

Usefulness of Electron Beam Tomography to Detect Progression of Coronary and Aortic Calcium in Middle-Aged Women

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Electron beam tomography (EBT) permits the noninvasive quantification of coronary and aortic calcium as a marker of atherosclerosis. Coronary and aortic calcium are strongly related to premenopausal cardiovascular risk factors in middle-aged women. This report evaluates changes in coronary and aortic calcium over an average of 18 months in 80 women. Measurement variation over time and between readings is also evaluated in these women who were followed through the menopausal transition. Eight years after menopause, 80 women (average age 63 years) underwent serial EBT of the coronary arteries and aorta separated by 18 months. Calcium scores were based on the number and density of calcific deposits. Duplicate readings were obtained to evaluate the effect of reading variation on

calcium scores. At baseline, the median calcium score was 0 in the coronary arteries and 58 in the aorta. Average change in coronary (+11) and aortic (+112) calcium were significantly different from zero ($p < 0.001$). Reading variability did not contribute significantly to the variation in calcium scores. Extent of calcium in the coronary arteries was associated with progression of calcium in the aorta ($p = 0.013$). Both coronary and aortic calcium were significantly associated with premenopausal cardiovascular risk factors. Thus, progression of coronary and aortic calcium using EBT can be observed over a short time in healthy middle-aged women. ©2001 by Excerpta Medica, Inc.

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We have previously reported a strong association between electron beam tomographic measures of coronary and aortic calcium and cardiovascular risk factors in 154 middle-aged women.¹ Elevated levels of low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, higher body mass index, waist circumference, apoprotein B, and lower levels of high-density lipoprotein cholesterol were associated with higher coronary and/or aortic calcium scores. There was a strong correlation between aortic and coronary calcium scores ($r = 0.44$, $p = 0.001$), and the prevalence of any detectable calcium was much higher for the aorta (63%) than for coronary arteries (27%). This report evaluates changes in coronary and aortic calcium over an average of 18 months in 80 of these women. Only limited data have been reported on progression of coronary calcium by EBT, and this article represents the first report of progression of aortic calcium by EBT.

METHODS

Healthy Women Study: Detailed descriptions of the Healthy Women Study have been previously published.^{2,3} Beginning in 1983, 541 premenopausal women aged 42 to 50 years, living in Pittsburgh, Pennsylvania, were recruited. Eligible women had diastolic blood pressures < 100 mm Hg, were free from chronic disease requiring medication (including blood pressure medication), were not taking hormone replacement therapy, and were menstruating within 3 months of the baseline examination. These women were followed until they ceased cycling and/or used hormone replacement therapy in combination for 12 months, at which time they were considered postmenopausal and reevaluated. Evaluations were also performed at 2, 5, and 8 years after menopause.

Clinic visits: The baseline clinic visit included measurement of height, weight, blood pressure, and a fasting blood sample for determination of insulin, glucose, and lipoproteins. Assays were performed at a central laboratory that adheres to the quality control standards recommended by the Centers for Disease Control and the National Heart, Lung, and Blood Institute. Standard assays were used to measure total serum cholesterol,⁴ total high-density lipoprotein cholesterol,⁵ and triglycerides.⁶ Low-density lipoprotein cholesterol was estimated using the Friedewald equation.⁷ Serum glucose was determined by enzymatic assay.⁸ Blood pressures were measured twice using a random-zero sphygmomanometer, and the results were averaged. Similar data were collected at visits 1, 5, and 8 years after menopause.

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Women were invited to undergo EBT of the heart and the aorta after their 8-year postmenopausal examination; only 7 of 274 refused. Repeat scans were done an average of 18 months after the initial scan. Women have been invited back sequentially, and none had refused to date. The baseline characteristics of the women in the electron beam tomographic study were similar to all women visiting the clinic for their 8-year postmenopausal examinations. All women signed an informed consent approved by the University of Pittsburgh Institutional Review Board.

Electron beam tomographic methods: Electron beam tomographic scans were performed using an Imatron C-150 (Ultrafast CT) scanner (Imatron, South San Francisco, California). For evaluation of the coronary arteries, 30 to 40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart. Images were obtained during maximal breath-holding using electrocardiographic triggering so that each 100-ms exposure was obtained at 80% of the RR interval. During a second pass, 6-mm contiguous images of the aorta were obtained from the aortic arch to the iliac bifurcation using a 300-ms exposure time. The radiation exposure associated with the coronary scan is 407 mrad, and with the aortic scan is 2,200 mrad. The study protocol was reviewed and approved by the Radiation Health Committee of the University of Pittsburgh.

Calcium scores for both the coronary arteries and aorta were calculated by the method of Agatston et al,⁹ resulting in both a total score and a total number of calcifications. Calcium was considered present in the coronary arteries or aorta when at least 3 contiguous pixels of 130 Hounsfield units were present on a 30-cm matrix. Initial image analysis was performed with a densitometric program available on the Imatron C-150 workstation. Repeat scans were performed on a DICOM workstation using software provided by Accuimage Diagnostics Corp. (South San Francisco, California). The total calcium score determination was identical for the 2 software packages and the reproducibility between replicate readings is described later. Volumetric measures of calcium are available for 29 subjects. The Spearman correlation between the Agatston and volumetric scores was 0.99 for the aorta and 0.94 for the coronary score.

We have previously evaluated the reproducibility of the coronary and aortic calcium scores in 40 consecutive subjects from another study selected to have a wide range of calcium. The intraclass correlation of the coronary and aortic scores was 0.99 and 0.98, respectively.

Statistical analysis: For coronary and aortic calcium scores, the baseline score was subtracted from the follow-up score to obtain a continuous measure of change in calcium. To determine whether the number of positive changes significantly outweighed the number of negative changes, a Wilcoxon signed-rank test was used. To determine the association between change in calcium score and premenopausal risk factors, change was defined as either absent (change score of ≤ 0) or present (change score of > 0). Continuous

TABLE 1 Population Characteristics at Time of Eighth Postmenopausal Examination (Healthy Women Study, 80 women)

	Minimum	Maximum	Mean	Median
Age (yrs)	61	66	63	63
Systolic BP (mm Hg)	90	171	122	119
Diastolic BP (mm Hg)	52	92	73	73
Pulse pressure (mm Hg)	31	79	49	48
Total cholesterol (mg/dl)	152	362	217	211
HDL cholesterol (mg/dl)	32	112	60	57
LDL cholesterol (mg/dl)	45	222	130	128
Fasting glucose (mg/dl)	68	211	91	88
Triglycerides (mg/dl)	38	314	85	70
Body mass index (kg/m ²)	17	43	27	26
Waist circumference (cm)	64	126	84	82
% Smokers	10.3			
% HRT use	50.0			

BP = blood pressure; HDL = high-density lipoprotein. HRT = hormone replacement therapy; LDL = low-density lipoprotein.

measures of premenopausal risk factors were compared between these 2 groups using *t* tests or Wilcoxon tests if not normally distributed. A *p* value < 0.05 was considered significant.

To determine the effect of the change in workstation and any "reader drift" over the 18-month follow-up period, duplicate readings of baseline and follow-up scans were undertaken in 32 consecutive women with nonzero aortic calcium scores. Readings were performed by a single observer who reread both the baseline and follow-up scans without knowledge of scan order or previous scores. Reliability of the coronary and aortic calcium scores was evaluated using the Pearson intraclass correlation coefficient.¹⁰ This is calculated as the ratio: $\sigma_p^2 / (\sigma_p^2 + \sigma_e^2)$, where σ_p^2 is the variability of the calcium score between patients, and σ_e^2 is the variability due to various sources of error. The components of this error were broken down into that originating from between-scan differences (over time) and between-reading differences (using SAS software [SAS Inc., Cary, North Carolina] procedure VARCOMP). High values of the intraclass correlation indicate that most of the measurement variation is due to differences between patients and very little of the variation to the different sources of error. For both the coronary and aortic calcium scores, a fourth root transformation was used for this analysis. For the coronary calcium scores, the analysis was restricted to non-zero values so that an approximate normal distribution could be achieved. For both analyses, time was considered a fixed effect and reading was considered a random effect.

RESULTS

Eighty participants for the Healthy Women Study underwent their second set of electron beam tomographic scans. The time between scans ranged from 12 to 26 months (average 18). At the time of the first scan, average age was 63 years, and women were, on average, 8 years postmenopausal. The risk factor lev-

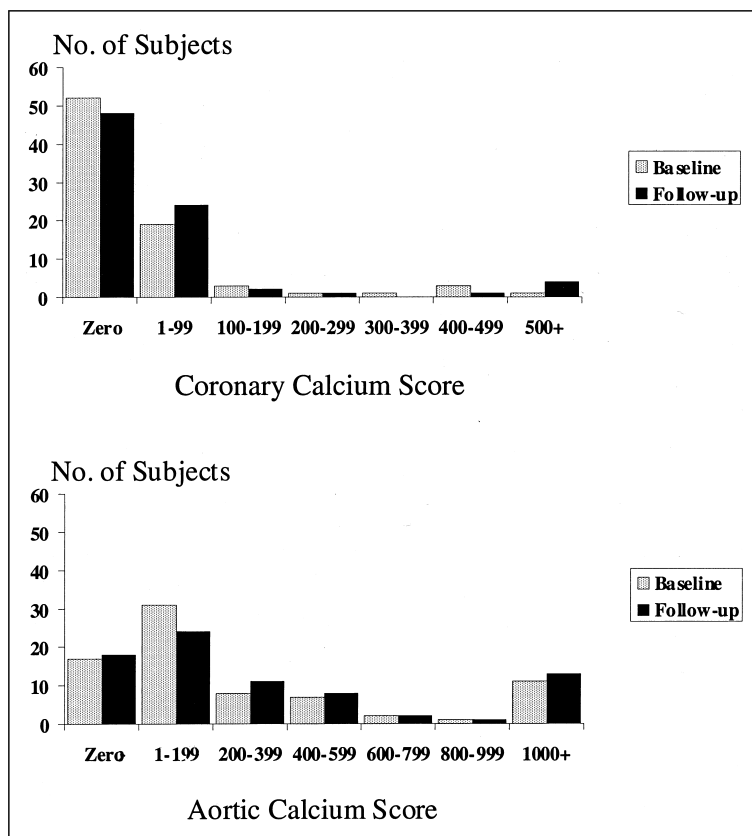


FIGURE 1. Distribution of coronary and aortic calcium scores at baseline and at follow-up.

els of these women at the time of the initial electron beam tomographic evaluation were well within the normal range (Table 1).

Of the 80 women, 52 (65%) had a coronary calcium score of 0 and scores ranged from 0 to 678. Among the 52 women with a baseline coronary score of 0, 35 (67%) had evidence of aortic calcium. Aortic scores ranged from 0 to 3,551. For coronary and aortic scores, baseline values of 0 tended to remain 0 at follow-up.

The distributions of the coronary and aortic calcium scores were skewed (Figure 1), and there were clear differences between baseline and follow-up values reflecting disease progression. The median coronary score was zero at baseline and the mean change over follow-up was +11 ($p < 0.001$ for change). The positive changes clearly outnumbered the negative changes (Table 2). The median aortic score was 82 at baseline and the mean change was +112 ($p < 0.001$ for change). Again, the positive changes clearly outnumbered the negative changes (Table 2). The correlation between baseline and follow-up calcium scores was 0.92 for the coronary arteries and 0.97 for the aorta.

For the 32 women in the reproducibility study, we also evaluated change in the number of calcifications. At baseline, the average number of aortic calcifications was 6.6, and at follow-up this increased to 7.7. The average change in the number of aortic calcifications was 1.1, with a range of -1 to 8. There were 5

negative differences, 11 zero differences, and 13 positive differences, indicating a significant increase in number of aortic calcifications ($p = 0.006$).

Replicate readings of the baseline coronary and aortic calcium scores were evaluated to determine if the observed changes in calcium scores were due to changes in how the scans were read. The readings were done randomly without knowledge of prior scores or ordering of examination. There was no significant difference in calcium score values between the initial and repeat coronary or aortic calcium readings. For the baseline scan, the average difference in calcium scores between the first and second readings was +5 for the aorta and -3 for the coronary score. For both, the number of positive and negative differences was roughly equal and the Wilcoxon signed-rank test was not significant. Results were similar for duplicate readings of the follow-up scans. The intraclass correlation for replicate scans defined by time (baseline vs follow-up) and reading (first vs second) was 0.98 for the aortic calcium score and 0.99 for the non-zero coronary calcium scores, suggesting that the variation due to measurement error is very small relative to between-patient differences.

For both the coronary arteries and aorta, there was a high correlation between baseline calcium scores and progression of these scores (Figure 2 and Table 2). Similarly, extent of calcium in the coronary arteries was associated with progression of calcium in the aorta. Among the 49 women who had coronary calcium scores of zero at baseline, the median increase in aortic calcium was 17, compared with an increase of 79 among women with scores greater than zero at baseline ($p = 0.013$).

We have previously reported that risk factors measured at premenopause are significant predictors of coronary and aortic calcium scores measured at the approximate eighth postmenopausal examination. Even with the small sample size presented here ($n = 80$), increase in coronary and aortic calcium was significantly associated with premenopausal risk factors (Table 3). An increase in coronary calcium was significantly associated with lower high-density lipoprotein cholesterol levels, higher triglycerides, and cigarette smoking, whereas an increase in aortic calcium was associated with higher pulse pressure, total cholesterol, and low-density lipoprotein cholesterol (Table 3).

DISCUSSION

This study demonstrates that progression of calcium can be observed over an 18-month period in both the coronary arteries and the aortas of healthy, middle-aged women. The prevalence of non-zero calcium

TABLE 2 Distribution of Change in Coronary and Aortic Calcium Scores by Baseline Scores

	No.	Mean Change	Median Change	No. of Negative Changes	No. of Zero Changes	No. of Positive Changes
Baseline coronary score						
Zero	52	0.4	0	0	47	5
1-99	19	11	6	3	0	16
100+	9	72	103	3	0	6
Total	80	11	0	6	47	27
Baseline aortic score						
Zero	17	0.4	0	0	15	2
1-199	31	45	19	6	0	25
200-59	15	105	76	1	0	14
600+	14	402	326	0	0	14
Total	77	180	58	7	15	55

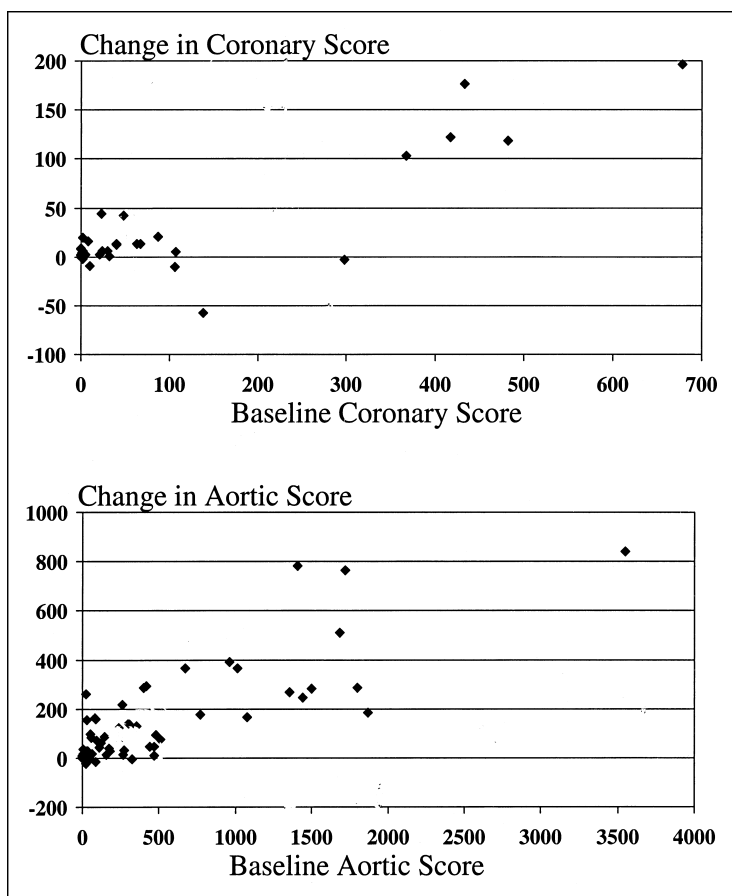


FIGURE 2. Association between baseline calcium score and change in calcium score for the coronary arteries (*top panel*) and the aorta (*bottom panel*). For the coronary calcium graph, 47 subjects are represented by the point at the 0.0 coordinate. For the aortic calcium graph, 13 subjects are represented by the point at the 0.0 coordinate.

scores was higher in the aorta than in the coronary arteries, suggesting that aortic calcium may provide a more sensitive measure of atherosclerosis in populations with minimal disease. Our data indicate high reproducibility of aortic and coronary calcium scores within patients between scans and between readings.

Although this is the first report of aortic calcium progression by EBT, other investigators have reported progression of coronary calcium. Janowitz et al¹¹ reported coronary calcium progression in a smaller group of 25 subjects followed for 13 months. Significant progression was restricted to patients with calcium at baseline, and those with obstructive coronary disease showed greater progression than asymptomatic patients. Investigators from the Mayo Clinic have documented progression in coronary calcium scores¹² over a longer period of 3.5 years. In 81 men and women (mean age 46 years) from the community-based electron beam tomographic study in Rochester, Minnesota,

the average coronary calcium score increased from 18.4 to 44.6. There was a high correlation between calcium scores over time (0.71, $p = 0.001$), indicating high within-patient reproducibility. Changes in coronary calcium scores have been found to be associated with lipid lowering in an observational study of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.¹³ The 44 untreated subjects showed a significant net increase in mean calcium score (mean change +52%, $p < 0.001$), while 65 successfully treated subjects (low-density lipoprotein < 120 mg/dl) had an average change of -7% ($p = 0.01$) over 12 to 15 months. Finally, Budoff et al¹⁴ recently reported 299 clinically selected but asymptomatic persons who underwent 2 consecutive electron beam tomographic scans at least 12 months apart.¹⁴ The average change in calcium score was 33.2 annually, and subjects receiving statin therapy had significantly lower progression rates than patients who did not receive statins. Thus, early concerns regarding insufficient reproducibility of the electron beam tomographic technique to accurately detect progression of calcium¹⁵ may no longer be warranted. These studies have demonstrated progression, although the Agatston scoring method was used in most studies. Better precision reported with a volumetric scoring¹⁶ method is likely to allow even more accurate assessment of progression.

Scores in only a few women with zero coronary calcium scores at baseline progressed in our study, as in the Mayo Clinic series. This suggests that by age 60, we may be able to identify groups of women who are at very low risk of subsequent coronary events, assuming that women with no calcium are unlikely to go on to have clinical events.

Women have more atherosclerosis as well as

TABLE 3 Baseline Premenopausal Risk Factors by Change in Calcium Score (n = 80)

	Coronary			Aortic		
	Increase (n = 27)	No Change (n = 53)	p Value	Increase (n = 55)	No Change (n = 22)	p Value
Age at time of scan (yrs)	63	64	0.210	63	63	0.979
Systolic BP (mm Hg)	108	108	0.894	109	105	0.080
Diastolic BP (mm Hg)	73	73	0.870	73	72	0.559
Pulse pressure (mm Hg)	35	36	0.661	36	33	0.031
Total cholesterol (mg/dl)	191	185	0.443	193	178	0.052
HDL cholesterol (mg/dl)	54	63	0.004	58	64	0.068
LDL cholesterol (mg/dl)	117	107	0.159	116	99	0.015
Fasting glucose (mg/dl)*	88	88	0.278	88	88	0.238
Triglycerides (mg/dl)*	85	64	0.005	74	64	0.261
Body mass index (kg/m ²)	24	25	0.192	25	24	0.368
Waist circumference (cm)	78	76	0.602	76	78	0.671
% Smokers	40.7	18.9	0.036	30.9	18.2	0.257
% HRT use [†]	5.0	50.0	1.000	32.0	57.1	0.323

*Median values.
[†]Hormone replacement therapy at time of baseline EBT scan.
Abbreviations as in Table 1.

greater amounts of calcium in the aorta than in the coronary arteries. Although coronary and aortic calcium are correlated within the same person, atherosclerotic disease is known to begin earlier in the aorta.^{17,18} Accordingly, in younger women (even up to the age of 65 years), the measurement of aortic rather than coronary calcium may provide the earliest and most accurate evaluation of the underlying atherosclerotic burden and may best measure changes induced by therapeutic modalities, particularly over a limited period of time.

Traditional cardiovascular risk factors were strongly related to the extent of aortic and coronary calcium and to changes in calcium over time. Similar observations have been made using radiographic evaluation of aortic calcium progression.¹⁹ Thus, a logical use of serial electron beam tomographic measurements is to assess efficacy of risk factor interventions. The recently published American College of Cardiology/American Heart Association Expert Consensus Document on EBT²⁰ has concluded that this is a promising use for EBT, and that further research in this area is needed.

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