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Influence of Atherosclerosis Risk Factors on Carotid Intima, Media, and Intima-Media thickness

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Abstract

We intended to measure the IT, MT, and the IMT of carotid artery separately and tried to analyze the clinical significance. Two hundred and fifty consecutive patients (125 males, 125 females) underwent carotid artery scanning using high-resolution ultrasound. The images were off-line analyzed using B-mode ultrasound image processing, devised in our research. We measured the IT, MT, and IMT semi-automatically at the far wall of designated 1cm length of the right common carotid and calculated the average values over the 200 points. The IT ($p < 0.05$), MT ($p < 0.05$) as well as IMT ($p < 0.01$) of patients with atherosclerotic disease were significantly thicker than that of the patients without atherosclerotic disease. Patients with hypertension showed significantly thicker IT ($p < 0.05$), MT ($p < 0.01$), and IMT ($p < 0.01$) than that of the patients without hypertension. However, only IT was thicker in patients with smoking ($p<0.05$) than that of the patients without smoking. Smoking was associated only with intima while hypertension was associated with the all three layer's thickness. This result suggests the atherosclerotic process can be different by cardiovascular risk factors.

Keywords: Carotid artery, Intima thickness (IT), Media thickness (MT), Intima-media thickness (IMT), Ultrasound

Introduction

The severity of carotid intima-media thickness (IMT), which is the sum of intima thickness (IT) and media thickness (MT), is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction. Evaluation of IMT using ultrasonography is a validated quantitative method for assessing atherosclerosis[1], since IMT is independently associated with atherosclerotic risk factors and adverse cardiovascular events.[2-5] The appearance of atherosclerosis in the carotid artery has been highly associated with atherosclerosis in the aorta and the incidence of coronary heart disease.[4] Therefore, the severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction.[5] Arterial intima layer is the innermost coat of blood vessels, consisting of a thin lining of endothelial cells oriented longitudinally and arterial media layer is the middle coat of blood vessel walls, composed principally of thin cylindrical smooth muscle cells and elastic tissue, accounting for the bulk of the wall of most arteries. Abnormal neointima formation is the main pathophysiology of obliterative vascular disease, although atherosclerotic changes of vessel wall also include smooth muscle proliferation and inflammatory process in media and adventitia. We

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hypothesized that IT and MT have a different clinical significance with regards to development and pathophysiology of atherosclerosis.

However, most studies used carotid IMT as a surrogate marker rather than separate measurement of IT and MT due to probably technical problems. It defines carotid IMT as the distance between the luminal border of the intima and the outer border of the media using high-resolution ultrasound. The border of intima layer can be identified as the first echogenic line from the lumen and the outer border of media layer as the second echolucent line in the high-resolution ultrasound. The measurement of carotid IMT is getting more precise by semiautomatic measurement rather than manual measurement.[6] And these semiautomatic measurements of carotid IMT give us more reliability in understanding many clinical studies as well as more important clinical significance about that. The neointima is developed by a migration, proliferation, and accumulation of vascular smooth muscle cells in the intima.[7] Medial thickness relates statistically to necrosis indirectly through associations with foam cells and fibroplasia.

We performed this study to evaluate the individual clinical significance of the intima layer and the media layer of the common carotid artery (CCA) by individual measurement using high-resolution ultrasound and newly devised image processing algorithm

Methods

Subjects

Two hundred and fifty consecutive patients (125 males, 125 females) underwent carotid artery scanning using high-resolution ultrasound. Patients were included in this study if they gave an informed consent after fully explanation and did not have the following exclusion criteria. Exclusion criteria included history of neck radiation, carotid arterial surgery, dissection of aorta or carotid artery, and cervical trauma. Patients demographic and laboratory data within 2 weeks including lipid profile, glucose, homocysteine, and fibrinogen were obtained. This study was approved by the hospital ethics committee and also in accordance with the Declaration of Helsinki. Fifty patients from the 250 patients enrolled were excluded due to poor delineation of the borders between intima and media layers by new method. The rest 200 patients were analyzed in this study. The clinical characteristics of the patients are shown in Table 1. The mean age of the study population was 56 +/– 12 years (102 males, 98 females). Most patients had an atherosclerotic disease such as coronary artery disease or ischemic stroke, or atherosclerotic risk factors. The subjects' clinical characteristics are represented in Table 1.

Table 1 Characteristics of the Study Subjects

Variables	Values
Age (yrs)	56±12
Male, n (%)	102 (51.0%)
BMI (kg/m^2)	24.6±4.1
Hypertension, n (%)	107 (53.5%)
Diabetes, n (%)	49 (24.5%)
Smoking, n (%)	40 (20.0%)
Systolic blood pressure (mm Hg)	127.6±23
Diastolic blood pressure (mm Hg)	79±13
Diagnosis	
Without atherosclerotic disease, n (%)	99(49.5%)
With atherosclerotic disease, n (%)	101(50.5%)
Total cholesterol (mg/dl)	185±42
Triglyceride (mg/dl)	162±103
HDL cholesterol (mg/dl)	44.0±12.5
LDL cholesterol (mg/dl)	109±28
Fasting blood glucose (mg/dl)	133±54
Homocysteine (mg/dl)	11.5±5.6
Fibrinogen (mg/dl)	3.1±0.7
Hs-CRP (mg/dl)	0.22±0.26
Blood urea nitrogen (mg/dl)	22±17
Creatinine (mg/dl)	2.3±2.1
Uric acid (mg/dl)	5.4±1.7

BMI= body mass index; LV= left ventricular; HDL= high-density lipoprotein; LDL= low-density lipoprotein; Hs-CRP= high sensitivity C-reactive protein.

Carotid Artery Scanning and Image Processing

Common Carotid arterial (CCA) scanning with a high-resolution ultrasound system (Hewlett-Packard Sonos 5500; 7.5 MHz peripheral probe) was done by a certified blinded sonographer in a dark, air-conditioned room. The far wall of the right CCA was longitudinally scanned while patient was in supine position and head extension, and then the image was controlled by adequate gain control and depth control. The depth control was fixed during the whole analysis to set the calibration. The gain control was adjusted according to the carotid artery image in order to get a clear delineation of the intima, media, and adventitia layers of the carotid artery far wall. After getting a clear carotid artery image, the image was digitally captured for off-line analysis (Figure 1).

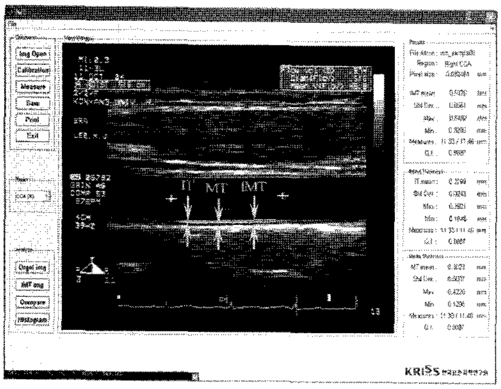

Figure1. Separate measurements of intima (IT), media (MT), and intima-media thickness (IMT).

To measure IT, MT, and IMT effectively, a new method of CCA image processing was devised in our previous study.[8] Image processing was carried out as follows: first, the CCA image was loaded, and the size per pixel was determined with electronic caliper, which was previously calibrated at 4 cm depth in axial direction of multipurpose phantom by using the broadband linear array transducer (Figure 2).

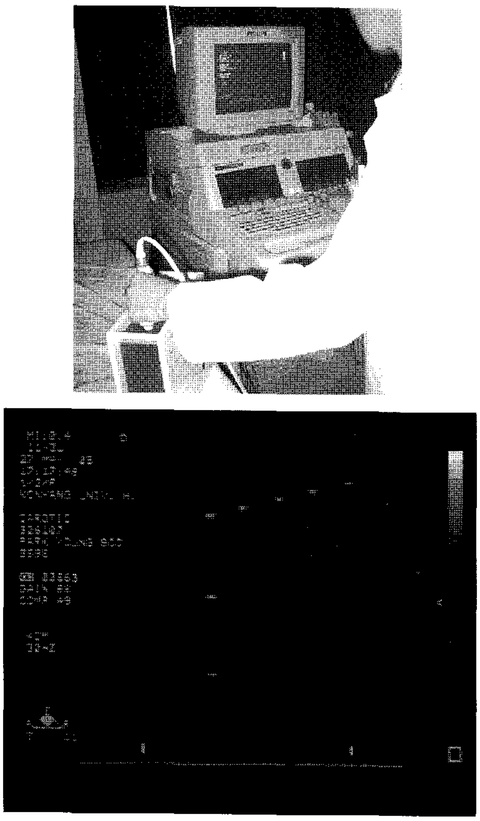

Figure2. Calibration of ultrasound image obtained with 7.5 MHz at 4 cm depth in multipurpose phantom.

Next, a region of interest (ROI) for each CCA image was selected from distal to proximal, starting from 1 cm proximal to the carotid bifurcation and extending at least 1 cm distal. The staring point was adjusted to exclude any plaque if present in this region. The quality of ROI image was evaluated, and the noise removed with a filtering algorithm.[9] Three layers (intima, media, and adventitia) were identified after acquiring the edge images using edge detection algorithm.[10] To evaluate the thickness of each layer, the numbers of the pixels corresponding to the thickness of each three layers were calculated. Finally, the IT, MT, and IMT were measured by multiplying the calibration factor with the number of pixels (applying calibration factor) for each three layers.

The reproducibility of scanning CCA image was validated in other's research.[11] The reliability of the new method devised in this study can be estimated indirectly by comparing the IMTs measured using this method with that of using commercial software which was previously validated. Therefore, to validate the reliability, the IMT values measured for 200 CCA images by new method were compared with that of by M'ATH.

Statistical Analysis

All analyses were done using SPSS (version 12.0; SPSS Inc., Chicago, Illinois). Values are expressed as mean ± standard deviation. Comparison of each layer thickness according to the presence of risk factors was done with independent *t*-test. Linear regression analysis was performed to determine independent predictor of intima, media, and intima-media thickness. Statistical significance was accepted when $p<0.05$.

Results and Discussion

To evaluate the reliability of new method for IMT measurement, the relationship between new method and M'ATH in the IMT measurements for 200 CCA images were compared. The IMT ranged from 0.46 to 1.08 mm, with a mean value of 0.75 ± 0.11 mm, when measured with M'ATH and from 0.48 to 1.12 mm, with a mean value of 0.76 ± 0.12 mm, when measured with new method. The correlation between the two methods was excellent with the correlation coefficient of 0.960 (Figure 3).

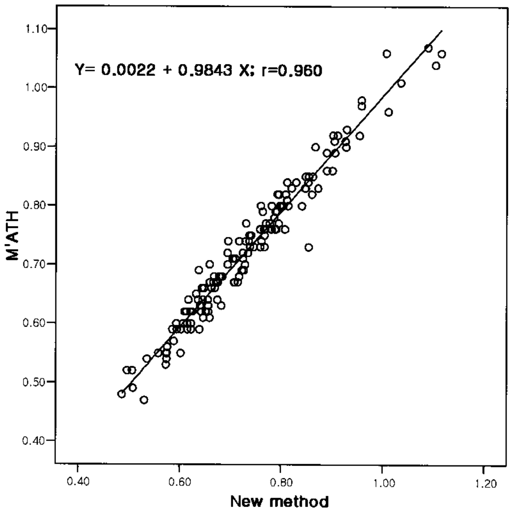

Figure3. Correlation between M'ATH and new method for IMT measurement of common carotid artery (n=200).

Table 2 Comparison of carotid intima (IT), media (MT), and intima-media thicknesses (IMT) in patients with and without atherosclerosis

	Without atherosclerosis (n = 99)	With atherosclerosis (n = 101)	t	p
IT (mm)	0.32 ± 0.07	0.33 ± 0.09	-2.24	0.0
MT (mm)	0.40 ± 0.09	0.44 ± 0.10	-2.50	0.0
IMT (mm)	0.72 ± 0.08	0.77 ± 0.09	-2.67	0.0

* p<0.05 ; ** p<0.01

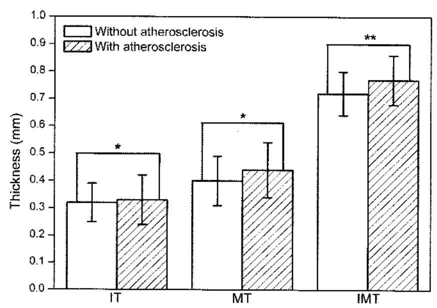

Figure4. Comparison of carotid intima (IT), media (MT), and intima-media thicknesses (IMT) in patients with and without atherosclerosis.

The IT ($p < 0.05$), MT ($p < 0.05$) as well as IMT ($p < 0.01$) of patients with atherosclerotic disease (n=101) were significantly thicker than that of the patients without atherosclerotic disease (n=99) (Table 2 and Figure 4).

Thickness of all 3 layers was significantly higher in patients with hypertension than in those without hypertension ($p<0.05$) (Table 3). Among smokers, only the intima layer was significantly thicker compared with that in nonsmokers ($p<0.05$). The presence of other risk factors such as diabetes and hypercholesterolemia were not significantly correlated with thickness of each layer of the carotid wall (Table 3 and Figure 5).

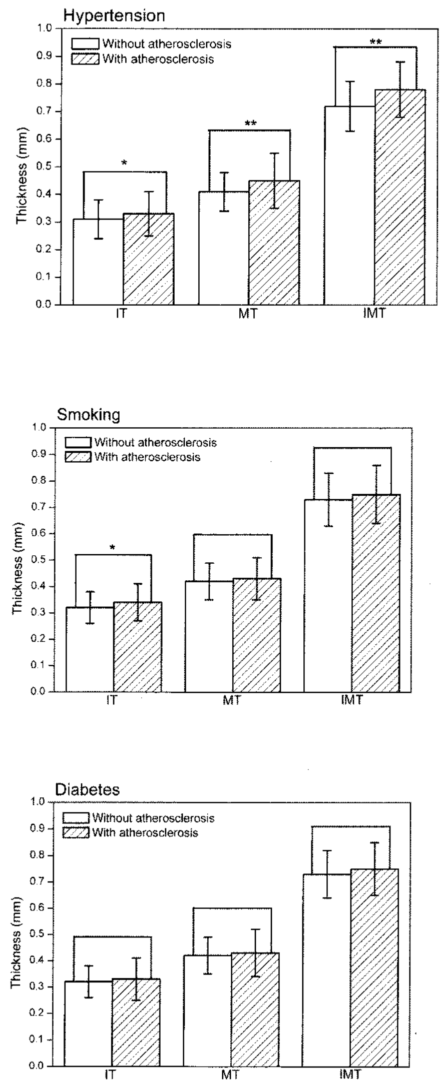

Figure5. Comparison of carotid intima (IT), media (MT), and intima-media thicknesses (IMT) according to atherosclerosis risk factors.

Table 3 Relationship between carotid intima (IT), media (MT), and intima-media thicknesses (IMT) and atherosclerosis risk factors

Risk Factor	IT (mm)		MT (mm)		IMT (mm)	
	(+)	(-)	(+)	(-)	(+)	(-)
Hypertension	0.33±0.08	0.31±0.07*	0.45±0.10	0.41±0.07**	0.78±0.10	0.72±0.09**
Smoking	0.34±0.07	0.32±0.06*	0.43±0.08	0.42±0.07	0.75±0.11	0.73±0.10
Diabetes	0.33±0.08	0.32±0.06	0.43±0.09	0.42±0.07	0.75±0.10	0.73±0.09

(+)= with risk factor; (-) = without risk factor; * $p<0.05$; *$p<0.01$ compared with that of patients with risk factor

We determined the edge between lumen and intima for IT and the edge between intima and media for MT, respectively, by using not only the Canny edge detection algorithm but also the statistical signal processing method.[8,10,12] The IT and MT determined in our research may slightly differ from the real thickness, possibly due to the lack of histological examination. However, the correlation of IT or MT with the atherosclerosis risk factors is valid because it inspects the relative variation of IT or MT depending on the atherosclerosis risk factors. Our results suggest that each layer of the CCA wall can be affected by specific cardiovascular risk factors in different ways. As our previous study[8], smoking was associated only with intima while hypertension was associated with the all three layer's thickness. Therefore, clinical study with specific risk factors such as hypertension or smoking as in our study needs to focus on specific layer of vessel wall using this technique. Because the IMT depends on the site measured, existence of plaque, and etc., the measurement protocol of IMT should be standardized. The separate measurement of IT and MT confirms that atherosclerosis risk factors affect the arterial wall in its own way. This novel noninvasive method for individual measurement of carotid artery IT, MT, and IMT will be useful in the future clinical studies and helpful in many in-vivo human trials.

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