CHAPTER

208

To Assess Predictive Value of Carotid Artery Intima Media Thickness as a Non-Invasive Marker for Coronary and Cerebral Artery Disease

Gurmukh S Sainani, Mitul A Shah

INTRODUCTION

There is a great interest in identifying asymptomatic patients at high risk who might be candidates for more intensive, evidence based medical interventions that reduce cardiovascular disease (CVD) and cerebrovascular disease risk. Measurement of carotid intima media thickness (CIMT) with B-mode ultrasound is a non-invasive and reproducible technique for identifying subclinical vascular disease and for evaluating CVD risk.

Earlier endothelium was thought to be a smooth, intact non-thrombogenic lining of the arterial wall but now it is known that the endothelium produces vasoactive factors which are divided into 2 groups. Endothelial derived relaxing factors (EDRF) eg nitric oxide (No) and prostacyclin (PG12) and Endothelial derive constricting factors (EDCF) like Endothelin-1 and Thromboxane A2 (TXA2). These factors balance the effects of vascular tone and vascular structure and preserve a smooth non-thrombogenic luminal surface. The alterations in these factors, if allowed to become chronic, are responsible for changes in vascular structure and growth and adhesions to platelets and leukocytes leading to atherosclerosis.[1]

ENDOTHELIAL CELL DYSFUNCTION CAN BE ASSESSED BY 3 METHODS

1. Intima media thickness (IMT)
2. Brachial artery flow mediated dilatation (FMD)
3. Ankle brachial index (ABI)

Atherosclerotic vascular disease begins in childhood and progresses over decades. Symptomatic, clinical cardiovascular disease (CVD) events generally occur when atherosclerosis progresses to flow limiting disease that causes ischemia or when thrombus forms on an existing plaque as a result of rupture or erosion[2]. The greater the degree of subclinical atherosclerosis, the greater is the risk of future cardiovascular events[3-7]. To prevent morbidity and death from CVD, there is great interest in identifying asymptomatic patients at high risk who would be candidates for more intensive, evidence based medical interventions that reduce CVD risk.

Measurement of carotid intima media thickness (CIMT) with B-mode ultrasound is a non-invasive, sensitive and reproducible technique for identifying and quantifying atherosclerotic burden and CVD risk. It is a well validated research tool that has been translated increasingly into clinical practice[8-12]. Measuring CIMT and identifying carotid plaque can be useful for refining CVD risk assessment. CIMT testing can reclassify patients at intermediate risk, discriminate between patients with and without prevalent CVD and predict major adverse CVD events.

CIMT measurements should be limited to the far wall of the common carotid arteries and should be supplemented by a thorough scan of the extra cranial carotid arteries for the presence of carotid plaque to increase sensitivity for identifying subclinical vascular disease. Carotid plaque is defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or at a focal region with CIMT greater than 1.5 mm that protrudes into the lumen which is distinct from the adjacent boundary. The presence of carotid plaque or CIMT greater than or equal to 75th percentile for patient's age, sex, race and ethnicity are indicative of increased CVD risk and may signify the need for more aggressive risk reduction interventions.

According to the recommendations of American Society of Echocardiography (ASE), patients with the following clinical circumstances also might be considered for CIMT testing: (1) Family history of premature CVD in a first-degree relative (2) Individuals younger than 60 years with severe abnormalities with a single risk factor who otherwise would not be candidates for pharmacotherapy or (3) Women younger than 60 years of age with at least two CVD risk factors. This test can also be considered if the level of aggressiveness of therapy is uncertain and additional information about the burden of subclinical vascular disease or future CVD risk is needed.

AIMS AND OBJECTIVES

1. To ascertain whether there is any correlation between the grade of CIMT and the severity of coronary artery disease. (CAD as assessed by coronary angiography).
2. To ascertain whether there is any correlation between the CIMT and severity of cerebrovascular disease.

Table 1: Group wise CIMT values

	RCCA Mean-Max CIMT (MM)		LCCA Mean-Max CIMT (MM)	
	Mean	Standard Deviation	Mean	Standard Deviation
Group A (CAD)	0.860	0.224	0.858	0.247
Group B (CVA)	0.752	0.183	0.808	0.222
Group C (Controls)	0.544	0.143	0.554	0.146

RCCA (right common carotid artery); LCCA (left common carotid artery); The mean CIMT (carotid intima media thickness) in RCCA and LCCA in coronary artery disease (CAD) and cerebrovascular disease (CVA) are significantly higher than controls.

3. To establish the range of CIMT in normal persons (controls).

MATERIAL AND METHODS

We carried out the study in a large accredited institute (Jaslok Hospital and Research Centre) serving as a tertiary care centre. The subject was approved by scientific committee and ethnical committee of Jaslok Hospital and Research Centre.

Total 125 subjects in the age group of 30-75 years were selected from the inpatient and outpatient departments of the Jaslok Hospital and Research Centre, Mumbai. We selected 3 groups of subjects

Group A (CAD) : Coronary artery disease patients – These patients underwent coronary angiography and were documented as having coronary artery disease (50 cases)

Group B (CVA): Cerebrovascular disease patients: Patients admitted with stroke (cerebrovascular accidents and confirmed by CT, CT-angio and/or MRI - 25 cases)

Group C (Controls) – These subjects were selected from health check-up, staff members of the hospital who had no complaints, no abnormal physical findings with normal BP, normal ECG and normal blood reports (50 subjects). All 125 subjects were studied as per the protocol enquiring about complaints, any history of smoking, tobacco chewing or alcohol intake, past history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease or cerebrovascular disease.

After obtaining a written and informed consent from each individual selected for this project, carotid ultrasound study was performed in the department of ultrasonography at the Jaslok Hospital and Research Centre.

We recorded age, sex, body mass index, pulse, blood pressure, fasting and 2 hours post lunch blood sugar, lipid profile, ECG, X-ray chest. Coronary angiographies for CAD cases and CT, CT angio and/or MRI for stroke cases were done.

As recommended by Stein J H et al,[3] while describing the consensus statement from the American Society of Echocardiography, Carotid Intima Media Thickness Task Force, the maximum CIMT (CIMT-Max) was measured in the far wall of the proximal, middle and distal segments of both common carotid arteries and the mean of the three CIMT-Max values or the highest value was taken as the final Mean-Max CIMT. These measurements were supplemented by a thorough scan of the extra cranial carotid arteries for the presence of carotid plaque which is supposed to increase sensitivity for identifying subclinical vascular disease. Carotid plaque is defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or at a focal region with CIMT greater than 1.5 mm that protrudes into the lumen and is distinct from the adjacent boundary.

The various parameters were analysed statistically. We studied the demographic distribution of the patients taken in the study and also compared the CIMT values among all three groups along with various cardiovascular disease (CVD) risk factors. We also studied whether the presence or absence of carotid plaque had any correlation with CAD or CVD along association with various CVD risk factors.

RESULTS

There was a significant increase in CIMT on both sides in those with CAD (Group A) as compared to the normal individuals (Group C) (P value 0.000) (Table 1).

The group A (CAD) was further subdivided into three subgroups as per the number of coronary arteries involved (1 vessel, 2 vessels and 3 vessels) and the CIMT values were compared (Figures 1 & 2). It was found that there was a significant difference in the CIMT between those with 1 vessel and 3 vessels CAD on right side (p value <0.001). Also it was found that there was significant difference in the CIMT between those with 1 vessel and 3 vessels CAD and those with 2 and 3 vessels CAD on left side (P valve<0.001)

Also a significant increase in CIMT was observed on either side in those with CVA (Group B) as compared to the normal individuals (Group C) (P value 0.000) (Table 1 and Figure 3).

The number of hypertensive individuals in Group A and Group B were 37 and 15 respectively while the others were non-hypertensive. We found that there was a significant difference in CIMT on either side in hypertensive versus non-hypertensive individuals (P value 0.000 for both sides).

The number of diabetic individuals in Group A and Group B were 18 and 10 respectively while the others were non-diabetics. Here also a significant difference was found in CIMT on either side in diabetic versus non-diabetic

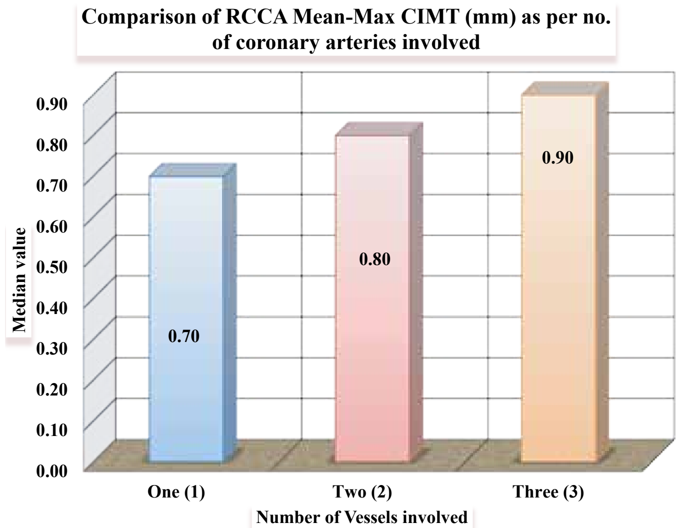

Fig. 1: There was a significant difference in the CIMT between those with 1 vessel CAD and 3 vessels CAD on right side (P value <0.016)

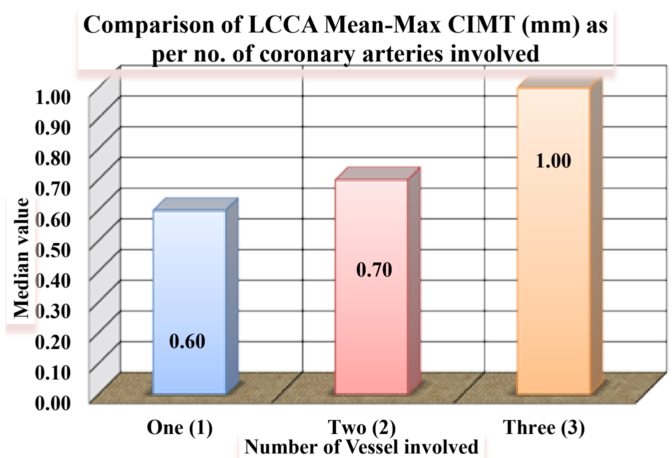

Fig. 2: A significant difference in the CIMT was noted between those with 1 vessel CAD versus 3 vessels CAD and 2 vessels CAD versus 3 vessels CAD on left side (P value <0.001)

individuals (P value <0.004 and <0.012 for right and left side respectively).

DISCUSSION

Coronary Artery Disease and CIMT

In the ARIC (Atherosclerosis Risk in Communities) Study conducted by Nambi V et al.[4] it was concluded that adding plaque and CIMT to traditional risk factors improves CHD (Coronary Heart Disease) risk prediction. In another study conducted by Yoshida M at al[5], it was concluded that Carotid IMT is a significant predictor of CVD (Cardiovascular diseases) in asymptomatic type II diabetic patients and the combination of Framingham Risk Score (FRS) and IMT improves the prediction of CVD in these patients. Bots ML et al.[6] studied whether common carotid IMT is related to future stroke and myocardial infarction and found that an increased common carotid IMT is associated with future cerebrovascular and cardiovascular events.

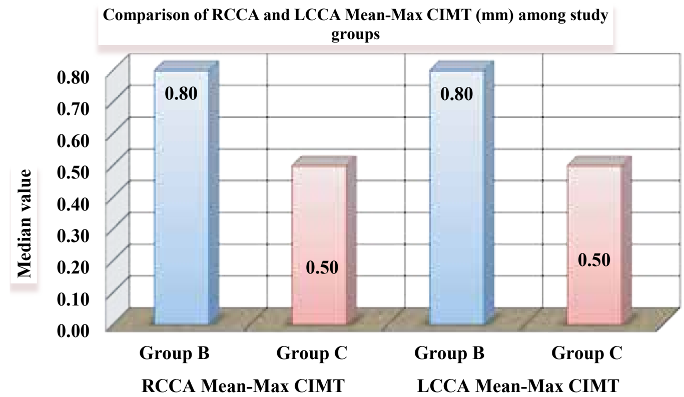

Fig. 3: There was a significant increase in CIMT on either side in those with CVA as compared to the normal individuals (P value 0.000 for both sides)

Cerebrovascular Accidents and CIMT

In a study performed by Sahoo R et al.,[7] it was found that the CIMT was independently associated with the presence of carotid plaques and strokes. Thus the findings of our study that the CIMT is positively correlated with the presence of CVA are supported by the above study.

Hypertension and CIMT

In a study conducted by Yarynkina et al[8], the relationship between CIMT and other cardiovascular disease risk factors in 77 patients with mild and moderate essential hypertension (EH) was assessed and it was concluded that common carotid artery IMT changes are related with BP elevation, in part with pulsatile component of BP (Systolic BP, Pulse Pressure). In another study conducted by Sharma P et al[9], the CIMT was evaluated in 203 hypertensive cases and 101 normotensive individuals (controls). Mean IMT was significantly high in hypertensive patients compared to the control group ($p < 0.001$). In addition they found a significant difference in IMT of bilateral common carotid arteries between the smokers and non-smokers hypertensive patients ($p < 0.02$). In conclusion, the study revealed a strong correlation between IMT of common carotid arteries and hypertension. Thus, our observations are in echo with the above mentioned studies.

Diabetes Mellitus and CIMT:

Sainani G S and Khan N[10], found a very strong correlation of diabetes mellitus and CIMT and they concluded that: (1) Post-prandial hyperglycemia is directly responsible for increase in CIMT and as the level of post-prandial blood sugar increases there is proportionate increase in the CIMT; (2) With increasing age, there is proportionate increase in CIMT in patients with post prandial hyperglycemia as compared to those without post prandial hyperglycemia; (3)There is increase in CIMT with increase in the duration of diabetes mellitus; (4) There is no gender bias in CIMT among patients with post prandial hyperglycemia; (5) Smoking and alcohol accelerate CIMT in patients with post prandial hyperglycemia.

There is a study conducted by Inohara T et al[11] in which they found CIMT >or=1.6 as the independent predictor of coronary artery plaque and it was proven that the CIMT is a useful screening tool to detect coronary artery plaque in type II diabetic patients with Calcium Score of zero. In another study by Irie Y et al[12], it was concluded that in type II diabetic patients without apparent cardiovascular disease, the addition of max-IMT to conventional risk factors substantially improves the risk stratification for CAD.

Carotid Plaque and its Various Associations:

Here we found that the presence of carotid plaque has a very strong association with the presence of CAD and CVA and is supported by previous studies.

CONCLUSIONS

1. The mean CIMT in the normal healthy individuals (controls) in this study population on the right side is (0.544 ± 0.143) mm and on the left side is (0.554 ± 0.146) mm.
2. CIMT is positively correlated with the presence of coronary artery disease, severity of coronary artery disease, presence of cerebrovascular accidents, presence of hypertension and diabetes mellitus.
3. It was also found that the presence of carotid artery plaque has a very strong association with CAD and CVA.

REFERENCES

1. Sainani GS, Bhatia MS, Sainani RG. Endothelial Cell Dysfunction-A Key Factor in Atherogenesis and its Reversal (laboratory and Clinical Study); Atherosclerosis, Hypertension and Diabetes; Edited by Pierce G N, Nagano Makoto, Zahradka P, Dhalla N S; Kluwer Academic Publishers; 2003; p. 27-51.
2. Virman R, Burke AP, Farb A. Kolodgie FD – Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006; 47:C13-8
3. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. *J Am SocEchocardiogr* 2008; 21:93–111.
4. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol* 2010; 55:1600 –7.
5. Yoshida M, Mita T, Yamamoto R, Shimizu T, Ikeda F, Ohmura C, Kanazawa A, Hirose T, Kawamori R, Watada H. *Diabetes Care* 2012; 35:178-80.
6. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997; 96:1432–7.
7. Sahoo R, Krishna MV, Subrahmaniyan DK, Dutta TK, Elangovan S. *Neurol India* 57:627-30.
8. Yarynkina O, Svyshchenko E, Mishchenko L, Tchyrulneva N, Mospan M, Yegorushkin V. Relationship Between Carotid Intima-Media Thickness and Cardiovascular Risk Factors in Hypertensive Patients; *Journal of Hypertension* 28 e-–Supplement A:e592, June 2010.
9. Sharma P, Lohani B and Chataut S P; Ultrasonographic evaluation of carotid intima-media thickness in hypertensive and normotensive individuals; *Nepal Med Coll J* 2009; 11:133-135.
10. Sainani G S, Khan N; Carotid Artery Intima Media Thickness – A Correlative Study of Diabetics with Postprandial Hyperglycemia versus Controls with Euglycemia; Medicine Update 2012; 22:298-303.
11. Inohara T, Niinuma H, Niwa K. *J Am Coll Cardiol* 2012; 59(13s1):E1155-E1155. doi:10.1016/S0735-1097(12)61156-5.
12. Irie Y, Katakami N, Kaneto H, Kasami R, Sumitsuji S, Yamasaki K, Tachibana K, Kuroda T, Sakamoto K, Umayahara Y, Ueda Y, Kosugi K, Shimomura I. *Atherosclerosis* 2012; 221:438-44. Epub 2012 Jan 21.