Advanced Coronary Artery Calcification and Cerebral Small Vessel Diseases in the Healthy Elderly

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Background: Coronary artery calcification (CAC) scores are widely accepted to predict risk of coronary heart diseases and are associated with atherosclerosis in other vasculatures. Cerebral small vessel diseases (SVDs), including white matter lesions (WML), silent lacunar infarction (SLI) and cerebral microbleeds (CMB), are considered to develop in conjunction with pro-atherogenic conditions, measured by CAC scores.

Methods and Results: Of 672 individuals aged ≥ 65 years that underwent health screening, 312 subjects with brain magnetic resonance imagings (MRIs) were enrolled in this study. The distribution of baseline characteristics among individuals with or without MRIs was not different. Clinical and laboratory information was collected and CAC scores were measured using multi-detector computed tomography. Cerebral SVD were independently assessed by 2 raters who were unaware of the CAC scores. The prevalence of CAC (CAC > 0) was 71.7% in men and 50.0% in women. The associations between moderate-to-extensive CAC (CAC score ≥ 100) and WML (adjusted odds ratio and 95% confidence interval, 4.99 and 1.33–18.73), SLI (5.04 and 1.86–13.63) and CMB (6.07 and 1.54–23.94) remained significant after adjusting for relevant confounders.

Conclusions: This study documents significant associations between CAC and cerebral SVDs. The findings suggest that SVDs in the brain and CAC in the heart may develop under similar systemic pathogenic processes. (*Circ J* 2011; **75**: 451–456)

Key Words: Cerebral microbleeds; Cerebral small vessel disease; Coronary artery calcification; Silent lacunar infarction; White matter lesion

Coronary artery calcification (CAC) scores have recently gained a reputation for estimating the future risk of coronary heart disease and have been recommended for the assessment of individuals with intermediate cardiovascular risks.¹ CAC measurements are able to quantify subclinical coronary artery atherosclerosis and predict the future risk of coronary heart disease^{2,3} and cerebrovascular disease,^{4,5} and the progression of atherosclerotic coronary artery disease.^{6,7} The predictive power of CAC scores was successfully evaluated in a multi-ethnic group,⁸ and is more accurate than conventional cardiovascular risk factors.⁹ Recent advances have also revealed an association between CAC scores and atherosclerotic diseases in other vasculatures, which implies that CAC scores could be used to estimate systemic subclinical atherosclerotic burden.^{10–14}

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In the brain, various subclinical lesions involving small arteries to arterioles develop before clinical manifestation of diseases. Cerebral small vessel diseases (SVDs), which include white matter lesions (WML), silent lacunar infarction (SLI) and cerebral microbleeds (CMB), are detected in 4–6% of the general population. Cerebral SVDs develop in close relation to traditional cardiovascular risk factors and increases the future risk of stroke and cognitive impairment.¹⁵

In this context, we speculated that a close relation exists between CAC and cerebral SVDs, and that both subclinical phenomena may share similar systemic pathological processes, such as pro-atherogenic internal milieu. Accordingly, we investigated the association between CAC scores and

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Figure. A representative figure of cerebral small vessel diseases: white matter lesions (A), silent lacunar infarction (B) and cerebral microbleed (C).

Table 1. Baseline Characteristics of All Participants ≥ 65 -Years Old and Participants That Underwent Brain MRI

	All participants (n=672)	Participants with brain MRI (n=312)
Demographic variable		
Male gender	443 (65.9%)	198 (63.5%)
Age (years)	69.0 $\pm$ 4.0	68.7 $\pm$ 3.7
Clinical variables		
Hypertension	389 (57.9%)	183 (58.7%)
Diabetes	188 (28.0%)	81 (26.0%)
Hypercholesterolemia	109 (16.2%)	48 (15.4%)
Exposure to smoking*	215 (37.0%)	117 (37.5%)
Anthropometric variables		
SBP (mmHg)	128.4 $\pm$ 17.7	129.0 $\pm$ 17.8
DBP (mmHg)	77.7 $\pm$ 10.9	78.1 $\pm$ 10.5
Body mass index (kg/m ²)	24.2 $\pm$ 3.3	24.4 $\pm$ 2.9
Waist circumference (cm)	89.7 $\pm$ 8.1	90.2 $\pm$ 2.9
Laboratory variables		
Glucose (mmol/L)	5.9 $\pm$ 1.5	5.9 $\pm$ 1.4
Total cholesterol (mmol/L)	5.1 $\pm$ 0.9	5.1 $\pm$ 0.9
Triglyceride (mmol/L)	1.3 $\pm$ 0.7	1.4 $\pm$ 0.8
HDL cholesterol (mmol/L)	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4
LDL cholesterol (mmol/L)	3.4 $\pm$ 0.9	3.4 $\pm$ 0.8
CRP (mg/L)	1.8 $\pm$ 4.0	1.7 $\pm$ 3.5
Coronary artery calcification score (M/F)		
25 th percentile	0/0	0/0
50 th percentile	45/3	36/1
75 th percentile	246/74	229/56
90 th percentile	719/230	669/230

Values are presented as means $\pm$ standard deviations or numbers (%).

MRI, magnetic resonance imaging; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

*Information regarding exposure to smoking was missing in 91 (13.5%) of the 672 "All-participants" (17.9%) and in 16 (5.1%) of the 312 subjects with a brain MRI.

cerebral SVDs in healthy, elderly individuals that were free of neurologic and cardiac diseases.

Methods

Study Population

Seoul National University Hospital Healthcare System Gangnam Center provides detailed health screening services for individuals with no overt diseases in need of instant medical attention and who requests this service at their own expense. Between October 2003 and December 2008, 5,420 individuals underwent health screening including CAC scoring. Health screening participants consisted of 3,542 (65.4%) male and 1,878 (34.6%) female subjects, and their mean age was 53.6 $\pm$ 9.5 years. From a total of 672 participants ≥ 65 years old without alleged cardiac or neurological disease, 312 subjects (46.4%), who requested brain magnetic resonance imaging (MRI) as a health screening, were enrolled in this study. Participants < 65 years of age were excluded due to the rarity of cerebral SVDs in this population. This study was approved by the institutional review board at Seoul National University Hospital and all included subjects provided informed consent.

Measurement of CAC

Computed tomographic scanning of the coronary artery was performed using a 16-slice multidetector system (SOMATOM Sensation 16, Siemens Healthcare, Erlangen, Germany). Images were acquired in 3.0-mm slices throughout coronary artery regions using a prospectively ECG-triggered scan acquisition at a 50% of the RR interval and slice collimation of 4 $\times$ 2.5 mm at 120 kV and 120 mAs.¹⁶ All images were transferred to a stand-alone workstation and CAC scores were calculated using an automated computer program (Wizard VB10B, SynGo, Siemens Healthcare). CAC scores were produced using the Agatston method.¹⁷ Briefly, the area of CAC is defined as at least 1 mm² with a computed tomography density ≥ 130 Hounsfield Units (HU). A score for each region was calculated by multiplying the area size and the density score, which derived from the peak intensity of this focus ((1) 130–199HU; (2) 200–299HU; (3) 300–399HU; (4) ≥ 400 HU). The total CAC score was computed by adding

Table 2. Distribution of Baseline Characteristics in Relation to Severity of CAC

	No CAC (CACS, 0; n=113)	Mild CAC (CACS, 1–99; n=104)	Moderate-to-extensive CAC (CACS, ≥100; n=95)	P for trend
Demographic variable				
Male gender	56 (49.6%)	67 (64.4%)	75 (78.9%)	<0.01
Age	67.9±3.2	69.0±3.7	69.3±4.1	<0.01
Clinical variables				
Hypertension	54 (47.8%)	68 (65.4%)	61 (64.2%)	0.01
Diabetes	20 (17.7%)	22 (21.2%)	39 (41.1%)	<0.01
Hypercholesterolemia	19 (16.8%)	20 (19.2%)	9 (9.5%)	0.16
Exposure to smoking*	29 (27.6%)	36 (36.0%)	52 (57.1%)	<0.01
Anthropometric variables				
SBP (mmHg)	125.6±17.0	130.5±17.2	131.4±19.0	0.02
DBP (mmHg)	77.6±10.3	77.7±10.4	79.3±10.8	0.25
Body mass index (kg/m ²)	24.6±3.0	24.0±2.9	24.5±2.8	0.75
Waist circumference (cm)	91.0±7.9	89.8±8.7	89.8±8.2	0.30
Laboratory variables				
Glucose (mmol/L)	5.6±1.0	5.7±1.1	6.3±1.9	<0.01
Total cholesterol (mmol/L)	5.2±0.8	5.1±0.9	4.9±0.9	0.07
Triglyceride (mmol/L)	1.2±0.6	1.5±1.2	1.4±0.6	0.21
HDL cholesterol (mmol/L)	1.4±0.4	1.3±0.4	1.3±0.3	0.15
LDL cholesterol (mmol/L)	3.5±0.8	3.5±0.9	3.3±0.9	0.11
CRP (mg/L)	1.9±4.7	1.7±2.9	1.3±2.0	0.20
Cerebral small vessel disease				
Advanced white matter lesion	4 (3.5%)	8 (7.7%)	14 (14.7%)	<0.01
Silent lacunar infarction	10 (8.8%)	18 (17.3%)	24 (25.3%)	<0.01
Cerebral microbleed	5 (4.4%)	9 (8.7%)	14 (14.7%)	0.01

Values are presented as means±standard deviations or as numbers (%).

CAC, coronary artery calcification; CACS, coronary artery calcification score. Other abbreviations see in Table 1.

P values for trend were calculated by analyses of variance test or chi-square tests trend, as appropriate.

*Information regarding the exposure to smoking was missing in 16 subjects.

up each of the scores for all calcified lesions in the epicardial coronary system.

Measurement of Cerebral SVD and Cardiovascular Risk Factors

MRI studies were performed using a 1.5-Tesla superconducting magnet (CHORUS, ISOL Technology, Seoul, Republic of Korea). The standardized MRI protocol included axial T2-weighted spin echo, T1-weighted spin echo, fluid-attenuated inversion recovery (FLAIR) and axial T2*-weighted gradient-echo (GRE) sequences. WML were classified as absent or present as punctuate, early confluent, or confluent lesions based on FLAIR image evaluations,¹⁸ and the early confluent or confluent lesions were defined as advanced WML. SLI were defined as focal lesions measuring 3–15 mm in diameter with signal intensities corresponding to liquor, and surrounded by a hyperintense gliotic rim on FLAIR images.¹⁹ CMBs were defined as homogeneous, round signal loss lesions of diameter up to 5 mm on GRE images (Figure).²⁰ Cerebral SVD were rated by 2 independent reviewers (W.-S.R. and C.K.K.) who were unaware of clinical information or CAC scores with good inter-rater agreement (κ -values of agreement were 0.70, 0.66 and 0.86, respectively). Disagreements were settled by discussion with a third rater (B.J.K.).

Baseline information on demographic and cardiovascular risk factors was collected during health examinations on the following: gender, age, hypertension (previous use of anti-hypertensive medication, or systolic blood pressure (BP)

≥140 mmHg or diastolic BP≥90 mmHg), diabetes (previous use of antidiabetic medication or fasting blood glucose >7.0 mmol/L), hyperlipidemia (previous use of lipid-lowering medication, total cholesterol (TC) >6.0 mmol/L or low-density lipoprotein cholesterol >4.14 mmol/L) and exposure to smoking (current smoker or having a regular smoking habit in the past). We also measured anthropometric variables, which included systolic and diastolic BP, waist circumference and body mass index. Laboratory assessments included glucose, TC, high-density lipoprotein cholesterol, triglyceride and C-reactive protein (CRP) levels. Low-density lipoprotein cholesterol levels were calculated using the Friedewald equation.²¹

Data Analysis

We first compared the characteristics of the 672 ≥65 year-old health screened participants and the 312 subjects with brain MRI studies to ensure comparability between subjects with and without brain MRI. CAC scores were categorized as no CAC (CAC score of 0), mild CAC (CAC score of 1–99) and moderate-to-extensive CAC (CAC score of ≥100).²² The distribution of clinical and laboratory variables in relation to increased CAC severity was also examined. Trends across categorized CAC severity were performed using the Mantel-Haenszel chi-square test and by analysis of variance. Univariate analysis was performed using the t-test or the chi-square test, as appropriate, to investigate associations between cerebral SVD and baseline characteristics. Associa-

Table 3. Comparison of Groups With Respect to Cerebral Small Vessel Diseases

	Advanced white matter lesion			Silent lacunar infarction			Cerebral microbleeds		
	Present (n=26)	Absent (n=286)	P value	Present (n=52)	Absent (n=260)	P value	Present (n=28)	Absent (n=284)	P value
Demographic variable									
Male gender	12 (46.2%)	186 (65.0%)	0.06	31 (59.6%)	167 (64.2%)	0.53	17 (60.7%)	181 (63.7%)	0.75
Age	70.9±4.8	68.5±3.5	<0.01	69.4±4.3	68.6±3.6	0.15	68.6±3.6	69.5±4.4	0.23
Clinical variables									
Hypertension	21 (80.8%)	162 (56.6%)	0.02	35 (67.3%)	148 (56.9%)	0.16	20 (71.4%)	163 (57.4%)	0.15
Diabetes	8 (30.8%)	73 (25.5%)	0.56	16 (30.8%)	65 (25.0%)	0.39	8 (28.6%)	73 (25.7%)	0.74
Hypercholesterolemia	5 (19.2%)	43 (15.0%)	0.57	12 (23.1%)	36 (13.8%)	0.09	4 (14.3%)	44 (15.5%)	1.00†
Exposure to smoking*	8 (32.0%)	109 (40.2%)	0.42	19 (39.6%)	98 (39.5%)	0.99	11 (42.3%)	106 (39.3%)	0.76
Anthropometric variables									
SBP (mmHg)	136.3±21.5	128.3±17.3	0.03	135.2±21.4	127.8±16.8	<0.01	134.2±15.1	128.5±18.0	0.11
DBP (mmHg)	79.3±11.1	78.0±10.4	0.56	78.7±11.7	78.0±10.2	0.67	80.7±10.5	77.9±10.4	0.18
Body mass index (kg/m ²)	24.3±2.4	24.4±3.0	0.80	24.0±2.6	24.5±3.0	0.34	24.6±2.6	24.4±2.9	0.71
Waist circumference (cm)	89.6±7.4	90.3±8.3	0.69	89.4±7.8	90.4±8.4	0.45	90.9±6.3	90.1±8.4	0.64
Laboratory variables									
Glucose (mmol/L)	5.9±1.0	5.9±1.4	0.98	5.9±1.3	5.8±1.4	0.91	5.6±1.1	5.9±1.4	0.36
Total cholesterol (mmol/L)	4.9±1.0	5.1±0.9	0.42	5.0±1.1	5.1±0.9	0.43	4.9±0.9	5.1±0.9	0.27
Triglyceride (mmol/L)	1.5±1.3	1.3±0.8	0.30	1.4±0.7	1.3±0.9	0.44	1.3±0.7	1.4±0.8	0.82
HDL cholesterol (mmol/L)	1.3±0.3	1.4±0.4	0.73	1.3±0.3	1.4±0.4	0.04	1.4±0.4	1.4±0.4	0.41
LDL cholesterol (mmol/L)	3.3±0.8	3.4±0.9	0.35	3.4±1.1	3.4±0.8	0.74	3.2±0.8	3.5±0.8	0.13
CRP (mg/L)	0.8±0.8	1.7±3.6	0.19	1.6±3.2	1.7±3.5	0.91	1.5±2.4	1.7±3.6	0.83
CACS†									
Median [interquartile range]	172 [5, 468]	17 [0, 149]	<0.01	62 [9, 376]	11 [0, 136]	<0.01	133 [4, 789]	17 [0, 148]	<0.01

Values are presented as means±standard deviations or as numbers (%).

Abbreviations see in Tables 1,2.

*Information regarding exposure to smoking was missing in 27 subjects.

P values were calculated using Mann-Whitney U test† or Fisher's exact test‡ for categorical variables, and t-test for continuous variables.

tion between CAC scores and cerebral SVDs were evaluated using the nonparametric Mann-Whitney U test due to the skewed distribution of CAC scores. Binomial logistic regression analyses were used to study relations between cerebral SVDs and CAC by treating each cerebral SVD as a dependent variable. The initial models consisted of adjusting variables, which included gender, age, hypertension, diabetes, hypercholesterolemia and exposure to smoking. The extended models further included systolic BP, glucose, TC and CRP. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC, USA) and SPSS 17 (SPSS Inc, Chicago, IL, USA). Two-tailed P values of <0.05 were considered significant and values are presented as frequencies (percentages), means±standard deviations, or as medians [interquartile ranges], as appropriate.

Results

We first compared the distribution of baseline variables and risk factor profiles between the original ≥65-year-old cohort (n=672) and the enrolled subjects with brain MRI (n=312). Overall, the distribution of baseline demographic variables and risk factor profiles are not significantly deviated (Table 1).

In the 312 subjects with a brain MRI, the prevalence of CAC (CAC score of >0) was 71.3% for males and 50.0% for females. The distributions of baseline characteristics in relation to CAC severity are presented in Table 2. The prevalence of advanced WML, SLI and CMB increased significantly as CAC severity increased (P for trends; P<0.01, P<0.01 and P=0.01, respectively). Clinical and laboratory

profiles according to each cerebral SVD are described in Table 3. Subjects with advanced WML, SLI, or CMB had higher CAC scores (P<0.01). As shown in Table 4, subjects with moderate-to-severe CAC (CAC score of ≥100) were found to have an increased odds of having advanced WML (adjusted odds ratio and 95% confidence interval; 4.69 and 1.30–16.98; P=0.02), SLI (5.04 and 1.86–13.63; P<0.01) and CMB (6.07 and 1.54–23.94; P=0.01) after adjusting for relevant clinical and laboratory factors, in both initial and extended model of multivariate analysis.

Discussion

In this study, we have documented a robust association between moderate-to-extensive CAC (CAC score of ≥100) and increased odds of having cerebral SVDs, including WML, SLI and CMB. Furthermore, these relations remained true after adjusting for gender, age, hypertension, diabetes, hypercholesterolemia and exposure to smoking, as well as systolic BP, glucose, TC and CRP.

The virtue of CAC scoring lies in its ability to predict coronary heart disease in healthy individuals with intermediate cardiovascular risks, not in the quantification of the amount of calcium in coronary arteries per se. Similarly, cerebral SVD are closely related to the development of future stroke, cognitive impairment, or antithrombotic-related fatal complications in the brain. WML is associated with information processing speed and executive function deficits,^{23–25} gait disturbance in the elderly,²⁶ the risk of ischemic and hemorrhagic stroke,^{27–29} and anticoagulation-related cerebral

Table 4. Multivariate Analysis of the Relation Between Severity of CAC and Cerebral Small Vessel Diseases

	Adjusted OR (95%CI)		
	Advanced white matter lesion	Silent lacunar infarction	Cerebral microbleeds
Initial model			
No CAC (CACS, 0)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Mild CAC (CACS, 1–99)	1.84 (0.51–6.63)	2.39 (0.95–6.01)	3.02 (0.78–11.78)
Moderate-to-extensive CAC (CACS, ≥100)	4.69 (1.30–16.98)*	4.59 (1.76–11.92)†	5.67 (1.47–21.86)*
Extended model			
No CAC (CACS, 0)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Mild CAC (CACS, 1–99)	1.96 (0.53–7.23)	2.37 (0.92–6.13)	3.01 (0.76–11.87)
Moderate-to-extensive CAC (CACS, ≥100)	4.99 (1.33–18.73)*	5.04 (1.86–13.63)†	6.07 (1.54–23.94)*

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

Initial model was adjusted for age, gender, hypertension, diabetes, hypercholesterolemia and exposure to smoking.

The extended model was additionally adjusted for systolic blood pressure, glucose, total cholesterol and CRP.

*P<0.05, †P<0.01 for comparison with no CAC.

hemorrhage.³⁰ SLI is an arterial occlusive lesion per se, and the presence of SLI in asymptomatic individuals implies increased risks of subsequent stroke,^{31,32} mild cognitive impairment and apparent dementia including Alzheimer's disease.^{33,34} CMB, a minute bleeding focus with surrounding tissue damage, has been also suggested to predict the future risk of symptomatic cerebral hemorrhage after stroke,^{35,36} and to contribute to clinical deficit and executive dysfunction.³⁷

CAC is considered a part of subclinical atherosclerosis and the development of CAC is also related to cardiovascular risk factors.^{1,38} Recent progress has further elucidated associations between CAC and the development of atherosclerosis in other vascular beds, such as hypertensive retinopathy, carotid intima-media thickness, peripheral artery disease and early stage nephropathy.^{10–13} The development of cerebral SVDs is also closely related to cardiovascular risk factors including hypertension and reflects arteriolosclerosis in smaller cerebral vasculatures.^{15,39} Furthermore, endothelial dysfunction may also provide an explanatory bridge between cerebral SVDs and CAC. The initial developments of atherosclerotic plaque and CAC are also related to the endothelial dysfunction and to the presence of stimuli noxious to vascular walls.^{40,41} Endothelial dysfunction has been proposed to interact with the development of cerebral WML via the extravasation of toxic plasma constituents into cerebral parenchyma, which induce localized inflammation, arteriolar thickening and eventually sublethal ischemia.⁴² SLI is related to lipohyalinosis and fibrinoid necrosis of cerebral arteriolar walls,⁴³ and CMB involves the extravasation of blood at the microscopic level through fragile vascular walls.⁴⁴ In spite of different radiological phenotypes in each cerebral SVDs, risk factors and genetic factors trigger accumulation of vascular wall pathology and loss of smooth muscle cells with luminal narrowing, and ultimately lead to blood brain barrier damage and microscopic vascular rupture, thus causing cerebral SVDs.⁴⁵

The association between cerebral SVDs and CAC supports the notion that a shared pathophysiologic process, such as systemic atherosclerosis, may contribute to coronary artery diseases and microvascular diseases in cerebral arterioles. At present, we cannot conclude an exact common mechanism for CAC and cerebral SVDs, or mechanisms underlying asymptomatic disease processes that involve arteries of different sizes. However, in view of the high incidence of coexisting coronary heart disease and stroke, a common mechanism involving both CAC and cerebral SVDs has been

suggested.⁴⁶

Our study should be interpreted with caution because of its retrospective nature, the limited size of our study population and because of its cross-sectional design. In spite of the well-known rarity of SVD in the younger population, excluding the <65-year-old population to maximize statistical comparability in our analyses may have introduced bias. Furthermore, the healthy volunteer effect may have introduced bias and limits generalizations based on our results.⁴⁷ In addition, we failed to collect information on the medication history and cognitive status of the included individuals.

From our study, the association between cerebral SVDs and CAC was detected after adjusting for cardiovascular risk factors and other relevant laboratory parameters. We are not here to argue that either CAC or SVDs cause each other, or that CAC may predict future risk of stroke or dementia. Only sufficiently powered prospective studies could prove such a hypothesis. Rather, we were able to document the shared pathogenesis of both subclinical phenomena and thereby pulling cerebral SVDs into the risk pools of systemic cardiovascular diseases and high CAC scores.

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Disclosure

Conflict of Interest: The authors have no potential conflict of interest to report concerning this article.

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