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Review Article

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Measurement and Clinical Analysis of Carotid Intima, Media and Intima-Media Thickness

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Abstract

Individual clinical significance of each layer of CCA (common carotid artery) has not been well studied. We intended to measure the intima thickness (IT), media thickness (MT), and intima-media thickness (IMT) of CCA separately and tried to analyze the clinical significance. One hundred fifty one consecutive patients (mean age: 57 ± 15 years; 77 males, 74 females) underwent CCA scanning using high-resolution ultrasound. The images were off-line analyzed using B-mode ultrasound image processing, devised for individual measurement of IT and MT as well as IMT. The mean coefficients of variation of new method measuring IT, MT, and IMT separately were 0.16% for IMT and 0.21% for both IT and MT. The IT ($p < 0.01$), MT ($p < 0.01$) as well as IMT ($p < 0.001$) of patients with atherosclerotic disease were significantly thicker than that of the patients without atherosclerotic disease. Patients with hypertension showed significantly thicker IT ($p < 0.01$), MT ($p < 0.001$), and IMT ($p < 0.001$) than that of the patients without hypertension. However, only IT was thicker in patients with smoking ($p<0.01$) than that of the patients without smoking.

Key words: Carotid artery, Intima thickness (IT), Media thickness (MT), Intima-media thickness (IMT), Ultrasound.

Introduction

Features of atherosclerosis include foam cell infiltrates, fibroplastic intimal thickening, and atheronecrosis.[1] The neointima is developed by a migration, proliferation, and accumulation of vascular smooth muscle cells in the intima.[2] Medial thickness relates statistically to necrosis indirectly through associations with foam cells and fibroplasia. These findings are based on histology of autopsy or animal study.[1-3] Evaluation of carotid intima media wall thickness (IMT) using ultrasonography is a validated quantitative method for assessing atherosclerosis,[4] that is closely correlated with pathological findings observed in the carotid artery.[5] Moreover, the appearance of atherosclerosis in the carotid artery has been highly associated with atherosclerosis in the aorta [6] and the incidence of coronary heart disease.[7-9] Therefore, the severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction.[10] Carotid IMT, which is the sum of intima thickness (IT) and media thickness (MT), is independently associated with the several risk factors and adverse cardiovascular events.[7,10-12] Abnormal neointima formation is the main pathophysiological consequences of obliterative vascular disease, although atherosclerotic changes may also includes smooth muscle proliferation and inflammatory process in both media and adventitia.[13,14] Therefore, we hypothesized that IT and MT have different clinical responses to cardiovascular risk factor exposure and the development and pathophysiology of atherosclerosis.

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

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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.[15] 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.

In this study, we aimed to measure the carotid IT, MT, and IMT separately using high-resolution ultrasound and newly devised image processing algorithm and tried to analyze the clinical significance.

Matrials and Methods

Study population

One hundred seventy consecutive patients referred for ischemic heart disease screening were studied prospectively. 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.

Common Carotid Artery Scanning

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(Fig. 1).

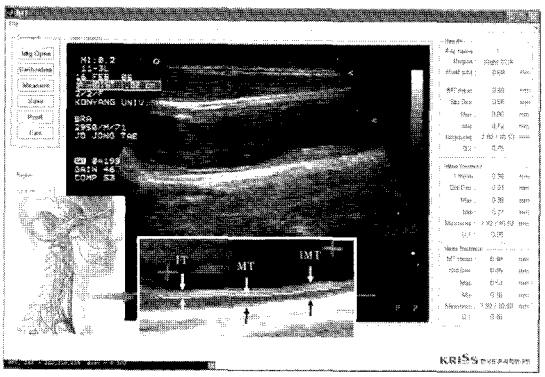

Figure 1 Separate measurements of intima (IT), media (MT), and intima-media thickness (IMT) using new method software devised in this study.

Image Processing for Separate Measurement of Intima and Media Layer

To measure IT, MT, and IMT effectively, a new method of CCA image processing was devised in this study. Image processing was carried out as follows (Fig. 2): first, the CCA image scanned was loaded from hard disk of the computer. Pixel calibration was performed with electronic calipers using the B-mode ultrasound system to determine a calibration factor. 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.[16] Three layers (intima, media, and adventitia) were identified after acquiring the edge images using edge detection algorithm.[17] 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.

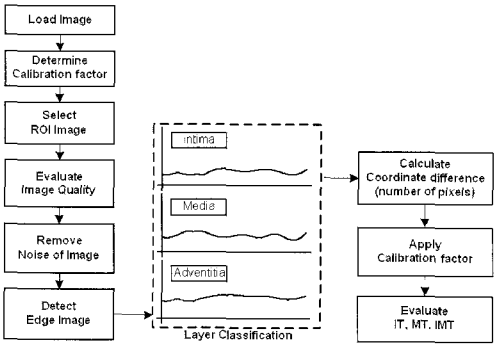

Figure 2. Block-diagram of image processing for separate measurements of intima, media, and intima-media layers. ROI= region of interest; IT= intima thickness; MT= media thickness; IMT= intima-media thickness.

Validation of Separate Measurement of Intima and Media Layers

The reproducibility of scanning CCA image was validated in our previous research.[18] In this study, therefore, the reproducibility of new method for IMT measurement including image processing was validated as follows. For 15 images selected randomly from 151 CCA images, two sonographers measured IMTs two times independently using commercial software M'ATH (Version 2.01; METRIS Inc., France). After then the same measurements were carried out using new method devised in this study. For M'ATH and new method software respectively, for the same 15 CCA images, the reproducibility of IMT measurements was evaluated by the two different sonographers while the repeatability was estimated by one sonographer with two successive measurements. The reliability of the new method devised in this study can be estimated indirectly by comparing the IMTs measured using new method with that of using validated commercial software.[15,18] Therefore, to validate the reliability, the IMT values measured for 151 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. Identifying the potential clinical predictors of the intima, media, and intima-media thickness was done with Pearson correlation coefficient analysis. 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

Patients Characteristics

Forty three patients from the 194 patients enrolled were excluded due to poor delineation of the borders between intima and media layers by new method. The rest 151 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 57 ± 15 years (77 males; 74 females). Most patients had an atherosclerotic disease such as coronary artery disease or ischemic stroke, or atherosclerotic risk factors

Table 1. Clinical Characteristics of the Study Subjects

Variables	Values
Age (yrs)	57±15
Male, n (%)	77 (51.0%)
BMI (kg/m^2)	24.7±3.3
Hypertension, n (%)	82 (54.3%)
Diabetes, n (%)	37 (24.5%)
Smoking, n (%)	31 (20.5%)
Systolic blood pressure (mm Hg)	127.7±21
Diastolic blood pressure (mm Hg)	78±14
Diagnosis	
Without atherosclerotic disease, n (%)	75(49.7%)
With atherosclerotic disease, n (%)	76(50.3%)
Total cholesterol (mg/dl)	185±41
Triglyceride (mg/dl)	162±107
HDL cholesterol (mg/dl)	44.0±12.8
LDL cholesterol (mg/dl)	109±32
Fasting blood glucose (mg/dl)	133±61
Homocysteine (mg/dl)	11.7±6.8
Fibrinogen (mg/dl)	3.2±0.8
Hs-CRP (mg/dl)	0.22±0.26
Blood urea nitrogen (mg/dl)	22±18
Creatinine (mg/dl)	2.1±3.1
Uric acid (mg/dl)	5.5±1.8

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

Reproducibility and Reliability of New method for the Separate Measurement of Intima and Media Layer

The coefficient of variation (CV), standard deviation divided by mean, is useful to evaluate the reproducibility and repeatability of measurement systems.[19,20] Therefore, to evaluate the reproducibility for 15 CCA images, the CVs of interobserver were calculated in percent for each set of duplicate new method and M'ATH measurements (Table 2). The mean CVs of new method were 0.16% for IMT and 0.21% for both IT and MT. The mean CV of M'ATH was 0.21% for IMT. Eighty-seven percent of the CVs from the duplicate new method IMT measurements were < 0.3%. Of the CVs for duplicate M'ATH IMT measurements, 73% were < 0.3%. Eighty

percent of the CVs form the duplicate new method MT measurements were < 0.3%. Of the CVs for duplicate new method IT measurements, 73% were < 0.3%. Any of the CVs from the duplicate new method IT, MT, or IMT measurements were < 1%. The repeatability was evaluated by calculating the mean CV of intraobserver with two successive measurements for each 15 CCA images, and resulted in < 0.3% for IT, MT, and IMT using new method and for IMT using M'ATH software.

Table 2. Reproducibility Data Summary of New method vs. M'ATH

CV (%)	New Method			M'ATH
	IMT	IT	MT	IMT
0 - < 0.05	2(13%)	2(13%)	5(33%)	2(13%)
0.05 - < 0.1	4(27%)	1(7%)	2(13%)	1(7%)
0.1 - < 0.15	3(20%)	4(27%)	1(7%)	5(33%)
0.15 - < 0.2	2(13%)	1(7%)	2(13%)	1(7%)
0.2 - < 0.25	1(7%)	2(13%)	0	0
0.25 - < 0.3	1(7%)	1(7%)	2(13%)	2(13%)
≥ 0.3	2(13%)	4(27%)	3(20%)	4(27%)
Mean	0.16%	0.21%	0.21%	0.21%
SD	0.14%	0.15%	0.26%	0.14%
Range	(0.0%, 0.46%)	(0.0%, 0.51%)	(0.0%, 0.98%)	(0.0%, 0.51%)

To evaluate the reliability of new method for IMT measurement, the relationship between new method and M'ATH in the IMT measurements for 151 CCA images were compared. The IMT ranged from 0.47 to 1.07 mm, with a mean value of 0.73 ± 0.12 mm, when measured with M'ATH and from 0.49 to 1.12 mm, with a mean value of 0.74 ± 0.12 mm, when measured with new method. The correlation between the two method was excellent with the correlation coefficient of 0.979 (Figure 3).

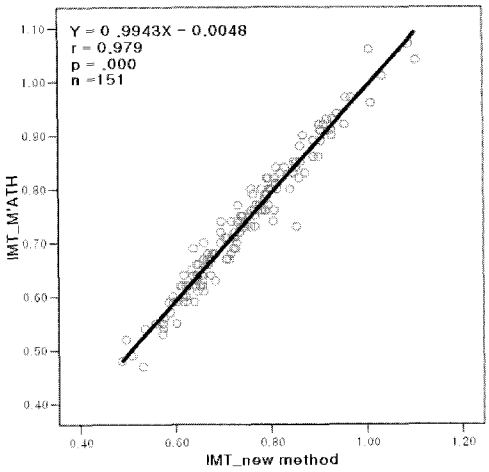

Figure 3. Correlation between M'ATH and new method for IMT measurement of common carotid artery (n=151).

Univariate Analysis

The IT ($p < 0.01$), MT ($p < 0.01$) as well as IMT ($p < 0.001$) of patients with atherosclerotic disease(n=76) were significantly thicker than that of the patients without atherosclerotic disease(n=75)(Fig. 4).

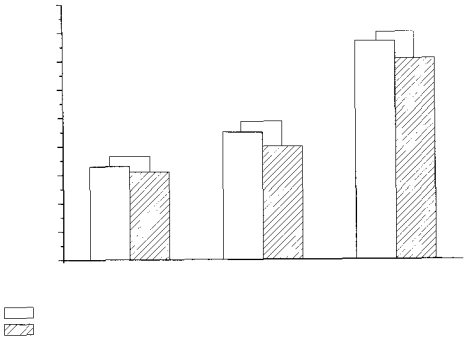

Figure 4. Comparison of carotid intima (IT), media (MT), and intima-media thicknesses (IMT) in patients with and without atherosclerosis.

All three layers thickness were significantly higher in patients with hypertension than those without hypertension. In regarding to smoking, only the intima layer thickness was significantly higher in smokers than in non-smokers, while the other risk factors such as diabetes and hypercholesterolemia did not show any significant changes in each layer according to the its presence (Fig. 5, Table 3).

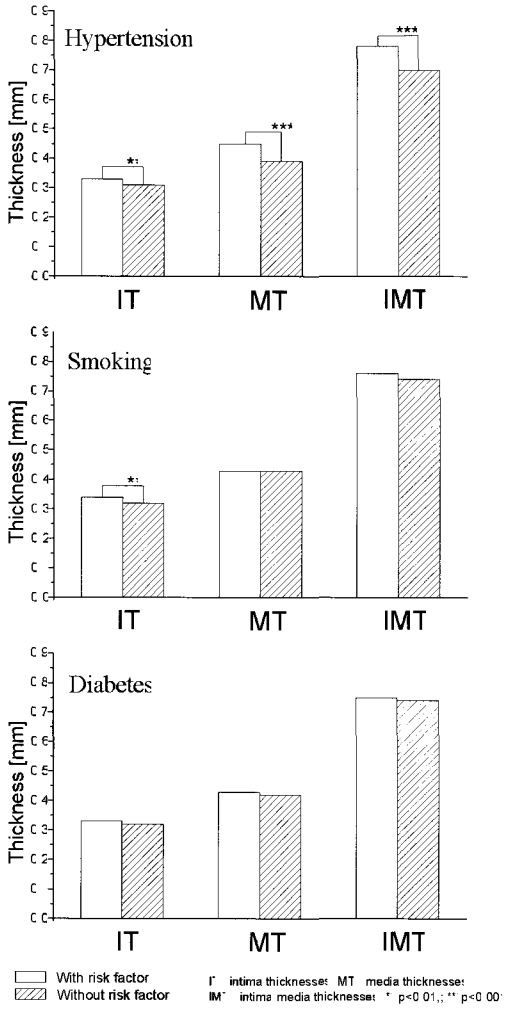

Figure 5. Relationship between carotid intima (IT), media (MT), and intima-media thicknesses (IMT) and atherosclerosis risk factors.

Table 3. ANOVA results from comparison in Fig. 5 including the interaction effect between risk factors and atherosclerotic disease

	IT(F)	MT(F)	IMT(F)
Hypertension (+ vs. -)[a]	9.122**	13.711***	15.110***
Hypertension (+ vs. -)[a] × Atherosclerosis (+ vs. -)[b]	2.180	0.690	1.467
Smoking (+ vs. -)[a]	8.114**	0.080	0.307
Smoking (+ vs. -)[a] × Atherosclerosis (+ vs. -)[b]	0.618	1.391	0.967
Diabetes (+ vs. -)[a]	1.511	0.146	0.324
Diabetes (+ vs. -)[a] × Atherosclerosis (+ vs. -)[b]	1.216	0.278	0.815

(+ vs. -)[a] = with versus without the risk factor; (+ vs. -)[b] = with versus without the atherosclerotic disease; x = interaction between atherosclerotic risk factors and atherosclerotic disease; **p<0.01; ***p<0.001

Discussion

The new method devised in this study has excellent repeatability (CV of intraobserver < 0.3%) and reproducibility (CV of interobserver < 1%). The reliability is compatible as that of the commercial software M'ATH (correlation coefficient of IMT measurements between using new method and M'ATH is 0.979; p< 0.001). Moreover, this is the first study showing the differential significance of carotid arterial intima and media thickness using the newly devised B-mode image signal processing.

To inspect the reliability of our IMT measurements furthermore, we compared our results with other's. Diez-Roux AV(U.S.A)[21]reported the IMT as 0.71 ± 0.01 mm for non-smokers with no environmental tobacco smoke and 0.81 ± 0.01 mm for smokers. In our research, the IMT was 0.74 ± 0.12 mm for no smoker and 0.76 ± 0.11 mm for smoker. Diez-Roux AV(U.S.A) measured the IMT manually at the far wall of designated 1cm length of the common carotids, the carotid bifurcations, and the internal carotids. The average intima media thickness over the six sites (three for the left and three for the right carotid arteries) was used. In our study, we measured the IMT semi-automatically at the far wall of designated 1cm length of the right common carotid and we used the average IMT over the 200 points. The main difference between the two results arouse from the different measurement methods as well as whether considering the environmental tobacco smoke or not.

Bonithon-Kopp(France)[22] found that the IMT tend to be thicker as atherosclerotic plaques in carotid arteries become severe. They reported the IMT as 0.68 ± 0.14 mm (male) and 0.64 ± 0.11 mm (female) for no plaque; 0.71 ± 0.12 mm (male) and 0.66 ± 0.11 mm (female) for unilateral plaque ≤2 mm; 0.73 ± 0.16mm (male) and 0.68 ± 0.09 mm (female) for unilateral plaque >2 mm or bilateral plaques ≤2 mm; 0.76 ± 0.08 mm (male) and 0.70 ± 0.10 mm (female) for bilateral plaques >2 mm. In our study, the IMT was 0.71 ± 0.12 mm for without atherosclerosis and 0.77 ± 0.11 mm for with atherosclerosis. In this case, the reason why the IMT of

without atherosclerosis was thicker than that of the no plaque is that patients without atherosclerosis in our study include the risk factors.

Bae JH[23] measured the IMT of Korean as our study with similar method of ours. They reported that the IMT of patients with risk factors group thicker than that of the normal control group. The IMT was 0.65 ± 0.12 mm (male) and 0.62 ± 0.11 mm (female) at right CCA, and 0.65 ± 0.12 mm (male) and 0.64 ± 0.11 mm (female) at left CCA for control group; 0.72 ± 0.15 mm (male) and 0.68 ± 0.11 mm (female) at right CCA, and 0.72 ± 0.14 mm (male) and 0.70 ± 0.13 mm (female) at left CCA for patients with risk factors. Because about 70% of patients without atherosclerosis had risk factors in our study, the IMT value from our study (approximately 0.71 mm) was similar to that of the risk factor group of Bae JH et al.

To find a clinical significance of the each layer of vessel wall, we inspect the correlation between atherosclerotic risk factors and IT, MT, and IMT. 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. 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.

Interestingly, only intima thickness was independently associated with smoking, while media thickness and IMT failed to show the independent association with smoking. The detailed smoking history was not obtained such as a total pack year and the duration of smoking. This can explain why carotid IMT did not show the association with smoking. Nevertheless, IT showed the independent association with smoking, which may be a stronger relation with smoking than MT and IMT. In other words, the association between smoking and the increased carotid IMT may be resulted from the association between smoking and the increased carotid IT. This result is similar to the autopsy findings by Berenson et al[24] in some way. They reported that smoking was associated with increased percentage of intimal surface involved with fibrous plaques in the aorta and fatty streaks in the coronary vessels, although there was no mention about the diabetes or hyperlipidemia possibly due to limitation of an autopsy study.

This study has limitations inherent to study populations. The study population needs to be homogeneous, that is control group versus patients with single risk factor or atherosclerotic disease, to identify the pure impact of atherosclerosis risk factors or atherosclerotic disease on the each vessel wall such as carotid IT, MT, and IMT. Despite of this limitation, there were some significant findings in this study group. And we could not evaluate why some risk factors affect the specific vessel layer. It should be studied in future with histological findings.

Conclusion

The separate measurement of IT and MT confirms that atherosclerosis risk factors affect the arterial wall in its own way. Because the IMT depends on the site measured, existence of plaque, and etc., the measurement protocol of IMT should be standardized.

The IMT values measured in our study can be reliable from comparing to other studies. 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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