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# Carotid Intima-Media Thickness, Not Carotid Plaque, is Associated With Large Territory Cerebral Infarction in Patients With Ischemic Stroke

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## ABSTRACT

**Background and Objectives:** Carotid intima-media thickness (IMT) has been associated with an increased risk of ischemic stroke. To better understand this association, we evaluated the relationships of vascular risk factors, including carotid IMT and carotid plaque, and large territory cerebral infarction and small vessel stroke. **Subjects and Methods:** A total of 502 patients with acute ischemic stroke were divided into two groups according to neurologic examinations and imaging studies; 1) a large territory infarction group (group I: n=126, 64.4 ± 11 years, 78 males) and 2) a small vessel stroke group (group II: n=376, 62.5 ± 11 years, 242 males). We evaluated associations between (a) territory and non-territory strokes and (b) age, sex, potential vascular risk factors, carotid image and cardiac function (by echocardiography). **Results:** We did not find significant between group differences of age, sex, diabetes, previous history of ischemic stroke, plaque (presence, site and size of carotid plaque), and velocity of carotid blood flow and left ventricle ejection fraction. However, group I had a higher incidence of hypertension (p=0.006), smoking (p=0.003), and dyslipidemia (p=0.001). Group I had thicker carotid IMT than group II (right carotid: 0.81 ± 0.21 mm vs. 0.76 ± 0.19 mm, p=0.035; left carotid: 0.88 ± 0.23 mm vs. 0.80 ± 0.20 mm, p=0.014) and a higher e/e' level (12.08 vs. 9.66, p<0.001). Dyslipidemia, thicker carotid IMT and elevated E/E' ratios were significant independent predictors for large territory infarction in patients with ischemic stroke. **Conclusion:** Carotid IMT is significantly increased in patients with large territory infarction compared with those with small vessel stroke. (*Korean Circ J* 2010;40:272-276)

**KEY WORDS:** Cerebral infarction; Stroke; Carotid arteries.

## Introduction

The carotid arteries are responsible for providing blood flow to the brain. If the carotid artery is blocked, or if a piece of carotid artery plaque dislodges and travels

to the brain, the individual can suffer a stroke. This can lead to paralysis, loss of ability to speak, blindness, loss of independence, and even death. Stroke is currently a leading cause of disability and the major leading cause of death in developing countries.<sup>1)</sup> A large portion of stroke cases result from cerebral ischemia; the remainder is from hemorrhage. Large territory cerebral infarction tends to be the result of ischemic insult more than small vessel lacunar infarction.

In earlier studies, carotid atherosclerosis was confirmed by autopsy or by angiography.<sup>2-5)</sup> However, over the last decade, the development of noninvasive ultrasound techniques has made the visualization and measurement of the layers of the arterial wall and plaques possible in large population samples.<sup>6-9)</sup> It has been suggested that the intima-media thickness (IMT) of the common carotid artery (CCA) is one of the most sensitive markers for the

Received: August 23, 2009

Revision Received: November 23, 2009

Accepted: December 25, 2009

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earliest stages of atherosclerosis.<sup>10)</sup>

Increases in carotid IMT have been associated with increased risk of ischemic stroke.<sup>11)</sup> We did this study to evaluate the relationship of vascular risk factors, including carotid IMT and carotid plaque, with large territory cerebral infarction, one of the common subtypes of ischemic stroke and small vessel stroke.

## Subjects and Methods

### Study population

A total of 502 patients with acute ischemic stroke were enrolled in our study between April 2007 to September 2008.

Neurologists and radiologists diagnosed ischemic stroke by neurologic examination and imaging study. If patients had any embolic source such as infective endocarditis and intracardiac thrombi, they were excluded. Patients with ischemic stroke were divided into two groups according to infarct territory: Group I was defined by large territory infarctions ( $n=126$ ,  $64.4 \pm 11$  years, 78 males). Group II was defined by small vessel strokes including lacunar infarction ( $n=376$ ,  $62.5 \pm 11$  years, 242 males). We evaluated the association of territory and non-territory strokes with age, sex, potential vascular risk factors, carotid image and cardiac function (by echocardiography).

### Definition of hypertension, diabetes, dyslipidemia and territory infarction

Subjects were considered to have hypertension if their blood pressure was  $\geq 140/\geq 90$  mmHg as recommended by the Joint National Committee (JNC) VII,<sup>12)</sup> or if they were on treatment for hypertension. The American Diabetes Association criteria<sup>13)</sup> were used to define diabetes mellitus (DM). We considered a subject to have DM when the fasting plasma glucose levels were  $\geq 126$  mg/dL in 2 consecutive assessments or if they were on treatment for DM. Dyslipidemia was diagnosed according to the 2004 update of National Cholesterol Education Program guidelines.<sup>14)</sup>

According to these guidelines, we included in the study patients with a level of low density lipoprotein-cholesterol  $\geq 160$  mg/d, a level of high density lipoprotein-cholesterol  $\leq 40$  mg/dL and a level of triglycerides  $\geq 150$  mg/dL.<sup>15)</sup> Large territory cerebral infarction was defined if a major cerebral artery territory infarction was shown by a neurologic examination and an imaging study. This included anterior, middle and posterior cerebral infarction. Lacunar, cortical or subcortical infarction were classified as small vessel stroke.

### Laboratory tests

Blood sampling for serum lipid profiles and glucose were obtained after at least 14 hours of fasting.

### Measurement of carotid intima-media thickness and carotid flow velocity

Carotid B-mode ultrasound was performed on both common carotid arteries and internal carotid arteries using a 10 MHz linear probe (VIVID 7, GE, USA). Images were interpreted at the last centimeter of the CCA prior to the carotid bulb. We first described the presence or absence of plaques or of atheromas, which were defined as a focal widening relative to adjacent segments protruding into the lumen more than 1.5 mm, with or without calcifications. On a longitudinal two-dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery appear as two bright white lines separated by a hypoechoic space. End-diastolic images were frozen, and the far wall IMT was identified as the region between the lumen-intima interface and the media-adventitia interface.<sup>16)</sup> Peak systolic and end diastolic carotid flow velocity was measured by pulse wave Doppler on the CCA and the internal carotid artery (ICA).<sup>17)</sup>

### Measurement of aortic intima-media thickness

Transesophageal echocardiography was done using an Acuson 128 XP or Sequoia C256 ultrasonograph (Siemens, Mountain View, CA, USA) equipped with a 3.5- to 7.0-MHz multiplane probe. To ensure imaging of the entire thoracic aorta, the probe was rotated posteriorly and advanced to the distal esophagus and withdrawn slowly to scan the descending aorta and aortic arch. The probe was then rotated and advanced again to image the ascending aorta. The maximal value of the aortic IMT was collected for each patient.<sup>18)</sup> Transesophageal echocardiography was performed by experienced investigators who had no knowledge of the results of our other analyses.

### Statistical analysis

Data are reported as mean  $\pm$  SD. In univariate analysis, risk factors for different end-points were analyzed using the Chi-square test for discrete variables and Student's *t*-test for continuous variables. Multiple logistic regression analysis was used to determine a model with independent predictive factors. A  $p < 0.05$  was considered statistically significant. The software for statistical analysis was Statistical Package for the Social Sciences 13.0.

## Results

### Baseline characteristics

We did not find any significant between group differences for age, sex, diabetes, or previous history of ischemic stroke. However, group I patients with large territory cerebral infarct had a significantly higher percentage of hypertension ( $p=0.006$ ), smoking ( $p=0.003$ ), and dyslipidemia ( $p=0.001$ ) (Table 1). Also, group I had thicker carotid IMT values than did group II (right CCA:

**Table 1.** Baseline clinical characteristics

	Group I (n=126)	Group II (n=376)	p
Age (years)	64.4±11.0	62.5±11.0	0.138
Sex (male, %)	78 (61.9)	241 (63.2)	0.433
Height (cm)	162.8±9.8	162.9±9.5	0.952
Weight (kg)	62.6±12.1	64.4±11.4	0.850
Hypertension (%)	83 (65.8)	209 (55.5)	0.027
Diabetes (%)	43 (34.1)	110 (29.3)	0.127
Dyslipidemia (%)	90 (71.4)	189 (50.6)	0.020
Smoking (%)	36 (28.5)	65 (17.2)	0.021
Old CVA (%)	16 (12.2)	38 (14.6)	0.383

CVA: cerebrovascular accident

**Table 2.** Comparison of IMT and plaque in patients with ischemic stroke

	Group I (n=126)	Group II (n=376)	p
Right IMT (mm)	0.82±0.21	0.76±0.19	0.005
Plaque (%)	27 (36.9)	83 (34.1)	0.386
Plaque site (bulb, %)	24 (85.7)	59 (70.2)	0.082
Plaque size (mm)	2.77±0.88	2.37±0.71	0.319
Left IMT (mm)	0.88±0.23	0.79±0.20	0.001
Plaque (%)	25 (34.2)	78 (32.2)	0.434
Plaque site (bulb, %)	18 (81.8)	57 (76)	0.400
Plaque size (mm)	1.5±1.20	1.46±1.21	0.588
Descending aorta IMT	1.47±0.39	1.53±0.41	0.498

IMT: intima-media thickness

**Table 3.** Comparison of carotid blood flow velocity in the patients with ischemic stroke

	Group I (n=126)	Group II (n=376)	p
Right CCA PS (m/sec)	45.3±20.0	50.3±27.0	0.068
CCA ED	12.9±7.2	14.4±7.4	0.034
ICA PS	46.2±27.2	51.8±31.2	0.086
ICA ED	16.6±11.1	18.5±12.3	0.152
ICA/CCA	1.01±0.8	1.12±1.3	0.381
Left CCA PS (m/sec)	48.3±24.1	53.1±27.0	0.087
CCA ED	13.4±7.5	15.7±9.7	0.017
ICA PS	44.1±24.5	49.2±34.6	0.160
ICA ED	16.4±9.5	18.4±1.5	0.203
ICA/CCA	0.92±0.9	0.88±0.5	0.093

CCA: common carotid artery, ICA: internal carotid artery, PS: peak systolic velocity, ED: end diastolic velocity

0.81±0.21 mm vs. 0.76±0.19 mm,  $p=0.035$ ; left CCA: 0.88±0.23 mm vs. 0.80±0.20 mm,  $p=0.014$ ) despite the absence of significant differences between the two groups for the presence of carotid plaque, the site of carotid plaque, the size of carotid plaque and the velocity of carotid blood flow (Table 2 and 3). Regarding echocardiographic parameters, group I showed higher E/E' ratios-which indicate diastolic dysfunction-than did group II, whereas there was no significant between group difference for left ventricle ejection fraction, which indicates systolic dysfunction (Table 4).

**Table 4.** Comparison of echocardiographic parameters in patients with ischemic stroke

	Group I (n=126)	Group II (n=376)	P
LVEDD (mm)	47.9±5.6	48.8±4.5	0.056
LVESD (mm)	31.3±4.9	31.6±4.6	0.637
IVS (mm)	9.45±1.4	9.46±1.5	0.940
LVPW (mm)	9.26±1.3	9.32±1.4	0.698
EF (%)	63.8±7.0	64.0±6.9	0.853
AOD (mm)	32.5±3.9	32.8±5.6	0.531
LAD (mm)	39.9±7.7	37.6±6.5	0.001
E (m/s)	0.63±0.3	0.58±0.24	0.080
A (m/s)	0.69±0.1	0.71±0.2	0.437
E/A	0.77±0.3	0.81±0.3	0.230
DT (msec)	238.9±156	204.0±68	0.001
E' (m/s)	0.061±0.1	0.071±0.1	0.495
A' (m/s)	0.092±0.1	0.099±0.1	0.980
S' (m/s)	0.079±0.1	0.082±0.1	0.744
E/E'	11.41±8.3	9.67±4.0	0.002

LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, IVS: interventricular septal thickness, LVPW: left ventricular posterior wall thickness, EF: ejection fraction, AOD: aortic diameter, LAD: left atrial diameter, E: mitral inflow E velocity, A: mitral inflow A contraction velocity, DT: deceleration time, E': mitral septal annular velocity, A': mitral septal annulus A' velocity, S': mitral septal annulus systolic velocity

**Table 5.** Independent predictors of large territory infarction in patients with ischemic stroke

	Hazard ratio	Confidence interval	p
Hypertension	1.359	0.869-2.127	0.179
Dyslipidemia	2.066	1.312-3.254	0.002
Smoking	1.673	1.014-2.761	0.051
CCA IMT	4.710	1.754-12.645	0.002
E/E'	1.039	1.004-1.074	0.027

CCA: common carotid artery, IMT: intima-media thickness, E/E': mitral inflow E velocity/mitral septal annular velocity

### Correlation of carotid and aortic atherosclerosis

We found a positive and significant correlations between carotid IMT and descending thoracic aortic IMT (right CCA  $r=0.261$ ,  $p=0.009$ ; left CCA  $r=0.232$ ,  $p=0.021$ ) (Fig. 1). But, there were no significant correlations between descending thoracic aorta IMT and infarction territory. Descending thoracic aorta plaques were also not associated with infarct subgroup.

### Independent predictors of territory infarction

By multivariate regression analysis, dyslipidemia, thicker carotid IMT and elevated E/E' were significant independent predictors of large territory infarction in patients with ischemic stroke (Table 5).

## Discussion

In this study, we compared CCA IMT and plaque for the risk assessment of respective stroke subtypes. Caro-

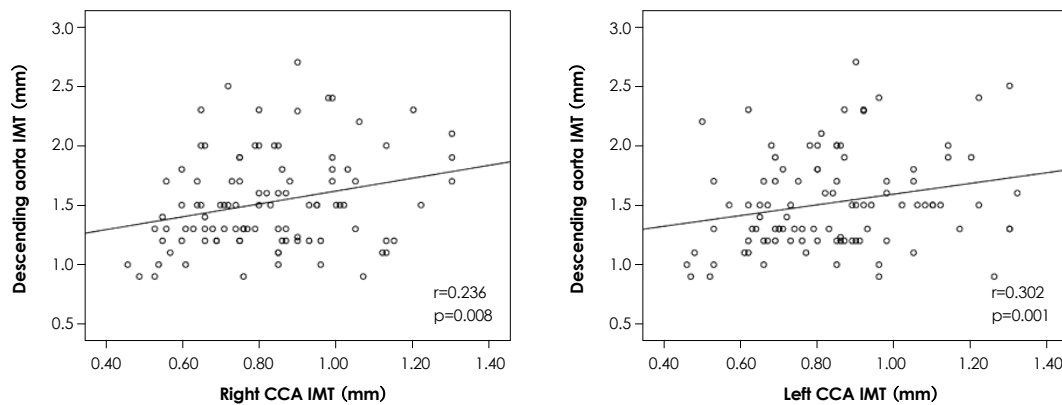


Fig. 1. Correlation of descending thoracic aortic intima-media thickness (IMT) and common carotid artery (CCA) IMT.

tid IMT was significantly increased in patients with large territory infarction compare with those with small vessel stroke. Various noninvasive imaging has been recommended by the American Heart Association for evaluation of risk in primary prevention.<sup>19)</sup> Carotid IMT is well known as a noninvasive surrogate marker of coronary atherosclerosis. IMT is increased in patients who are at risk for cardiovascular disease and in those patients with atherosclerotic disease.<sup>20-23)</sup> O'Leary et al.<sup>24)</sup> reported that an increased carotid IMT is associated with a higher risk of stroke and acute myocardial infarction in an elderly population and it is also a more powerful predictor of cardiovascular disease than the conventional risk factors for atherosclerosis. Similarly, Touboul et al.<sup>25)</sup> demonstrated a greater CCA IMT in patients with all major cerebral infarction subtypes compared with controls. In contrast, Nagai et al.<sup>26)</sup> reported a greater plaque score only for atherothrombotic and lacunar infarction patients compared to nonstroke patients. Consequently, the implications of carotid atherosclerosis remain to be established for each stroke subtype.

Certain known risk factors exist for the development of carotid artery atherosclerosis. These include smoking, diabetes, high blood pressure, high cholesterol, family history of cardiac or vascular disease and advanced age. The present results indicated that hypertension, smoking and dyslipidemia are more common in patients with large territory cerebral infarct.

Some previous investigators reported that carotid plaque was superior to carotid IMT for stratification of cardiovascular risk, and that carotid IMT was not a significant predictor for myocardial infarction and stroke.<sup>27)28)</sup> However, carotid IMT was different from carotid plaque as a predictor for developing stroke subtypes in this study. Also, IMT of the descending thoracic aorta showed a strong correlation with coronary atherosclerosis and was a good predictor for stroke and peripheral arterial disease in some reports.<sup>29)</sup> In our study, descending thoracic aorta IMT was correlated with carotid IMT as in the previous study, whereas they did not find a significant

correlation with infarction subtype. Therefore, we thought that the atherosclerosis of the descending thoracic aorta was related to ischemic stroke, but this variable did not differentiate infarct subtype. Based on our findings, carotid IMT evaluation was more sensitive than other surrogate markers such as carotid plaque or descending aorta IMT for differentiating stroke subtypes in patients with ischemic stroke.

Additionally, diastolic dysfunction was more common in patients with large territory cerebral infarcts. Many investigators insist that diastolic dysfunction is not a disease but a step of the aging process resulting from decreasing left ventricle compliance.<sup>30)31)</sup> Left ventricular systolic function tends to be preserved compared with diastolic function until old age. Although age differences were not significant between groups, the large territory infarction group showed higher E/E' than did the small vessel infarction group. This finding suggests a large infarction effect on diastolic function rather than on systolic function in patients with ischemic stroke.

The current study has several limitations, both in the diagnosis of stroke subtypes and in the transferability of conclusions to the general population. Because this study had a cross-sectional design, whether it can be applied to all individuals with stroke is not clear. Large prospective studies are still necessary to establish a link between these measures and future risk of stroke subtypes.

#### Acknowledgments

This study was supported by a grant from the Korea Healthcare technology R&D project (A084869), Ministry for Health, Welfare & Family Affairs, Republic of Korea, and the Cardiovascular Research Foundation, Asia.

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