Indian Heart J 2000; 52: 395–399

Review Article

Role of Carotid Intimal-Medial Thickness in Assessment of Pre-Clinical Atherosclerosis

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Introduction

Atherosclerosis is a multifactorial and dynamic process and until now there is no generally agreed hypothesis explaining this process. One of the early features of atherosclerosis is the presence of fatty streaks along the vessel wall. These fatty streaks are characterised by accumulation of lipid-filled smooth muscle cells and macrophages and fibrous tissue in focal areas of the intima. Consequent to endothelial damage over time, fibrin, platelets, cellular debris and other substances get deposited along the arterial wall. This build-up of plaque on the wall of arteries leads to a reduction in the calibre of the vessel. Over a period of several years cholesterol, fat and the smooth muscle cell lining of blood vessels get transformed into a thickened and sometimes calcified mass. This ultimately results in constriction of the artery; eventually the elasticity of the artery disappears and the volume of blood able to travel through it at a given time is reduced[1,2].

The process of atherosclerosis may start as early as childhood, but it may progress rapidly in high risk individuals[2]. Atherosclerosis tends to target the aorta, the body's largest artery which leaves from the heart, and the arteries leading to the heart, brain, liver and the kidney. Depending on the location and severity of the arterial damage, the symptoms and signs of pathology of that particular organ emerge. Thus, coronary artery disease (CAD) leads to angina or myocardial infarction; in the carotid artery it may cause cerebral thrombosis leading to cerebrovascular sequelae including transient ischaemic attacks or an established stroke. In the aorta, atherosclerosis can lead to development of aneurysmal dilatation of the thoracic abdominal segment. Atherosclerosis in the kidney can lead to high blood pressure and renal failure. Atherosclerosis in the lower limbs can lead to intermittent claudication, ischaemic ulcers and eventually, gangrene[2,3].

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Prevalence of Atherosclerotic Disease

Atherosclerosis is a leading cause of death and impairment in US and Europe[4]. Recent estimates indicate that 12 million deaths annually worldwide are due to CAD and in 1990 approximately 25 percent of the deaths in India were attributed to CAD[5,6]. This is greater than that caused by diarrhoeal disease and respiratory and other infectious diseases[5,6].

Recognition/Documentation of Atherosclerosis

Angiography

Coronary angiography as a tool to assess the genesis of this pathology was first reported by Sones et al[7] in 1959 and is, since considered one of the best methods to document atherosclerosis. Angiography facilitates visualisation and assessment of arteries as small as 0.5 mm in diameter. Recent progress in this field has led to computer-assisted methods for measuring and quantifying severity of this obstruction. However, the major drawbacks with this technique are that it is invasive, expensive, has some degree of morbidity or mortality even at the best centres and is clearly unsuitable for repeat studies to assess progression or regression, effects of drugs and also for large scale epidemiological studies.

Intracoronary Ultrasound Doppler

Doppler ultrasound measures flow velocity and focuses on the change in frequency resulting from reflection of the ultrasound beam from a moving target blood. This method has been shown to have a high degree of correlation with angiography. However, the major limitation, again, is its invasive character[8].

Imaging of Carotid Arteries

The normal artery wall has a smooth glistening surface which prevents blood from sticking to it. With progression of atherosclerosis, the artery wall thickens, narrows and becomes irregular. Turbulence and

sediment commonly occur at the branches of the major arteries. It has been identified that the turbulence occurs more specifically and markedly at the carotid artery, aorta and the peripheral vessels. Atherosclerosis of the carotid artery mainly occurs at its major branching point within the neck, namely the carotid bifurcation, where the external and internal carotid arteries branch off from the common carotid artery (Fig. 1).

Intimal-Medial Thickness Technique

As atherosclerosis is asymptomatic in the early stages, techniques identifying atherosclerosis in the early stage are of great significance. Additionally, as atherosclerosis predominantly affects the intimal layer of the artery, techniques which facilitate the study of intima of the artery are necessary. This is the principle behind the intimal-medial thickness (IMT) technique[9,10].

Carotid Intimal-Medial Thickness

High resolution B mode ultrasonography can accurately measure intimal-medial thickness. B mode ultrasound relies on acoustic characteristics of tissues to generate cross sectional images of the near and far walls of the artery and of the lumen. The major advantage of this method is its non-invasiveness and its reproducibility.

Ultrasonographic scanning of the carotid arteries is usually performed using an electrical linear transducer (mid frequency of 7.5mHz is usually used). Scanning of the extracranial common carotid (or internal carotid) arteries in the neck is performed bilaterally according to the anterior - posterior projection. The intimal plus medial thickness (IMT) as defined by Pignoli et al[9] is the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. The first line represents the lumen-intimal interface and the second line is produced by the collagen-containing upper layer of the tunic adventitia (Fig. 2). At each longitudinal projection, three determinations of IMT are conducted at the site of the maximum thickness and at two points, 1 cm upstream and 1 cm downsteam from the site of maximum thickness. The three values are then averaged to get the IMT (Fig. 3).

Reliability and Validity of IMT

O'Leary et al[11] compared the capabilities of carotid B mode ultrasound and angiography as diagnostic methodology and suggested that B mode has a good reproducibility for lesion thickness. Ricotta et al[12] performed a correlation analysis of the human carotid bifurcation by B mode ultrasound, angiography and pathological examination in 900 patients. This study revealed an excellent correlation in thickness of lesions obtained by ultrasound compared to angiography and in fact ultrasound was graded as superior to angiography for quantifying atherosclerotic plaques. Moreover, while angiography provides information about flow patterns, it does not provide any information of the vessel wall.

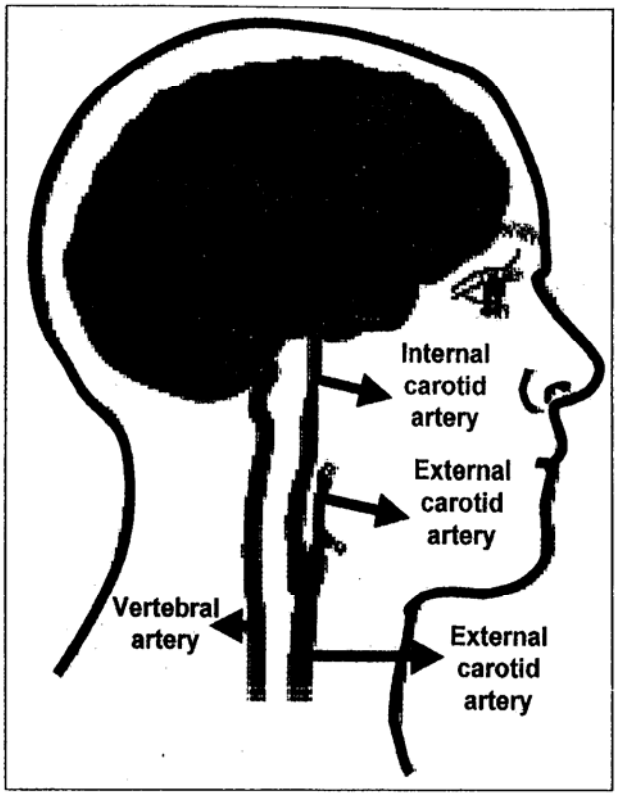

Fig. 1. *Carotid arteries are used to measure the intimal medial thickness, as they are superficial and easily accessible.*

Comparison of carotid stenosis by doppler and carotid angiography in the same patients showed 84 percent sensitivity and 99 percent specificity for differentiation of angiographically demonstrable stenosis of 50 percent or more or less than 50 percent[13]. In the Rotterdam study[14], it was shown that reliable data on intimal-medial thickness of the carotid artery can be obtained in approximately 99 percent of all the subjects. Similar reports have been obtained from large studies like the Kuopio Ischaemic Heart Disease Risk Factor Study[15] and the Cardiovascular Health Study[16]. Although there could be significant inter-observer differences due to placing of the probe and other variables, the results are excellent and reproducible if done by the same observer[17].

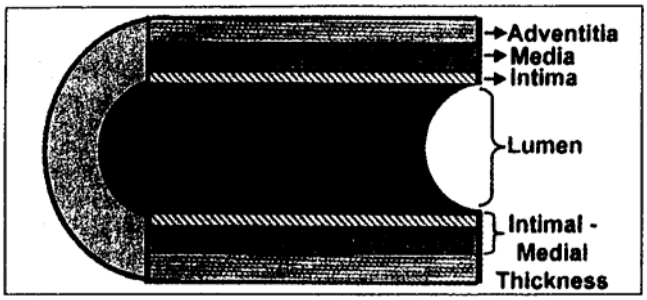

Fig. 2. *Measurement of intimal medial-thickness.*

Chikos et al[18], O'Leary et al[11] and the ARIC Study Group[19] reported an inter-observer correlation coefficient ranging from 0.78 - 0.93 between readers. The elegant studies of Pignoli[20] established the validity of B mode method for measurement of IMT with tissue specimens. A recent longitudinal study by the National Institute of Health & Medical Research (INSERM), Paris[21] has shown that IMT of common carotid artery predicts carotid plaque occurrence. The validity and high degree of reproducibility in these studies have established beyond doubt that B mode ultrasonography is a reliable method to assess atherosclerosis non-invasively.

IMT as a Predictor of CAD

Various studies have examined the association of carotid atherosclerosis using B mode ultrasound with the risk factors for CAD[22-24]. The carotid B mode score had a strong, consistent and independent association with CAD. A study by Wofford et al[25] on 434 patients undergoing cardiac catheterisation showed that patients in the lowest quartile of IMT had normal coronary arteries whereas patients in the higher IMT quartile were 10 times more likely to have triple-vessel CAD.

The predictive power of IMT for the risk of myocardial infarction and stroke was well established by O'Leary et al[26]. In this classic study it was shown that intimal-medial thickness of both, the common carotid artery and internal carotid artery are strongly associated with the risk of myocardial infarction and stroke in asymptomatic older adults. Recently studies were performed on correlation of asymptomatic CAD assessed by exercise ECG with carotid IMT[27]. The results showed that each 0.1 mm increase in IMT was associated with 1.91 fold increase in the risk for positive exercise test.

Further, several studies have also confirmed that intimal-media thickness of the common carotid arteries is a marker for generalised atherosclerosis and may be useful for identification of subjects at risk of cardiovascular disease even at an early stage[28,29].

Fig. 3. *Intimal-medial thickness of carotid artery.*

IMT Measurement in Diabetic Subjects

Diabetic patients are known to have a two- to three-fold higher risk for CAD and studies by Kawamori et al[30] have shown that diabetic subjects show atherosclerosis in carotid arteries 20-30 years earlier than in non-diabetic subjects. Prospective results from the Bruneck study[31] show that impaired glucose tolerance and type 2 diabetes are strong independent predictors of advanced carotid atherosclerosis. Results from the Atherosclerosis Risk in Communities (ARIC) study[32] found the mean IMT to be about 0.08 mm greater in diabetics compared to non-diabetic individuals after adjustments for age, sex, smoking and body mass index. Correlation between the intimal-medial thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes reveals that diabetic patients have more advanced changes as compared to age- and sex-matched control subjects[33].

Studies on insulin resistance and IMT on 53 type 2 diabetic patients by Watarai et al[34] suggest that insulin resistance in the peripheral tissues independently contributes to the carotid arterial wall thickness and especially to plaque lesions. Insulin resistance has been reported to be associated with cardiovascular risk and with IMT is some studies[35,36].

Even in non-diabetic individuals, mild hyperglycemia is associated with atherosclerosis, as measured by the increased intima-media thickness of the common carotid artery[37].

Ethnic Differences in Carotid IMT

It is well known that there are marked ethnic differences in the prevalence of CAD[38-40]. Similarly,

carotid IMT also differs in different populations studied. A large epidemiological study on black and non-Hispanic whites showed that blacks had increased IMT values[41]. A recent study at the Morphometric Reference Centre of WHO and World Heart Foundation (WHF)[42] indicates that the mean IMT differs in arterial wall specimens from various geographic locations. Individuals from countries with high prevalence rates of CAD tend to have greater mean IMT[42]. This prompted us to take up a study on IMT as Indians have high rates of CAD and to our knowledge there are no studies of IMT in Indians.

The Chennai Urban Population Study

The Chennai Urban Population Study (CUPS) is an ongoing epidemiological study in Chennai, the fourth largest city in India with a population of about 6 million. The aim of CUPS is to obtain prevalence data on diabetes and its complications, hypertension, hyperlipidemia and CAD and their risk factors among people of different socio-economic strata in urban Chennai. Briefly, two defined residential colonies representing the middle and lower income groups in the city were selected for their geographic convenience, social differences and local support available which would facilitate future incidence studies. An initial survey was done in all family members using a questionnaire to obtain the basic census details such as number of individuals, age, sex and presence or absence of diabetes. Out of total of 1339 individuals above the age of 20 years living in the two colonies, 1262 (90%) individuals participated in the initial screening programme. Of these 1262 subjects, 152 were identified as diabetic. All the diabetic subjects were invited to participate in the studies on carotid intimal-medial thickness. 140/152 diabetic subjects (92.1%) and 103 healthy age- and sex-matched non-diabetic control subjects selected from the same population participated in the study. IMT was assessed using high resolution B mode ultrasound and colour doppler imaging of the common carotid arteries at three different sites on the anterior and posterior walls and the average values were taken. The results have recently been published in Diabetologia[43] and a brief summary is given below.

The mean IMT values of the diabetic subjects (0.95±0.31 mm) were higher than the non-diabetic subjects (0.74±0.14 mm) ($p<0.001$). At any age point, the IMT values of diabetic subjects were significantly greater than among non-diabetic subjects. Pearson's correlation analysis showed that age and duration of diabetes strongly correlated with IMT in diabetic subjects while in non-diabetic subjects, IMT showed a correlation with age, serum cholesterol, low-density lipoprotein (LDL) and triglyceride levels. Multivariate linear regression analysis revealed that age and diabetes were the major risk factors for increased IMT. The prevalence of carotid atherosclerosis diagnosed on the criteria of Kawamori et al[30] namely IMT above 1.1 mm, was 1 percent among non-diabetic subjects and 20 percent among diabetic subjects. Table 1 summarises mean IMT measurements in various diabetic populations studied.

TABLE 1

Mean IMT Values in Various Diabetic Populations

Country	Authors (Reference)	Normal Glucose Tolerance	Diabetes
Italy	Bonora et al[36]	1.19±0.15	1.44±0.15
Japan	Kawamori et al[30]	0.52±0.07	0.73±0.27
Netherlands	Kanters et al[44]	-	1.00±0.43
India (CUPS)	Mohan et al[43]	0.74±0.14	0.95±0.31

To our knowledge this is the first data on IMT in Indians in the world literature.

Conclusion

To conclude, measurement of carotid IMT offers an excellent, quick, reliable and reproducible method of assessing atherosclerosis non-invasively. It (i) correlates strongly with CAD and PVD, (ii) is an excellent predictor of future myocardial infarction and strokes, (iii) is increased in diabetics compared to non-diabetics, (iv) correlates with serum lipids and other CAD risk markers, (v) can be used to look at drugs which retard/regress atherosclerosis, (vi) appears to have increased IMT, and (vii) should be used more extensively for the clinical and research purposes.

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