and diabetes mellitus were not predictors (5). In the Cardiovascular Health Study, age, male gender, hypertension, smoking, lipoprotein (a) and low-density lipoprotein were independent predictors of AVS (4). A report by Aronow et al. (7) showed that adults age >62 years with calcified aortic cusps or root had a higher prevalence of hypercholesterolemia, history of hypertension, diabetes mellitus and serum high-density lipoprotein level <35 mg/dl than those with normal aortic cusps and root. In the Framingham Study, the presence of aortic calcified plaques was most strongly related to hypertension and was weakly related to other risk factors (17). Although the significant factors have varied among reports, these reports show that cardiovascular calcifications are associated with a high prevalence of coronary risk factors as well as generalized atherosclerosis. Diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking and male gender which

Table 4. Coronary Artery Disease (or Summed Stress Score ≥4) According to the Multiple Calcium Deposits (or Sclerosis) and DM or Multiple Risk Factors of Coronary Artery Disease

	No Multiple Calcium Deposits		Multiple Calcium Deposits	
	No DM or Multiple Cardiac Risk Factors	DM or Multiple Cardiac Risk Factors	No DM or Multiple Cardiac Risk Factors	DM or Multiple Cardiac Risk Factors
Total	1*	2.37 (1.17–4.79)	2.59 (1.31–5.1)	4.28 (2.30–7.98)
Male	1*	1.80 (0.75–4.33)	2.25 (0.94–5.37)	2.56 (1.17–5.58)
Older male (age >55 yrs)	1*	1.38 (0.36–5.34)	1.16 (0.35–3.84)	1.13 (0.37–3.43)
Younger male (age ≤55 yrs)	1*	2.21 (0.65–7.54)	3.40 (0.80–14.44)	5.55 (1.59–19.38)
Female	1*	4.83 (1.12–20.82)	5.06 (1.25–20.42)	13.81 (3.72–51.33)
Older female (age >55 yrs)	1*	1.95 (0.27–13.98)	4.50 (0.81–24.97)	10.00 (1.93–51.77)
Younger female (age ≤55 yrs)	1*	13.33 (1.28–138.85)	4.00 (0.31–51.03)	20.00 (2.16–184.87)

*Reference category. Data are expressed as odds ratio (95% confidence interval).
DM = diabetes mellitus.

Table 5. Predictors of Coronary Artery Disease (or Summed Stress Score ≥4) in Multivariate Analyses

		Gender		Age, yr	
	Total (n = 338)	Male (n = 198)	Female (n = 140)	≤55 (n = 136)	>55 (n = 202)
Age	1.03 (1.01–1.06)*	1.04 (1.01–1.08)*	0.99 (0.95–1.05)	1.04 (0.98–1.09)	1.04 (0.94–1.15)
Male	2.85 (1.73–4.72)‡	—	—	2.31 (1.03–5.18)*	3.68 (1.88–7.22)‡
Hypertension	0.95 (0.58–1.55)	1.02 (0.54–1.92)	0.65 (0.25–1.49)	1.10 (0.49–2.46)	0.80 (0.42–1.54)
Hypercholesterolemia	1.66 (1.03–2.67)*	1.92 (1.05–3.52)*	1.23 (0.52–2.91)	1.90 (0.85–4.25)	1.57 (0.85–2.89)
Diabetes	2.60 (1.50–4.49)‡	1.56 (0.73–3.30)	6.16 (2.59–14.70)‡	3.15 (1.30–7.59)*	2.35 (1.14–4.83)†
Current smoking	1.15 (0.63–2.10)	0.88 (0.45–1.74)	3.08 (0.81–11.67)	2.86 (1.01–8.10)*	0.66 (0.31–1.41)
Multiple calcium deposits	2.08 (1.27–3.41)†	1.50 (0.80–2.81)	4.88 (1.92–12.37)‡	2.41 (1.08–5.38)*	1.89 (0.99–3.60)

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$. Data are expressed as adjusted odds ratio (95% confidence interval).

are commonly associated with cardiac calcifications were the risk factors evaluated in our study (3–7,17). Our data show that MAC is associated with a higher prevalence of systemic hypertension, diabetes mellitus and an older age group. Patients with AVS are older and had a higher prevalence of hypertension, diabetes mellitus and current smoking than those without AVS, and the presence of ARC was associated with increasing age and hypertension. There is a greater prevalence of both hypertension and diabetes mellitus as the number of sites with calcium deposits increases.

CAD and cardiac calcification. Patients with MAC or AVS undergoing coronary angiography have a higher prevalence of CAD (15,19). In addition, patients with MAC have a higher incidence of new coronary events than those without MAC (20,21). Aortic valve sclerosis is associated with an approximately 50% increase in the risk of cardiovascular death or myocardial infarction in adults age >65 years (16). In our study, we utilized abnormal myocardial perfusion SPECT as a surrogate for angiographically significant CAD. Multiple logistic regression analyses revealed that the multiple calcium deposits remained a statistically significant predictor for abnormal SPECT, in addition to conventional coronary risk factors. In the subgroup analyses, the statistical significance of this observation was maintained in women and patients age ≤55 years but not in men and patients age >55 years. The Framingham Study showed that aortic calcific plaques are associated with CAD. But the predictive value of aortic calcific plaques for CAD generally diminishes with age and a significant increase in the prevalence of CAD was not found among men age ≥65 years (17). Adler et al. (6) reported a more prominent difference in the prevalence of CAD between women with or without MAC but no significant differences in men. These studies showed that the risk of CAD associated with the presence of MAC and ARC was generally stronger in women than in men. Similarly, our study also showed a stronger association of calcium deposits with abnormal SPECT in female and younger age groups. Electron-beam computed tomography is a sensitive technique for detecting coronary calcium (22,23). While the prevalence of electron-beam computed tomography detected calcium increases markedly with age (23), the specificity to detect obstructive CAD with electron-beam computed tomography is higher in the younger patient population (24). In the present study, the association of multiple calcium deposits with SSS ≥4 was most evident in female subjects and in male subjects age ≤55 years with diabetes or multiple coronary risk factors. Mitral annulus calcification or AVS is known to be more closely related to age than any other coronary risk factors (2,3). The findings suggest that multiple calcium deposits, found in patients ≤65 years old with diabetes as well as multiple coronary risk factors, reflect not merely the aging process but an epiphenomenon of atherosclerosis. As atherosclerosis is a generalized degenerative vascular process, patients who have more generalized calcium deposits in these structures are more likely to have atherosclerotic involvement in the coronary artery, especially in women age ≤65 years and men age ≤55 years.

Study limitations. This study was a retrospective study of patients who underwent both TTE and SPECT for clinical indications. Consequently, there was a substantial time interval between the two studies (276.1 ± 398.2 days). Although atherosclerosis is a chronic disease, some atheromatous plaques in the coronary artery may have progressed to a more significant lesion or may even have undergone plaque rupture and thrombotic occlusion during this time interval. Such progression over time may affect the association of echocardiographic calcium deposits with an abnormal SPECT. As coronary risk factors were evaluated at the time of the SPECT study, this time interval also may have affected the prevalence of coronary risk factors at the time of echocardiographic study. Because of the sample size, there may not have been sufficient power to demonstrate that some coronary risk factors were predictive of an abnormal SPECT. We did not use a digitized method to identify cardiac calcification. This could have caused a verification bias and may have affected the reproducibility in identifying cardiac calcifications. Although the sensitivity and specificity for SSS ≥4 are high for CAD, there may be a false positive and false negative diagnosis of CAD with SPECT; nevertheless, a large body of literature has been developed supporting the excellent prognostic discrimination of patients with no CAD or low-risk CAD when SSS <4 compared to patients at higher risk with SSS ≥4 (10,25,26). Our study did not consider the characteristics of chest pain, such as typical or atypical angina. The value of cardiac

calcification in identifying patients with coronary artery disease may vary according to the presence or characteristics of the chest pain.

CONCLUSIONS

In the patients with suspected CAD age ≤65 years, MAC, AVS and/or ARC on TTE are associated with coronary risk factors and the presence of multiple sites with calcium deposits appears to be an independent predictor of an abnormal myocardial SPECT, an indicator of angiographically significant CAD. In addition, when multiple coronary risk factors are present, calcium deposits at two or more of these sites may help in identifying patients with obstructive coronary artery disease in men ≤55 years old and women.

Reprint requests and correspondence: Dr. Robert J. Siegel, Cardiac Non-Invasive Laboratory, Room 5335, Cedars-Sinai Medical Center, Los Angeles, California 90048. E-mail: Siegel@cshs.org.

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