pISSN 1975-4612/ eISSN 2005-9655

www.kse-jcu.org
http://dx.doi.org/10.4250/jcu.2013.21.1.12
ORIGINAL ARTICLE J Cardiovasc Ultrasound 2013;21(1):12-17

Differences of Aortic Stiffness and Aortic Intima-Media Thickness According to the Type of Initial Presentation in Patients with Ischemic Stroke

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Background: Aortic stiffness and intima-media thickness (IMT) are known to be associated with ischemic stroke. The aim of the present study was to investigate the differences of aortic stiffness and IMT between cerebral infarction (CI) and transient ischemic attack (TIA).

Methods: A total of 500 patients with acute stroke were divided into 2 groups: the TIA group (n = 230, 62.4 ± 12 years, 144 males) versus CI group (n = 270, 63.4 ± 11 years, 181 males). Aortic stiffness index and IMT, as well as conventional cardiovascular risk factors, were compared.

Results: The prevalence of hypertension, diabetes, and dyslipidemia were significantly higher, and left atrial volume and E/E' were significantly elevated in the CI group than in the TIA group. Carotid IMT was significantly thicker in the CI group than in the TIA group. Aortic stiffness index β was significantly higher (7.99 ± 2.70 vs. 7.02 ± 4.30, $p = 0.043$) and aortic IMT was significantly thicker (1.53 ± 0.41 vs. 1.45 ± 0.39 mm, $p = 0.040$) in the CI group than in the TIA group. Aortic stiffness index β was significantly correlated with the IMT of the aorta (r = 0.279, $p = 0.014$), right (r = 412, $p < 0.001$) and left carotid artery (r = 441, $p < 0.001$).

Conclusion: Aortic stiffness index β and IMT were significantly higher in patients with CI than TIA. The result of the present study suggested that CI is associated with more advanced degree of atherosclerotic and arteriosclerotic process than TIA.

KEY WORDS: Aorta · Stiffness · Stroke.

Introduction

Arterial stiffness in large arteries is a significant predictor of cardiovascular morbidity and mortality.[1)] Previous studies have shown that abnormal vascular tone plays a significant role for ischemic stroke and coronary heart disease.[2)3)]

With the advance in noninvasive ultrasound techniques, the direct visualization and measurement of the arterial wall structure, including the presence of plaques, became possible.[4)5)] The intima-media thickness (IMT) of the common carotid artery (CCA) is demonstrated a strong and sensitive surrogate marker of the earliest changes of atherosclerosis.[6)]

Aortic distensibility is an elasticity index of the aorta, and it can reflect aortic stiffness.[7)] As the aortic elasticity decreased, aortic distensibility is also decreased, and stiffness index became elevated. Aortic distensibility can be measured by obtaining the cyclic diameter changes of the ascending aorta on transthoracic echocardiography (TTE).[8)9)] Aortic distensibility can also be evaluated by obtaining the cyclic diameter change

• Received: October 31, 2012 • Revised: January 29, 2013 • Accepted: February 13, 2013
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of the descending thoracic aorta during a transesophageal echocardiography (TEE). Based on these measurements on TEE, elastic modulus and Young's circumferential static elastic modulus of the descending thoracic aorta can be calculated.[10][11] The previous studies have shown that aortic stiffness and IMT are associated with ischemic stroke,[12][13] but the differences of these parameters, according to the type of stroke, has been poorly studied. Therefore, the aim of the present study was to investigate the differences of aortic stiffness and IMT between advanced cerebral infarction (CI) and earlier manifested transient ischemic attack (TIA).

Methods

Study population

The present study was an retrospective observational study performed in a single tertiary center. From April 2007 to December 2010, a total of 635 patients with acute stroke underwent comprehensive echocardiographic examination including TTE, TEE, and carotid ultrasound. One hundred thirty five patients were excluded from the present study, and the reasons of exclusion were as follows; 121 patients who suspected cryptogenic stroke with intra or extracardiac shunt including patent foramen ovale (117 patients), atrial septal defect (2 patients), or pulmonary arteriovenous malformation (2 patients), 11 with left atrial thrombus, 3 patients with vegetations on left side cardiac valves. A total of 500 patients were enrolled finally and divided into 2 groups: the TIA group (n = 230, 62.4 ± 12 years, 144 males) versus the CI group (n = 270, 63.4 ± 11 years, 181 males). The type of stroke was classified into TIA and CI by a neurologist based on neurologic examination and magnetic resonance imaging study. TIA was defined as a brief episode of neurologic dysfunction, resulting from a focal temporary cerebral ischemia, not associated with CI, and CI was defined as the focal brain necrosis due to complete and prolonged ischemia with radiologic lesion.

Measurement of echocardiographic parameters on TTE

All echocardiographic parameters were measured by standardized method according to the guideline of American Society of Echocardiography.

Measurement of aortic stiffness on TEE

All consecutive patients were taken TEE using a multiplane 5-MHz TEE probe (Sequoia, Siemens, Malvern, PA, USA) after mild sedation with intravenous midazolam. TEE probe was advanced to the mid to lower esophageal level (about 30 to 35 cm from the incisors), and then slowly withdrawn to the aortic arch level to scan the descending thoracic aorta. Digital cine loops and continuous video recordings form transverse and longitudinal images of the descending thoracic aorta were obtained for subsequent off-line analysis.

IMT was measured in a region free of plaque at the level of the aortic far wall of 26 to 30 cm from the incisors and was defined as the mean value of the thickness of 3 points in longitudinal image.

Distensibility of the aorta was evaluated by measuring the systolic (SD) and diastolic diameter (DD) of the descending thoracic aortic diameters. SD and DD were measured at the time of maximum aortic anterior motion and at the peak of the QRS complex, respectively. The following aortic elastic indices were calculated:

Aortic strain = (SD - DD) / DD

Aortic stiffness index (β) = ln [systolic blood pressure (SBP) / diastolic blood pressure (DBP)] / [(SD - DD) / DD], where SBP and DBP are the systolic and diastolic blood pressures measured at pre-examination, and "ln" is the natural logarithm.

Aortic distensibility = 2 × (SD - DD) / [(SBP - DBP) × DD]

Measurement of carotid IMT

Carotid B-mode ultrasound was performed on both common carotid arteries using a 10 MHz linear probe (VIVID 7, GE, Milwaukee, WI, USA). Images were interpretation of the one last centimeters of the CCA, prior to the carotid bulb, consisted first to describe the presence or absence of plaques of atheroma, defined as a focal widening relative to adjacent segments, protruding the lumen of 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 hypoechogenic space. End-diastolic images were frozen, the far wall IMT was identified as the region between the lumen-intima interface and the media-adventitia interface.[14]

Statistical analysis

Data were reported as the mean ± standard deviations. In the univariate analysis, risk factors for different end-points were analyzed using a chi-square test for discrete variables and Student's t-test for continuous variables. Multiple logistic regression analysis was used to determine the model with independent predictive factors. A p-value < 0.05 was considered statistically significant. The software for statistical analysis was SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The results are summarized in Table 1. The prevalence of hypertension, diabetes, and dyslipidemia were significantly higher in the CI group than in the TIA groups.

Echocardiographic parameters

Echocardiographic findings are summarized in Table 2. Left atrial volume was significantly larger, and the ratio of early (E) and late diastolic velocity (A) (E/A) and the ratio of E and ear-

Table 1. Baseline clinical characteristics of the patients

	TIA group (n = 230)	CI group (n = 270)	*p*-value
Age (yr)	62.4 ± 12	63.4 ± 11	0.138
Male, n (%)	144 (62.6)	181 (67.0)	0.522
Hypertension, n (%)	118 (51.3)	185 (68.5)	0.005
Diabetes, n (%)	57 (24.7)	99 (36.6)	0.022
Dyslipidemia, n (%)	98 (42.6)	189 (70.0)	0.001
Smoking, n (%)	38 (16.5)	65 (24.2)	0.160
Atrial fibrillation, n (%)	24 (10.4)	35 (12.9)	0.082

TIA: transient ischemic attack, CI: cerebral infarction

Table 2. Echocardiographic findings of the patients

	TIA group (n = 230)	CI group (n = 270)	*p*-value
LVEDD (mm)	48.51 ± 5.2	48.4 ± 5.2	0.812
LVESD (mm)	32.92 ± 1.8	31.31 ± 1.6	0.522
IVS (mm)	9.34 ± 1.5	9.54 ± 1.3	0.936
LVPW (mm)	9.29 ± 2.3	9.31 ± 1.6	0.817
EF (%)	63.61 ± 6.8	64.22 ± 5.2	0.355
LA volume (mL)	56.12 ± 1.8	79.20 ± 1.2	0.041
E/A	0.80 ± 0.3	0.82 ± 0.2	0.019
E/E'	9.40 ± 56.2	10.61 ± 6.9	0.016

TIA: transient ischemic attack, CI: cerebral infarction, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, IVS: interventricular septum, LVPW: left ventricular posterior wall, EF: ejection fraction, LA: left atrium, E: early diastolic mitral inflow velocity, A: late diastolic mitral inflow velocity, E': early diastolic septal annular velocity

Table 3. Laboratory findings of the patients

	TIA group (n = 230)	CI group (n = 270)	*p*-value
Hemoglobin (mg/dL)	13.3 ± 2.7	13.4 ± 2.7	0.792
Creatinine (mg/dL)	0.95 ± 0.7	0.98 ± 0.7	0.671
Total cholesterol (mg/dL)	177 ± 42	186 ± 36	0.017
Triglyceride (mg/dL)	131 ± 80	135 ± 74	0.600
LDL cholesterol (mg/dL)	111 ± 40	122 ± 39	0.005
HDL cholesterol (mg/dL)	49 ± 15	42 ± 11	0.440
HbA1c (%)	6.2 ± 1.0	6.4 ± 1.3	0.174
hs-CRP (mg/dL)	1.65 ± 2.8	1.93 ± 2.6	0.595
Homocystein (mg/dL)	10.3 ± 8.1	12.2 ± 10.3	0.080

TIA: transient ischemic attack, CI: cerebral infarction, LDL: low density lipoprotein, HDL: high density lipoprotein, HbA1C: hemoglobin A1C, hs-CRP: high sensitivity C-reactive protein

ly diastolic velocity of mitral septal annulus (E') (E/E') were significantly higher in the CI group than in the TIA group. Intra-cardiac thrombus or unexpected hyper-mobile materials on heart valve were not seen in this examination.

Laboratory findings

Laboratory findings are summarized in Table 3. The levels of total and low density lipoprotein cholesterol were significantly higher in the CI group than in the TIA group. Other laboratory findings were not different between the groups.

Arterial stiffness and IMT

The results of aortic stiffness index and IMT between the groups were summarized in the Table 4.

The IMT of the descending thoracic aorta and carotid artery were significantly thicker in the CI group than in the TIA group. Aortic stiffness index β of the descending thoracic aorta was also significantly higher in the CI group compared to the TIA group. On multivariate regression analysis, aortic stiffness index β, carotid IMT, and dyslipidemia were independently associated with CI, whereas aortic IMT was not associated with CI (Table 5).

Aortic stiffness index β showed significant moderate correlation with the IMT of the descending thoracic aorta, right, and left carotid artery ($r = 0.279$, $p = 0.014$, $r = 0.412$, $p < 0.001$, $r = 0.441$, $p < 0.001$, respectively) (Fig. 1).

Table 4. Aortic stiffness index and intima-media thickness of the patients

	TIA group (n = 230)	CI group (n = 270)	*p*-value
Aortic stiffness index β	7.02 ± 4.3	7.99 ± 2.7	0.043
Descending aortic IMT (mm)	1.45 ± 0.39	1.53 ± 0.41	0.040
Right carotid IMT (mm)	0.75 ± 0.18	0.80 ± 0.20	0.011
Left carotid IMT (mm)	0.79 ± 0.22	0.84 ± 0.22	0.005

TIA: transient ischemic attack, CI: cerebral infarction, IMT: intima-media thickness

Table 5. Relative risk of cerebral infarction as compared to transient ischemic attack on linear regression analysis

	RR	95% CI	*p*-value
Hypertension	0.994	0.663-1.490	0.975
Diabetes	1.473	0.972-2.232	0.068
Dyslipidemia	0.476	0.312-0.725	0.008
Aortic stiffness index β	1.073	1.008-1.142	0.027
Descending aortic IMT	0.802	0.416-1.545	0.510
Left carotid IMT	2.882	1.116-7.444	0.029

RR: relative risk, CI: confidence interval, IMT: intima-media thickness

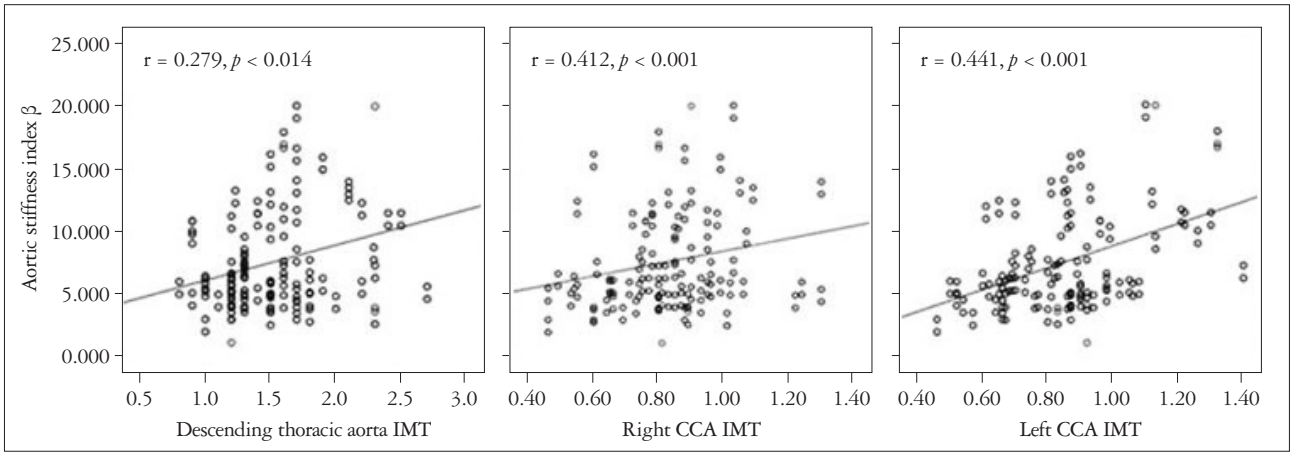

Fig. 1. Correlations between aortic stiffness index β and intima-media thickness (IMT) of carotid and descending thoracic aorta. CCA: common carotid artery.

Discussion

In the present study, the authors evaluated the differences of aortic stiffness and IMT between CI and TIA, and the main finding of the present study was that aortic stiffness was significantly increased and IMT of the aorta and carotid artery were significantly thicker in patients with CI than TIA. Based on these observations, therefore, it is suggested that CI is associated with more advanced degree of atherosclerotic and arteriosclerotic process than TIA.

Arterial stiffness is the most important cause of cardiovascular complications and a major contributor to atherosclerosis, and thus, it is associated with the development of stroke and myocardial infarction.[15] Direct measurement of arterial stiffness requires invasive techniques, which are unsuitable for a routine clinical practice. In previous studies, it has been demonstrated that pulsatile changes in ascending aortic diameter can be measured during a routine transthoracic echocardiography.[16] Non-invasively evaluated β index as a determinant of aortic stiffness is comparable with invasive methods with a high degree of accuracy.[11] Decreased arterial distensibility was associated with older age, hypertension, and African American ethnicity. Additionally, known atherosclerotic risk factors, such as current smoking and higher high density lipoprotein cholesterol levels, were related with arterial stiffness.[17]

Ischemic stroke, including TIA and CI, is well known amongst the atherosclerotic disease of the cerebral arterial system. In the present study, the prevalence of diabetes, hypertension, and dyslipidemia were more frequent in the CI group than in the TIA group. Although both TIA and CI are subtypes of ischemic stroke, atherosclerotic progression was different between the groups in the present study. Generally, CI was regarded to relatively severe symptomatic form with radiologic lesion, compare to that of TIA. Atherothrombotic infarcts are often preceded by TIA. A TIA is a focal neurological deficit that lasts less than 24 hours and resolves. The mechanism of TIAs is not clear until now. It may be caused by criti-

cal reduction of perfusion that impairs neurological function but falls short of causing permanent tissue damage, or by emboli that breaks up soon after they occlude vessels. Our data showed that advanced diastolic dysfunction was found in a more severe form of ischemic stroke. Diastolic dysfunction rather than systolic function more affected in the infarction group. Arterial distensibility, descending thoracic aorta IMT and carotid IMT were more decreased in the CI group than in the TIA group. In a previous study, increased arterial stiffness was associated with more severe left ventricular diastolic dysfunction, although the strength of the association varied according to the specific measure used in this elderly cohort.[18] This results suggest that cardiovascular risk factors interact to affect arterial stiffness and left ventricular relaxation, and therefore, support the importance of screening using atherosclerotic surrogate and early intervention in this patient population.

Impaired elasticity index of aorta were correlated with the proven surrogate for atherosclerosis, such as aortic IMT and carotid IMT in this study. It might be the manifestations of common atherosclerotic process, in addition to the arterial wall nutrition hypothesis.[19][20] It is a very interesting finding that aortic distensibility is more closely associated with carotid IMT than aortic IMT in those with ischemic stroke. There may be some affect from the lack of methodological standardization for IMT measurement of descending thoracic aorta compared with carotid artery.[21] Uncontrolled risk factors of atherosclerosis impose future burden of vascular diseases in our health system, which should implement earlier stratification of risk factor management. Therefore, measurement of carotid IMT rather than descending thoracic aortic IMT would be a sufficient role for screening atherosclerotic arterial stiffness in patients with ischemic stroke.

The current study has several potential limitations. Firstly, because the present study was an retrospective observational study and included only patients who underwent TEE examination, lots of stroke patients without TEE examination were not included. Therefore, the results of the present study cannot be generalized to all type of stroke. Secondly, the authors tried to exclude the patients with cryptogenic or embolic stroke, but not all patients with cryptogenic or embolic stroke could be excluded in the present study. Thirdly, the prevalence of atrial fibrillation was slightly higher in the CI than in the TIA group, it would also affect the results of statistical analysis. Large prospective studies will be needed to establish the relationships between these measures and the future risk of stroke subtypes.

• Acknowledgements

This work was supported by a grant of the new investigator funded by the Chonnam National University (2011-0588).

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