Calcification of the Aortic Arch: Risk Factors and Association With Coronary Heart Disease, Stroke, and Peripheral Vascular Disease

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Calcification of the Aortic Arch

Risk Factors and Association With Coronary Heart Disease, Stroke, and Peripheral Vascular Disease

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Context Calcium deposits in coronary and extracoronary arterial beds may indicate the extent of atherosclerosis. However, the incremental predictive value of vascular calcification, beyond traditional coronary risk factors, is not clearly established.

Objective To evaluate risk factors for aortic arch calcification and its long-term association with cardiovascular diseases in a population-based sample.

Design and Setting Cohort study conducted at a health maintenance organization in northern California.

Participants A total of 60393 women and 55916 men, aged 30 to 89 years at baseline who attended multiphasic health checkups between 1964 and 1973 and for whom incidence of hospitalizations and/or mortality data were ascertained using discharge diagnosis codes and death records through December 31, 1997 (median follow-up, 28 years).

Main Outcome Measure Hospitalization for or death due to coronary heart disease, ischemic stroke, hemorrhagic stroke, or peripheral vascular disease, as associated with aortic arch calcification found on chest radiograph at checkup from 1964-1973.

Results Aortic arch calcification was present in 1.9% of men and 2.6% of women. It was independently associated with older age, no college education, current smoking, and hypertension in both sexes, but it was inversely related to body mass index and family history of myocardial infarction. In women, aortic arch calcification was also associated with black race and elevated serum cholesterol level. After adjustment for age, educational attainment, race/ethnicity, cigarette smoking, alcohol consumption, body mass index, serum cholesterol level, hypertension, diabetes, and family history of myocardial infarction, aortic arch calcification was associated with an increased risk of coronary heart disease (in men, relative risk [RR], 1.27; 95% confidence interval [CI], 1.11-1.45; in women, RR, 1.22; 95% CI, 1.07-1.38). Among women, it was also independently associated with a 1.46-fold increased risk of ischemic stroke (95% CI, 1.28-1.67).

Conclusion In our population-based cohort, aortic arch calcification was independently related to coronary heart disease risk in both sexes as well as to ischemic stroke risk in women.

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CALCIUM DEPOSITS IN THE coronary and extracoronary arterial beds may indicate the extent of atherosclerotic lesions,[1-4] and may be a marker of subclinical cardiovascular disease. Although several studies have shown that coronary[5,6] and extracoronary calcification[7-10] are associated with increased risk of cardiovascular events, the incremental predictive value of vascular calcification, beyond traditional coronary risk factors, is unclear.[11]

We undertook this study to characterize the risk profile of patients with aortic arch calcification detected on a chest radiograph and to evaluate the long-term association of aortic arch calcification with incidence of hospitalization or death by coronary heart disease (CHD), stroke, and peripheral vascular disease in a large cohort of men and women followed up for a median of 28 years. The results of this study suggest that aortic arch calcification is an important predictor of cardiovascular outcomes, and that it has prognostic value beyond traditional risk factors.

METHODS

Study Population and Procedures

The study cohort is 139849 subscribers (66922 men and 72927 women) of the Kaiser Permanente Medical Care Program of northern California, aged 30 to 89 years, who attended voluntary periodic multiphasic health checkups in San Francisco, Calif, and Oakland, Calif, between 1964 and 1973. If subscribers attended more than 1 multiphasic health checkup,

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only the data from the first checkup were used.

Kaiser Permanente is a nonprofit, group-practice health maintenance organization that covers more than one quarter of the population in the geographic areas served. Kaiser Permanente subscribers are representative of the local population, except for the extremes of wealth and poverty, which are underrepresented.[12]

Information on demographic, lifestyle, and physiological characteristics was collected at the multiphasic health checkup.[13,14] Serum cholesterol levels were measured with an Auto-Analyzer (Technicon Co, White Plains, NY) from 1964 through 1968, with an Autochemist (AGA Corp, Stockholm, Sweden) from 1969 through 1972, and with an Auto-Analyzer (model SMA-12, Technicon Co) in 1973. Weight, height, and systolic and diastolic blood pressures were measured following standardized procedures.[14] Body mass index was computed as weight in kilograms divided by height in meters squared. Persons were classified according to their consumption of alcoholic drinks in the past year as nondrinkers, drinkers who drank less than 3 drinks per day, and drinkers who drank 3 or more drinks per day. Personal history of physician-diagnosed hypertension, diabetes, use of antihypertensive medication, insulin or oral hypoglycemic agents, as well as family history of myocardial infarction (in father or mother) were ascertained by self-report. No information was collected on age at myocardial infarction in first-degree relatives. Hypertension was defined as systolic blood pressure higher than 140 mm Hg and diastolic blood pressure higher than 90 mm Hg; or as self-reported or physician-diagnosed hypertension; or as self-reported use of antihypertensive medication. Diabetes was defined as self-reported physician-diagnosed diabetes; and/or as self-reported use of insulin or hypoglycemic agents. Multiphasic patients underwent a VDRL test (slide flocculation tests using a nontreponema antigen) for the serodiagnosis of syphilis.[14] At that time, this was the standard screening test for syphilis.

As part of the health checkups between 1964 and 1973, 70-mm minifilm, posterior-anterior chest radiographs were obtained during deep inspiration in a standing position using an Odelca machine (Philips Co, Eindhoven, the Netherlands). The radiographs were read by Kaiser Permanente Medical Group radiologists in the Oakland and San Francisco Kaiser Permanente hospitals according to routine clinical practice. Films were not reread for the purpose of this study and the radiologists were not blinded to other clinical information about the study participants. The reporting of radiological findings, including evidence of calcification in the aortic arch, was standardized by the use of mark sense cards.[14] The x-ray film report was available in electronic format, thus no information was abstracted from patients' charts.

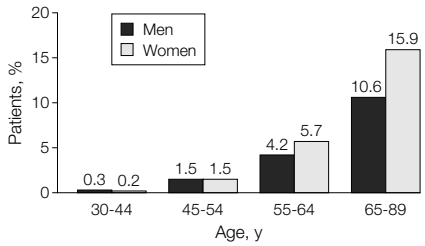
Excluded from the study were 3723 men and 4458 women who did not undergo chest radiography. The main reasons for not participating were refusal, pregnancy, or recent x-ray film examination. An additional 7283 men and 8076 women were excluded from the analysis because their radiographic film was judged to be unsatisfactory (the main reason being poor quality of the film due to overexposure or underexposure). Thus, the final sample consisted of 55916 men and 60393 women.

The incidence of hospitalizations for CHD (*International Classification of Diseases, Eighth Revision [ICD-8], Ninth Revision [ICD-9]* codes 410-414), ischemic stroke (*ICD-8* codes 432-438 and *ICD-9* codes 433-438), hemorrhagic stroke (*ICD-8* codes 430-431 and *ICD-9* codes 430-432), and peripheral vascular disease (*ICD-8* and *ICD-9* codes 440-448) was ascertained using an automated database of hospital discharge diagnoses beginning January 1, 1971.[15,16] When rehospitalizations occurred, only the first was selected. In a previous study, the ascertainment of CHD using our automated hospital discharge files was shown to be consistent with the physician's diagnostic impression noted at chart review.[17] Fatal outcomes through the end of 1997 were ascertained using the California Automated Mortality Linkage System, which has a sensitivity of 0.97 vs the National Death Index.[18] The underlying cause of death was categorized according to the same *ICD-8* and *ICD-9* codes noted above. Person-time was calculated as years elapsed from baseline (January 1, 1971) to hospitalization event, fatal event, closing date of the study (December 31, 1997), or termination of health plan membership. The termination of health plan membership was determined as failure to appear in the mid-year membership roster for 2 consecutive years (even if the subscriber rejoined the health plan thereafter), with censoring date at the end of the year before the 2-year membership gap. This was done because we did not consider out-of-plan hospitalizations. About 36% of study participants were followed up until the closing date. Attrition due to changes in insurance provider and death was 3% per year and the median follow-up time was 28 years (mean [SD], 26 [7] years).

Statistical Analysis

Logistic regression models were used to identify independent risk factors for aortic arch calcification by sex. Sex-specific, age-adjusted, and multivariate-adjusted associations of aortic arch calcification with CHD, ischemic stroke, hemorrhagic stroke, and peripheral vascular disease were determined with proportional hazards models.[19] The multivariate models included covariates for age, race (black, Asian, and other/unknown vs white, the race referent), education level (no college vs at least some college education), cigarette smoking status (former and current vs never), alcohol consumption status (nondrinker, ≥3 drinks per day, and unknown vs 1-2 drinks per day, the alcohol consumption referent), body mass index, serum total cholesterol level, hypertension, diabetes, and family history of myocardial infarction.

Figure. Prevalence of Aortic Arch Calcification



Data based on patients enrolled in the northern California Kaiser Permanente Medical Care Program who had multiphasic health checkups between 1964 and 1973.

Data on body mass index and serum cholesterol level were missing in 7% of men and in 7.5% of women, whereas data on systolic or diastolic blood pressure were missing in about 0.5% of men and women. Body mass index and serum cholesterol level were treated as categorical variables representing quartiles, with the lowest quartile as the reference level and dummy variables representing missing values.

To determine whether the associations between aortic arch calcification and study outcomes varied by age, we added a cross-product interaction term (continuous age × categorical aortic arch calcification) to the multivariate models, separately for men and women. Statistical analyses were performed using statistical software (SAS version 6.11, SAS Institute Inc, Cary, NC).

RESULTS

Aortic arch calcification was present in 1.9% of men and in 2.6% of women. Its prevalence increased with age in both sexes (FIGURE). The sex difference was particularly apparent in participants who were 65 years and older; 10.6% of men and 15.9% of women in this age range had aortic arch calcification.

Risk Factors for Aortic Arch Calcification

Compared with counterparts without aortic arch calcification, men who had aortic arch calcification were older, more likely to have at least some college education, and slightly more likely to be white (TABLE 1). Men with aortic calcification also tended to have a history of hypertension; but were less likely to be current smokers; consumers of 1 to 2, or of 3 or more alcoholic drinks per day; or to have a family history of myocardial infarction. Women with aortic arch calcification were older, weighed more, and had greater serum cholesterol levels than women without calcification (Table 1). They also tended to have received more years of education, were more likely to be white, and less likely to be current cigarette smokers or consumers of alcohol. They also were more likely to have hypertension and less likely to have a family history of myocardial infarction. About 1.7% of men and 1.6% of women had a positive or weakly reactive VDRL test; these small percentages did not vary importantly by aortic arch calcification status (Table 1).

Older age, having no college education, and current cigarette smoking were independently associated with aortic arch calcification in both sexes (TABLE 2). Contrary to expectation, aortic arch calcification was inversely related to body mass index and to family history of myocardial infarction in both sexes. In women, aortic arch calcifica-

Table 1. Distribution of Risk Factors by Presence of Aortic Arch Calcification and Sex*

	Aortic Arch Calcification			
	Men		Women	
Risk Factor	None (n = 54 824)	Present (n = 1092)	None (n = 58 803)	Present (n = 1590)
Age, y†	45.8 (11.1)	60.6 (10.8)	46.4 (10.8)	62.3 (8.8)
Body mass index, kg/m²†	25.8 (3.4)	25.7 (3.2)	24.5 (4.5)	25.2 (4.4)
Serum cholesterol, mmol/L†‡	5.9 (1.1)	6.0 (1.0)	5.9 (1.1)	6.5 (1.2)
Educational attainment				
No college	40	24	30	19
At least some college	45	68	56	75
Unknown	15	8	14	6
Race/ethnicity				
White	78	85	78	88
Black	13	10	14	9
Asian	4	2	4	1
Other/unknown	5	2	4	1
Cigarette smoking				
Never	29	28	44	54
Former	24	28	13	10
Current	39	34	34	23
Unknown	8	9	9	13
Alcohol consumption, drinks/d				
0	15	24	27	37
1-2	56	46	51	38
≥3	17	13	6	4
Unknown	12	14	19	21
Hypertension§	21	35	22	44
Diabetes‖	3	6	2	5
Family history of myocardial infarction	17	9	19	16
VDRL serologic test				
Positive	0.6	0.7	0.4	0.1
Weakly reactive	1.1	2.1	1.2	1.7

*Data based on patients enrolled in the northern California Kaiser Permanente Medical Care Program between 1964 and 1973 who had multiphasic health checkups. Values are expressed as percentages unless otherwise indicated.
†Values are expressed as mean (SD).
‡To convert cholesterol from mmol/L to mg/dL, divide by 0.0259.
§Diagnosed as having hypertension if patient had a systolic blood pressure higher than 140 mm Hg and diastolic blood pressure higher than 90 mm Hg; or if self-reported or if diagnosed by a physician; or if a patient self-reported his/her use of antihypertension medication.
‖Diagnosed as having diabetes if self-reported or if diagnosed by a physician, or if a patient self-reported his/her use of insulin or hypoglycemic agents.

tion was independently related to black race and to elevated serum cholesterol level. No association was apparent between positive or weakly reactive VDRL serologic test results and aortic calcification. Null results were also obtained comparing positive with negative or weakly reactive VDRL test results in men (data not shown; this comparison could not be made in women because there was only 1 case of aortic calcification among women with a positive VDRL test result).

Effects of Aortic Arch Calcification on Cardiovascular Outcomes

Among men, except for hemorrhagic stroke (in which no difference existed), the crude rates per 1000 person-years of all cardiovascular outcomes were higher in those with than in those without aortic arch calcification (TABLE 3). Among women, all rates were higher among those with than among those without calcification of the aortic arch.

After multivariate adjustment for age, race/ethnicity, educational attainment, cigarette smoking, alcohol consumption, body mass index, serum cholesterol level, hypertension, diabetes, and family history of myocardial infarction, aortic arch calcification was associated with a 1.27-fold increased risk of CHD in men (95% confidence interval [CI], 1.11-1.45), with a 1.22-fold increased risk of CHD in women (95% CI, 1.07-1.38), and with a 1.46-fold increased risk of ischemic stroke in women (95% CI, 1.28-1.67). No significant associations were found for ischemic and hemorrhagic stroke in men, but associations of borderline statistical significance were seen for peripheral vascular disease in both men and women.

The only significant age by aortic arch calcification status interaction was in the model of CHD among men. Given the high level of statistical significance ($P<.001$), this interaction is not likely due to multiple testing. When the analysis was stratified by age, we found that aortic arch calcification is more strongly related to CHD among men aged 65 years and older (relative risk, 1.48; 95% CI, 1.20-1.83) than among men aged 30 to 64 years and older (relative risk, 1.09; 95% CI, 0.92-1.29).

COMMENT

Aortic arch calcification seen on chest radiograph obtained as part of a voluntary health examination was positively associated with traditional cardiovascular risk factors, including age, race/ethnicity, hypertension, and cigarette smoking, but inversely related with body mass index and family history of myocardial infarction. Moreover, calcification of the aortic arch was significantly and independently related to increased risk of CHD in both sexes and with increased risk of ischemic stroke among women.

Table 2. Adjusted Associations Between Selected Risk Factors and Aortic Arch Calcification*

Risk Factor	Odds Ratio (95% Confidence Interval) Men (n = 55 916)	Women (n = 60 393)
Age†	2.74 (2.58-2.91)	3.52 (3.32-3.74)
Race/ethnicity‡		
Black	1.17 (0.94-1.43)	1.35 (1.11-1.63)
Asian	0.73 (0.47-1.08)	0.79 (0.48-1.22)
Other/unknown	0.65 (0.42-0.96)	0.69 (0.44-1.03)
No college vs at least some college education	1.17 (1.00-1.36)	1.31 (1.14-1.50)
Quartile of serum cholesterol, mmol/L§‖		
Men		
5.2-5.6	0.97 (0.80-1.17)	. . .
5.7-6.5	1.07 (0.89-1.30)	. . .
>6.5	1.16 (0.97-1.38)	. . .
Women		
5.1-5.6	. . .	1.13 (0.92-1.40)
5.7-6.6	. . .	1.19 (0.98-1.45)
>6.6	. . .	1.28 (1.06-1.55)
Quartile of body mass index, kg/m^2§		
Men		
23.6-25.4	1.01 (0.85-1.21)	. . .
25.5-27.6	0.97 (0.81-1.16)	. . .
>27.6	0.82 (0.68-0.98)	. . .
Women		
21.5-23.6	. . .	0.97 (0.82-1.15)
23.7-26.6	. . .	0.86 (0.73-1.01)
>26.6	. . .	0.82 (0.69-0.96)
Cigarette smoking vs never		
Former	1.13 (0.95-1.33)	1.04 (0.86-1.25)
Current	1.30 (1.10-1.53)	1.16 (1.01-1.33)
Unknown	1.04 (0.77-1.38)	1.33 (1.08-1.64)
Alcohol consumption vs 1-2 drinks/d		
0	1.08 (0.92-1.27)	1.00 (0.88-1.14)
≥3	0.84 (0.69-1.02)	0.89 (0.67-1.16)
Unknown	1.09 (0.87-1.36)	0.99 (0.83-1.17)
Hypertension vs no hypertension¶	1.27 (1.11-1.46)	1.38 (1.23-1.54)
Diabetes vs no diabetes#	1.19 (0.91-1.54)	1.21 (0.94-1.54)
Family history of myocardial infarction vs no family history	0.59 (0.46-0.74)	0.75 (0.64-0.88)
Positive or weakly reactive VDRL serologic test vs negative	1.06 (0.71-1.52)	0.82 (0.54-1.20)

*Data based on patients enrolled in the northern California Kaiser Permanente Medical Care Program between 1964 and 1973 who had multiphasic health checkups. Ellipses indicate data not applicable.
†Referent category is per 10 years.
‡Referent category is white.
§Values based on comparisons with those in the lowest quartile.
‖To convert cholesterol from mmol/L to mg/dL, divide by 0.0259.
¶Diagnosed as having hypertension if patient had a systolic blood pressure higher than 90 mm Hg; or if self-reported or if diagnosed by a physician; or if a patient self-reported his/her use of antihypertension medication.
#Diagnosed as having diabetes if self-reported or if diagnosed by a physician; or if a patient self-reported his/her use of insulin or hypoglycemic agents.

Consistent with prior studies,[20,21] aortic arch calcification was more common in women than in men, particularly after age 65 years. There are 3 possible nonmutually exclusive explanations for this finding. First, it could be that the sex difference might be related to technical aspects of testing. For example, the body habitus of women may make it easier to see a calcified aortic arch on chest radiograph. Second, atherosclerotic calcification reflects not only the atherosclerotic process but also bone calcium metabolism. Elderly women develop osteoporosis and some calcium is redistributed from bones to soft tissues, including atherosclerotic arteries. Third, there is the possibility of selective survival if men with aortic calcification tended to die at an earlier age than women with similar radiographical findings.

Aortic arch calcification was inversely related to body mass index, perhaps in part because it may be more difficult to detect vascular calcification with increasing body mass index. It is not clear why family history of myocardial infarction was inversely related to aortic arch calcification. Chance is an unlikely explanation, given the high level of statistical significance. A possible explanation is that those with a family history of myocardial infarction did not live long enough to develop aortic arch calcification. This unexpected finding deserves further scrutiny in another study.

Another noteworthy finding was that low educational attainment, a surrogate measure of socioeconomic status, remained significantly associated with the presence of aortic arch calcification in both sexes even after adjustment for age, race/ethnicity, health behaviors, hypertension, and diabetes. Disparities in cardiovascular risk across socioeconomic status are fairly well established, and remain an issue of considerable public health importance.[22]

Although syphilis is a known cause of aortitis,[23-25] we found no evidence in our population for an association between syphilis serology and calcification of the aortic arch.

Our results are consistent with prior studies in this area. Aortic calcification on routine radiographs,[8] and in the lumbar region,[7,10] were associated with increased risk of cardiovascular mortality, whereas thoracic aortic plaques identified by transesophageal echocardiography were associated with ischemic stroke.[9,26,27]

The co-occurrence of osteoporosis and manifestations of cardiovascular disease in postmenopausal women is a well-known phenomenon, including findings of associations between low bone mineral density after menopause with cardiovascular[28] and nontrauma mortality.[29] Both vascular calcification and low bone mineral density may result from estrogen deficiency.[30] Supporting a possible link between low estrogen level and arterial calcification, a recent study has found a decreased prevalence of coronary artery calcification assessed by double helical computed tomography among users of hormone replacement therapy.[31] The sharp increase in atherosclerosis among women as they develop osteoporosis suggests that these 2 processes may be closely related,[32-34] although probably not causally.[35-37] Another hypothesis is that common processes involving lipid peroxidation and extracellular matrix proteins may underlie both osteopenia and cardiovascular risk.[38-40]

Insoluble crystalline calcium phosphate, which is ubiquitous in the body, precipitates relatively early in atherosclerotic lesions.[3,41] Furthermore, it is now well established that calcification of vascular beds is regulated by some of the same processes that regulate bone calcification.[2]

The limitations of our study include the lack of data in other segments of the aorta (thoracic or lumbar) and the low sensitivity of the conventional chest

Table 3. Rates and Risk of Cardiovascular Outcomes According to Presence of Aortic Arch Calcification and Sex*

	Aortic Arch Calcification			
	Men (n = 55 916)		Women (n = 60 393)	
Outcome	None	Present	None	Present
Coronary heart disease				
No events	7954	242	4901	264
Rate per 1000 person-years	7.6	14.6	4.1	9.6
Relative risk (95% confidence interval)				
Age-adjusted		1.25 (1.09-1.42)		1.22 (1.07-1.39)
Multivariate-adjusted†		1.27 (1.11-1.45)		1.22 (1.07-1.38)
Ischemic stroke				
No events	3089	110	3243	258
Rate per 1000 person-years	2.9	6.6	2.7	9.3
Relative risk (95% confidence interval)				
Age-adjusted		1.17 (0.96-1.42)		1.50 (1.32-1.71)
Multivariate-adjusted†		1.17 (0.97-1.42)		1.46 (1.28-1.67)
Hemorrhagic stroke				
No events	634	10	689	37
Rate per 1000 person-years	0.6	0.6	0.6	1.3
Relative risk (95% confidence interval)				
Age-adjusted		0.67 (0.36-1.25)		1.37 (0.97-1.92)
Multivariate-adjusted†		0.67 (0.35-1.25)		1.33 (0.94-1.87)
Peripheral vascular disease				
No events	3688	104	3148	130
Rate per 1000 person-years	3.5	6.3	2.6	4.7
Relative risk (95% confidence interval)				
Age-adjusted		1.19 (0.97-1.45)		1.17 (0.98-1.40)
Multivariate-adjusted†		1.20 (0.98-1.46)		1.16 (0.97-1.39)

*Data based on patients enrolled in the northern California Kaiser Permanente Medical Care Program between 1964 and 1973 who had multiphasic checkups. Patients were followed up through December 31, 1997.
†Adjusted for age, race/ethnicity, educational attainment, cigarette smoking, alcohol consumption, body mass index, serum cholesterol, hypertension, diabetes, and family history of myocardial infarction.

x-ray film result compared with electron-beam and/or spiral computed tomography assessments of vascular calcification. The incremental prognostic significance of aortic calcification merits further study with these more precise techniques.

In conclusion, the results of the current study suggest that aortic arch calcification is independently associated with an increased risk of cardiovascular outcomes. The implications of our findings are 2-fold. First, patients with aortic arch calcification may be at higher risk for cardiovascular events, and should be candidates for aggressive risk factor management. Second, these data raise the question of whether therapies that prevent vascular calcification would have value in reducing the incidence of cardiovascular events.

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