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Association of Thoracic Aorta Calcium Score With Exercise Blood Pressure Response and Clinical Outcomes in Elderly Individuals: Differential Impact of Aorta Calcification Compared With Coronary Artery Calcification

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Background—The structure of the aorta is considered to influence exercise systolic blood pressure (SBP) response, which, in turn, might impact upon adverse outcomes. The current study sought to investigate the relationship of aortic calcification and exercise SBP with adverse outcomes among elderly individuals.

Methods and Results—We retrospectively reviewed 702 elderly individuals (>65 years of age) without obstructive coronary artery disease (CAD; luminal stenosis <50%) who underwent coronary computed tomography (CT) and exercise treadmill testing. ΔSBP_{stage2} and ΔSBP_{peak} were defined as the difference in systolic blood pressure (SBP) between rest and stage 2 or peak exercise, respectively. Thoracic aortic calcium score (TACS) and coronary artery calcium score (CACS) were measured using CT scanning procedures. The primary endpoints were defined as all-cause death, admission for heart failure, obstructive CAD requiring coronary intervention, and stroke. In multivariable models, ΔSBP_{stage2} and ΔSBP_{peak} were positively related with $_{log}(TACS+1)$, even after adjusting for various clinical variables, baseline SBP, and CACS ($P<0.001$). During a median follow-up period of 65 months, there were 59 events (8.4%). In a multivariate Cox regression model, independent predictors for all events were age (hazard ratio [HR], 1.12; 95% CI, 1.05–1.19; $P<0.001$), dyslipidemia (HR, 1.96; 95% CI, 1.14–3.37; $P=0.015$), and the 4th quartile of TACS (HR, 1.24; 95% CI, 1.03–1.49; $P=0.024$). Among individual events, the 4th quartile of TACS was the only independent predictor for stroke (HR, 2.15; 95% CI, 1.09–5.13; $P=0.044$), whereas CACS ≥400 mm^3 was an independent predictor for obstructive CAD requiring intervention (HR, 7.04; 95% CI, 1.58–31.36; $P=0.010$).

Conclusions—Aortic calcification was related to SBP response during exercise and was an independent predictor for outcomes, especially stroke, regardless of resting SBP or CACS. (*J Am Heart Assoc*. 2016;5:e003131 doi: 10.1161/JAHA.115.003131)

Key Words: aorta • blood pressure • calcification • exercise

D ynamic exercise typically elicits a substantial rise in systolic blood pressure (SBP) without much alteration in diastolic blood pressure (DBP).[1] An early elevation in SBP during exercise provides further prognostic information toward cardiovascular outcomes and is known to be an important marker of various cardiovascular diseases,

including incident hypertension, myocardial infarction, and stroke, as well as cardiovascular mortality in persons without overt coronary artery disease (CAD).[2–5]

Some plausible mechanisms are perhaps responsible, in part, for the observed exaggerated rise in SBP during exercise. Past studies documented that an exaggerated rise in SBP is associated with failure to reduce total peripheral resistance and impaired endothelial vasodilator function.[6] An exaggerated exercise SBP response is also associated with other established cardiovascular risk factors, such as insulin resistance, hypercholesterolemia, and carotid atherosclerosis.[7–9] Arterial stiffening has also been proposed as a potential mechanism for an elevated exercise SBP response observed during both peak[10] and submaximal exercise intensities.[11]

The aorta is an active participant of the cardiovascular system, and arterial stiffness has been suggested to be a predictor of cardiovascular morbidity and mortality.[12] Aortic calcification has previously been independently associated

with arterial stiffening, isolated systolic hypertension, left ventricular (LV) hypertrophy, and diastolic dysfunction in various study populations.[13–18] However, the relationship between exercise SBP and aortic calcification, and how it might adversely impact upon health, has not been fully elucidated, even though a significant interaction might exist between aorta and SBP response during exercise. Computed tomography (CT) is a useful tool for quantifying aortic calcification by aorta calcium scanning,[14] and it is possible that calcification of the thoracic aorta assessed by CT scanning may be associated with a higher SBP during exercise and, subsequently, with poor clinical outcomes. In this study, we set out to evaluate the role of aortic calcification on exercise SBP response and how it might impact on mortality and various cardiovascular events among elderly individuals without significant CAD who underwent coronary CT and exercise treadmill testing. Specifically, we hypothesized that aortic calcification would be associated with greater exercise SBP changes and poor clinical outcomes in the elderly.

Methods

Study Population

We retrospectively reviewed 990 elderly individuals (≥65 years of age) who underwent both coronary CT and exercise treadmill testing for evaluation of suspected CAD within 90 days between tests during 2003 through 2009 at Severance Cardiovascular Hospital. We excluded 229 individuals with obstructive CAD on coronary CT (luminal stenosis ≥50%), 31 individuals whose CT scan did not include whole thoracic aorta from aortic arch to diaphragm level, 25 individuals who did not complete 2 stages of the Bruce protocol at treadmill test, and 3 individuals with atrial fibrillation. Patients with obstructive CAD were excluded to abolish the effect of coronary ischemia on exercise blood pressure and capacity. Hence, 702 elderly individuals without obstructive CAD comprised the study population. The median number of days between coronary CT and exercise test was 7 (interquartile range [IQR], 2–14). At the time of index visit, clinical data were collected from routine medical history, physical examination, and laboratory tests. Body mass index (BMI) was calculated from height and weight. Diabetes mellitus was defined as receiving antidiabetic treatments or a fasting plasma glucose of ≥126 mg/dL. Current cigarette smoking was defined as any cigarette smoking in the past month. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or use of antihypertensive agents. Dyslipidemia was defined as use of cholesterol-lowering medications or having serum total cholesterol of ≥200 mg/dL. Primary endpoints were defined as all-cause death, inpatient admissions for heart failure, obstructive CAD requiring coronary

artery intervention or bypass surgery, stroke, and a composite of all endpoints. Occurrence of a clinical event was ascertained by review of hospital records and by telephone interview, if necessary. This study was approved by the institutional review board of Yonsei University, Severance Hospital (Seoul, Korea), and all individuals provided informed consent.

CT Protocol and Image Analysis

Patients were scanned using a 64-section CT scanner (Sensation 64; Siemens Healthcare, Forchheim, Germany). For calcium scanning, unenhanced CT was performed with prospective electrocardiography (EGC)-triggered acquisitions in mid-diastole using 120 to 140 kV with 150 to 220 mAs, depending on the patient's size; 240-ms exposure time per rotation; 330-ms gantry rotation time; and 64×0.6 mm slice collimation. Calcium scans were reconstructed at 70% of the R-R interval using a slice thickness of 3 mm with an increment of 3 mm. Coronary artery and thoracic aorta calcium scoring was performed on reconstructed images. Foci of coronary artery, aortic valve, and thoracic aorta were identified and scored by an experienced technician who was masked to the patient's medical records, using semiautomatic software (Vitrea 2.0; Vital Images, Minnetonka, MN) and verified by imaging cardiologists.[19] Lesion-specific calcium scores were summed across all lesions identified within left main, left anterior descending, left circumflex, and right coronary arteries to provide coronary artery calcium score (CACS). The thoracic aorta calcium score (TACS) included calcium scored in the ascending aorta, aortic arch, and descending aorta to the diaphragm level. An objective volume scoring method included in the system software was determined, which provided a score in cubic millimeters.[20]

Subsequently, standard CT angiography was performed. Patients without a contraindication to beta-adrenergic blocking agents and with initial heart rates higher than 65 beats/min received a single oral dose of 40 mg of propranolol hydrochloride 1 hour before coronary CT angiography. Two types of CT system configurations were employed: (1) a 64-slice CT scanner (Sensation 64; Siemens Medical Solutions, Forchheim, Germany) using retrospective ECG gating with tube current modulation from 2003 through 2009 with the following parameters: (1) rotation time: 330 ms, tube voltage: 100 to 120 keV, tube current: 400 to 800 mA, and pitch factor: 0.2; and (2) a 64-row CT scanner (LightSpeed VCT XT; GE Healthcare, Milwaukee, WS) using a prospectively ECG-gated axial technique from 2008 through 2009 with the following parameters: rotation time: 350 ms, tube voltage: 100 to 120 keV, and tube current: 300 to 900 mA. A real-time bolus-tracking technique was applied to trigger the initiation of the scan.

Exercise Testing

A symptom-limited exercise treadmill test was performed according to the Bruce protocol.[21] Resting SBP and DBP were measured in the brachial artery in the seated position. During the exercise stress test, heart rhythm, SBP, and DBP were recorded at the end of each stage of exercise, at peak stress, and during recovery (5 minutes after completion of the exercise). ΔSBP was defined as the difference between SBP at rest and exercise (ΔSBP_{stage2}, stage 2 exercise; ΔSBP_{peak}, peak exercise). Pulse pressure (PP) was defined as the difference between SBP and DBP. ΔPP was defined as the difference in PP between rest and exercise (ΔPP_{stage2}, stage 2 exercise; ΔPP_{peak}, peak exercise). A 12-lead ECG was obtained every minute, and a 3-lead ECG for heart rhythm was monitored continuously. Indications for terminating the exercise test are previously described.[22]

Statistical Analysis

Distributions of all relevant variables are reported as percentages or as means±SD for normally distributed variables and median (with 25−75%) for non-normally distributed variables. To minimize skewness, we transformed CACS and TACS before analysis by adding 1 and obtaining the natural logarithm of the value (ie, $_{log}[CACS+1]$ and $_{log}[TACS+1]$). We evaluated the linear relationships by use of univariate linear regression analysis to determine the independent correlates of exercise ΔSBP_{stage2}, ΔSBP_{peak}, ΔPP_{stage2}, and ΔPP_{peak}. We performed a univariate analysis before the multivariate analysis in an effort to ascertain candidate variables, which might be associated with exercise changes of SBP and PP. After that, variables that had a $P<0.2$ in univariate analysis were retained for subsequent multivariate linear regression,[23] with sex, age, and resting heart rate forced entry into all models. Multivariate Cox proportional-hazards regression analysis was employed to determine independent variables for event-free survival after acquisition of coronary CT. Kaplan−Meier survival curves were employed to plot all clinical events according to the time to first event. A $P<0.05$ was considered statistically significant.

Results

Population Characteristics

Demographic characteristics and CT variables of all patients enrolled in this study are shown in Table 1. Mean age was 69±4 years, and there were 298 males (42%). Diabetes, smoking, dyslipidemia, and hypertension were observed in 125 (18%), 95 (14%), 348 (50%), and 392 patients (56%), respectively. Among those enrolled, 269 (38%), 249 (35%), and 177 (25%) patients were receiving beta-blockers (BBs),

Table 1. Baseline Characteristics

Variable	Participants (n=702)
Baseline characteristics	
Age, y	69±4
Men, n (%)	298 (42)
Diabetes, n (%)	125 (18)
Smoking, n (%)	95 (14)
Dyslipidemia, n (%)	348 (50)
Hypertension, n (%)	392 (56)
Medications n (%)	
Beta-blocker	269 (38)
Calcium-channel blocker	249 (35)
ACEi/ARB	177 (25)
BMI, kg/m^2	24.5±2.7
Total cholesterol/HDL ratio	3.7±0.9
Resting systolic BP, mm Hg	125.0±15.7
Resting diastolic BP, mm Hg	76.5±9.2
Resting PP, mm Hg	48.2±14.6
Resting heart rate, bpm	57.9±7.4
CT variables	
CACS, mm^3	4 (0−56)
$_{log}$(CACS+1)	2.1±2.2
TACS, mm^3	442 (125−1235)
$_{log}$(TACS+1)	5.9±1.9

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; BMI, body mass index; BP, blood pressure; CACS, coronary artery calcium score; CT, computed tomography; HDL, high-density lipoprotein; PP, pulse pressure; TACS, thoracic aorta calcium score.

calcium-channel blockers (CCBs), and angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). Mean seated SBP and DBP at rest were 125±16 and 77±9 mm Hg, respectively. Median CACS and TACS were 4 (IQR, 0−56) and 442 mm^3 (IQR, 125−1235), respectively.

SBP Changes During Exercise Test

Because there are no accepted thresholds or cut-off points for TACS risk categories, we arbitrarily stratified TACS into quartiles to compare BP changes during exercise. Cutoffs for TACS quartiles were 0 to 125 (first quartile), 125 to 442 (second quartile), 442 to 1235 (third quartile), and >1235 (fourth quartile). Trend of changes in ΔSBP and ΔPP during exercise test and at peak exercise according to quartiles of TACS values are displayed in Table 2. ΔSBP and ΔPP were not significantly different among the quartiles of TACS at stage 1 exercise. However, ΔSBP and ΔPP were significantly higher during stage 2 and peak exercises and during the recovery

Table 2. Change in Systolic Blood Pressure and Pulse Pressure According to Quartiles of TACS

Variable	TACS Quartiles				P Value			
	1st	2nd	3rd	4th	P for Trend	1st vs 2nd	1st vs 3rd	1st vs 4th
ΔSBP								
Stage 1	12.9±21.4	11.2±20.4	14.0±24.7	12.4±21.5	0.864	0.864	0.644	0.824
Stage 2	24.3±22.4	24.3±23.8	26.2±25.9	30.8±25.0	0.101	0.987	0.471	0.011
Peak exercise	51.2±21.6	52.1±24.1	52.2±22.0	56.8±21.7	0.027	0.713	0.677	0.017
Recovery	20.5±20.8	23.5±20.4	21.7±20.2	26.0±20.8	0.039	0.183	0.595	0.016
ΔPP								
Stage 1	18.4±21.3	17.3±19.6	18.3±23.9	18.7±22.3	0.809	0.603	0.948	0.908
Stage 2	30.7±21.6	29.3±20.4	30.2±23.8	37.4±25.8	0.013	0.546	0.859	0.012
Peak exercise	50.6±20.9	51.1±22.7	50.1±23.0	58.0±22.9	0.006	0.838	0.813	0.002
Recovery	22.0±19.2	24.4±19.7	22.5±19.2	28.7±20.2	0.008	0.244	0.813	0.002

ΔPP indicates change in pulse pressure during exercise; ΔSBP, change in systolic blood pressure during exercise; TACS, thoracic aorta calcium score.

phase for the fourth quartile as compared with the lowest quartile (all $P<0.05$).

Relationship Between Aortic Calcification and Blood Pressure Response During Exercise Testing

Mean SBP, DBP, and PP during the second stage of exercise were 152±27, 72±13, and 80±25 mm Hg, respectively. $ΔSBP_{stage2}$ and $ΔPP_{stage2}$ were 31.8±23.1 and 27.3±23.9 mm Hg, respectively. $ΔSBP_{peak}$ and $ΔPP_{peak}$ were 53.4±22.3 and 52.4±22.6 mm Hg, respectively. The relationship of standard risk factors and aortic calcification to resting and $ΔSBP_{stage2}$ or $ΔSBP_{peak}$ are summarized in Table 3. Multivariate regression analysis revealed that $_{log}(TACS+1)$ was independently related to resting SBP, even after adjusting for sex, age, resting heart rate, diabetes, and hypertension ($P=0.048$). $_{log}(TACS+1)$ was also related to $ΔSBP_{stage2}$ or $ΔSBP_{peak}$, after adjusting for sex, age, resting SBP, resting DBP, resting heart rate, other comorbidities, and $_{log}(CACS+1)$ ($P=0.001$ and 0.010, respectively). No significant associations were observed between $_{log}(TACS+1)$ and ΔDBP both at rest and at stage 2 of exercise. The relationship between standard risk factors and aortic calcification to resting and $ΔPP_{stage2}$ or $ΔPP_{peak}$ is shown in Table 4. Similar to SBP, $_{log}(TACS+1)$ was independently associated to resting PP, after adjusting for sex, age, resting heart rate, diabetics, and $_{log}(CACS+1)$ ($P=0.049$). $_{log}(TACS+1)$ also demonstrated a relationship with $ΔPP_{stage2}$ and $ΔPP_{peak}$, even after adjusting sex, age, resting heart rate, other comorbidities, and $_{log}(CACS+1)$ (all $P=0.004$).

Predictors for Primary Endpoint

During a median follow-up period of 65 months (IQR, 19–90), there were 59 events (8.4%), including 11 all-cause deaths

(1.6%), 13 inpatient admissions for heart failures (1.9%), 11 CADs requiring coronary intervention (1.6%), and 24 strokes (3.4%). TACS was higher in patients with events as compared with those without an event (2628±1952 vs 1742±995 mm³; $P=0.008$). However, no significant differences in $ΔSBP_{stage2}$ (26.6±23.8 vs 23.6±29.6 mm Hg; $P=0.455$) or $ΔSBP_{peak}$ (53.5±21.9 vs 48.9±26.8 mm Hg; $P=0.208$) were observed in patients with versus without events. Table 5 reports the multivariate analysis of variables as potential predictors of all endpoints in the studied population. In univariate analysis, age and 4th quartile of TACS were associated with all events ($P<0.001$ and $=0.001$, respectively). CACS over 400 mm³ demonstrated a borderline statistical significance ($P=0.059$). In multivariate analysis, age (hazard ratio [HR], 1.12; 95% CI, 1.05–1.19; $P<0.001$), dyslipidemia (HR, 1.96; 95% CI, 1.14–3.37; $P=0.05$), and the 4th quartile of TACS (HR, 1.24; 95% CI, 1.03–1.49; $P=0.024$) were independent predictors for all-cause events, even after adjusting for sex and CACS. Among individual events, the 4th quartile of TACS was the only independent predictor for stroke (HR, 2.15; 95% CI, 1.09–5.13; $P=0.044$), whereas CACS ≥400 mm³ was independently associated with obstructive CAD requiring intervention (HR, 7.04; 95% CI, 1.58–31.36; $P=0.010$). Although the 4th quartile of TACS was a predictor for heart failure admission in univariate analysis, in multivariate analysis adjusting for age, sex, dyslipidemia, resting heart rate, and CACS, it demonstrated a nonsignificant relationship with heart failure admission ($P=0.119$).

Figure 1 demonstrates Kaplan–Meier curves showing differences in all event-free survival rates according to quartiles of TACS. Event-free survival rate was significantly lower for individuals within the 4th quartile of TACS when compared with the lower quartiles (log-rank, $P=0.002$). Figure 2 displays Kaplan–Meier curves for incident stroke and obstructive CAD

Table 3. Relationship of Standard Risk Factors and Aortic Calcification to Resting and Change in Systolic Blood Pressure During Exercise

Variable	Resting SBP				ΔSBP_{stage2}				ΔSBP_{peak}			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value
Male sex	0.042	0.270	0.044	0.321	−0.139	<0.001	−0.092	0.043	0.150	<0.001	0.149	0.001
Age	0.097	0.011	0.041	0.403	−0.032	0.423	−0.124	0.009	−0.077	0.042	−0.085	0.070
Resting SBP	—	—	—	—	−0.071	0.070	−0.044	0.401	−0.151	<0.001	−0.165	0.001
Resting DBP	—	—	—	—	−0.114	0.004	−0.096	0.056	−0.104	0.006	−0.041	0.417
Resting heart rate	0.203	<0.001	0.193	<0.001	0.024	0.606	0.010	0.821	−0.029	0.514	0.027	0.548
Diabetes	0.079	0.038	0.011	0.869	0.037	0.352	—	—	0.085	0.025	0.113	0.013
Hypertension	0.091	0.017	0.058	0.207	0.079	0.047	0.115	0.012	0.031	0.415	—	—
Dyslipidemia	−0.008	0.839	0.002	—	−0.024	0.550	—	—	−0.084	0.027	−0.048	0.283
Use of BB	−0.007	0.865	—	—	−0.091	0.020	−0.113	0.012	−0.002	0.950	—	—
Use of CCB	−0.012	0.747	—	—	0.053	0.272	—	—	−0.018	0.641	—	—
Use of ACEi/ARB	0.084	0.033	0.033	0.479	0.035	0.377	—	—	0.005	0.905	—	—
BMI	0.013	0.738	—	—	0.060	0.128	—	—	0.050	0.190	0.049	0.266
Smoking	−0.034	0.365	—	—	0.040	0.312	—	—	0.045	0.240	—	—
Total cholesterol/HDL	0.055	0.188	—	—	0.034	0.435	—	—	−0.035	0.402	—	—
$\log(CACS+1)$	0.110	0.004	0.074	0.138	−0.002	0.954	−0.077	0.126	0.020	0.595	−0.084	0.087
$\log(TACS+1)$	0.149	<0.001	0.096	0.048	0.132	0.001	0.175	0.001	0.071	0.060	0.100	0.010

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; CACS, coronary artery calcium score; CCB, calcium-channel blocker; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TACS, thoracic aorta calcium score; ΔSBP_{peak}, change of systolic blood pressure during peak exercise; ΔSBP_{stage2}, change of systolic blood pressure during stage 2 exercise.

requiring intervention according to quartiles of TACS or CACS. Incidence of stroke was higher in patients belonging to the 4th quartile of TACS as compared with the lower quartiles (log-rank, P=0.009), whereas incidence of obstructive CAD requiring intervention was higher in patients with CACS ≥400 mm³ as compared with those whose CACS was <400 mm³ (log-rank, P=0.004).

Discussion

In the current study, the high presence of aortic calcification was positively correlated with an SBP raise and PP widening during exercise. Foremost, these relationships remained significant after controlling for potential confounders, including CACS and resting blood pressure. In addition, aortic calcification was also related with adverse cardiovascular events, especially stroke, whereas CACS only predicted obstructive CAD events. Quantitative assessment of aortic calcification by use of TACS was feasible, associated with exercise SBP, and proved a useful surrogate for long-term clinical outcomes other than obstructive CAD, in elderly individuals without obstructive CAD determined by coronary CT angiography, regardless of CACS.

Aortic Calcification in Populations Without Obstructive CAD

Aortic calcification has been reported to be associated with isolated systolic hypertension in healthy individuals[13] and suggested to be a potential reason for developing arterial stiffening.[24] Aortic calcification and progressive stiffening of the large arteries with advancing age results in a widening of PP and leads to development of isolated systolic hypertension in the elderly.[25,26] Arterial stiffening is one of the suggested mechanisms for a rise in exercise SBP. We previously demonstrated that heavy aortic calcification was associated with arterial stiffening and also resulted in LV hypertrophy and diastolic dysfunction in elderly male patients with hypertension, most likely owing to increased LV afterload associated with heavily calcified aortic wall and decreased aortic compliance.[24] In the present study, we also verified that aortic calcification, which might be a surrogate for arterial stiffness, could predict exercise SBP response and cardiovascular outcomes in the elderly who are prone to aortic calcification, irrespective of coronary atherosclerosis.

The pathology of aortic calcification differs to that of coronary artery calcification, which is associated with CAD.

Table 4. Relationship of Standard Risk Factors and Aortic Calcification to Resting and Change in Pulse Pressure During Exercise

Variable	Resting PP Univariate β	P Value	Resting PP Multivariate β	P Value	ΔPP_{stage2} Univariate β	P Value	ΔPP_{stage2} Multivariate β	P Value	ΔPP_{peak} Univariate β	P Value	ΔPP_{peak} Multivariate β	P Value
Male sex	0.011	0.771	0.021	0.643	−0.086	0.030	−0.125	0.060	0.098	0.010	0.056	0.217
Age	0.151	<0.001	0.079	0.087	−0.027	0.492	−0.081	0.094	−0.066	0.085	−0.065	0.175
Resting PP	—	—	—	—	−0.033	0.411	—	—	−0.110	0.004	−0.121	0.010
Resting heart rate	0.152	0.001	0.135	0.003	0.028	0.553	−0.003	0.952	−0.005	0.914	0.007	0.877
Diabetes	0.157	<0.001	0.102	0.023	0.076	0.056	0.080	0.088	0.117	0.002	0.138	0.003
Hypertension	0.061	0.112	—	—	0.042	0.300	—	—	0.018	0.647	—	—
Dyslipidemia	0.021	0.579	—	—	−0.050	0.209	—	—	−0.069	0.072	−0.021	0.642
Use of BB	−0.035	0.363	—	—	−0.085	0.038	−0.121	0.009	−0.022	0.570	—	—
Use of CCB	0.012	0.753	—	—	0.032	0.426	—	—	−0.019	0.621	—	—
Use of ACEi/ARB	0.098	0.011	0.038	0.393	0.044	0.274	—	—	0.041	0.290	—	—
BMI	0.003	0.942	—	—	0.074	0.063	0.125	0.007	0.053	0.164	0.047	0.304
Smoking	−0.035	0.351	—	—	0.024	0.541	—	—	0.033	0.391	—	—
Total cholesterol/HDL	0.046	0.265	—	—	0.002	0.959	—	—	−0.045	0.280	—	—
$_{log}$(CACS+1)	0.108	0.005	0.070	0.153	0.034	0.397	−0.030	0.566	0.018	0.640	−0.101	0.055
$_{log}$(TACS+1)	0.173	<0.001	0.097	0.049	0.105	0.008	0.128	0.004	0.086	0.023	0.144	0.004

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; CACS, coronary artery calcium score; CCB, calcium-channel blocker; HDL, high-density lipoprotein; PP, pulse pressure; TACS, thoracic aorta calcium score; ΔPP_{peak}, change of pulse pressure during peak exercise; ΔPP_{stage2}, change of pulse pressure during stage 2 exercise.

Aortic calcification reflects calcification in both the intimal and medial tunica layers of the artery, in contrast to coronary artery calcification, which generally occurs in the intimal layer of an atherosclerotic plaque.[27] Medial calcification is not associated with atherosclerotic plaque, but is strongly associated with aging, diabetes, and end-stage renal disease.[28] Interestingly, in the current study, TACS and CACS demonstrated different prognostic roles in the elderly without obstructive CAD. TACS predicted adverse cardiac events other than CAD, whereas CACS mainly predicted significant obstructive CAD. Therefore, aortic calcification as represented by TACS might not always reflect a sole indicator for atherosclerosis, which is in contrast to CACS that is often associated with atherosclerotic plaque on coronary arteries.

Aortic Calcification, Exercise Blood Pressure, and Adverse Outcomes

In the present study, heavy aortic calcification (eg, 4th quartile of TACS) was related with composite of adverse outcomes, including all-cause death, stroke, heart failure, and ischemic heart disease during median follow-up of 65 months, although the studied population constituted individuals without significant CAD at study entrance. Interestingly, stroke was the most frequent adverse event of all

endpoints. It has been reported that descending thoracic aorta calcification was associated with incidence of stroke, and it has been proposed that thoracic aortic calcification is a surrogate marker for generalized atherosclerosis whereby plaques in the aorta itself might be a potential stroke origin.[29]

In addition, we may add that increased SBP might further provoke stroke and adverse events in individuals with a heavy calcium deposit. In a population-based study, Kurl et al.[4] reported an increased risk of stroke in subjects with increased SBP, and suggested that an increase in the risk of endothelial injury from high exercise SBP, as well as underlying arteriosclerotic disease or structural vascular changes, may reflect some of the plausible mechanisms involved. The association between ΔSBP and aortic calcification was similarly demonstrated during both submaximal and maximal exercise. Yet, ΔSBP and ΔPP during exercise did not predict clinical outcomes in the current study population. This discrepancy might be, in part, attributed to the fact that the population examined in this study was elderly, and most patients were only capable of completing the exercise test at a low-intensity workload. Further still, most of the enrolled population was prescribed antihypertensive medication, including BB and CCB, which could have also altered the SBP response to exercise.

Although not statistically significant in multivariate analysis, TACS was associated with incidence of heart failure

Table 5. Cox Proportional Hazards Regression for Predictors of Outcomes

Outcome	Predictor	Univariate		Multivariate	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All events	Age	1.14 (1.08–1.22)	<0.001	1.12 (1.05–1.19)	<0.001
	Male sex	1.20 (0.72–2.01)	0.488	1.06 (0.62–1.81)	0.826
	Hypertension	1.15 (0.68–0.95)	0.603	—	—
	Diabetes	0.82 (0.41–1.61)	0.557	—	—
	Dyslipidemia	1.60 (0.95–2.70)	0.081	1.96 (1.14–3.37)	0.015
	Resting heart rate	1.01 (0.97–1.05)	0.722	—	
	BMI	0.97 (0.88–1.06)	0.461	—	
	Smoking	1.19 (0.58–2.42)	0.635	—	
	CACS ≥400 mm³	2.26 (0.97–5.27)	0.059	1.83 (0.75–4.48)	0.184
	TACS 4th vs 1st to 3rd quartiles	2.41 (1.44–4.04)	0.001	1.24 (1.03–1.49)	0.024
All-cause death	Age	1.27 (1.12–1.44)	<0.001	1.26 (1.09–1.46)	0.002
	Male sex	1.08 (0.33–3.53)	0.904	0.77 (0.22–2.78)	0.694
	Hypertension	1.02 (0.31–3.33)	0.980	—	—
	Diabetes	0.38 (0.05–2.99)	0.360	—	—
	Dyslipidemia	0.96 (0.29–3.16)	0.949	—	—
	Resting heart rate	0.93 (0.83–0.13)	0.155	0.96 (0.85–1.08)	0.468
	BMI	0.69 (0.55–0.86)	0.001	0.66 (0.50–0.87)	0.003
	Smoking	0.66 (0.08–5.16)	0.692	—	—
	CACS ≥400 mm³	0.99 (0.21–4.59)	0.991	0.47 (0.65–1.74)	0.814
	TACS 4th vs 1st to 3rd quartiles	1.67 (0.49–5.72)	0.412	0.93 (0.25–3.49)	0.908
Heart failure	Age	1.16 (1.02–1.32)	0.029	1.08 (0.88–1.33)	0.483
	Male sex	1.71 (0.54–5.40)	0.360	1.89 (0.33–10.69)	0.473
	Hypertension	0.61 (0.19–1.91)	0.392	—	—
	Diabetes	1.34 (0.36–4.94)	0.665	—	—
	Dyslipidemia	2.32 (0.70–7.72)	0.170	3.63 (0.62–21.28)	0.152
	Resting heart rate	1.04 (0.99–1.09)	0.155	1.03 (0.15–7.25)	0.957
	BMI	0.98 (0.80–1.20)	0.848	—	—
	Smoking	2.18 (0.59–8.04)	0.244	—	—
	CACS ≥400 mm³	1.80 (0.23–13.96)	0.574	1.06 (0.15–7.25)	0.957
	TACS 4th vs 1st to 3rd quartiles	3.20 (1.03–9.93)	0.044	4.13 (0.69–24.62)	0.119
Obstructive CAD	Age	1.06 (0.91–1.23)	0.450	1.03 (0.88–1.21)	0.707
	Male sex	1.56 (0.48–5.13)	0.460	0.04 (0.29–3.77)	0.956
	Hypertension	0.69 (0.21–2.26)	0.537	—	—
	Diabetes	2.31 (0.68–7.89)	0.183	0.58 (0.17–1.94)	0.373
	Dyslipidemia	1.29 (0.39–4.22)	0.678	—	—
	Resting heart rate	0.99 (0.89–1.10)	0.825	—	—
	BMI	1.02 (0.83–1.26)	0.826	—	—
	Smoking	1.40 (0.32–6.48)	0.667	—	—
	CACS ≥400 mm³	7.12 (1.89–26.87)	0.004	7.04 (1.58–31.36)	0.010
	TACS 4th vs 1st to 3rd quartiles	1.67 (0.49–5.70)	0.414	1.45 (0.39–5.39)	0.583

Continued

Table 5. Continued

Outcome	Predictor	Univariate		Multivariate	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Stroke	Age	1.12 (1.02–1.23)	0.014	1.10 (0.99–1.22)	0.076
	Male sex	0.935 (0.42–2.17)	0.871	0.80 (0.34–1.89)	0.613
	Hypertension	2.35 (0.93–5.97)	0.072	0.33 (0.76–5.04)	0.139
	Diabetes	0.35 (0.08–1.49)	0.155	1.96 (0.76–5.04)	0.163
	Dyslipidemia	1.87 (0.82–4.30)	0.139	1.83 (0.77–4.37)	0.171
	Resting heart rate	1.02 (0.97–1.07)	0.402	—	—
	BMI	1.07 (0.94–1.23)	0.312	—	—
	Smoking	0.92 (0.28–3.10)	0.896	—	—
	CACS $\geq$400 mm^3	1.733 (0.41–7.38)	0.457	1.89 (0.42–8.56)	0.410
	TACS 4th vs 1st to 3rd quartiles	2.89 (1.30–6.42)	0.009	2.15 (1.09–5.13)	0.044

BMI indicates body mass index; CACS, coronary artery calcium score; CAD, coronary artery disease; CI, confidential interval; HDL, high-density lipoprotein; HR, hazard ratio; TACS, thoracic aorta calcium score.

admission during follow-up in univariate analysis—an observation that perhaps warrants further study, given that heart failure has been reported to be associated with arterial stiffening in the elderly.[30] Albeit, because our data did not include the measurement of arterial stiffening, further larger studies are clearly required to assess the association, if any, between aortic calcification, arterial stiffening, and incidence of heart failure. However, we might speculate that aortic calcification represents not only atherosclerotic burden, but also resultant vascular structural changes, which can cause stiffening of the aorta, a rise in exercise SBP, and may exacerbate poor clinical outcomes, such as heart failure and stoke. The role of anticalcification strategies as a novel

Figure 1. Kaplan–Meier curves displaying the differences in all event-free survival rates according to thoracic aorta calcium score quartiles.

therapeutic approach for exaggerated SBP response and heavy aortic calcification may warrant further investigation.

CT as a Screening Test Using Aortic Calcium Scoring

In current practice, the use of noncontrast CT of the chest is rapidly emerging as a screening tool for identifying asymptomatic patients at high risk of CAD, as well as for lung cancer screening.[31] Coronary CT angiography is gaining further consideration as a gatekeeper or useful alternative for invasive coronary angiography.[32] Although information regarding thoracic aortic calcification can also be assessed from CT of the thoracic area, it does not currently have a role in clinical decision making. Notably, it has been previously reported that TACS does not further improve prediction of events over and above CACS.[33] Albeit, the current study findings indicate that the measurement of TACS, rather than CACS, might reflect a novel surrogate for detection of vulnerable aortas that may provoke a raised SBP during exercise and possibly lead to poor clinical outcomes in elderly individuals other than obstructive CAD. Therefore, calculation of TACS in addition to coronary CT angiography, and not CACS, might prove more beneficial for screening populations who are at high risk for future cardiovascular disease, especially among elderly individuals without obstructive CAD. Though clearly, further studies are needed to test this speculation.

Study Limitations

The current study findings were based on a retrospective analysis, which may have inferred some biases. Despite this, we carefully reviewed all medical records, along with CT
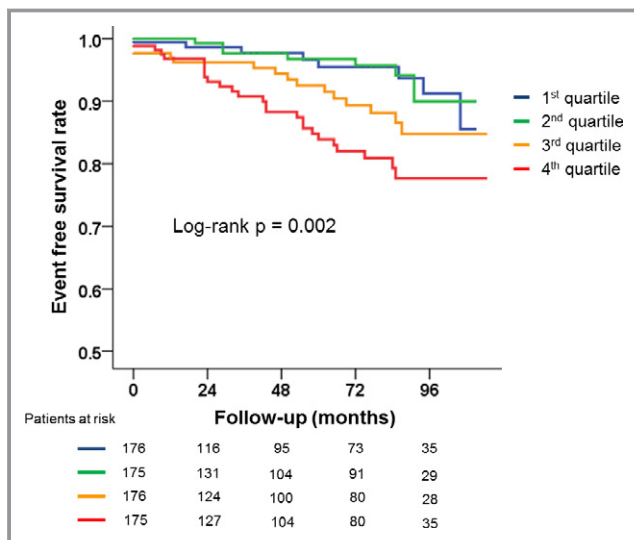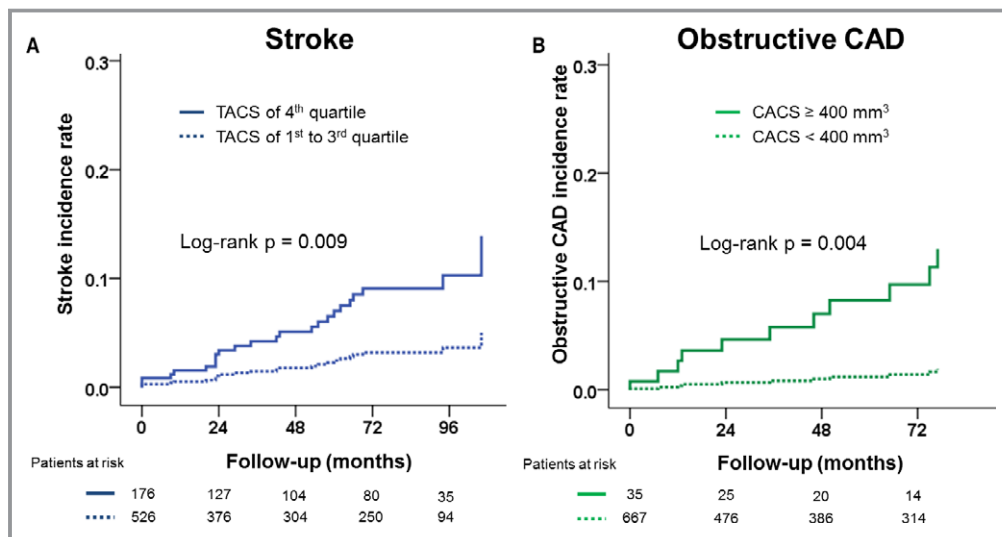
Figure 2. Kaplan–Meier curves displaying the differences in (A) stroke rates and (B) obstructive coronary artery disease according to quartiles of thoracic aorta calcium score (TACS) or coronary artery calcium score (CACS).

images, in an effort to avoid any of the possible biases that may have arisen. It remains uncertain precisely how much of the calcification detected in the aorta reflects calcified atherosclerotic plaque or nonatherosclerotic plaque, given that intimal calcification cannot be differentiated from medial calcification through CT scanning. Also, considering that our findings are based upon an observational cohort of elderly patients (≥65 years) without obstructive CAD, these observations may not be generalizable to other populations, and therefore our results should be interpreted with caution. Considering ΔSBP was not statistically different between individuals with and without an event in the current study, it is not clear whether a rise in exercise SBP mainly mediated poor clinical outcomes in the background of high TACS. However, one of the possibilities why TACS displayed better prediction of outcomes than ΔSBP would be attributed to the fact that there was relatively more variance in ΔSBP than in TACS measurement. Arterial stiffness was not measured, and therefore further studies with concurrent measures of arterial stiffness, aortic calcification, and exercise blood pressure are warranted to support our hypothesis. In addition, forthcoming studies with larger populations are required, given that we examined multiple endpoints, which can cause numerous issues attributed to multiple testing, and may heighten the probability of a type 1 error. Given that fitness is one of the most important factors for influencing SBP change during exercise, it would also be beneficial to perform the latter analysis while controlling for physical fitness, although because of the retrospective nature of the current study, it was beyond the scope of our investigation to obtain additional data regarding patients' fitness. Despite this, resting heart rate is a well-known surrogate of cardiorespiratory fitness and

has been utilized in several previous studies.[34,35] Moreover, TACS demonstrated an independent association with resting and exercise SBP, even after controlling for resting heart rate. Hence, we speculate that presence of an association between TACS and SBP might persist even after adjusting for physical fitness. Though clearly, additional studies with better-defined measures of physical fitness are needed to reinforce this contention.

Conclusion

In this study, presence of aortic calcification was related to elevated SBP during exercise and was a robust predictor of clinical outcomes in elderly individuals without obstructive CAD. Though additional studies are needed to confirm these associations, measurement of TACS from coronary CT scanning may prove useful for predicting exercise SBP response and subsequent adverse clinical outcomes, especially stroke, at least in elderly individuals without obstructive CAD.

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Disclosures

None.

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