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Research Article

Usefulness of Carotid Ultrasound in Patients with Intermediate Pretest Probability of Coronary Artery Disease

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Abstract

Objective: We aimed to investigate the clinical significance of carotid ultrasound in subjects with chest pain had intermediate pretest probability of CAD.

Methods: Eighty consecutive patients presented with chest pain and had intermediate pretest probability for CAD were subjected to carotid intima media thickness (CIMT) and carotid plaque evaluation with the use of carotid ultrasound. The presence and evaluation of CAD was performed with CCTA.

Results: 37% of the study cohort had CCTA documented. Of patients with CCTA documented coronary stenosis > 50%, the CIMT was significantly higher ($p < 0.001$). Furthermore, the calcium score was significantly higher in those with obstructive CAD ($p < 0.005$). Multivariate analysis demonstrated that increased CIMT was associated with an increased risk of coronary stenosis > 50% (odds 1.56 [1.22 - 1.93], $p < 0.03$), whilst carotid plaque thickness was associated with coronary stenosis (odds ratio 2.85 [1.25 - 3.72], $p < 0.001$) after adjusting for traditional risk factors. ROC analysis showed that the best cutoff CIMT value for predicting CAD was 0.89 mm, while the cutoff value of plaque thickness was 1.95 mm.

Conclusion: Carotid plaque and CIMT were significantly associated with coronary plaque burden in subjects presented with chest pain and had intermediate pretest probability of CAD. Thus, we suggest that carotid ultrasound might provide a useful noninvasive tool for risk stratification of subjects presented with acute chest pain and deemed to have intermediate pretest probability of CAD.

Keywords: *Carotid Ultrasound; Coronary Plaque Burden; Coronary CT Angiography*

Introduction

Noninvasive testing are generally recommended by most of guidelines in assessment of subjects presented with chest and have intermediate pretest probability of coronary artery disease (CAD) [1]. Yet, the results are normal or equivocal in a considerable percentage of most of the functional tests and in more than 95% of patients will not experience an adverse clinical outcome along two years of follow-up, spite of they had intermediate pretest likelihood of coronary artery disease [2-5].

Several studies found a significant relation between carotid atherosclerosis evidenced by increased carotid intima media thickness (CIMT) and higher incidence of cardiovascular diseases. Thus, CIMT assessment was suggested to be considered a surrogate marker of cardiovascular atherosclerosis [6-9].

Previous studies found a significant correlation between carotid atherosclerosis and CAD on invasive studies and coronary artery calcium on CCTA [10-12]. However, the usefulness of carotid ultrasound in detecting coronary atherosclerosis in the setting of chest pain of patients with intermediate pretest probability of CAD is not clearly studied. Hence, we investigated the presence of any coronary artery diseases based on CCTA and CIMT in patients with chest pain and have intermediate pretest probability for CAD.

Subjects and Methods

Eighty subjects, who presented with atypical chest pain were included in a prospective study. They deemed to have intermediate pretest probability for CAD. Subjects supposed to have intermediate pretest probability of CAD included men with atypical pain who were > 30 years old, and for women with atypical pain who were > 50 years old. CAD risk factors assessment for all individuals included: (i) Diabetes mellitus; (ii) Hypercholesterolaemia; (iii) Hypertension; (iv) Obesity; (v) Positive family history; and (vi) Smoking. All patients were referred to CCTA for CAD exclusion. The pretest probability of CAD was determined by age, sex and the nature of chest pain during initial presentation, and classified as low (< 10%), intermediate (10 - 90%) and high (> 90%) [13]. Patients with acute myocardial infarction, documented CAD, and/or previous coronary revascularization, severe coronary artery calcification, chronic liver disease, asthma and those with allergy to contrast material were excluded. Blood pressure was recorded using sphygmomanometer. In all the patients, two readings were taken at the same visit, in sitting position in the right arm with 10 - 15 minutes interval by the same physician. Echocardiographic evaluation was performed for all participates to obtain ejection fraction, mitral flow velocity, E/A ratio, mitral annular velocities (e' and a') and the E/e' ratio as an indication of left ventricular filling pressure and diastolic function was calculated. Blood urea, serum creatinine, fasting and postprandial blood sugar, and lipid profile and high sensitive C-reactive protein (hs-CRP) were obtained using standard laboratory techniques. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Each participate gave an informed written consent.

Carotid ultrasound

Two-dimensional ultrasound scans were performed with the use of vascular ultrasonography device (GE Healthcare) equipped with a two-dimensional transducer. Both right and left common carotid arteries (CCAs) were imaged and a full carotid ultrasound assessment was obtained as previously described by the American Society of Echocardiography (ASE) was carried out on every patient. The maximum height (thickness) from either bulb was used for analysis. The presence of carotid plaque, at least two of the following criteria were required: localized region with CIMT greater than 1.5 mm, change in the carotid wall surface outline, or focal change in the carotid wall echogenicity. The presence of plaque was coded as yes or no [14].

Coronary CCTA evaluation

CCTA was carried out with A 64-slice MDCT scanner (LightSpeed VCT; GE Medical Systems, Milwaukee, WI) to obtain CAC and MDCT Image acquisition as follows: collimation 64 × 0.625 mm, tube rotation 0.35s and electrocardiogram (ECG)-modulated tube current 110 - 550 mA at 120 kV. Non-ionic contrast material was injected at 5 - 6.5 ml s^{-1}. Aggressive dose modulation was utilized for all appropriate patients, with the maximal tube current centered at 75% of the R-R interval. Beta blocker (5 mg Bisoprolol) was given for all patients to optimize heat rate less than 60 bpm. The CT examinations were carried out during breath holding in inspiration, of approximately 10 - 20s.

Calcium score was calculated as previously described in Agatston scoring method [15]. The score of individual lesion was calculated by multiplying the lesion area by the density factor obtained from the maximal HU in that specific area. The sum of each score of all lesions detected along entire coronary artery tree obtained was obtained and was considered as total calcium score.

Measurement of plaque burden

We analyzed only coronary artery segments with diameters > 2 mm. morphologically, plaques were defined as structures > 1 mm^2 within and/or adjacent to the vessel lumen, that were clearly distinguished from the lumen and adjacent pericardial fat tissue. Each coronary segment was assigned one coronary plaque regardless of the number of lesions in that specific segment. The amount of stenosis in all coronary segments was visually assessed according to the Society of Cardiovascular Computed Tomography guidelines and was reported as no obstruction, luminal obstruction < 25% (mild CAD), luminal obstruction 25 - 50% (moderate), luminal obstruction 50 - 70% (moderately severe) and luminal obstruction > 70% (severe) for each segment. Plaque characteristics were described as calcified plaque (> 130 HU), non-calcified plaque (< 130 HU) and mixed plaque for each segment. A detailed analysis of the extent and severity of the CAD were performed using previously validated scores. We used the segment involvement score (SIS), which is calculated with the sum of the number of segments with CAD, ranging from 0 to 17 [16] and the segment severity score (SSS). Regarding the diameter stenosis, normal or no stenosis was assigned a score of 0, non-obstructive CAD was assigned a score of 1, 50 - 70% stenosis was assigned 2, whilst, a stenosis more than 70% was assigned 3. lastly the score is the sum of each individual score, ranging from 0 to 51 [17].

Statistical analysis

Continuous variables were presented as mean± standard deviation (SD) and categorical variables were expressed as percentages. The analysis of covariance was used to compare groups adjusted for sex, age and hypertension, with log-transformed variables for non-normally distributed variables. The correlation analysis was performed with the of Spearman's correlation methods. Multivariable logistic regression analysis was performed to assess independent variables that predict obstructive CAD. Receiver-operating characteristic (ROC) curve analysis was used to investigate the cutoff values of carotid atherosclerotic variables predict obstructive CAD in the study cohort. The SPSS 18.0 (Chicago, IL, USA) was utilized for statistical analysis.

Results

CCTA evidence of any obstructive CAD was present in 37 (42.5%) patients. The calcified or mixed coronary plaque was observed in 23 (62%), while the noncalcified plaques were found in 14 (38%). Among of vessels with coronary artery stenosis > 50%, 22 (59%) had single vessel disease, 11 (30%) had two vessel disease and 4(11%) had three vessel disease. Moreover, the total plaque score (TPS) was 8.5 ± 3.3, segment stenosis score (SSS) was 7.3 ± 4.1 and the segment involvement score (SIS) was 5.3 ± 2.2. Whilst, the CACS was 299 ± 245. Then the study cohort were classified into two groups according to the presence or absence of CCTA coronary artery disease. The demographic characteristics of both groups were summarized in table 1.

Variable	n = 80
Age	49 ± 11
Male (%)	51 (64%)
Body mass index (kg/m^2)	24.9 ± 2.5
Smoking (%)	39 (49%)
Family history of premature CAD	38 (47.5%)
Hypertension (%)	45 (56%)
Diabetes mellitus	35 (44%)
Total cholesterol mg/dL	207 ± 25
LDL-C (mg/dL)	133 ± 21
HDL-C (mg/dL)	40 ± 3

TG (mg/dL)	175 ± 46
Hs-CRP (mg/L)	3.3 ± 1.5
CCTA	
Coronary calcium score, mm^3	299 ± 245
Negative coronary artery disease	50 (57.5%)
Positive coronary artery disease (> 50% stenosis)	37(42.5%)
Calcified plaque or Mixed plaque	62 (66%)
Noncalcified plaque	32 (34%)
Segment stenosis score	7.3 ± 4.1
Segment involvement score	5.3 ± 2.2
Number of stenosed vessels	
One-vessel disease	22
Two vessel disease	11
Multivessel disease	4

Table 1: *Demographic characteristics and CCTA data of all studied cohort.*
CCTA: Coronary Computed Tomographic Angiography; HDL-C: High Density Lipoprotein Cholesterol;
LDL-C: Low Density Lipoprotein Cholesterol; TG: Total Glycosides; Hs-CRP: High Sensitive C-Reactive Protein.

All the demographic data were comparable among subjects with and without CAD except LDL-cholesterol which was slightly higher ($p < 0.05$) and hs-CRP which was significantly elevated ($p < 0.001$) in those with CAD. In addition, left ventricular filling pressure (E/e') was significantly increased in patients with positive CAD ($p < 0.001$).

Carotid ultrasound examination was obtained in 100% of all patients, with a good image quality allowing assessment of the carotid atherosclerotic parameters. Patients with CAD had CIMT of 0.98 ± 0.34 mm, while those without CAD had CIMT of 0.61 ± 0.21 mm ($P < 0.001$). The prevalence of carotid plaque was approximately (76.6% versus 13%; $p < 0.001$). In particular as regards the maximal plaque thickness (CPT) (Figure 1), it was 2.85 ± 0.79 mm in subjects with CAD versus 1.4 ± 0.31 mm ($p < 0.001$) in those without CAD (Table 2).

Variable	CAD (+) n = 37	CAD (−) n = 43	P value
Age (years)	51.5 ± 11	48.6 ± 12	> 0.05
Body mass index (kg/m^2)	25.1 ± 3.3	24.2 ± 2.1	> 0.05
Hypertension	68 (72%)	64 (60)	> 0.05
Diabetes mellitus	13 (35%)	16 (37)	> 0.05
Total cholesterol (mg/dl)	231 ± 48	189 ± 31	> 0.05
LDL-cholesterol (mg/dl)	148 ± 33	95 ± 29	< 0.05
HDL-cholesterol (mg/dl)	39 ± 8	45 ± 9	> 0.05
hs-CRP (mg/L)	4.5 ± 1.2	1.2 ± 1+0.09	< 0.01
Triglycerides (mg/dl)	179 ± 45	153 ± 42	> 0.05
Family history of CAD	18 (19%)	16 (15%)	> 0.05
Smokers	21 (57%)	22 (51%)	> 0.05
Ejection fraction%	66 ± 5	68 ± 4	> 0.05
E/e'	9.2 ± 1.1	4.8 ± 0.3	< 0.01
Carotid plaque %	72/94 (76.6%)	14/106 (13%)	< 0.001
Maximum thickness of plaque (mm)	2.85 ± 0.79	1.4 ± 0.31	< 0.001
Mean CIMT (mm)	0.98 ± 0.34	0.61 ± 0.21	< 0.001

Table 2: *Characteristics of CCTA positive coronary artery disease and negative patients.*
CCTA: Coronary Computed Tomographic Angiography.

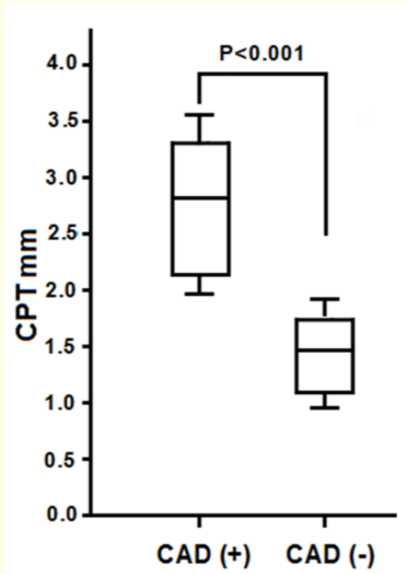

Figure 1: *Distribution of the carotid plaque thickness [CPT] in coronary artery disease [CAD] positive and negative patients with coronary computed tomographic angiography.*

All carotid atherosclerotic parameters were significantly correlated with correlated with segmental stenosis score (SSS); segment involvement score (SIS); and total plaque score (TPS) (Table 3).

	SSS		SIS		TPS	
	r	P	r	P	r	P
CIMT	0.193	< 0.05	0.311	0.01	0.243	< 0.03
Number of Carotid plaques	0.321	< 0.001	0.405	< 0.001	0.318	< 0.003
Carotid plaque thickness (mm)	0.375	< 0.001	0.511	< 0.001	0.429	< 0.001

Table 3: *Correlation analysis of variable for coronary plaque burden in patients with intermediate pretest probability of CAD.*
SSS: Segmental Stenosis Score; SIS: Segment Involvement Score; TPS: Total Plaque Score; CIMT: Carotid Intima Media Thickness.

Carotid intima media thickness and carotid plaque thickness were significantly ($p < 0.001$) correlated with E/e' ratio as a marker of diastolic filling pressure and diastolic function of the left ventricle.

Univariate analysis showed that hypertension ($p < 0.05$), smoking ($p < 0.05$), dyslipidemia ($p < 0.05$), hs-CRP ($p < 0.05$), CIMT ($p < 0.003$) and carotid plaque number ($p < 0.001$) and CPT (< 0.001) were significantly associated with CAD. On the other hand multivariate analysis only the carotid atherosclerotic parameters were independent predictors for coronary plaque burden in subjects with chest pain and had intermediate probability of CAD, with the plaque thickness is the strongest predictor (OR: 2.85, 95% CI: 1.25 - 3.72; $p < 0.001$) (Table 4).

	Univariate regression			Multivariate regression		
	OR	95% CI	p	OR	95% CI	p
Hypertension	1.75	1.23 - 2.96	< 0.05	1.19	0.85 - 1.62	> 0.05
Smoking	1.52	1.15 - 2.64	< 0.05	1.05	0.79 - 1.55	> 0.05
LDL-C	1.62	1.17 - 2.21	< 0.05	0.99	0.81 - 1.75	> 0.05
hs-CRP (mg/L)	1.85	1.15 - 2.85	< 0.05	1.24	0.91 - 1.53	> 0.05
CIMT mm	1.94	1.43 - 2.35	< 0.003	1.56	1.22 - 1.93	< 0.03
Carotid plaque number	2.61	1.48 - 2.65	< 0.001	1.95	1.34 - 2.73	< 0.01
Plaque thickness	3.99	1.53 - 4.82	< 0.001	2.85	1.25 - 3.72	< 0.001

Table 4: *Univariate and multivariate logistic regression analysis to determine the independent predictor for plaque burden.*
LDL-C: Low Density Lipoprotein Cholesterol; hs-CRP: High Sensitive C-Reactive Protein;
CIMT: Carotid Intima Media Thickness Lipoprotein Cholesterol.

ROC analysis showed that carotid plaque thickness (CPT) > 1.95 mm was the best cutoff value for predicting CAD with a sensitivity of 95% and specificity of 83% (Figure 2). On the other hand CIMT > 0.89 mm was the best cutoff value predicted CAD with a sensitivity of 89% and specificity of 78% (Figure 3).

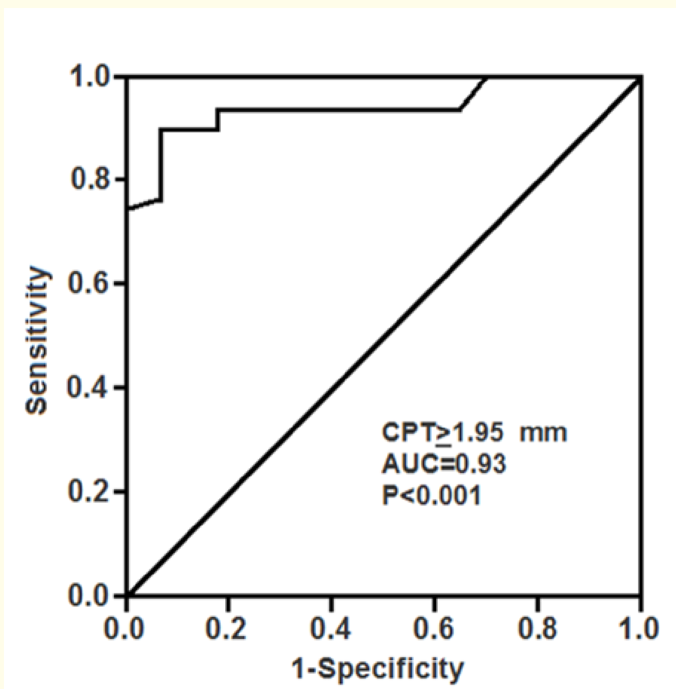

Figure 2: *Receiver operating characteristic (ROC) curve analysis to identify positive coronary artery disease with CCTA. The cut-off value of carotid plaque thickness [CPT] was set at 1.95 mm.*

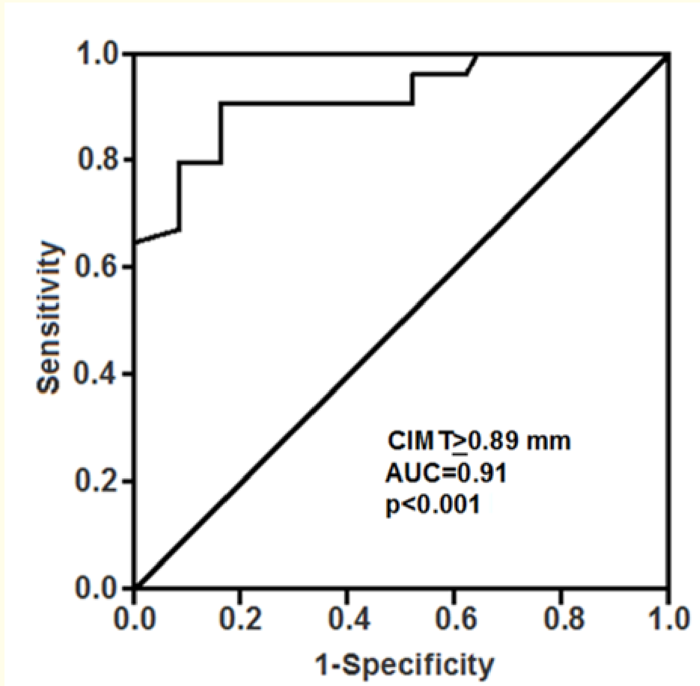

Figure 3: *Receiver operating characteristic (ROC) curve analysis to identify positive coronary artery disease with CCTA. The cut-off value of mean carotid intima-media thickness was set at 0.89 mm.*

Discussion

In patients without known CAD and supposed to have an intermediate risk of CAD, the detection of any coronary artery disease may have a critical importance. CCTA as a noninvasive tool has a great value in the assessment of coronary artery calcium score and coronary plaque burden. This value provides a great importance for detection and evaluation of high-risk atherosclerotic plaques [18] and might increase the efficiency of diagnosis of significant coronary stenosis in the assessment of acute chest pain [19]. Nevertheless, it is costly and not available everywhere. Herein, we investigated the association between carotid ultrasound as a simple easily available tool and CCTA findings for risk stratification of subjects presented with chest pain.

We found a higher prevalence of carotid plaques and greater CIMT in patients with any CCTA evidence of CAD, compared with those without CAD. Interestingly we investigated the cut-off level of CIMT and carotid plaque thickness for identifying the presence of CAD in the setting of intermediate pretest probability for CAD, when the cut-off value of CIMT set at > 0.89 mm and CPT at 1.95 mm, we might predict the presence of CAD. Furthermore, we observed that patients with increased CIMT and higher percentage of carotid plaques had higher values of hs-CRP and higher levels of LDL-cholesterol, spite of comparable others cardiovascular risks factors among both groups. These findings suggests that both carotid atherosclerosis and coronary atherosclerosis are sharing a systemic mechanisms. Moreover, in the current study, patients with carotid atherosclerosis has significant impaired left ventricular diastolic function evidenced by increased E/e' ratio spite of normal ejection fraction and mitral E/A ratio on conventional echo-Doppler assessment. The association between carotid atherosclerosis and diastolic dysfunction might be explained by the presence of CAD in our cohort.

Chest pain is a nonspecific complain that have several causes of cardiac and noncardiac origin [20]. Chest pain due to CAD is the commonest type of cardiac pain in subjects present to emergency departments. Besides about 1 in every 5 deaths is attributed to CAD constituting the single most common cause of mortality worldwide. The socioeconomic burden, morbidity and mortality of CAD are critical considerations for risk stratification, and the in make timely accurate diagnosis and cost-effective management of CAD of the utmost importance [21-23].

Few previous studies tried to introduce a set of findings that help to risk stratification of patients with chest pain and have an intermediate-likelihood probability for CAD who are likely to receive little or no benefit from noninvasive testing. This concept of not testing subjects with intermediate pretest probability for CAD goes in line with guideline recommendations to not test unless the pretest probability of obstructive CAD is greater than 10% [24,25].

CIMT evolution provides useful information for risk stratification of symptomatic patients undergoing exercise stress testing. Moreover, carotid ultrasound might be used in risk stratification of patients without coronary plaques, with a negative predictive value nearly 100% [26].

Limitation of the Study

All the coronary artery lesions on coronary computed tomographic angiography were not confirmed by invasive coronary angiography. Secondly, we did not set a control group for the coronary artery disease screening, and we did not follow up patients with negative carotid ultrasound findings.

Conclusion

Our findings suggest that carotid plaque height and CIMT are independent predictors of coronary plaque burden in patients presented with chest pain and have an intermediate pretest probability for CAD. Thus, carotid ultrasound to assess CIMT and carotid plaques is of great importance in risk stratification of subjects with chest pain and have a low to intermediate probability for coronary artery disease.

Conflict of Interest

All Authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional.

Consent

An informed consent was obtained from all individual participants included in the study.

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