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Effect of age on aortic atherosclerosis

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Abstract

Objective To examine the association of atherosclerosis burden in the survivors of an asymptomatic elderly cohort study and its relationship to other coronary risk factors (specifically, age) by evaluating aortic atherosclerotic wall burden by magnetic resonance imaging (MRI). **Methods** A total of 312 participants in an ongoing observational cohort study underwent cardiac and descending thoracic aorta imaging by MRI. Maximum wall thickness was measured and the mean wall thickness calculated. Wall/outer wall ratio was used as a normalized wall index (NWI) adjusted for artery size difference among participants. Percent wall volume (PWV) was calculated as NWI × 100. **Results** In this asymptomatic cohort (mean age: 76 years), the mean (SD) aortic wall area and wall thickness were 222 ± 45 mm^2 and 2.7 ± 0.4 mm, respectively. Maximum wall thickness was 3.4 ± 0.6 mm, and PWV was 32% ± 4%. Women appeared to have smaller wall area, but after correcting for their smaller artery size, had significantly higher PWV than men ($P = 0.03$). Older age was associated with larger wall area ($P = 0.04$ for trend) with similar PWVs. However, there were no statistically significant associations between standard risk factors, Framingham global risk, or metabolic syndrome status, therapy for cholesterol or hypertension, coronary or aortic calcium score, and the aortic wall burden. Aortic calcification was associated with coronary calcification. **Conclusions** Asymptomatic elderly in this cohort had a greater descending thoracic aortic wall volume that correlated with age, and women had a significantly increased PWV compared to men. In these survivors, the atherosclerotic aortic wall burden was not significantly associated with traditional risk factors or with coronary or aortic calcium scores or coronary calcium progression. Results suggest that age, or as yet unidentified risk factor(s), may be responsible for the increase in atherosclerosis.

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Keywords: Aging; Aortic atherosclerosis; Magnetic resonance imaging; Atherosclerotic risk factors

1 Introduction

Age is an important risk factor in atherosclerosis. Some even consider atherosclerosis to be a part of the aging process.[1] What influence age alone has on the atherosclerosis burden is uncertain, as is the relationship between atherosclerosis burden and traditional or nontraditional risk factors in a relatively healthy elderly population.

The South Bay Heart Watch (SBHW) is a prospective cohort study designed to evaluate the importance of subclinical atherosclerosis represented by coronary artery calcium (CAC) and both traditional and nontraditional risk factors for predicting cardiovascular outcomes and calcium progression in an asymptomatic elderly population. The study design of the SBHW has been reported previously.[2]

The objective of this investigation was to evaluate survivors of the SBHW cohort to prospectively evaluate the atherosclerosis burden as assessed by magnetic resonance

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imaging (MRI) and examine the association of risk factors, specifically age, the Framingham global risk score, and metabolic syndrome/diabetes status with atherosclerosis burden in this subset of an asymptomatic elderly cohort.

2 Methods

2.1 Subjects

The SBHW cohort comprises respondents to a community based mailing campaign in the early 1990s. The original cohort consisted of 1,461 asymptomatic individuals > 45 years old with multiple cardiac risk factors (> 10% 8-year risk of developing coronary heart disease by the Framingham risk equation), but without evidence of coronary heart disease at the time of enrollment. Participants were initially screened and enrolled between December 1990 and December 1992. Participants with electrocardiogram (ECG) evidence of myocardial infarction, or clinical history of myocardial infarction, coronary revascularization, or typical angina were excluded.

Of 1,461 participants initially screened and 11.4 ± 0.6 years later, 386 (26%) with a mean age 75 years were locatable and able and willing to have cardiac magnetic resonance imaging (CMR). These scans were performed to evaluate the use of computer tomography assessed coronary calcium (CT CAC) scores in the prediction of cardiovascular events and cardiac function.[3] The reasons for non-participation were: deceased 503 (46.8%); too ill to participate or other medical reason 53 (4.9%); lost to follow-up or reason unknown 253 (23.5%); declined to participate 197 (18.3%); no baseline calcium score 8 (< 1%); and MRI contraindication 61 (5.7%). MRI contraindications included: 17 pacemakers, 31 with claustrophobia, 4 with internal metal, and 9 that were too large to scan. Of 386 participants who underwent CMR, 312 also received scans of their descending thoracic aorta.

2.2 Aortic magnetic resonance imaging and analysis

The aortic and CMR scans were performed using a General Electric (Milwaukee, WI), 1.5 tesla Horizon Echospeed EXCITE system with a 6-channel cardiac coil. The aortic images were obtained using a cardiac gated, triple inversion black blood imaging sequence with flow and fat suppressions. The parameters were: Repetition time (TR) = 2000 ms, Echo time (TE) = 40.5 ms, matrix = 256 × 256, field of view = 40 cm, echo train = 32. The first of four consecutive cross-sectional images with 8 mm thickness and 2 mm gap was positioned immediately after the aortic arch as shown in Figure 1. Total aortic wall coverage was 40 mm.

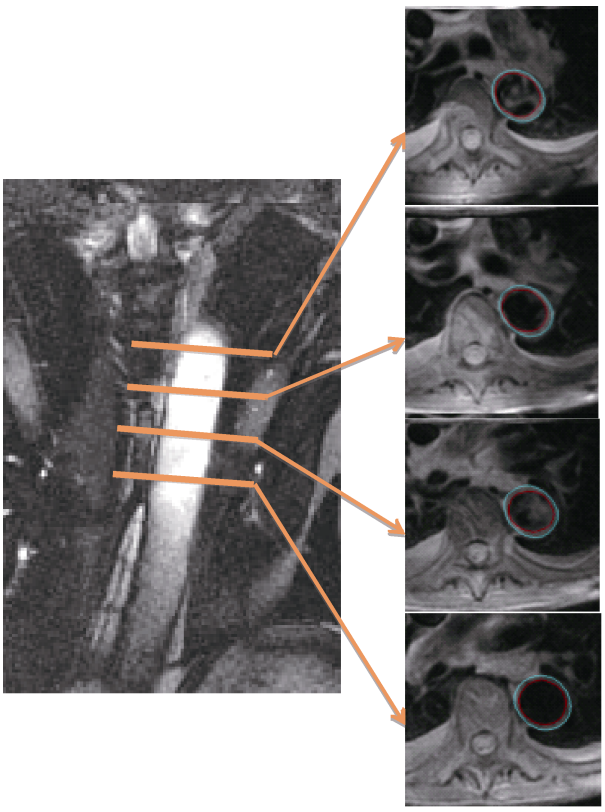

Figure 1. Aortic atherosclerosis imaging and analysis by magnetic resonance imaging. The aortic images were obtained using a cardiac gated triple inversion black blood imaging sequence with flow and fat suppressions as shown on the left. The first of 4 consecutive cross-sectional images with 8 mm thickness and 2 mm gap was positioned immediately after the aortic arch. Total aortic wall coverage was 40 mm. On the right, images show that cross-sectional aortic wall area was quantified by placing contours around lumen and outer-wall boundaries of the aorta and subtracting lumen area from outer-wall area.

As illustrated in Figure 1, cross-sectional aortic wall area was quantified by placing contours around lumen and outer-wall boundaries of the artery and subtracting the lumen area from the outer-wall area. Maximum wall thickness was identified and measured and mean wall thickness was calculated. Wall/outer wall ratio was used as a normalized wall index (NWI) that is adjusted for artery size difference among subjects. Percent of wall volume (PWV) = NWI × 100. These MRI measurements have been used previously in carotid atherosclerosis assessment.[4,5]

2.3 Statistical analysis

Socio-demographic and risk characteristics, coronary calcium (by CT) and myocardial function status (by CMR) were summarized for the 312 participants who underwent aortic MRI scans. Coronary calcium was categorized into 4

groups: 0, 1–99, 100–399, ≥ 400. Abnormality of Left ventricular ejection fraction (LVEF) was defined as LVEF < 50%, or LVEF < 40%. An abnormality of diastolic peak filling rate was defined as < 2.2 end-diatolic volume per second, and regional wall motion abnormalities (RWMA) were evaluated on vertical long axis and short axis cine views by consensus of two experienced reviewers. A 17 segment wall motion model was applied with wall motion scores recorded as: normal = 2, hypokinesia = 1, akinesia = 0, and dyskinesia = –1. A completely normal 17 segment wall motion study received a score of 17 segments × 2 points = 34.[6]

Analysis of variance with Tukey pairwise comparisons was used to contrast aortic atherosclerosis burden parameters (mean aortic wall area, mean/maximum aortic wall thickness and normalized wall index) by gender and across age groups (61–69, 70–79, 80–91 years). Tests for trends across age groups utilized the Wald test. Similar analyses were conducted to compare atherosclerosis burden parameters across traditional CAC groups (0, 1–99, 200-399, ≧ 400) and stratified by quartiles (or medians) of aortic calcium for all 312 participants, and for the 108 participants not on lipid lowering medication.

All analyses were conducted at the 0.05 significance level and utilized SAS (SAS Software, version 9.1, Cary, NC).

3 Results

3.1 Patient characteristics

Demographic and risk characteristics, coronary calcium by CT and myocardial function status by CMR of the 312 participants who underwent aortic MRI scans are presented in Table 1. In this cohort, 95% were males, the average age

Table 1. Participant demographic characteristics and atherosclerosis burden.

	Baseline		*P* value	At the time of aortic MR scan
	No MR Scan	MR Scan		
	n = 1,148	*n* = 312		*n* = 312
Demographic & Risk factors				
Age, yrs	65.9 ± 8.1	63.5 ± 6.5	< 0.0001	75.6 ± 6.4
Male gender	756 (66%)	296 (95%)	< 0.0001	297 (95%)
Total cholesterol, mg/dL	229.1 ± 44.6	233.7 ± 38.6	0.08	186.8 ± 43.3
HDL cholesterol, mg/dL	44.8 ± 15.6	46.1 ± 14.9	0.19	45.7 ± 28.0
Systolic blood pressure, mmHg	144.0 ± 21.0	137.4 ± 17.8	< 0.0001	131.1 ± 17.5
Diastolic blood pressure, mmHg	80.1 ± 11.9	79.6 ± 9.7	0.46	70.9 ± 9.7
Hypertension*	382 (35%)	77 (25%)	0.0007	209 (67%)
Hypertension 2#	667 (58%)	137 (44%)	< 0.0001	227 (73%)
Current smoking	194 (18%)	51 (16%)	0.58	27 (9%)
Family history†	503 (44%)	140 (45%)	0.75	140 (45%)
Diabetes§	288 (25%)	30 (10%)	< 0.0001	63 (20%)
Lipid lowering medication	214 (20%)	71 (23%)	0.21	204 (65%)
Framingham risk score, %	18.2 ± 7.3	17.1 ± 7.0	0.01	21.3 ± 6.5
Body Mass Index, kg/m^2	31.3 ± 5.5	30.5 ± 4.5	0.01	27.8 ± 4.2
Coronary calcium	*n* = 1006	*n* = 305		
= 0	274 (27%)	105 (34%)	0.009	40 (13.6%)
1–99	299 (30%)	98 (32%)		78 (26.5%)
100–399	227 (23%)	61 (20%)		74 (25.2%)
≥ 400	206 (20%)	41 (13%)		102 (34.7%)
Descending aortic calcium (*n* = 129)‖	NA	NA	---	752 ± 1661
Myocardial function				
LVEF				
Abnormal (LVEF < 50%)	NA	NA	---	37 (11.9%)
Abnormal (LVEF < 40%)				7 (2.2%)
Diastolic PFR < 2.2 EDV/s	NA	NA	---	152 (48.7%)
RWMA	NA	NA	---	34 (10.9%)

Data are mean ± SD or frequency (%). *hypertension med use; #hypertension med use or SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg; † Collected baseline only; §Diabetes medication use; ‖From the initial CT scan. DBP: diastolic blood pressure; EDV: End diastolic velocity; HDL: high density lipoprotein; LVEF: Left ventricular ejection fraction; MR: magnetic resonance; NA: Not available; PFR: Peak filing rate; RWMA: Regional wall motion abnormality; SBP: systolic blood pressure.

was 75.6 years, 73% were hypertensive or treated for hypertension, 45% had a family history of cardiovascular disease, 20% had diabetes, and 65% were on lipid-lowering therapy. The overall Framingham risk score was 21%, while 35% of the cohort had coronary calcium scores of 400 or higher, and a mean aortic calcium score of 752 ± 1661, 12% had LVEF < 50%, 49% had diastolic peak filling rate < 2.2 end-diatolic volume per second, and 11% had at least one regional wall motion abnormality.

Table 1 shows that subjects who received MRI scans were at significantly lower cardiovascular risk as assessed by the presence of hypertension and/or diabetes, and had lower overall Framingham Risk and coronary calcium scores than those who did not undergo MRI scans.

3.2 Atherosclerotic burden in the descending thoracic aortic wall

Table 2 describes the aortic wall burden in this asymptomatic elderly cohort. Overall, the mean aortic wall area was 222 ± 45 mm^2, the mean wall thickness was 2.7 ± 0.4 mm, the maximum wall thickness was 3.4 ± 0.6 mm, and PWV was 32% ± 4%. Women appeared to have smaller wall area, but after correcting for their smaller artery size, they had significantly (P = 0.03) higher PWV than men. Older age was associated with larger wall area (P = 0.04 for trend) with similar PWV.

3.3 Association of atherosclerotic burden in the descending thoracic aortic wall with traditional atherosclerotic risk factors

There were no statistically significant associations between the standard risk factors, Framingham global risk, or metabolic syndrome status, therapy for cholesterol or hypertension, and the atherosclerotic aortic wall burden as identified in this population.

Furthermore, the aortic wall burden was not correlated with calcium scores in either the coronary arteries or the aorta as shown in Table 3 for subjects who were not treated with statin. Although mean aortic wall area appeared to be significantly larger with an increased coronary calcium score, PWV did not differ significantly between subjects with lower and higher coronary calcium scores. However, there was a significant correlation between coronary calcium scores and aortic calcification (Spearman correlation coefficient 0.32, $P < 0.001$).

4 Discussion

Subclinical atherosclerosis as presented by CAC and carotid intima-media thickness (CIMT) is clearly associated with aging.[7,8] In this report, we described MRI-assessed aortic wall thickness, area, and percent wall volume in a relative healthy elderly population with mean age of 76 years (Table 1). There are a number of factors that support the population being particularly healthy. The study population was a group of survivors from the SBHW study who then consented to have cardiac MRIs. The manner that the original SBHW cohort was recruited (by a community mailer) could have biased towards participants who had a greater interest in cardiovascular health and might be more compliant with recommended lifestyle changes and medications, and thus, be less prone to adverse cardiac events

Table 2. Aortic atherosclerosis burden overall and stratified by gender and age.

	Mean aortic wall area (mm^2)	Mean aortic wall thickness (mm)	Max aortic wall thickness (mm)	Percent wall volume
Overall	222.2 (44.5)/213.3	2.65 (0.39)/2.58	3.42 (0.62)/3.28	31.9 (3.9)/31.5
(n = 312)	(139.0, 191.6, 245.1, 420.9)	(1.83, 2.38, 2.86, 4.02)	(2.16, 2.99, 3.75, 5.73)	(23.1, 29.1, 34.3, 44.8)
Gender				
Male	223.1 (44.7)/213.3	2.65 (0.39)/2.58	3.42 (0.62)/3.27	31.8 (3.9)/31.2
(n = 296)	(139.0, 192.8, 246.9, 420.9)	(1.83, 2.38, 2.86, 4.02)	(2.16, 2.98, 3.76, 5.73)	(23.1, 29.0, 34.0, 44.8)
Female	205.1 (38.3)/195.9	2.63 (0.35)/2.63	3.34 (0.52)/3.28	34.0 (3.4)/32.8
(n = 16)	(148.1, 175.2, 235.0, 270.8)	(2.02, 2.42, 2.83, 3.23)	(2.47, 3.03, 3.54, 4.43)	(26.2, 32.0, 36.8, 39.7)
P-value (t-test)	0.12	0.85	0.59	0.03
By age, yr				
61–69	212.3 (45.8)/202.7	2.62 (0.37)/2.52	3.38 (0.60)/3.22	32.3 (3.8)/31.6
(n = 70)	(144.1, 180.3, 233.0, 420.9)	(2.05, 2.34, 2.82, 4.02)	(2.39, 2.95, 3.69, 5.73)	(23.1, 29.4, 34.4, 42.6)
70–79	222.2 (43.7)/213.3	2.64 (0.40)/2.58	3.41 (0.65)/3.27	31.7 (4.0)/31.2
(n = 163)	(139.0, 191.6, 248.6, 386.5)	(1.83, 2.39, 2.83, 3.96)	(2.16, 2.99, 3.66, 5.73)	(23.8, 29.0, 34.0, 44.8)
80–91	231.0 (43.9)/225.6	2.70 (0.37)/2.67	3.48 (0.58)/3.45	32.0 (4.0)/32.0
(n = 79)	(148.1, 197.5, 253.5, 356.5)	(2.06, 2.40, 3.00, 3.60)	(2.56, 3.00, 3.98, 5.14)	(23.5, 29.0, 34.4, 39.9)
P-value (ANOVA)	0.04*/0.01	0.39/0.19	0.58/0.93	0.64/0.64

Data presented as: Mean (SD)/Median (min, 25 percentile, 75 percentile, max). *Tukey pairwise comparison shows: age (61–69) *vs*. age (80-91), P = 0.03.

Table 3. Aortic atherosclerosis burden stratified by coronary calcium and aortic calcium (Participants not on lipid lowering medication only).

	Mean aortic wall area (mm^2)	Mean aortic wall thickness (mm)	Max aortic wall thickness (mm)	Percent wall volume
Overall (n = 108)	226.7 (50.6)/213.9	2.69 (0.44)/2.59	3.49 (0.72)/3.29	32.0 (4.3)/31.4
	(139.0, 192.0, 254.7, 420.9)	(1.83, 2.37, 2.88, 4.02)	(2.16, 2.98, 3.82, 5.73)	(23.5, 29.1, 35.1, 44.8)
By CAC (n = 105)				
0	213.2 (43.6)/200.1	2.62 (0.47)/2.54	3.41 (0.76)/3.42	32.7 (4.9)/31.5
(n = 19)	(148.1, 174.6, 255.3, 305.4)	(2.02, 2.29, 2.94, 3.92)	(2.47, 2.79, 3.78, 5.62)	(26.2, 29.5, 34.6, 44.8)
1–99	215.2 (43.2)/198.2	2.63 (0.40)/2.53	3.38 (0.66)/3.17	32.2(3.8)/31.8
(n = 30)	(161.5, 186.5, 240.9, 308.1)	(2.13, 2.33, 2.74, 3.61)	(2.58, 2.90, 3.65, 5.13)	(26.6, 29.0, 35.0, 41.1)
100–399	228.2 (53.8)/216.4	2.65 (0.43)/2.54	3.42 (0.65)/3.27	30.9 (4.3)/31.2
(n = 25)	(139.0, 191.9, 241.5, 345.5)	(1.83, 2.39, 2.83, 3.52)	(2.16, 3.01, 3.62, 4.88)	(23.5, 27.5, 33.7, 38.5)
≥ 400	244.2 (53.5)/229.1	2.82 (0.44)/2.66	3.69 (0.75)/3.42	32.7 (4.4)/33.0
(n = 31)	(171.7, 199.3, 273.6, 420.9)	(2.15, 2.56, 3.00, 4.02)	(2.67, 3.24, 3.97, 5.73)	(25.3, 29.6, 36.3, 44.0)
P-value (ANOVA/trend)	0.08/0.02	0.28 / 0.13	0.30 / 0.17	0.40 / 0.72
By aortic calcium (n = 38)				
0.00–35.48	204.6 (38.6)/206.1	2.43 (0.33)/2.36	3.10 (0.56)/2.99	30.0 (3.7)/29.4
(n = 19)	(139.0, 172.7, 220.6, 298.9)	(1.83, 2.30, 2.54, 3.49)	(2.16, 2.88, 3.19, 5.04)	(24.0, 27.3, 31.9, 41.1)
35.48–5041.24	217.1 (50.6)/197.8	2.45 (0.35)/2.40	3.09 (0.47)/2.96	29.1 (2.9)/28.0
(n = 19)	(148.1, 182.5, 251.5, 333.8)	(2.02, 2.20, 2.63, 3.47)	(2.47, 2.76, 3.46, 4.47)	(25.4, 27.1, 30.9, 35.3)
P-value (t-test)	0.40	0.88	0.97	0.40

Data are Mean (SD)/Median (min, 25 percentile, 75 percentile, max). CAC: coronary artery calcium.

(or atherosclerosis). In addition, as with other long-term studies of elderly patients lost to follow-up, creates a survival population of even healthier subjects. In this case, 26.4% of the original sample underwent MRI scanning, those scanned also were younger (63.8 *vs*. 66.6 years old at recruitment) than those who did not undergo scanning. Furthermore, MRI scanned subjects had lower prevalence of hypertension, diabetes mellitus, elevated baseline CAC scores and they had lower Framingham risk scores.

In this selected, healthier population, we found that older age was significantly associated with larger aortic wall area and non-significantly associated with increased wall thickness. However, older age did not seem to be associated with percent wall volume, which suggested that older people may have a larger aortic artery. This is consistent with previous studies showing a mild increase in the aortic root diameter with increasing age by echocardiography,[9] and by chest X-ray.[10] This finding is also somewhat consistent with what is seen in recent reported results from the multi-ethnic study of atherosclerosis using CAC, that CIMT and ankle brachial indices as markers of subclinical atherosclerotic vascular disease,[1] and with the Rotterdam Study,[11] showing age as an independent factor for arterial calcification. Not surprisingly, aortic calcification was also significantly associated with coronary calcification in our study.

Interestingly, women in this study had a significantly increased percent wall volume compared to men. Clinical and autopsy observations have suggested that women seem to develop vascular disease later than men, which could be related to factors specific to women that resist atheroma growth, and delay plaque rupture and other acute vascular complications.[12] However, when women enter their 70's, they are no longer protected, as suggested in this study that women had larger percent wall volumes.

Unlike coronary calcium, which has been identified as associated with other risk factors,[2,7] MRI-assessed aortic wall burden was not associated with traditional risk factors (such as hypertension, diabetes, smoking, or cholesterol levels) despite the fact that the overall Framingham risk score was 21% in these survivors of the original study population. This may reflect an unknown protective mechanism against traditional risk factors that resulted in successful (event-free) cardiovascular aging in this selected population of healthy survivors of an asymptomatic elderly cohort. It is possible that atherosclerosis progression may occur *via* different pathways, with risk factors representing one pathway and normal aging by another (not necessarily independent) pathway. Although this study cannot specifically elucidate these pathways, it is nonetheless one of the first reports on the atherosclerotic aortic wall burden in a relatively healthy elderly population, and thus can serve as a reference for future studies which may be able to elucidate

the mechanisms that underlie atherosclerosis progression with increasing age.

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