

Carotid intima-media thickness and plaque occurrence in predicting stable angiographic coronary artery disease

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Background: Carotid intima-media thickness (CIMT) and plaque formation have been used as surrogate end-points for evaluating the regression and/or progression of atherosclerotic cardiovascular disease, but their predictive value for stable coronary artery disease (CAD) is inconclusive.

Methods: Carotid ultrasonography was performed in patients who underwent noninvasive multislice computed tomography (MSCT) angiography for CAD suspected, due to chest pain. CIMT and plaque formation on the left and right common carotid arteries (CCAs), carotid bulb (CB), and proximal internal carotid arteries (ICAs) were evaluated, and the relationship between angiographic CAD, CIMT, and plaque formation was determined.

Results: 120 patients (95 male; 25 female), with a mean age \pm standard deviation of 61 ± 11 years (range: 35–89 years) were recruited. Because age had a significant impact on CAD ($r = 0.191$; $P = 0.036$), CCA plaques ($r = 0.368$; $P = 0.001$), ICA plaques ($r = 0.334$; $P = 0.004$), and mean CIMT ($r = 0.436$; $P = 0.001$), patients were divided into two groups aged <60 years and ≥ 60 years. In the <60 years group, CIMT-CB was significantly higher in patients with CAD ($P = 0.041$), while in the ≥ 60 years group, mean CIMT, CIMT-CCA, and CIMT-CB were significantly higher in patients with CAD ($P < 0.05$, for each). In both groups, the occurrence of carotid plaques was significantly higher in patients with CAD than in those without CAD ($P < 0.007$, for each). After controlling for other risk factors, carotid plaques were an independent predictor of CAD in both groups ($P < 0.05$, for each), while CIMT-CB could independently predict CAD only in patients ≥ 60 years old ($P = 0.031$).

Conclusion: Our findings suggest that carotid plaques are a strong predictor of stable CAD. However, CIMT-CB could predict stable CAD only in patients over 60 years of age.

Keywords: carotid plaque, intima-media thickness, coronary artery disease, ultrasonography

Introduction

Coronary artery disease (CAD) is a common and disabling disorder. It remains the leading cause of mortality worldwide, resulting in the deaths of 3.8 million men and 3.4 million women annually.¹ Most individuals with stable CAD show no symptoms and signs for decades, until the sudden onset of coronary events, such as myocardial infarction. Therefore, it is desirable to identify patients at an early stage of CAD, to enable preventive interventions and to promote lifestyle modifications as early as possible.

Traditional risk factors for CAD, such as family history of CAD, age, smoking, hypertension, diabetes mellitus, hyperlipidemia, and obesity have been used to identify asymptomatic individuals who are at higher risk of cardiovascular events.^{2,3}

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However, these risk factors can only identify approximately 50% of patients at risk of CAD.⁴ Carotid ultrasonography has become a prominent focus of clinical research in the last two decades, and the relationship between cardiovascular events, and carotid intima-media thickness (CIMT) and plaque formation, has been studied widely. Many large epidemiological studies have shown a strong relationship between cardiovascular events, and CIMT and plaques.^{5–8} Overall, evidence for the predictive value of carotid plaques for CAD seems consistent,^{9–13} but evidence for the use of CIMT in clinical practice is incomplete, because the predictive value of CIMT for CAD is inconsistent, especially in patients with stable CAD. Some studies have suggested that CIMT could be used as a predictive marker for cardiovascular events,^{14–16} while others have reported that CIMT was not an independent predictor for CAD, after adjustment for traditional risk factors.^{17,18} Such conflicting results may be due to considerable variation between studies in relation to measurement methods and cut-off values for CIMT. In addition, most studies have used severe cardiovascular events, such as myocardial infarction, CAD death, or coronary revascularization, as study end-points. However, it is not suitable to apply the results derived from these studies to patients with asymptomatic CAD. A genome-wide study also showed a strong genetic effect on CIMT.¹⁹ Unfortunately, very few studies are available regarding the age-related predictive value of CIMT and plaques for stable CAD in the Chinese population. Thus, the purpose of this prospective study was to investigate the predictive value of CIMT and plaques for the occurrence of stable CAD.

Material and methods

Patients

Patients who were referred to Cathay General Hospital, Taipei, Taiwan with suspected CAD due to chest pain were consecutively recruited from January 2008–January 2010. Exclusion criteria included a history of myocardial infarction, unstable angina, coronary-artery bypass surgery, stroke, ventricular and supraventricular arrhythmias, contraindications for the use of iodinated contrast medium, history of cervical spine injuries, wounds on the neck, and poor echo imaging. All participants underwent physical examination, noninvasive multislice computed tomography (MSCT) coronary angiography for the diagnosis of CAD, and ultrasonography for the assessment of CIMT and plaques. Hypertension was defined as a blood pressure $>140/90$ mmHg, or treatment with any antihypertensive agent. Hyperlipidemia was defined as a total cholesterol level >5.0 mmol/L, or the

use of any antihyperlipidemic agent. Diabetes mellitus was defined as a fasting plasma blood glucose level >7.0 mmol/L on two different days, a postprandial blood glucose level >11.1 mmol/L, or the use of antidiabetic medications.

All participants provided informed, written consent. The study was conducted in accordance with the Helsinki II Declaration and approved by the Scientific Ethics Committee of Cathay General Hospital.

MSCT coronary angiography

MSCT coronary angiography was performed with a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Otawara-shi, Japan). A nonenhanced prospective electrocardiographically-gated scan was performed first, to determine the start and end position of the following helical scan, through which coronary angiography was performed. The presence of coronary atherosclerosis was visually evaluated based on axial images and curved multiplanar reconstructions in two orthogonal planes. Obstructive coronary atherosclerosis was defined as a luminal narrowing $>50\%$ in one or more coronary arteries.

Carotid ultrasonography

Carotid ultrasonography was performed within 24 hours following MSCT coronary angiography. The carotid arteries were evaluated using a high resolution B-mode color Doppler and pulse Doppler ultrasound system (iE33 xMATRIX, Philips Healthcare, Andover, MA, USA) with a transducer frequency of 11–13 MHz, by an examiner who was blind to the subjects' characteristics. The near and far wall of the right and left common carotid arteries (CCAs) (at least 1.5 cm proximal to the origin of the carotid bulb [CB], bifurcations at the CB), and proximal internal carotid arteries (ICAs) were scanned. Using an automated edge detection algorithm, the maximum IMT was determined as the distance between the lumen–intima interface and the media–adventitia interface at a plaque-free segment in end-diastole. The maximum IMT of the CCA, ICA, and CB was recorded. Mean CIMT was defined as the average of IMT values at the right and left sides of the CCA, ICA, and CB. A carotid plaque in the CCA, CB, or ICA was defined either as (1) a thickening of the focal wall that was at least 50% greater than the thickening of the surrounding vessel wall (relative plaque), or (2) a focal region with an IMT of >1.5 mm (absolute plaque).²⁰

Statistical analysis

Statistical analysis was conducted using SPSS software version 19.0 (IBM Corporation, Armonk, NY, USA). Continuous

variables were expressed as mean \pm standard deviation, and categorical variables were expressed as number (%). The Student's *t*-test or Mann–Whitney *U* test was performed for between-group comparisons of continuous variables (according to distribution characteristics), while the chi-square test was used to perform between-group comparisons of categorical variables. Partial correlation analysis was performed to test the correlation between CAD and CIMT or plaques, controlling for age, diabetes mellitus, hyperlipidemia, hypertension, smoking, and family history of CAD. Multivariate logistic regression analysis (with CAD as the outcome variable) was performed to determine the independent predictors of CAD. Two-tailed tests were performed, and a value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 120 patients were recruited into the study, including 95 males and 25 females, with a mean age of 61 ± 11 years (range: 35–89 years). Age had a significant impact on CAD ($r = 0.191$; $P = 0.036$), CCA plaques ($r = 0.368$; $P = 0.001$), ICA plaques ($r = 0.334$; $P = 0.004$), and CIMT ($r = 0.436$; $P = 0.001$). As most Chinese retire at the age of 60 years, and their lifestyles may change dramatically after retirement, we separated patients into two groups (<60 years and ≥ 60 years) for further analysis. As shown in Table 1, compared with patients <60 years old, patients ≥ 60 years old had a higher incidence of hypertension ($P = 0.018$), and more severe CAD (involving three coronary arteries; $P = 0.015$). No difference was found between the two groups in terms of sex or CAD risk factors, such as family history of CAD, smoking, diabetes mellitus, and hyperlipidemia ($P > 0.05$, for each).

Table 1 Patient characteristics

	Total	<60 years (n = 61)	≥ 60 years (n = 59)	P
Age (years)	61 ± 11	52 ± 5	71 ± 7	0.000
Males	95 (79.2)	51 (83.6)	44 (74.6)	NS
CAD risk factors				
Family CAD history	21 (17.5)	10 (16.4)	11 (18.6)	NS
Smoking	65 (54.2)	35 (57.4)	30 (50.8)	NS
Diabetes	46 (38.3)	20 (33.3)	26 (44.1)	NS
Hypertension	88 (73.3)	39 (63.9)	49 (83.1)	0.018
Hyperlipidemia	57 (47.5)	32 (52.5)	25 (42.4)	NS
Number of diseased coronary arteries				
0	32 (26.7)	19 (31.1)	13 (22.0)	NS
1	19 (15.8)	12 (19.7)	7 (11.9)	NS
2	20 (16.7)	12 (19.7)	8 (13.6)	NS
3	49 (40.8)	18 (29.5)	31 (52.5)	0.015

Note: Data are presented as mean \pm standard deviation, or number (percentage).

Abbreviations: CAD, coronary artery disease; NS, not significant.

CIMT and its correlation with CAD

In the <60 year group, only IMT-CB was significantly higher in patients with CAD, as compared to those without CAD ($P = 0.041$), while in the ≥ 60 years group, mean CIMT, IMT-CCA, and IMT-CB were significantly higher in patients with CAD than in those without CAD ($P < 0.05$, for each). Comparing the two age groups, mean CIMT and IMT-CCA were significantly higher in the ≥ 60 years group than those in the <60 years group ($P < 0.0001$, for each) (Table 2). After controlling for other CAD risk factors (age, family history of CAD, smoking, diabetes mellitus, hypertension, and hyperlipidemia), partial correlation analysis showed that only IMT-CB was correlated with CAD in the <60 years group ($P = 0.041$), but that mean CIMT, IMT-CCA, and IMT-CB were all correlated with CAD in the ≥ 60 years group ($P < 0.05$, for each) (Table 3). These results suggest that IMT-CB was more specific for predicting the relationship between CIMT and CAD in both age groups, while mean CIMT and IMT-CCA were only valuable in patients ≥ 60 years old.

Carotid plaques and correlation with CAD

Of the 120 patients, 27 (22.5%) had no carotid plaques, and 93 (77.5%) had plaques, of whom 16 (13.3%) had plaques at one site, 40 (33.3%) had plaques at two sites, and 37 (30.8%) had plaques at three sites. As shown in Table 4, the proportion of patients with plaques at all sites (CCA, ICA, and CB) was significantly higher in patients with CAD than in those without CAD, in both age groups ($P < 0.007$, for each). However, the proportion was higher

Table 2 Difference in carotid intima-media thickness between the two age groups of patients, with and without coronary artery disease

	<60 years (n = 61)	≥ 60 years (n = 59)	P
Mean CIMT (mm)			
Non-CAD	0.65 ± 0.02	0.72 ± 0.04	NS
CAD	0.68 ± 0.02	0.81 ± 0.02	0.000
P	NS	0.028	
IMT-CCA (mm)			
Non-CAD	0.84 ± 0.02	0.88 ± 0.04	NS
CAD	0.85 ± 0.02	0.97 ± 0.02	0.000
P	NS	0.036	
IMT-CB (mm)			
Non-CAD	0.87 ± 0.02	0.85 ± 0.03	NS
CAD	0.93 ± 0.02	0.98 ± 0.02	NS
P	0.041	0.001	

Note: Data are presented as mean \pm standard deviation.

Abbreviations: CIMT, carotid intima-media thickness; CCA, common carotid artery; CB, carotid bulb; CAD, coronary artery disease; NS, not significant.

Table 3 The correlation between carotid IMT and plaque with the incidence of CAD, after controlling for other risk factors

	<60 years		≥60 years	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Mean CIMT	0.125	0.336	0.286	0.028
IMT-CCA	0.028	0.829	0.274	0.036
IMT-CB	0.263	0.041	0.424	0.001
CCA plaque	0.319	0.012	0.347	0.007
ICA plaque	0.168	0.195	0.288	0.027
CB plaque	0.255	0.047	0.481	0.000

Abbreviations: *r*, correlation coefficient; IMT, intima-media thickness; CIMT, common carotid intima-media thickness; CAD, coronary artery disease; CCA, common carotid artery; CB, carotid bulb; ICA, internal carotid artery.

in patients aged ≥60 years, compared against those aged <60 years ($P < 0.05$, for each). After controlling for other CAD risk factors (age, family history of CAD, smoking, diabetes mellitus, hypertension, and hyperlipidemia), partial correlation analysis showed that carotid plaques in the CCA and CB were significantly correlated with CAD in patients aged <60 years ($P < 0.05$, for each), whereas plaques in all sites were correlated with CAD in those aged ≥60 years ($P < 0.05$, for each) (Table 3).

CAD risk prediction

By controlling for other CAD risk factors, multivariate logistic regression analysis (with CAD as the outcome variable) showed that only IMT-CB was an independent predictor of CAD in patients ≥60 years old ($P = 0.031$), but not in patients <60 years old. However, carotid plaques were an independent predictor of CAD in patients <60 and ≥60 years old ($P = 0.006$ and $P = 0.045$, respectively) (Table 5).

Table 4 Difference of carotid plaque occurrence between the two age groups of patients, with and without coronary artery disease

	<60 years (n = 61)	≥60 years (n = 59)	P
CCA plaque			
Non-CAD	2 (3.3)	6 (10.2)	0.028
CAD	18 (28.7)	38 (64.4)	
P	0.000	0.000	
ICA plaque			
Non-CAD	4 (6.6)	5 (8.5)	NS
CAD	16 (25.4)	33 (55.9)	
P	0.007	0.000	
CB plaque			
Non-CAD	8 (13.2)	6 (10.2)	NS
CAD	29 (47.5)	42 (71.2)	
P	0.000	0.000	

Note: Data are presented as number (percentage).

Abbreviations: CAD, coronary artery disease; CCA, common carotid artery; ICA, internal carotid artery; CB, carotid bulb; NS, not significant.

Table 5 Prediction of coronary artery disease by carotid IMT and plaque

	<60 years		≥60 years	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Mean CIMT	1.42 (0.46–4.34)	0.540	1.79 (0.45–7.06)	0.408
IMT-CCA	2.23 (0.70–7.09)	0.174	0.92 (0.24–3.61)	0.905
IMT-CB	0.73 (0.25–2.13)	0.560	3.86 (1.13–13.23)	0.031
Carotid plaque	5.36 (1.63–17.63)	0.006	14.91 (1.06–209.84)	0.045

Abbreviations: OR, odds ratio; CI, confidence interval; CIMT, carotid intima-media thickness; CCA, common carotid artery; CB, carotid bulb.

Discussion

The present study analyzed the relationship between carotid atherosclerosis and stable angiographic CAD. We found that CIMT was not an independent predictor of CAD in patients <60 years old, but that IMT-CB could predict CAD in patients ≥60 years old, after adjustment for traditional risk factors. Carotid plaques in the CCA or CB were strongly correlated with CAD in all patients, and multivariate logistic regression analysis showed that this was an independent predictor of CAD in all patients.

Our findings regarding the predictive value of CIMT differ from those of previous studies. Kablak-Ziembicka et al¹⁸ examined IMT at the CCA, ICA, and CB in 558 consecutive patients referred for coronary angiography. They reported that CIMT was strongly correlated with the presence and severity of CAD, particularly in women. However, there were some significant limitations to that study. First, the CIMT maximum included plaque, which would significantly increase the predictive value of CIMT. Second, the mean CIMT values among patients with no disease and 1-, 2- and 3-vessel disease overlapped substantially. Moreover, many patients had a history of myocardial infarction, which places them in a high-risk group. In another study, Timoteo et al²¹ measured maximum IMT and plaques at the CCA in 300 patients with suspected stable CAD, and found that the maximum IMT at the CCA was an independent predictor of CAD, together with age, sex, and diabetes mellitus. The Atherosclerosis Risk in Communities (ARIC) study,²² which recruited subjects between 45–64 years old, also found that CIMT and plaque information can be used to improve CAD risk prediction, and was equal or superior to other contemporary markers.

Debate remains active as to which carotid segment should be used to measure IMT. The ARIC study examined whether IMT-CCA was as good as all-segment IMT for the prediction of vascular events, when added to traditional risk factor and plaque information. No difference between the two measures

was found, suggesting that IMT-CCA was sufficient for use in clinical risk assessment.²² However, in the Three-City Study,²³ IMT was examined at the CCA in 5,895 CAD-free adults aged 65–85, and the results indicated that CINT at a plaque-free site failed to predict CAD events, such as hospitalization for angina pectoris, myocardial infarction, CAD death, or a revascularization procedure (percutaneous intervention or coronary artery bypass or grafting). Although the measurement of IMT at the CCA is more reproducible than that measured at the ICA or bifurcation,²⁴ disease progression is more obvious in the ICA and bifurcation.⁵ Therefore, measuring only IMT-CCA may underestimate carotid atherosclerosis. In the present study, we measured IMT at the CCA, ICA, and CB, and found that CINT measured at all sites could not predict CAD in patients <60 years old, while in patients ≥60 years old, IMT-CB could weakly predict CAD. These results suggest that CINT should be assessed in all carotid segments in order to avoid underestimation of carotid atherosclerosis.

In the present study, CINT was assessed in the carotid segments free of plaques because, although correlated, increased CINT and the presence of plaques represent different stages and aspects of atherosclerosis. Diffuse adaptive thickening of the carotid wall reflects arteriosclerosis, responding to aging and hypertension, while plaque formation is a focal process, and is more related to atherosclerotic processes, such as inflammation, oxidation, and endothelial dysfunction,^{25,26} which may be more strongly associated with the pathology of CAD. A recent meta-analysis of eleven population-based studies by Inaba et al²⁷ showed that carotid plaques, compared against CINT, had a significantly higher diagnostic accuracy for prediction of future coronary events. In the present study, we found also that correlation between carotid plaques and the severity of CAD was consistent in patients below and above 60 years old.

We separated patients into two groups at 60 years of age because we had found, along with others,⁶ that age has a significant impact on CINT and plaque formation. In addition, in the People's Republic of China, most people have dramatic lifestyle changes following retirement at the age of 60, which can affect their health condition. We found that the predictive value of CINT for CAD was different in patients under and over 60 years of age, suggesting that age plays an extremely important role in CAD and plaque formation. This may help to explain why the predictive value of CINT for CAD is inconsistent in previous studies, as they included different age groups of patients. We believe the present findings, based on the comparison between these two age groups, will be more

useful for clinical decision making. The American Heart Association's Prevention Conference V recommended CINT scanning for patients who are older than 45, and requiring further clarification of their CAD risks.²⁸ Although carotid ultrasonography is easy and quick to perform, it requires expensive equipment and specific operator training. To perform carotid scanning for a target population older than 45 years would have an enormous cost. We think it may be more efficient and useful to target those aged over 60 years, with CAD risk factor assessment.

There are certain limitations to the present study. Firstly, the study sample is relatively small for multivariate logistic regression analysis, which may affect the significance of the results. For example, the ARIC Study²² recruited a population-based cohort of 15,792 subjects; the 25th and 75th percentile CINT values were only 0.65 mm and 0.84 mm, for men, and 0.58 mm and 0.74 mm, for women, respectively, which are much lower than our measurements. However, our results still suggest that CINT and plaque information can be used to improve CAD risk prediction, and may be equivalent or superior to other contemporary markers. Secondly, in our study, the proportion of women was small. It has been reported that patients with chest pain and normal coronary angiographies are predominantly women.²⁹ However, age- and sex-related differences in the prevalence of CAD are well recognized: male patients tend to have earlier onset of CAD;³⁰ therefore, male patients predominate. Finally, the incidence of plaques was relatively high in our study. This may reflect a true patient population in the People's Republic of China, because only patients who are considered to be at high risk of CAD will be referred for CT angiography.

Conclusion

Our findings suggest that carotid plaque formation is a strong predictor of stable CAD. However, CINT-CB could predict stable CAD only in patients aged over 60. Further study with a larger sample size is warranted.

Disclosure

The authors declare that they have no competing interests in this work.

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