THE ASSOCIATION BETWEEN CARDIOVASCULAR EVENTS AND CAROTID STRUCTURAL AND FUNCTIONAL CHARACTERISTICS

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ABSTRACT

Introduction*: Previous study found that carotid intima-media thickness (CIMT), arterial elasticity and plaque size would be changed during atherosclerosis development, indicating that the association between cardiovascular events and carotid structural and functional characteristics may be of significance in the clinic. The purpose of this study was to investigate whether the integration of carotid Young's modulus (YM), Young's modulus standard deviation (YM-std), CIMT), and presence/absence of plaque can promote the risk of cardiovascular event (CVE).*

Materials and methods: *Seventy-eight patients with CVE (age 62.85±9.23 years) and seventy-five patients at risk of atherosclerosis (age 63.49±5.95 years) were assessed in this study. Ultrasonic texture matching method was used to calculate the carotid YM and YM-std. CIMT was measured by MyLab 90 Ultrasound Platform employed dedicated software RF-tracking technology.*

Results: *YM in CVE patients was significantly higher than that in control group (p=0.022). YM had significantly positive correlation with CIMT (rs=0.226, p=0.005). By unvaried analysis, plaque (p=0.0001) and YM-std (p=0.015) were demonstrated to have significantly positive ORs. Whereas YM (p=0.009), YM-std plus plaque (p=0.019) were associated with reduced ORs for CVE. When examining the area under the receiver-operating characteristic curve (AUC), YM-std plus CIMT plus plaque improved the AUC significantly. Compared with single factor models, (YM-std + CIMT + plaque) model was demonstrated to have significant rises in ORs, which showed increase from 0.64 (plaque only) to 0.70, from 0.55 (CIMT only) to 0.70, from 0.61 (YM only) to 0.70, and from 0.55 (YM-std only) to 0.70.*

Conclusion: *Comprehensive consideration of structural and functional characteristics, such as model of YM-std coupled with CIMT and presence/absence of plaque, may improve risk prediction of cardiovascular events.*

Keywords: *Ultrasound, intima-media thickness, carotid stiffness, plaque, atherosclerosis.*

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Introduction

Recent studies have shown that cardiovascular events (CVEs) are the primary cause of death[1-2] globally. Investigations found that carotid intima-media thickness (CIMT), arterial elasticity and plaque size would be changed during atherosclerosis development[3-5] , indicating that the association between cardiovascular events and carotid structural and functional characteristics may be of significance in the clinic. With respect to vascular structures, CIMT was considered to be a strong predictor of CVEs, however, their relationship was proved to be nonlinear[6] . Other studies reported that presence/absence of carotid plaque and carotid plaque burden were reliable indicators of subclinical atherosclerosis, with a higher prediction value for CVEs than CIMT[7-8] . Furthermore, large artery stiffness is also proved to be a predictor of incident cardiovascular events. Since arterial walls are biologically heterogeneous, measurement of the elastic properties of the large arteries can be used to predict coronary atherosclerosis. Our previous study has shown that local Young's modulus (YM) of the common carotid artery (CCA) measured by the vessel texture matching method is a potent independent predictor of adverse cardiovascular outcomes.

Therefore, we hypothesized that the integration of carotid structural and functional characteristics, such as CIMT, YM-std and presence/absence of plaque, may have a closer relationship with CVEs. This study aimed to propose a dual-mode ultrasound imaging method to evaluate the carotid structural and functional characteristics, and investigated the relationship between these parameters and CVEs.

Materials and methods

Study population

Patients were eligible for the study if they had a history of CVEs or if they had at least one cardiovascular risk factor (such as hypertension, diabetes, dyslipidemia, smoking and overweight). The study population was made up of 78 patients with CVEs, and 75 patients with at least one cardiovascular risk factor as control group. All methods and experimental procedures were carried out in accordance with the approved guidelines of the Institutional Review Board of the Third Affiliated Hospital of Sun Yat-sen University. All participants signed informed consents before they were included in the study. Age, gender, blood pressure, body mass index (BMI), history of smoking, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol, triglyceride, fasting plasma glucose, and medication usage were available for all participants.

Cardiovascular risk assessment included the presence or absence of medically diagnosed hypertension, dyslipidemia, diabetes, overweight, and smoking status. The criteria used were guided by Adult Treatment Panel III and the World Health Organization[9-10]. Hypertension was defined as resting systolic blood pressure (SBP) ≥140mmHg and/or diastolic blood pressure (DBP) ≥90mmHg and/or the use of antihypertensive drugs.

Dyslipidemia was defined as using lipid-lowering drugs or having one or more conditions of the following: total cholesterol ≥5.2mmol/L, LDL cholesterol ≥3.4mmol/L, HDL cholesterol ≤1.0mmol/L, or triglyceride ≥1.70mmol/L. Diabetes was defined as fasting plasma glucose ≥7.0mmol/L or use of antidiabetic medication. Overweight was defined as a BMI ≥25.0kg/m^2. Smoking status was ascertained by a questionnaire that classified each subject as a non-smoker, former smoker, or current smoker. For the purpose of the present study, "ever-smoker" status (former or current) was used.

CVEs includes definite or probable myocardial infarction and stable ischemic heart disease that are indicated by electrocardiograms, characteristic symptoms, biomarkers of myocardial necrosis, or coronary arteriography, as previously described[2, 11]. Then, the detailed methods that ascertained the CVEs were classified.

Carotid ultrasonography

We used the Esaote MyLab 90 Ultrasound Platform (Esaote Medical Systems, Rome, Italy) that is equipped with a 4~13 MHz linear-array transducer (LA523). The ultrasound technician scanned the left CCA using a standardized protocol[12-13]. Then, the image was focused on the posterior (far) wall, and the image quality was optimized by gain settings. We record a series of image frames using a resolution zoom box function.

A moving scan of the CCA 1~2 cm proximal to the bifurcation that has a duration of 9 seconds was record and stored in digital format to be utilized for subsequent off-line analysis.

The CIMT of the far wall was measured on the frozen frame of a suitable longitudinal image. The image was magnified to achieve a much higher spatial resolution. We record the presence or absence of plaque, and when an area with CIMT ≥1.5mm, we defined it as presence of plaque. The CCA YM was evaluated by the vessel texture matching method that has been described and validated by Niu et al.

We used the vessel texture matching method to assess the CCA YM. This technique can be described by Niu et al[14-15]:

$$YM(x,y)=\frac{1}{2}\left(\frac{R_{il}}{h_0\cdot L}+\frac{L-x+1}{L}\right)\frac{\Delta P}{\Delta\varepsilon_{\max}(x,y)}$$

Here, the coordinates of a pixel in the image plane was (x, y). Then, the number of layers, thickness of each layer, the inner radius of the l-th layer, the maximum strain of each layer during one cardiac cycle, and pulse pressure measured at the brachial artery were defined as L, h0, Ril, Δεmax and ΔP respectively. The YM-std was computed as follows:

$$YM\_std=\left(\frac{1}{(M-1)(N-1)}\sum_{x=1}^{M}\sum_{y=1}^{N}\left(YM(x,y)-\overline{YM}\right)^2\right)^{1/2}$$

Where (M, N) and are the dimensions of YM, and its mean value, respectively.

Statistical analysis

We used the PASW Statistics 18 and the Medical for windows to evaluate all data. The p-values less than 0.05 were considered statistically significant. We expressed parametric data as mean ± standard deviation and qualitative data as percentages. Our primary hypothesis was tested with an analysis of covariance model, comparing differences in the demographic and clinical characteristics between the CVE and non-CVE groups. We calculated the association between independent variables and prevalent CVEs in two groups by using multivariate logistic regression analysis, and the odds ratio (OR) of CVE was presented with the 95% confidence interval (CI).

The model we considered was based on the (YM-std + CIMT + plaque) technique. We described the area under the receiver-operating characteristic curve (AUC) for CVE risk using methods that accounted for censoring for each of the models to describe the model predictively.

Results

Age and gender were adjusted so that there was no significant difference between CVE group and non-CVE group. Mean age of the CVE group was 62.85±9.23 years and that of the non-CVE group was 63.49±5.95years (p=0.609). Forty-seven males and thirty-one females were included in the CVE group, as well as 35 males and 40 females were included in the non-CVE group, without significant difference between two groups (p=0.093). Compared with non-CVE subjects, the CVE patients showed no increase in BMI (23.69±2.94 versus 24.44±3.15, p=0.134), diabetes (44.9% vs. 53.3%, p=0.298), hypertension (70.5% vs. 60.0%, p=0.174), dyslipidemia (52.6% vs. 77.3%, p=0.001), overweight (28.2% vs. 34.7%, p= 0.393). However, the CVE group had a significantly higher proportion of patients with smoking(37.2% vs. 20%, p=0.019). The other demographic and clinical characteristics of the groups were shown in Table 1.

No significant difference was found for CIMT (p=0.830) and YM-std (p=0.513) between two groups. YM in CVE patients was significantly higher than that in control group (p=0.022). There was significant difference in arterial diameter change between two groups, as shown in Figure 1.

Figure 2 showed the YM distributions for different groups of people at the same age and gender. A score of 0 to 1 was assigned to the subjects who had no plaque, whereas a score of 1 to 2 was assigned to the subjects who had a plaque.

	Non-Cardiovascular Event group (n=75)	Cardiovascular Event group (n=78)	*p*
Age (yrs)	63.49±5.95	62.85±9.23	0.609
Female (%)	53.3%	39.7%	0.093
BMI (kg/m^2)	24.44±3.15	23.69±2.94	0.134
SBP (mmHg)	134.52±16.25	135.47±18.3	0.745
DBP (mmHg)	79.19±8.04	80.33±11.96	0.498
PP (mmHg)	55.20±13.85	55.14±15.03	0.98
Diabetes (%)	53.3%	44.9%	0.298
Hypertension (%)	60.0%	70.5%	0.174
Dyslipidemia (%)	77.3%	52.6%	0.001
Smoking (%)	20.0%	37.2%	0.019
Overweight (%)	34.7%	28.2%	0.393

Table 1: Baseline characteristics of two groups.
CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index.

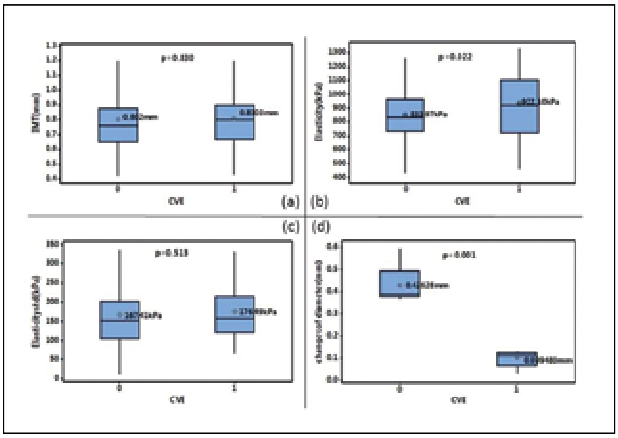

Figure 1: Box plot of IMT, elasticity and elasticity-std. a) and c): no significant difference was found for CIMT (p=0.830) and YM-std (p =0.513). b) YM in control group was significantly higher than that in CVE patients (p=0.022). d): there was significant difference in arterial diameter change between groups.

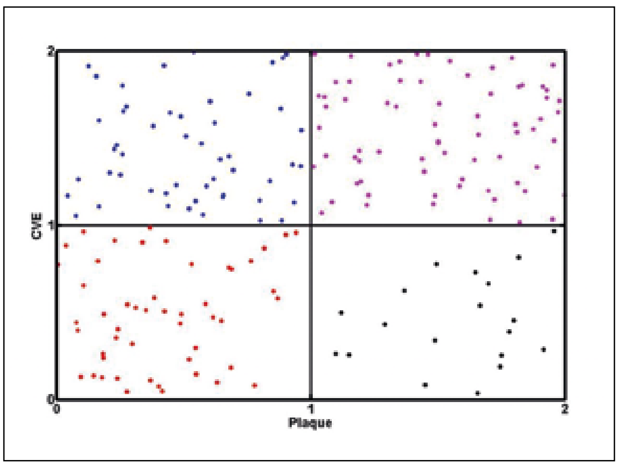

Figure 2: A scatter diagram of plaques. A score of 0 to 1 was assigned to the subject who had no plaque, whereas a score of 1 to 2 was assigned to the subject who had a plaque.

Figure 3 showed a scatter diagram of plaques. Here, we found the splashes uniformly distribute in the diagram and so, we were unable to see significant difference on the plaques. As shown in Figure 4, YM had significantly positive correlation with CIMT (rs=0.226, p=0.005).

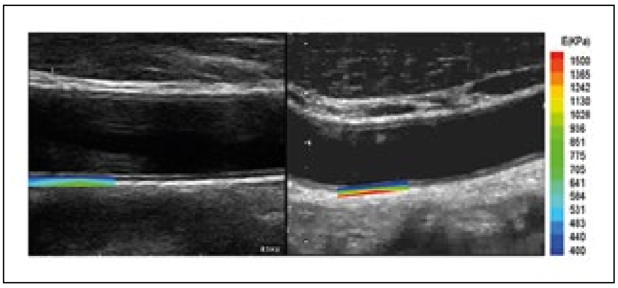

Figure 3: The distributions of Young's modulus of a 59-year-old male subject without cardiovascular events (left) and a 59-year-old male subject with cardiovascular events (right) calculated by the vessel texture matching method.

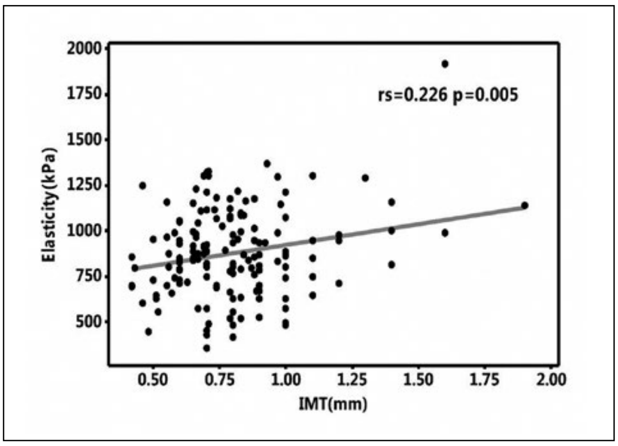

Figure 4: YM has significantly positive correlations with CIMT (rs=0.226, p=0.005).

A logistic regression analysis was performed using the variables including plaque, CIMT, YM, YM-std, and (YM-std + CIMT + plaque), as shown in Table 2.

	OR(95% CI)	*P*
Plaque	11.038(3.318-38.832)	0.0001
CIMT	2.383(0.379-14.968)	0.354
YM	0.998(0.996-0.999)	0.009
YM-std	1.008(1.001-1.014)	0.015
YM-std+CIMT+Plaque	0.991(0.984-0.999)	0.019

Table 2: Logistic regression analyses.

By unvaried analysis, plaque (OR: 11.038, CI: 3.318-38.832, p=0.0001) and YM-std (OR: 1.008, CI: 1.001-1.014, p=0.015) were demonstrated to have significantly positive ORs. Whereas YM (OR: 0.998, CI: 0.996~0.999, p=0.009), YM-std + CIMT + plaque (OR: 0.991, CI: 0.984-0.999, p=0.019) were associated with reduced ORs for CVE. When examining the area under the receiver-operating characteristic curve (AUC), YM-std plus CIMT plus plaque improved the AUC significantly (Table 3).

Model	Area under the curves CI 95% for difference)	Z	*p*
Plaque	0.64		
CIMT	0.55		
YM	0.61		
YM-std	0.55		
YM-std + CIMT + Plaque	0.70		
YM-std + CIMT + Plaque vs. Plaque	(0.00768~0.11100)	2.253	0.0243
YM-std + CIMT + Plaque vs. CIMT	(0.0304~0.2670)	2.463	0.0138
YM-std + CIMT + Plaque vs. YM	(0.0000419~0.1820000)	1.961	0.0499
YM-std + CIMT + Plaque vs. YM-std	(0.0333~0.1820)	2.502	0.0124

Table 3: Adjusted area under the curves.

Compared with single factor models, (YM-std + CIMT + plaque) model was demonstrated to have significant rises in ORs, which showed increase from 0.64 (plaque only) to 0.70 (95% CI: 0.00768~0.11100), from 0.55 (CIMT only) to 0.70 (95% CI: 0.0304~0.2670), from 0.61 (YM only) to 0.70 (95% CI: 0.0000419~0.1820000), and from 0.55 (YM-std only) to 0.70 (95% CI: 0.0333~0.1820).

Discussion

In this study, a comprehensive assessment of structural and functional characteristics was performed in patients with CVE using vessel texture matching method and carotid ultrasound imaging. The results suggested that the association between integrated structural and functional characteristics and prevalent CVEs may be closer than that with only one factor (Table 3). Other previous studies also considered that combining diagnosis with several factors could make cardiovascular disease prediction more accurately. For example, Jeevarethinam et al found that adding plaque and CIMT to traditional risk factors improves CVE risk prediction in asymptomatic patients with type 2 DM(16).

Some investigations have examined the utility of plaque in the risk prediction of CVE. Jeevarethinam et al indicated plaque and cIMT can be useful predictors of prevalence of CAD and its severity(17). In addition, ten Kate et al have also found a correlation between carotid plaque and coronary artery disease in patients[8]. This finding is consistent with our results. Table 2 showed that plaque was an independent predictor of CVE.

We had detected some differences of distribution in the Figure 2, but it is not remarkable. Therefore, plaque, CIMT and YM-std, when utilized alone for evaluation, could not improve risk prediction significantly in our study.

Most studies consider CIMT to be significantly correlated with cardiovascular risk[18-19]. However, Lorenz et al. examined the carotid atherosclerosis progression study and reported that CIMT did not improve CVE risk prediction[20]. Our results indicated that CIMT was not considered as an independent predictor of CVE (Table 2), and Figure 1 showed that there was no significant difference in CIMT between CVE and non-CVE patients. Furthermore, our study showed that CIMT was significantly associated with YM (Figure 4). Therefore, the application of CIMT as a screening tool may be more challenging as CIMT values should be considered with functional characteristics.

Recent studies indicated that the change of vascular elasticity was earlier than the change of structure, and the arterial elastic properties, particularly of large arteries, associated with the risk of cardiovascular disease[21-22]. Our previous study proposed using the vessel texture matching method (VTMM) technique to measure the YM in local region of a few millimeters in site on the arterial wall and to estimate the mechanical properties of arterial wall[23]. We implemented the VTMM technique in our previous study to estimate the mechanical properties of arterial wall, as well as to determine the YM in local region of a few millimeters in site on the arterial wall. In our study, the results indicated that CCA YM-std measured by the VTMM technique was an independent predictor of CVE.

Our experimental results showed that CCA YM-std measured by the VTMM technique seemed to be an independent predictor of CVE. Furthermore, Figure 3 did not show a significant difference in the plaque between the CVE and non-CVE groups. Obviously, some limitations have been discovered in our study. Firstly, there were no follow-up patient visits to assess the occurrence of clinical events. Based on the baseline (2012-2013) hospital visit (YM-std and plaque), the data is determined and used for the current analysis.

Then, the results might be affected by using information (including YM-std and plaque) from subsequent hospital visits. Additionally, the potential difference between plaque presences in one artery alone versus in multiple arteries was not taken into account. A higher risk may be existent because of the plaque presence in multiple carotid artery segments.

In conclusion, our results demonstrated that comprehensive diagnosis considering structural and functional characteristics (such as the model YM, CIMT and plaque) could improve risk prediction of cardiovascular events.

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