The frequency and risk of preclinical coronary artery disease detected using multichannel cardiac computed tomography in patients with ischemic stroke

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The Master's Thesis

Submitted to the Department of Medicine

The Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of Master of Medical Science

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December 2012

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December 2012

ACKNOWLEDGEMENTS

First of all, I would like to give unbounded gratitude to Professor Ji Hoe Heo who encouraged me to start and complete this thesis. This thesis would not be completed without his advice and supports.

I also give my thanks to Professor Yangsoo Jang and Professor Hyo Suk Nam who gave me helpful comments and suggestions.

Finally, I would like to mention my family. Thanks for my parents, sister and especially my wife, who always care me and love me.

Joonsang Yoo

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Background Atherosclerosis is a systemic disease. Many ischemic stroke patients may have concomitant coronary artery disease (CAD). Detection and treatment of preclinical CAD in stroke patients may improve long-term outcome and survival because CAD is a major cause of death during follow-up in stroke patients. However, association between coronary and cerebral artery atherosclerosis in stroke patients has not fully been investigated. This study aimed at examining the frequency and high-risk groups of CAD in ischemic stroke patients.

Methods Consecutive patients who were admitted due to acute ischemic stroke between July 2006 and June 2010 were prospectively enrolled in this study. A total of 1,304 patients who underwent multislice computed tomography (MSCT) coronary angiography and cerebral angiography were included in this study. By using 64-MSCT coronary angiography, we investigated the frequency of CAD and association between coronary and cerebral artery atherosclerosis in terms of location and burden (severity and extent) in stroke patients. We also sought to identify high risk groups for CAD among stroke patients.

Results The frequency of significant (≥50%) CAD was 32.3% and the frequency of any degree of CAD was 70.1%. Diabetes mellitus, serum levels of total cholesterol, high-density lipoprotein cholesterol and triglyceride, and significant stenosis of the extracranial carotid, intracranial vertebral and basilar arteries were independently associated with CAD. However, no association was found between CAD and significant stenosis of the anterior, middle and posterior cerebral arteries. The association between CAD and cerebral atherosclerosis was stronger with increased severity and extent of cerebral atherosclerosis. When compared to patients with <2 risk factors and without significant cerebral atherosclerosis, those with multiple (≥2) risk factors and atherosclerosis in both the carotid and the vertebrobasilar arteries had very high risks of CAD [odds ratio (OR) 8.36; 95% confidence interval (CI) 4.15 – 16.87]. The risk was also high in patients with multiple risk factors and atherosclerosis in either the carotid or the vertebrobasilar artery (OR 4.13; 95% CI 2.62 – 6.51), and in those with <2 risk factors but atherosclerosis in both the carotid and the vertebrobasilar arteries (OR 3.40; 95% CI 1.22 – 9.47).

Conclusions A substantial portion of stroke patients had preclinical CAD, and there was a clear relationship between coronary and cerebral artery atherosclerosis in terms of location and burden. The risk of CAD was particularly high in stroke patients with multiple risk factors and atherosclerosis of the carotid and/or vertebrobasilar arteries.

Key words: Angiography, Atherosclerosis, Computed tomography angiography, Coronary artery disease, Ischemic stroke

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I. INTRODUCTION

Patients with symptomatic atherosclerotic disease in one vascular bed may have symptoms in other vascular beds during follow-up.[1] In fact, coronary artery disease (CAD) is the major cause of death in ischemic stroke patients.[2-4] Detection and treatment of preclinical CAD in stroke patients may improve long-term outcome and survival. However, most stroke patients remain unevaluated for the presence of CAD during their initial evaluation. Moreover, there are limited diagnostic tools that can be effectively used for stroke patients. Diagnosis of CAD is based on the thallium-201 scan,[5] ultrasonography,[6] exercise test,[7] autopsy study[8] and conventional coronary angiography.[9] However, these studies have limitations for routine application in stroke patients. For example, conventional angiography is invasive and the exercise test and thallium-210 scan are inadequate to evaluate the individual coronary artery and have relatively low sensitivity and specificity.[10] In addition, the exercise test cannot be performed in stroke patients with weakness.

Atherosclerosis is a systemic disease,[11] and many patients may have concomitant atherosclerosis in the coronary and cerebral arteries. Although an association between coronary atherosclerosis and extracranial carotid atherosclerosis has been suggested,[12–14] the exact association between coronary and individual cerebral artery atherosclerosis is yet uncertain. Multislice computed tomography (MSCT) coronary angiography has recently been introduced to evaluate the coronary artery. MSCT coronary angiography is an attractive diagnostic tool for detecting coronary atherosclerosis because it is noninvasive and has a sensitivity of 85–97% and a specificity of 90–98% in the detection of obstructive CAD when compared with conventional coronary angiography.[15–18] Due to these advantages, MSCT coronary angiography was recently introduced to evaluate the presence of CAD in ischemic stroke patients.[19–21]

We investigated the frequency of CAD using MSCT coronary angiography and examined the relationship between atherosclerosis of the coronary and the cerebral artery in terms of location and burden in stroke patients without a history of CAD. Furthermore, we sought to determine the group of patients who are at high risk for CAD.

II. METHODS

1. Patients and Inclusion/Exclusion Criteria

Consecutive patients with acute ischemic stroke or transient ischemic attack (TIA) who were admitted to the neurology department within 7 days after onset of symptoms between July 2006 and June 2010 were prospectively enrolled for this study. Among them, those who underwent both MSCT coronary angiography and cerebral angiography were included for the analysis. This study was approved by the institutional review board of Severance Hospital, Yonsei University Health System, and informed consent was obtained from all patients.

Patients were indicated for MSCT coronary angiography when they had at least one of the following: (1) presence of atherosclerosis in the intracranial or extracranial cerebral artery, (2) presence of ≥2 risk factors for CAD such as hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and central obesity, and (3) old age (men >45 years, women >55 years). Exclusion criteria were: (1) known CAD (angiographically confirmed CAD, unstable angina, coronary artery stent or angioplasty, or coronary artery bypass graft), (2) high pulse rates (>64/min) that were not controlled with a beta blocker at the time of MSCT coronary angiography, (3) poor general condition, (4) impaired renal function, and (5) failure to obtain informed consent.

In addition to clinical evaluation including histories for cardiovascular diseases and vascular risk factors, all patients underwent brain CT and/or magnetic resonance imaging (MRI), cerebral angiographic study, 12-lead electrocardiography (ECG), 3-lead ECG monitoring during admissions to the stroke unit, standard blood tests, and a chest X-ray. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment classification.[22] Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mmHg on resting status, at least twice, or a history of taking antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/l or a history of taking oral hypoglycemic agents or insulin. Dyslipidemia was defined as serum total cholesterol level ≥6.2 mmol/l, low-density lipoprotein cholesterol ≥4.1 mmol/l or a history of taking lipid-lowering drugs after diagnosis of dyslipidemia. Lipid profiles and fasting glucose were measured at fasting status after admission, which was typically the morning following admission. Patients were considered to be smokers if they had smoked a cigarette within the 3 months prior to admission. Central obesity was defined as abdominal circumference >102 cm in men and >88 cm in women.[23]

2. MSCT Coronary Angiography

Patients underwent two-phase MSCT coronary angiography within 2 weeks after admission, using 64-multislice CT (Sensation 64; Siemens Medical Solutions, Forchheim, Germany). A betablocker (40 mg propranolol hydrochloride; Daewoong, Seoul, Korea) was administered 1–2 h before examination for patients with a resting pulse rate >64/min. Intravenous nonionic contrast agent (370 iodine mg/ml, Iopamiro; Bracco Diagnostics, Milano, Italy) was administered intravenously at a rate of 5 ml/s using a power injector (Envision CT; Medrad, Indianola, Pa., USA). For CT scanning, retrospective ECG gating was used, with 330 ms gantry rotation time, 120 kV tube voltage and 800 mA tube currents. Image reconstruction was performed with 0.8 mm slice thickness, 0.5 mm increment, 512 × 512 pixel image matrix, a medium-smooth kernel, and 18–20 cm field of view. The images were reformatted into various formats including volume rendering, curved multiplanar images, and routine cardiac axis views in a workstation (Wizard; Siemens Medical Solutions), which were interpreted by independent cardiac radiologists. Atherosclerotic stenosis <50% was classified as mild stenosis, and obstruction or stenosis ≥50% was classified as significant stenosis. The presence of stenosis was determined at three main coronary branches, which are the left anterior descending, left circumflex and right coronary arteries.

3. Cerebral Angiography

Cerebral angiography was performed within 1 week after admission by digital subtraction angiography, MR angiography or CT angiography. Any abnormalities in the extracranial and intracranial cerebral arteries were determined based on a neuroradiologist's report and the consensus of ≥2 stroke specialists. The presence of atherosclerosis was determined at arteries or segments, including the carotid artery (extracranial carotid artery, intracranial internal carotid artery), the vertebrobasilar artery (extracranial portion of the vertebral artery, intracranial portion of the vertebral artery, basilar artery), the anterior cerebral artery, the middle cerebral artery and the posterior cerebral artery. The stenotic degree was measured in each artery/segment based on the North American Symptomatic Carotid Endarterectomy Trial method[24] or the Warfarin-Aspirin Symptomatic Intracranial Disease Study Trial method.[25] Atherosclerotic stenosis <50% was classified as mild stenosis and significant stenosis was defined as occlusion or stenosis ≥50%.

4. Data Analysis and Statistical Analysis

Patients with cardioembolism were excluded in analysis for the frequency of cerebral artery atherosclerosis and relationships with CAD because nonatherosclerotic steno-occlusive lesions of the cerebral artery by embolism from the heart are occasionally indistinguishable from those of atherosclerosis.[26] The SAS statistics package (version 9.2; SAS Institute Inc., Cary, N.C., USA) was used for statistical analysis. The independent sample t test and the Pearson chi-square test were used for comparison of risk factors, severity, extent and location of cerebral artery atherosclerosis between the CAD and non-CAD groups. After univariate analysis, all the variables with p values <0.20 were entered into the for multiple logistic regression model to determine factors associated with CAD using the enter method. The relationships were assessed by odds ratios (ORs) with 95% confidential intervals (CIs). The association between number of cerebral arteries with significant atherosclerosis and CAD burden was analyzed by using analysis of variance. Chi-square test for trend was used to compare atherosclerosis in each cerebral artery according to CAD burden. A p values <0.05 were considered statistically significant.

III. RESULTS

1. Overall Baseline Characteristics of Patients

A total of 2,260 patients with acute ischemic stroke were admitted during the study period. Among them, 519 patients did not meet the inclusion criteria or met at least one of the exclusion criteria. Of the 1,741 eligible patients, MSCT coronary angiography was undertaken in 1,316 patients (fig. 1). After excluding 12 patients with coronary angiography that was not interpretable, 1,304 patients were included in this study. When compared to the participant group, 425 patients who were eligible but not included for analysis were older, more likely to be women, and less likely to be smokers. The other major risk factors did not differ. Cerebral angiographic study was performed using digital subtraction angiography in 405 patients (31.1%), MR angiography in 867 patients (66.5%), and CT angiography in 32 patients (2.5%). Of the 1,304 patients, 963 patients (73.8%) were admitted to the stroke unit. The mean age was 63.81 ± 11.11 years, and 827 patients were men (63.4%). Among 1,304 patients, 1,194 patients (91.6%) were admitted due to cerebral infarction and 110 patients (8.4%) due to TIA. The stroke subtypes in patients with cerebral infarctions were large artery atherosclerosis in 289 patients (22.2%), cardioembolism in 248 patients (19.0%), small-vessel occlusion in 148 patients (11.3%), stroke of other determined etiology in 15 patients (1.2%), and stroke of undetermined etiology in 494 patients (37.9%: ≥2 causes identified in 163 and negative evaluation in 331).

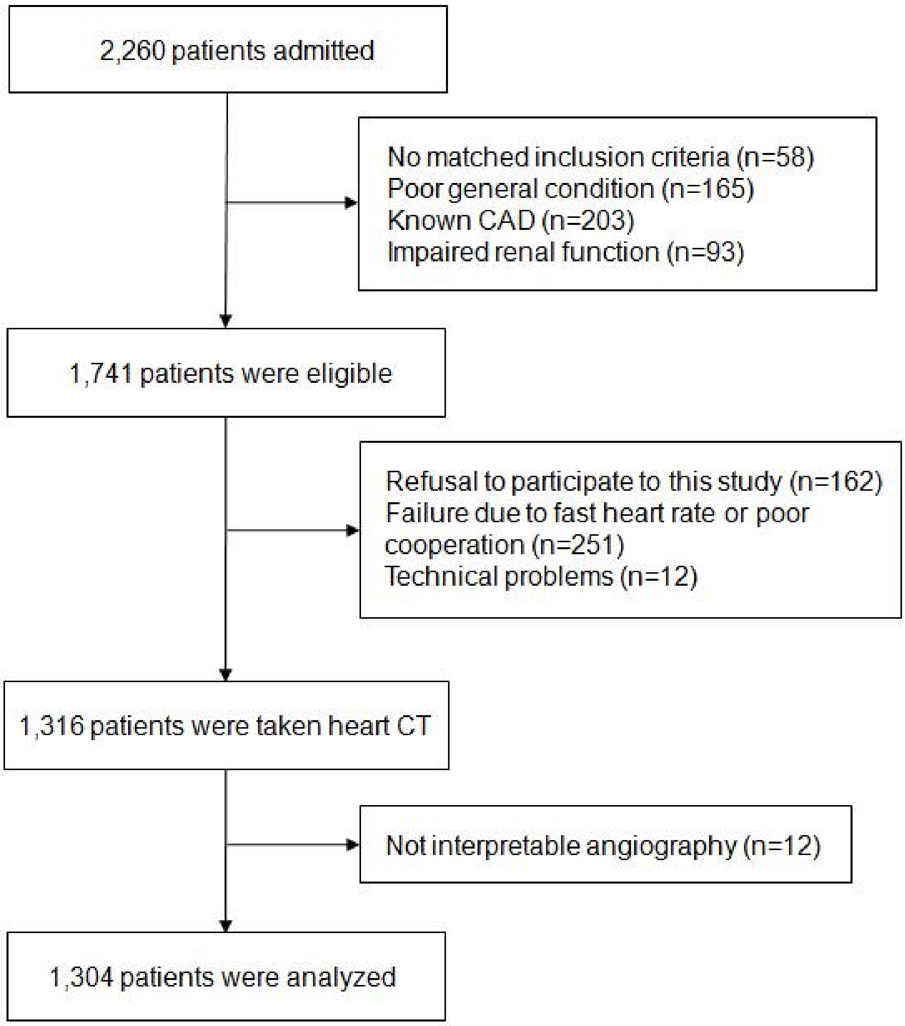

Fig. 1. Flow chart of patient enrollment.

2. Frequency of Coronary Artery Atherosclerosis

Any degree of coronary atherosclerosis was detected in 918 (70.4%) out of 1,304 patients. Among them, 431 patients (33.1%) had significant stenosis (≥50%) of at least one coronary artery (one-vessel disease in 225 patients, two-vessel disease in 137 patients, and three-vessel disease in 69 patients). On univariate analysis, patients with significant CAD were older than those without CAD, and were more likely to be men and smokers (table 1). Risk factors of hypertension and diabetes mellitus were more common in patients with CAD. Blood levels of triglyceride and fasting blood sugar were higher and those of high-density lipoprotein cholesterol were lower in patients with CAD than in those without CAD (table 1). After diagnosis of significant stenosis of the coronary artery on MSCT coronary angiography, 130 patients (10.0%) were further examined by conventional coronary angiography, 74 patients (5.7%) received coronary angioplasty and stent insertion, and 8 patients (0.6%) received a coronary artery bypass graft.

Table 1. Characteristics of patients with and without significant (≥50%) coronary artery disease (univariate analysis)

Characteristics	Patients without CAD (n=873)	Patients with CAD (n=431)	OR, 95% CI	P-value
Age, year (mean ± SD)	62.25 ± 11.59	66.96 ± 9.31	1.042, 1.030 – 1.055	<0.001
Male	516 (59.1)	311 (72.2)	1.793, 1.396 – 2.302	<0.001
Risk factors				
Hypertension	627 (71.8)	365 (84.7)	2.170, 1.606 – 2.931	<0.001
Diabetes	250 (28.6)	200 (46.4)	2.158, 1.698 – 2.741	<0.001
Smoking	348 (39.9)	213 (49.4)	1.474, 1.168 – 1.860	0.001
Dyslipidemia	119 (13.6)	74 (17.2)	1.313, 0.957 – 1.802	0.091
Central obesity	154 (18.4)	63 (15.6)	0.819, 0.595 – 1.129	0.223
Laboratory findings, mmol/L				
Total cholesterol	4.64 ± 1.04	4.76 ± 1.09	1.113, 0.998 – 1.242	0.053
Triglyceride	3.17 ± 2.23	3.79 ± 2.71	1.113, 1.056 – 1.172	<0.001
High-density lipoprotein	1.16 ± 0.61	1.08 ± 0.26	0.435, 0.283 – 0.669	0.001

Table 1. Characteristics of patients with and without significant (≥50%) coronary artery disease (univariate analysis) (continued)

Characteristics	Patients without CAD (n=873)	Patients with CAD (n=431)	OR, 95% CI	P-value
Low-density lipoprotein	2.91 ± 0.89	2.95 ± 0.96	1.043, 0.919 – 1.183	0.516
hs-CRP, mg/L	6.12 ± 19.53	7.47 ± 23.12	1.003, 0.997 – 1.008	0.317
Fasting glucose	6.18 ± 1.99	6.66 ± 2.40	1.104, 1.047 – 1.164	0.001
Significant cerebral atherosclerosis*	360 (53.0)	252 (66.8)	1.786, 1.375 – 2.322	<0.001

Numbers in parenthesis are percentages.

*Patients with cardioembolic stroke were excluded.

CAD = coronary artery disease; hs-CRP = high sensitivity C-reactive protein.

3. Frequency of Cerebral Artery Atherosclerosis

After excluding 248 patients with cardioembolic stroke, any degree of cerebral artery atherosclerosis was found in 855 (81.0%) of 1,056 patients, and there were 612 patients (58.0%) who had significant cerebral artery atherosclerosis. The frequency of significant stenosis of the cerebral artery was higher in the patients with significant CAD than in those without (66.8% vs. 53.0%, $p < 0.001$) (table 1).

4. Relationship between Atherosclerosis in the Cerebral and in the Coronary Arteries

The presence of significant atherosclerosis in the cerebral artery was associated with significant atherosclerosis in the coronary artery ($p < 0.001$). We divided CAD patients into five groups according to the presence, severity, and number of the arteries with significant atherosclerosis: no CAD, mild CAD (<50%), and significant CAD (one-vessel disease, two-vessel disease, and three-vessel disease), and compared the number of cerebral arteries with significant atherosclerosis in each of the groups. The number of cerebral arteries with atherosclerosis increased as the CAD burden increased ($p < 0.001$) (fig. 2).

We investigated the relationship between CAD and cerebral atherosclerosis in terms of location, severity (no stenosis, at least one mild stenosis and no significant stenosis, and at least one significant stenosis) and extent (no stenosis, one significant stenosis, and ≥2 significant stenoses). The association between CAD and cerebral atherosclerosis was stronger with increased severity and extent of cerebral atherosclerosis (table 2). Among cerebral arteries, significant stenosis of the carotid artery (extracranial and intracranial carotid arteries) and of the vertebrobasilar artery (extracranial and intracranial vertebral arteries and basilar artery) were associated with significant CAD (table 2). These associations were also significant as the CAD burden increased (table 3). In contrast, significant stenosis of the anterior, middle or posterior cerebral artery was not associated with significant CAD (table 2).

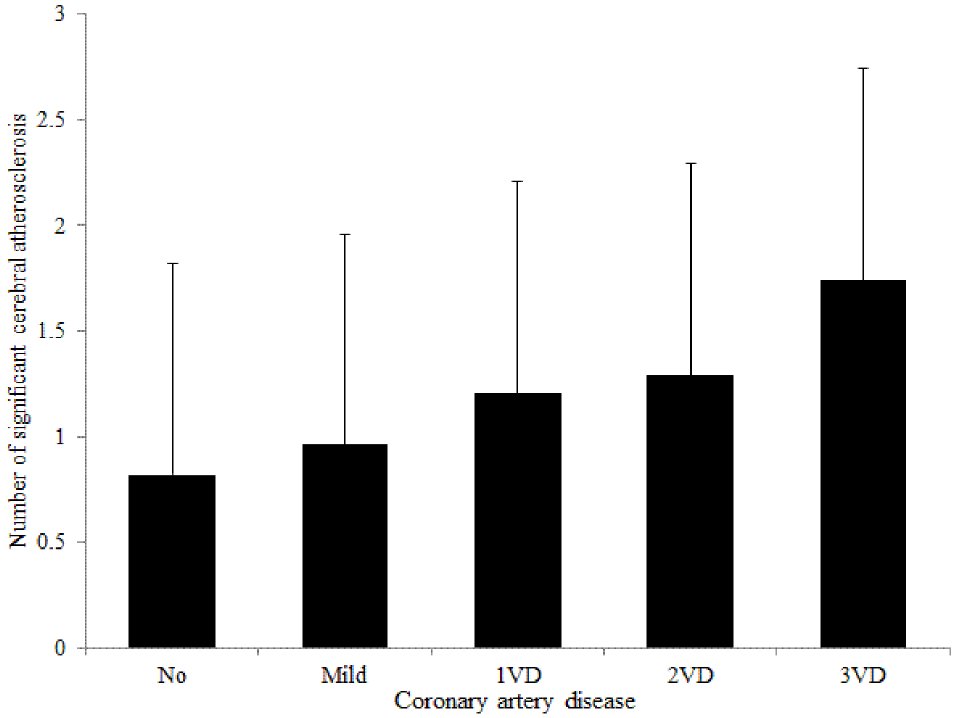

Fig 2. Number of arteries with significant atherosclerosis according to the burden of coronary artery disease. Number of cerebral arteries with significant (≥50%) stenosis increases as the burden of coronary artery disease increases. VD = vessel disease.

Table 2. Relationships between cerebral artery atherosclerosis and significant coronary artery disease (univariate analysis) by location, severity and extent

Cerebral artery atherosclerosis (≥50%)	Coronary artery atherosclerosis (≥50%)		OR, 95% CI	P-value
	Patients without CAD (n=679)	Patients with CAD (n=377)		
Extracranial carotid artery	54 (8.0)	71 (18.8)	2.685, 1.838 – 3.925	<0.001
Intracranial carotid artery	28 (4.1)	33 (8.8)	2.230, 1.326 – 3.753	0.002
Middle cerebral artery	149 (21.9)	83 (22.0)	1.004, 0.741 – 1.361	0.978
Anterior cerebral artery	34 (5.0)	22 (5.8)	1.176, 0.677 – 2.041	0.565
Posterior cerebral artery	77 (11.3)	37 (9.8)	0.851, 0.562 – 1.287	0.444
Extracranial vertebral artery	108 (15.9)	80 (21.2)	1.424, 1.033 – 1.964	0.031
Intracranial vertebral artery	43 (6.3)	55 (14.6)	2.526, 1.658 – 3.848	<0.001
Basilar artery	24 (3.5)	28 (7.4)	2.190, 1.250 – 3.835	0.005

Table 2. Relationships between cerebral artery atherosclerosis and significant coronary artery disease (univariate analysis) by location, severity and extent (continued)

Cerebral artery atherosclerosis (≥50%)	Coronary artery atherosclerosis (≥50%)		OR, 95% CI	P-value
	Patients without CAD (n=679)	Patients with CAD (n=377)		
Severity (stenosis)				<0.001
No	158 (23.3)	43 (11.4)	1	
At least one mild and no significant	161 (23.7)	82 (21.8)	1.871, 1.218 – 2.875	
At least one significant	360 (53.0)	252 (66.8)	2.572, 1.770 – 3.737	
Extent (number of arteries with significant stenosis)				<0.001
No significant	319 (47.0)	125 (33.2)	1	
1 significant	203 (29.9)	117 (31.0)	1.471, 1.081 – 2.000	
2 or more significant	157 (23.1)	135 (35.8)	2.194, 1.610 – 2.990	

Numbers in parenthesis are percentages.

Mild stenosis means stenosis <50% and significant stenosis means stenosis ≥50%.

Table 3. Significant cerebral atherosclerosis according to the burden of coronary artery disease

Cerebral artery atherosclerosis (≥50%)	Burden of coronary artery disease					P-value*
	No (n=295)	Mild (n=384)	1-vessel disease (n=197)	2-vessel disease (n=118)	3-vessel disease (n=62)	
Extracranial carotid artery	13 (4.4)	41 (10.7)	32 (16.2)	21 (17.8)	18 (29.0)	<0.001
Intracranial carotid artery	11 (3.7)	17 (4.4)	18 (9.1)	11 (9.3)	4 (6.5)	0.034
Middle cerebral artery	67 (22.7)	82 (21.4)	44 (22.3)	21 (17.8)	18 (29.0)	0.525
Anterior cerebral artery	16 (5.4)	18 (4.7)	15 (7.6)	4 (3.4)	3 (4.8)	0.512
Posterior cerebral artery	35 (11.9)	42 (10.9)	20 (10.2)	9 (7.6)	8 (12.9)	0.743
Extracranial vertebral artery	47 (15.9)	61 (15.9)	31 (15.7)	30 (25.4)	19 (30.6)	0.008
Intracranial vertebral artery	14 (4.7)	29 (7.6)	27 (13.7)	18 (15.3)	10 (16.1)	<0.001
Basilar artery	7 (2.4)	17 (4.4)	10 (5.1)	13 (11.0)	5 (8.1)	0.005
Total	147 (49.8)	213 (55.5)	124 (62.9)	81 (68.6)	47 (75.8)	<0.001

* P-value from Chi-square test for trend

5. Factors Associated with CAD

Multivariate analysis showed that old age, male sex, diabetes mellitus, high cholesterol levels, high triglyceride levels and low high-density lipoprotein levels were associated with significant CAD (table 4). After adjustment for age, sex, conventional vascular risk factors, and laboratory findings, significant atherosclerosis of the extracranial carotid (OR 1.856, 95% CI 1.214–2.836), intracranial vertebral (OR 2.182, 95% CI 1.364–3.489) and basilar arteries (OR 2.200, 95% CI 1.170–4.138) was associated with significant CAD. Significant atherosclerosis of the intracranial carotid artery showed a weak association with CAD. The association between CAD and cerebral atherosclerosis was stronger with increased severity and extent of cerebral atherosclerosis.

Table 4. Factors associated with significant (≥50%) coronary artery disease (multivariate analysis)

	Model 1			Model 2			Model 3		
Characteristics	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	1.057	1.041 – 1.074	<0.001	1.057	1.040 – 1.073	<0.001	1.058	1.042 – 1.074	<0.001
Male	1.995	1.356 – 2.934	<0.001	1.992	1.365 – 2.907	<0.001	2.005	1.373 – 2.928	0.001
Risk factors									
Hypertension	1.426	0.991 – 2.053	0.056	1.513	1.054 – 2.172	0.025	1.506	0.970 – 2.005	0.073
Diabetes	1.642	1.169 – 2.306	0.004	1.700	1.217 – 2.375	0.002	1.672	1.144 – 2.252	0.006
Smoking	1.403	0.981 – 2.007	0.064	1.392	0.978 – 1.981	0.067	1.371	0.976 – 1.992	0.068
Dyslipidemia	0.867	0.548 – 1.372	0.542	0.888	0.564 – 1.397	0.607	0.882	0.561 – 1.388	0.588
Laboratory findings									
Total cholesterol	1.241	1.047 – 1.471	0.013	1.254	1.060 – 1.484	0.008	1.250	1.057 – 1.477	0.009
Triglyceride	1.084	1.019 – 1.154	0.011	1.080	1.017 – 1.147	0.013	1.076	1.013 – 1.144	0.018
HDL cholesterol	0.482	0.270 – 0.861	0.014	0.464	0.263 – 0.818	0.008	0.459	0.260 – 0.810	0.007
Fasting glucose	1.033	0.960 – 1.110	0.389	1.019	0.948 – 1.096	0.606	1.025	0.954 – 1.102	0.498
Artery with significant stenosis (≥50%)									
Extracranial carotid	1.856	1.214 – 2.836	0.004						
Intracranial carotid	1.737	0.969 – 3.112	0.064						

Table 4. Factors associated with significant (≥50%) coronary artery disease (multivariate analysis) (continued)

	Model 1			Model 2			Model 3		
Characteristics	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Extracranial vertebral	1.220	0.853 – 1.746	0.276						
Intracranial vertebral	2.182	1.364 – 3.489	0.001						
Basilar	2.200	1.170 – 4.138	0.014						
Severity of cerebral atherosclerosis									
No stenosis				1					
Mild stenosis				1.631	1.018 – 2.613	0.042			
Significant stenosis				2.087	1.380 – 3.157	0.001			
Extent of cerebral atherosclerosis									
No significant							1		
1 significant							1.363	0.975 – 1.907	0.070
2 or more significant							1.782	1.267 – 2.505	0.001

* Variables with P<0.2 in univariate analysis were entered into these logistic models

HDL=high-density lipoprotein

6. Risk of CAD according to the Presence of Vascular Risk Factors and Cerebral Atherosclerosis

We investigated the risk levels of CAD according to the presence of vascular risk factors, and the presence and location of cerebral atherosclerosis. When compared to stroke patients with <2 risk factors and without significant cerebral atherosclerosis, those with atherosclerosis in the carotid and/or vertebrobasilar arteries and those with ≥2 risk factors had significantly higher risks of CAD (table 5). The risk of CAD was about twice as high in stroke patients with ≥2 risk factors than in those with <2 risk factors. In patients with ≥2 risk factors and atherosclerosis in both the carotid and the vertebrobasilar arteries, the risk of CAD was highest (OR 8.36, 95% CI 4.15–16.87). Almost all patients in this group (96.1%) showed any degree of CAD and about two thirds (68.6%) had significant stenosis of at least one coronary artery (table 5).

Table 5. Risk of coronary artery disease according to risk factors and significant (≥50%) cerebral atherosclerosis

Risk factors	Cerebral atherosclerosis	Number of Patients (n=1056)	Number of CAD patients		OR, 95% CI*	P-value
			Any (n=761)	Significant (n=377)		
Less than 2	No	164	98 (59.8)	34 (20.7)	1	
	Other than carotid and vertebrobasilar A.	77	45 (58.4)	15 (19.5)	0.93, 0.47 – 1.82	0.822
	Either carotid or vertebrobasilar A.	104	70 (67.3)	29 (27.9)	1.48, 0.84 – 2.62	0.180
	Both carotid and vertebrobasilar A.	17	12 (70.6)	8 (47.1)	3.40, 1.22 – 9.47	0.019
Two or more	No	280	198 (70.7)	91 (32.5)	1.84, 1.17 – 2.90	0.008
	Other than carotid and vertebrobasilar A.	128	92 (71.9)	43 (33.6)	1.93, 1.14 – 3.27	0.014
	Either carotid or vertebrobasilar A.	235	197 (83.8)	122 (51.9)	4.13, 2.62 – 6.51	<0.001
	Both carotid and vertebrobasilar A.	51	49 (96.1)	35 (68.6)	8.36, 4.15 – 16.87	<0.001

Numbers in parentheses are percentages.

A = artery; CAD = coronary artery disease; CI = confidence interval; OR = odds ratio.

*Odds ratios were calculated with data for significant CAD.

IV. DISCUSSION

This study showed that many ischemic stroke patients without a history of CAD have coronary artery atherosclerosis in that any degree of coronary artery atherosclerosis was detected in about 70% of patients and significant atherosclerosis was found in about one third of patients. The presence and burden (extent and severity) of cerebral artery atherosclerosis were clearly associated with those of coronary artery atherosclerosis. These results suggest that atherosclerosis is a systemic disease.

The frequency of significant CAD was estimated as 22.9–41.2% in studies using thallium myocardial scintigraphy.[5, 7, 27, 28] In a recent coronary angiography-based study, coronary plaques were found in 61%, and coronary stenosis ≥50% was present in 25.7% in patients with cerebral infarction.[29] A few studies have examined the frequency of CAD in stroke patients using coronary CT angiography. In 71 patients who were examined by 16-multislice coronary CT angiography, 25.4% had significant CAD.[19] The frequency was 37.5% in 104 patients who had a modified Rankin score <4 and were aged <80 years when they were examined by 8-multislice coronary CT angiography.[30] Recently, in 274 cases of nondisabling, noncardioembolic stroke or TIA in patients aged 45–75 years, CAD was detected in 18% using 64-multislice CT.[20] In an autopsy study, the frequency of significant CAD, which was assessed in 188 ischemic stroke patients, was 29.3% and that of coronary plaques was 68.2%.[8] The strengths of our study include the large sample size (1,304 patients), which is the largest to our knowledge of any similar studies, and homogeneity of the patient group, which was achieved by enrolling patients in a consecutive and prospective manner. Our findings clearly demonstrate that a substantial portion of stroke patients who have not been previously diagnosed with CAD actually have CAD.

It is noteworthy that a location-specific relationship between cerebral and coronary artery atherosclerosis in our study. Extracranial carotid and cervicocephalic artery atherosclerosis has been known to be associated with CAD.[12, 14, 20] However, in previous studies, atherosclerosis of the individual cerebral artery was not correlated with the CAD. Moreover, some studies were based on carotid duplex study for cerebral artery evaluation or were conducted in selected patients with coronary artery bypass graft surgery or heart surgery.[12–14] Our study, which was based on angiographic studies and assessed the relationships between the coronary artery and individual cerebral arteries, demonstrated that atherosclerosis of not only the extracranial carotid artery, but also of the intracranial vertebral and basilar arteries have strong associations with coronary artery atherosclerosis. Our study also clearly showed that atherosclerosis of the anterior, middle and posterior cerebral arteries was not associated with atherosclerosis of the coronary artery. It is uncertain why there is such a distinct pattern of association between coronary artery atherosclerosis and the cerebral artery. An explanation according to dichotomization of 'intracranial' and 'extracranial' cerebral arteries, which was attempted in many previous epidemiologic studies, was not applicable to our findings. The cerebral arteries that were associated with the coronary artery were larger and in closer proximity to the coronary artery than those that were not associated. However, this simple observation was not enough to explain the reason. Further studies are required to reveal this issue.

Although it is likely that many stroke patients have CAD, coronary artery evaluation has not been included in routine evaluation of stroke patients. At the guideline level, no specific recommendations for coronary evaluation in stroke patients are available, due to a lack of large studies regarding CAD in stroke patients. However, the American College of Cardiology/American Heart Association recommends exercise testing for asymptomatic persons without known CAD who had multiple risk factors, or for men >45 years and women >55 years who are at risk for CAD due to other diseases.[31] At the statement level, the American Heart Association/American Stroke Association recommends consideration for coronary heart disease (CHD) testing in patients with carotid or large artery atherosclerosis, and in those with high risk CHD risk factor scores based on Framingham algorithms (10-year CHD risk ≥20%).[11]

Based on previous guidelines and statements for ischemic stroke patients, we enrolled patients with multiple (≥2) risk factors, men >45 years and women >55 years of age, and those with cerebral artery atherosclerosis. We stratified risks of CAD according to the location of cerebral atherosclerosis and the presence of multiple risk factors because atherosclerosis of the carotid and vertebrobasilar arteries was significantly associated with the presence of CAD. It appeared that the risk of CAD was high in stroke patients with atherosclerosis (≥50%) of both the carotid and the vertebrobasilar artery, and those with multiple (≥2) risk factors and atherosclerosis (≥50%) of either the carotid or the vertebrobasilar artery. The risk was particularly high in patients who had ≥2 risk factors and atherosclerosis of both the carotid and the vertebrobasilar artery, as almost all of those patients showed mild or significant CAD.

Stroke/cerebral atherosclerosis and ischemic heart disease/coronary atherosclerosis share common risk factors. Although all of the patients enrolled in this study were stroke patients, and the frequency of cerebral atherosclerosis was higher than the frequency of CAD, risk factors such as diabetes mellitus, older age, high triglyceride levels, and low high-density lipoprotein cholesterol levels were independently associated with the presence of significant CAD. These findings suggest a dominant role of these vascular risk factors in developing CAD. Likewise, the risk of CAD was significantly higher instroke patients with multiple risk factors even though they did not have cerebral atherosclerosis in our study. Thus, coronary evaluation may be also considered in stroke patients with multiple risk factors without significant cerebral atherosclerosis.

Our study suggested that the frequency of preclinical CAD is substantial in stroke patients. When planning coronary evaluation in stroke patients, its yield may be improved by considering the presence of multiple vascular risk factors and the presence of atherosclerosis in the carotid, vertebral and basilar arteries.

REFERENCES

1. Alberts MJ, Bhatt DL, Mas JL, Ohman EM, Hirsch AT, et al. Three year follow-up and event rates in the international reduction of atherothrombosis for continued health registry. Eur Heart J 2009;30:2318–26.

2. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366:1773–83.

3. Touze E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. Stroke 2005;36:2748–55.

4. Man BL, Fu YP, Chan YY, Lam W, Hui CF, Leung WH, et al. Long-term outcomes of ischemic stroke patients with concurrent intracranial and extracranial stenoses and ischemic heart disease. Cerebrovasc Dis 2010;29:236–41.

5. Rokey R, Rolak LA, Harati Y, Kutka N, Verani MS. Coronary artery disease in patients with cerebrovascular disease: A prospective study. Ann Neurol 1984;16:50–3.

6. Wofford JL, Kahl FR, Howard GR, McKinney WM, Toole JF, Crouse JR 3rd. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. Arterioscler Thromb 1991;11:1786–94.

7. Di Pasquale G, Andreoli A, Pinelli G, Grazi P, Manini G, Tognetti F, et al. Cerebral ischemia and asymptomatic coronary artery disease: A prospective study of 83 patients. Stroke 1986;17:1098–1101.

8. Gongora-Rivera F, Labreuche J, Jaramillo A, Steg PG, Hauw JJ, Amarenco P. Autopsy prevalence of coronary atherosclerosis in patients with fatal stroke. Stroke 2007;38:1203–10.

9. Hertzer NR, Young JR, Beven EG, Graor RA, O'Hara PJ, Ruschhaupt WF 3rd, et al. Coronary angiography in 506 patients with extracranial cerebrovascular disease. Arch Intern Med 1985;145:849–52.

10. Wilterdink JL, Furie KL, Easton JD: Cardiac evaluation of stroke patients. Neurology 1998;51:S23–S26.

11. Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council On Clinical Cardiology of the American Heart Association/American Stroke Association. Circulation 2003; 108:1278–90.

12. Craven T, Ryu J, Espeland M, Kahl F, McKinney W, Toole J, et al. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis. A case control study. Circulation 1990;82:1230–42.

13. Kaden JJ, Eckert JP, Poerner T, Haghi D, Borggrefe M, Pillich M, et al. Prevalence of atherosclerosis of the coronary and extracranial cerebral arteries in patients undergoing aortic valve replacement for calcified stenosis. J Heart Valve Dis 2006;15:165–8.

14. Bae HJ, Yoon BW, Kang DW, Koo JS, Lee SH, Kim KB, et al. Correlation of coronary and cerebral atherosclerosis: Difference between extracranial and intracranial arteries. Cerebrovasc Dis 2006;21:112–9.

15. Ropers D, Baum U, Pohle K, Anders K, Ulzheimer S, Ohnesorge B, et al. Detection of coronary artery stenoses with thin-slice multidetector row spiral computed tomography and multiplanar reconstruction. Circulation 2003;107:664–6.
16. Martuscelli E, Romagnoli A, D'Eliseo A, Razzini C, Tomassini M, Sperandio M, et al. Accuracy of thin-slice computed tomography in the detection of coronary stenoses. Eur Heart J 2004;25:1043–8.
17. Hamon M, Morello R, Riddell JW, Hamon M. Coronary arteries: Diagnostic performance of 16- versus 64-section spiral CT compared with invasive coronary angiography-meta-analysis. Radiology 2007;245:720–31.
18. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.
19. Seo WK, Yong HS, Koh SB, Suh S, Kim JH, Yu SW, et al. Correlation of coronary artery atherosclerosis with atherosclerosis of the intracranial cerebral artery and the extracranial carotid artery. Eur Neurol 2008;59:292–8.
20. Calvet D, Touze E, Varenne O, Sablayrolles JL, Weber S, Mas JL. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. Circulation 2010;121:1623–9.
21. Cho HJ, Lee JH, Kim YJ, Moon Y, Ko SM, Kim HY. Comprehensive evaluation of coronary artery disease and aortic atherosclerosis in acute ischemic stroke patients: usefulness based on Framingham risk score and stroke subtype. Cerebrovasc Dis 2011;31:592–600.
22. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al.

Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.

23. Expert Panel on Detection Evaluation Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.

24. The North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445–53.

25. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, et al. The warfarin-aspirin symptomatic intracranial disease study. Neurology 1995;45:1488–93.

26. Kim YD, Choi HY, Jung YH, Nam CM, Yang JH, Cho HJ, et al. Mirror pattern of cerebral artery atherosclerosis in patients with ischaemic stroke. Eur J Neurol 2009;16:1159–64.

27. Love BB, Grover-McKay M, Biller J, Rezai K, McKay CR. Coronary artery disease and cardiac events with asymptomatic and symptomatic cerebrovascular disease. Stroke 1992;23:939–45.

28. Urbinati S, Di Pasquale G, Andreoli A, Lusa AM, Ruffini M, Lanzino G, et al. Frequency and prognostic significance of silent coronary artery disease in patients with cerebral ischemia undergoing carotid endarterectomy. Am J Cardiol

1992;69:1166–70.
29. Amarenco P, Lavallee PC, Labreuche J, Ducrocq G, Juliard JM, Feldman L, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. Stroke 2011;42:22–9.
30. Hoshino A, Nakamura T, Enomoto S, Kawahito H, Kurata H, Nakahara Y, et al. Prevalence of coronary artery disease in Japanese patients with cerebral infarction: impact of metabolic syndrome and intracranial large artery atherosclerosis. Circ J 2008;72:404–8.
31. Gibbons RJ, Balady GJ, Timothy Bricker J, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883–92.

ABSTRACT(IN KOREAN)

허혈뇌졸중 환자에서 다채널 컴퓨터단층촬영 관상동맥 혈관조영술을 이용하여 찾아낸 전임상단계의 관상동맥질환의 빈도와 위험요인

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유준상

죽상경화증은 전신적인 질환으로, 많은 허혈뇌졸중 환자들은 관상동맥질환을 같이 가지고 있는 경우가 많다. 관상동맥질환은 뇌졸중 환자의 주요한 사망 원인으로, 뇌졸중 환자에서 전임상 단계의 관상동맥질환을 발견하는 것은 장기적인 경과와 생존률의 향상에 도움을 줄 수 있다. 그러나, 뇌졸중 환자에서 심장혈관과 뇌혈관 죽상경화증 사이의 관계는 아직 완전히 밝혀지지 않은 상태이다. 이 연구는 허혈뇌졸중 환자에서 관상동맥질환의 빈도와 고위험군을 찾는 것을 목표로 하였다.

연구는 2006년 7월부터 2010년 6월 사이에 급성 허혈뇌졸중으로 입원한 환자를 대상으로 시행되었으며, 총 1,304명의 환자들이 64채널 컴퓨터단층촬영 관상동맥 혈관조영술과 뇌혈관 조영술을 시행받아 연구에 포함되었다. 이 환자들에서 관상동맥질환의 빈도,

위치와 심한정도를 조사하여 심장혈관과 뇌혈관 죽상경화증 사이의 관계를 밝히고 또한 뇌졸중 환자에서 관상동맥질환의 고위험군을 분석하였다.

관상동맥의 의미있는 (50% 이상) 협착이 있는 환자의 비율은 32.3%였으며, 모든 정도의 관상동맥질환을 가진 환자는 70.1%였다. 당뇨, 혈중 총콜레스테롤, 고밀도지질단백질-콜레스테롤, 중성지방 그리고 의미있는 두개강외 목동맥, 두개강내 척추동맥과 뇌바닥동맥의 협착이 관상동맥질환과 관련되어 있었다. 그러나 의미있는 전뇌, 중뇌, 후뇌동맥의 협착은 관상동맥질환과 유의한 관계가 없었다. 관상동맥의 죽상경화증은 뇌혈관 죽상경화증의 강도와 범위가 증가할수록 함께 증가하는 경향이 있었다. 2개 이상의 위험요인을 가지고 있으며, 목동맥과 척추-뇌바닥 동맥에 협착을 가지고 있는 환자는 그렇지 않은 환자군에 비하여 매우 높은 관상동맥질환의 위험을 가지고 있었다(교차비 8.36).

본 연구에서 뇌졸중 환자가 전임상단계의 관상동맥질환을 많이 가지고 있으며, 위치와 강도를 고려해 볼 때 관상동맥과 뇌혈관의 죽상경화증은 분명한 관계가 있음을 보여주었다. 관상동맥질환의 위험은 두개 이상의 위험요인을 가지고 있으며, 목동맥과 척추-뇌바닥 동맥의 죽상경화증을 가지고 있는 경우에 특히 높았다.

핵심되는 말 : 혈관조영술, 죽상경화증, 컴퓨터단층촬영 혈관조영술, 관상동맥질환, 허혈뇌졸중

PUBLICATION LIST

1. Yoo J, Yang JH, Choi BW, Kim YD, NAM HS, Choi HY, Cho HJ, Lee HS, Cha MJ, Choi D, Nam CM, Jang Y, Lee DH, Kim J, Heo JH. The frequency and risk of preclinical coronary artery disease detected using multichannel cardiac computed tomography inpatients with ischemic stroke. Cerebrovasc Dis. 2012;33(3):286-94