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Risk Factor Correlates of Coronary Calcium as Evaluated by Ultrafast Computed Tomography

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Coronary artery calcium is invariably associated with atherosclerosis and has been linked to an increased risk of coronary events. Ultrafast computed tomography (CT) was recently used to document the presence and relative quantity of coronary calcium. The use of the self-reported coronary risk factors to identify persons with coronary calcium as documented by ultrafast CT screening was examined in 458 men and 139 women aged 26 to 81 years (88% asymptomatic). All subjects underwent ultrafast CT scanning, and received a questionnaire and underwent an interview regarding medical and risk factor history. Total calcium score was calculated as the sum of lesion-specific scores, each calculated as the product of density ≥130 Hounsfield units and area ≥0.51 mm^2. The prevalence of coronary calcium increased significantly ($p < 0.01$) by age group, and the greater the number of risk factors present, the greater the likelihood of calcium. From multiple logistic regression, age ($p < 0.01$), male sex (relative risk [RR] 3.03; $p < 0.01$), and history of smoking (RR 1.85; $p < 0.01$) and hypertension (RR 1.65; $p < 0.05$) were independently associated with the probability of detectable calcium. Among asymptomatic subjects, an association with hypercholesterolemia was also seen (RR 1.56; $p < 0.05$). The results demonstrate that cardiovascular risk factors can help in identifying the likelihood of coronary calcium.

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Despite decreasing mortality rates, coronary artery disease remains the major cause of death among Americans.[1,2] Accurate diagnosis has been limited to either invasive methods, such as coronary angiography, or noninvasive methods, such as exercise treadmill testing that has significant false-positive and false-negative rates.[3,4] The ability of the standard risk factor profile to predict clinical coronary events is also limited.[5]

Coronary calcium deposits have been documented histologically to be a frequent component of atherosclerotic plaque.[6–9] Patients with radiographically detectable calcium have also been shown to be associated with as high as a fourfold increase in mortality compared with those without coronary calcium.[10] Although digital subtraction fluoroscopy provides a sensitive means to detect coronary calcium,[11] ultrafast computed tomography (CT) is probably more sensitive and is capable of quantitating relative amounts of coronary calcium. Furthermore, it is highly specific for the detection of nonobstructive[12] as well as obstructive[13] angiographic disease, and enables rapid image acquisition, the elimination of cardiac motion artifacts, and high-contrast resolution. Noninvasive ultrafast CT may, in conjunction with known risk factors, improve the sensitivity of identifying subjects at risk for coronary artery disease events. To determine which subjects are most likely to have coronary artery calcium by ultrafast CT, we evaluated the contribution of self-reported cardiovascular risk factors to predicting presence and extent of calcification.

METHODS

Study population and interview: The study group included 458 men and 139 women (age range 26 to 81 years, mean 52 ± 10; 84% asymptomatic and 7% with previously reported myocardial infarction), primarily self-referred (or by their physician) to a private medical clinic, who were consecutively studied between May 1991 and March 1992 by ultrafast CT coronary artery scanning. In general, these patients constituted a high-risk subset of the general population (53% of subjects had ≥2 reported risk factors). A questionnaire was given to all patients, which included questions regarding medical and risk factor history, including items on history of systemic hypertension, diabetes mellitus, hypercholesterolemia, chest pain suggestive of angina pectoris (by Rose questionnaire), myocardial infarction and tobacco use, and family history of premature (aged ≤55 years in a parent or sibling) myocardial infarction. A physician reviewed the completed responses with each subject to ascertain completeness and validity.

Procedures for ultrafast computed tomography: All studies were performed with a standard protocol previ-

TABLE I Mean ± SE Total Calcium Score and Prevalence of Detectable Calcium (score > 0) by Age Group

Age (year)	Mean ± SE (n)		Score > 0	
	Men	Women	Men	Women
<40	7 ± 5 (47)	0.1 ± 0.1 (8)	11%	13%
40–49	55 ± 17 (140)	10 ± 4 (42)	44%	29%
50–59	155 ± 26 (158)*	20 ± 7 (52)	70%	29%
60–69	362 ± 63 (20)†	71 ± 30 (6)‡	90%	67%
≥70	1,051 ± 245 (20)†	70 ± 57 (6)	90%	67%
Overall	191 ± 22 (458)§	29 ± 8 (139)	5,990	3,990

*p <0.05 compared with patients aged <40 and 40 to 49 years; †p <0.001 compared with all other groups; ‡p <0.05 compared with ages 50 to 59 years, and p <0.01 compared with ages 40 to 49 years; §p <0.001 compared with women.

ously described,[2] using an Imatron C-100 ultrafast CT scanner. Briefly, this involved subjects being positioned supine, head first, into the scanning aperture with no couch angulation, and instructed to take 3 deep breaths and hold their breath (at end-expiration) while a preview scan was performed. Positioning of the patient was checked and, if necessary, adjusted so that scanning began from near the lower margin of the bifurcation of the main pulmonary artery. Coronary visualization was achieved without contrast by using the high-resolution volume mode of the ultrafast CT scanner in conjunction with a 100 ms scan time, 3 mm slice thickness, electrocardiographic triggering (to 80% of the RR interval), and breath-holding for approximately 45 seconds. Twenty contiguous slices were obtained with no interslice gaps. Each of 20 levels (which encompassed the proximal portions of the coronary arteries where nearly all calcium is present)[12] were evaluated sequentially to determine presence and quantity of coronary calcium. From the established protocol,[12] the threshold for a calcified lesion was set at a CT density of 130 Hounsfield units and an area ≥0.51 mm^2. At each level, all pixels with a CT density ≥130 were displayed. A region of interest was manually encircled around each visible lesion within each coronary artery, and computer-acquired measurements of lesion area (mm^2) and maximal Hounsfield number of each region of interest were recorded. A lesion score was determined based on maximal Hounsfield number in the following manner: 1 = 130 to 199; 2 = 200 to 299; 3 = 300 to 399; and 4 = >400 Hounsfield units. A score of each region of interest was calculated by multiplying density score by area. A total calcium score was determined by adding each of these scores for all 20 slices. Total scores were also obtained for each of the following major coronary arteries: left main, left anterior descending, left circumflex and right.

Statistical analysis: Mean calcium score and prevalence of detectable calcium (total calcium score >0) were calculated initially for men and women separately across age groups (<40, 40 to 49, 50 to 59, 60 to 69 and ≥70 years). Analysis of variance and chi-square analyses were used (as appropriate) to examine age-related differences.

For men and women separately, the chi-square test was used to compare the proportions of subjects with detectable calcium (as defined previously) by reported history of high blood pressure, hypercholesterolemia, diabetes, chest pain and myocardial infarction (confirmed by physician), family history of premature (aged <55 years) myocardial infarction in sibling or parent, and any previous tobacco use. Mean calcium score and prevalence of detectable calcium were also compared for subjects with 0, 1, 2, 3, 4 or more principal risk factors (high blood pressure, hypercholesterolemia, diabetes, smoking or positive family history) by analysis of variance or chi-square analyses, as appropriate.

Stepwise multiple logistic regression analysis was used to examine the independent relation of each of the aforementioned potential risk factors (except previous infarction, which was not considered as a candidate variable, because it clinically indicates the presence of disease) to the probability of having calcium after adjusting for the effects of age, sex and other medical history and risk factor variables. Separate analyses were performed for all subjects (n = 597) and the subset who were asymptomatic and without previous myocardial infarction (n = 493). Alpha values of 0.15 and 0.10 were required for a variable to enter and remain, respectively, in the regression model.

RESULTS

The prevalence of detectable calcium varied significantly (p <0.01) by age group for both men and women (Table I). Mean calcium scores also increased by age group, although more significantly in men (p <0.01) than women (p = 0.03). There was a large increase in the prevalence of detectable calcium in men between the 40 to 49 year (44%) and 50 to 59 year (70%) age groups and in women between the 50 to 59 year (29%) and 60 to 69 year (71%) age groups. Whereas almost 90% of patients aged <40 years had no calcium, only a few subjects (10% of men) aged >70 had no calcium.

Hypercholesterolemia or family history of premature myocardial infarction were the most frequently reported risk factors in the patient population, each occurring in approximately half of subjects. A significantly higher prevalence of detectable calcium was found in men with than without diabetes, hypertension, previous smoking, reported history of chest pain, or previous myocardial infarction (p <0.05) (Table II). In women, the prevalence of detectable calcium was significantly greater in those with than without a reported history of hypercholesterolemia (p <0.05) or smoking (p <0.05).

There was a significant (p <0.01), continuous, graded relation of mean calcium score and prevalence of detectable calcium with an increasing number of risk factors in men (Table III). In men with no risk factors, prevalence of calcium was 37.8%, which doubled to 76% in those with ≥4 risk factors. A significant (p <0.01) relation between prevalence of calcium and number of risk factors was found in both men and women.

Table IV shows the results from multiple logistic regression analyses. Among all subjects, age, male sex, previous smoking, and high blood pressure were all independently associated with a significant (p <0.01 or <0.05) increased probability of detectable calcium. Men had 3 times (RR 3.03; p <0.01) the likelihood of having detectable calcium than did women. Subjects

TABLE II Prevalence of Detectable (calcium score > 0) and Significant Calcium by Self-Reported Cardiovascular Risk Factors

Risk Factor (% of men; women with risk factor)		Detectable Calcium (%) Men (n = 458)	Women (n = 139)
Hypercholesterolemia	Yes	64%*	47%†
(52.2; 54.7)	No	55%	29%
Diabetes	Yes	81%†	56%
(5.7; 6.5)	No	58%	38%
Hypertension	Yes	75%‡	44%
(25.1; 18.0)	No	54%	34%
Previous smoking	Yes	70%‡	54%‡
(36.7; 25.2)	No	53%	34%
Family history of premature MI	Yes	63%	42%
(45.9; 48.2)	No	56%	36%
Current chest pain	Yes	74%†	32%
(12.5; 15.8)	No	57%	40%
Previous MI	Yes	94%‡	50%
(7.0; 1.4)	No	57%	39%
Body mass index (kg/m^2)	Yes	26 ± 3	25 ± 3
(mean ± SD) by calcium status	No	26 ± 3	25 ± 4

*p <0.10; †p <0.05; ‡p <0.01 compared with subjects without indicated risk factor (except for body mass index, where comparison is with those without calcification).
MI = myocardial infarction.

TABLE III Mean ± SE Calcium Score and Prevalence (%) of Detectable (total score > 0) and Significant (total score ≥ 50) Calcification by Number of Risk Factors

No. of Risk Factors*	Men		Women	
0	109 ± 33 (82)	38%	6 ± 4 (22)	23%
1	143 ± 41 (129)	57%	32 ± 18 (47)	28%
2	188 ± 35 (139)	62%	26 ± 9 (49)	53%
3	275 ± 56 (83)	75%	62 ± 31 (17)	35%
≥4	442 ± 171 (25)	76%	29 ± 14 (4)	100%
	p <0.01	p <0.0001	p = 0.45	p <0.01

*Including reported history of high cholesterol and blood pressure, smoking and premature (aged ≤55 years) myocardial infarction.
p values indicate significance of test comparing means or prevalences across all risk factor categories.

TABLE IV Multiple Logistic Regression Analyses Evaluating Association of Cardiovascular Risk Factors to Probability of Detectable (score > 0) Calcium in All Subjects (n = 597), and in Those Asymptomatic and Without Previous Infarction (n = 493)

	All Subjects		Asymptomatic, No MI	
Risk Factor	Coefficient	RR	Coefficient	RR
Age (year)	0.11	1.12*	0.11	1.11*
Sex (women/men)	−1.11	3.04*†	−1.95	2.59*†
Previous smoking	0.61	1.85*	0.45	1.57‡
Hypercholesterolemia	0.35	1.42§	0.45	1.56‡
Hypertension	0.50	1.65‡	0.47	1.59§
Family history of premature MI	0.34	1.40		

*p <0.01; ‡p <0.05; §p <0.10.
†Relative risk for men compared with women.
MI = myocardial infarction; RR = relative risk.

with history of smoking had an 85% increased risk (RR 1.85; p <0.01), and those with high blood pressure had a 65% increased risk (RR 1.65; p <0.05). Analyses obtained among the subset of subjects who were asymptomatic and without previous infarction showed history of hypercholesterolemia also predictive (RR 1.56; p <0.05), but found a weaker relation with hypertension.

DISCUSSION

Important relations between cardiovascular risk factors and coronary artery disease as documented by coronary angiography have been the subject of previous investigations.[5,14] This is the first report from a large cohort of patients that examines the association of coronary atherosclerosis detected noninvasively by ultrafast CT calcium screening with a wide spectrum of cardiovascular risk factors.

The strong positive correlation of age with prevalence of coronary calcium in men and women, as well as the higher prevalence of calcium in men (59.4 vs 38.9%; p <0.01), is consistent with clinical data reported by other investigators.[15] However, it is not known whether the prognostic significance of coronary calcium diminishes with age. Long-term follow-up studies are needed to establish this.

History of hypercholesterolemia was independently associated with coronary calcium prevalence in asymptomatic subjects with no previous infarction. Self-reported history, rather than actual venepuncture-assessed lipid levels, may be more appropriate to use in subjects receiving lipid-lowering medications that would have lowered actual levels. Such patients may have had hyperlipidemia for many years. Other investigators have also shown coronary calcium to be associated with total (Detrano et al, unpublished observations) or low-density lipoprotein[15] cholesterol, which is consistent with our findings.

Diabetes was significantly associated with detectable calcium only in men by univariate analysis. The greater prevalence of calcium in diabetic patients is consistent with that reported previously from an autopsy series.[16]

History of hypertension was also associated with an increased probability of detectable calcium (but only in the entire cohort), conferring a 65% increased probability from multiple logistic regression analysis adjusted for other factors. This may relate to the finding that hypertension can aggravate the atherosclerotic process through arterial wall trauma.[17-19] Although we did not obtain actual resting blood pressures, a self-reported history of using antihypertensive medication may be more relevant to our study, because a number of subjects were currently controlled on antihypertensive medication.

Previous tobacco use was the strongest indicator, other than age or gender, for detectable calcium in both men and women. This was associated with an approximately two-fold increased probability of calcium in multivariate analysis. It has also been reported that tobacco use correlates with arterial atherosclerosis in autopsied men.[20]

History of myocardial infarction was also found to be associated with detectable calcium in men. If history of myocardial infarction (confirmed by treating physician) is used as the gold standard for coronary artery disease, this indicates a sensitivity in our study of 94% in men (30 of 32 with a previous infarction had calcification). Among subjects with current chest pain, 74% of men but only 32% of women had calcium in their arteries, possibly reflecting a lower prevalence of actual disease in women than in men with chest pain.

Finally, we noted that the mean calcium score and prevalence of detectable calcium in men and women increases in a graded fashion with the number of risk factors. Lee et al[15] also reported significantly greater calcium scores among patients with ≥3 risk factors than among those with ≤2.

The search for effective screening strategies for coronary artery disease is hampered by the imperfect sensitivity and specificity of currently available tests. Testing based on functional assessment has a reasonably good predictive value, but depends on the presence of significant coronary luminal narrowing for diagnosis and is therefore not useful for early detection of subclinical coronary artery disease in high-risk subjects.[3,4] Furthermore, it is now recognized that a significant proportion of myocardial infarctions are due to rupture of nonobstructive atherosclerotic plaques that would not be detected by any functional test.[21] Detection of calcium by fluoroscopy or nongated CT has been used as a screening test for coronary artery disease, but has limited sensitivity.[11,22,23] In contrast, ultrafast CT is more sensitive for detection of coronary calcium. Recent studies with ultrafast CT showed an excellent correlation between quantification of coronary calcium and angiographic extent of coronary artery disease.[13,24,25] Whether this sensitivity can be further enhanced by choosing a lower Hounsfield number (<130) for detection of possibly early calcific lesions needs further investigation.

Current strategies for detecting patients at increased risk of clinical events are based on screening for multiple risk factors. Although this strategy defines cohorts of patients with increased risk, it has poor predictive value when applied to an individual patient, because many subjects with the risk factor may never develop clinically evident coronary artery disease (unpublished observations). Larger prospective studies are needed to determine whether calcific deposits defined by ultrafast CT coronary artery scanning in combination with known risk factors can better enable physicians to evaluate subsequent risk of coronary events.

Until these data are available, we believe that patients with concomitant risk factors and prevalent coronary calcium could be targeted for more aggressive risk factor intervention to retard any likely progression of disease.

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