

A COMPARATIVE STUDY OF CAROTID INTIMA MEDIA THICKNESS AS A SURROGATE MARKER FOR CARDIOVASCULAR EVENTS IN RURAL DAKSHINA KANNADA POPULATION

Aishwarya K. C¹, Shrunga Tejasvi², Rudresh Hiremath³, Gowtham Gowda⁴, Mahesh⁵, Krishna Prashanti⁶

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ABSTRACT: BACKGROUND & PURPOSE: Carotid artery intima media thickness (CIMT) is used as a noninvasive surrogate marker to measure progression of atherosclerosis, but its relation to coronary events has not been fully explored. CIMT determined by B-mode ultrasonography (USG) is a valid and measurable index of atherosclerosis. Atherosclerosis is strongly associated with cardiovascular risk factors and thus CIMT has the ability to predict cardiovascular diseases. It possibly reflects the summative burden of atherosclerosis regardless of underlying risk factors like smoking, dietary factors, hypertension & diabetes mellitus. Thus measurement of CIMT by USG is a valuable, inexpensive, non-invasive screening tool in early identification and prevention of complications of cardiovascular events. **AIMS & OBJECTIVES OF THE STUDY:** **1.** To estimate common carotid arterial IMT and internal carotid arterial IMT. **2.** To determine if carotid arterial IMT is associated with cardiovascular events. **3.** Comparison of carotid artery IMT with risk factors for atherosclerosis. **MATERIALS AND METHODS:** Carotid B-Mode USG was performed prospectively in 200 individuals. Of these 100 were cases of myocardial infarction (MI) & acute coronary syndromes (ACS) and remaining 100 were healthy individuals with no past history of chest pain or ischemic heart disease. The IMT of the common and internal carotid arteries was measured bilaterally. A detailed medical history, electrocardiogram findings and biochemical data like the blood sugar, lipid profiles & cardiac enzymes were obtained in each individual and correlated with CIMT. **STATISTICAL ANALYSIS:** Statistical analysis was made with help of SPSS (Statistical Package for Social Science, Version.10.0.5) package. **RESULTS:** CIMT is a marker of atherosclerosis and raised values of CIMT are strongly associated with coronary artery disease (CAD). Risk factors for atherosclerosis like age, hypertension, diabetes mellitus, smoking, alcohol & coconut oil consumption increases value of CIMT. Average CIMT measurements: Controls: CCA-0.599 mm, ICA-0.518mm Cases: CCA-1.14mm, ICA- 1.043 mm. As average CIMT goes above 1 mm chances of having CAD increases. **CONCLUSION:** The current study propagates that carotid IMT increases with advancing CAD and that patients with mean IMT over 1mm have likelihood of CAD.

KEYWORDS: Atherosclerosis; Coronary artery disease; Carotid intima- media thickness; Coconut oil.

INTRODUCTION: Cardiovascular diseases (CVD) like Myocardial Infarction (MI) & Acute Coronary Syndrome (ACS) remains the main cause of death in developing and developed countries, despite several prevention programmes¹. MI and ACS are the initial manifestations of coronary artery disease (CAD) in more than 50% of all patients with CVD.^{1,2} During the past 30 years, CAD rates have doubled in both rural and urban India.³

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Assessment of association of conventional risk factors like hypertension & diabetes mellitus (DM) has already been dealt in many studies. Coconut oil is the major cooking medium of the people of coastal Karnataka,⁴ but however usage of coconut oil for cooking still stands for a debate, as there are two equal and opposite theories favoring it. Coconut oil contains saturated fatty acids. The link between excessive consumption of dietary saturated fats and coronary heart disease (CHD) is now well established. Due to its high content of saturated fatty acids, the consumption of foods containing coconut oil may therefore be a risk factor for CHD.⁵ Epidemiological studies usually attribute an increased risk of CAD to elevated levels of serum cholesterol, which in turn is due to increased intake of saturated fats.^{6,7}

Cardiovascular disease is the end result of the atherosclerotic process. Thus, early detection of atherosclerosis may indeed provoke early effective treatment and may in turn help in reducing mortality, for example, through plaque stabilization and with more aggressive control of atherosclerotic risk factors.¹

The various diagnostic modalities used currently (Exercise electrocardiography, stress echocardiography, thallium scanning, coronary angiography) can detect atherosclerotic disease only when it becomes well advanced and occlusive.

Thickening of the intima-media is identified as the initial stage in the pathogenesis of atherosclerosis.⁸ Non-invasive techniques such as B-mode ultrasound can directly assess the intima-media thickness (IMT), which corresponds to the thickness of the histologic intima and media. With the help of Doppler ultrasound machines, advanced operating software, IMT can be easily and noninvasively obtained by high-resolution transducers for better analysis of the IMT in the peripheral vessels like carotid & femoral arteries.⁶

This study was intended to know the value of sonographic measurement of IMT and its association with cardiovascular events, thereby helping in early identification of clinical and preclinical CAD and increasing the possibility of preventing complications.

AIMS AND OBJECTIVES OF THE STUDY:

1. To estimate common carotid arterial intima-media thickness and internal carotid arterial intima-media thickness.
2. To determine if carotid arterial intima-media thickness is associated with cardiovascular events.
3. Comparison of carotid artery IMT with risk factors for atherosclerosis.

MATERIALS AND METHODS: This was a hospital based case control study done between October 2012 & March 2014 in KVG Medical College, Sullia which includes 100 cases and 100 controls. Cases referred with MI and ACS with complaints of chest pain, positive ECG findings or elevated cardiac enzymes above the age of 30 years were included in this study. Controls included patients above the age group of 30 years with no previous history of chest pain. Patients less than 30 years of age were excluded from the study.

Detailed medical history was obtained and routine physical & systemic examination was done. Specific biochemical investigations like blood sugar, lipid profile & cardiac enzymes were obtained in each individual. Electrocardiography findings & echocardiography findings were also made note of in these individuals.

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Ultrasonographic Evaluation of Carotid Arteries: This study was performed using GE Voluson 730 Expert ultrasound scanner using Linear array probes with a frequency of 7 MHz or higher for B-mode, and 5MHz or higher for Doppler.

The examination was performed with the patient lying supine on the couch and the operator sitting on a stool facing the patient. The neck under examination was exposed, extended and placed in a relaxed position on a support as shown in Fig.1.

General Protocol: The anatomy under examination is checked in both transverse and longitudinal planes.

The transverse plane is used to identify vessels (Artery and vein) and further the common carotid artery (CCA) is identified as vessel adjacent to the internal jugular vein as a rounded, thick walled, non-compressible structure & then further orienting in longitudinal section the long axis of the CCA was obtained. Compression as minimal as possible is used. Further moving cephalad in longitudinal section Internal carotid artery (ICA) is identified after differentiating it from the external carotid artery as given in (table 1).⁹

CIMT was measured in the far wall of carotid artery from the inner echogenic to outer echogenic line as shown in Fig 2. CCA and ICA IMT was measured within 1cm from the carotid bulb.¹⁰ CIMT of only plaque free segments was recorded. Measurements were taken in both the carotid system. Carotid bulb region values were negated from the study as this region is more prone for plaque formation.

Normal Values: Normal IMT is less than 0.7 mm in both CCA and ICA.

IMT increases with age; a thickness of 0.8 to 1.0mm is considered indeterminate. A thickness of 1.1mm or greater is actually a more accepted abnormal value¹⁰.

In this study, age matched & sex matched cases and control groups underwent similar ultrasound examination at baseline to determine the IMT in two segments of the carotid arteries bilaterally.

A Total of Four Measurements are Taken which Includes the:

1. IMT far wall of right common carotid artery (RCCA).
2. IMT far wall of right internal carotid artery (RICA).
3. IMT far wall of left common carotid artery (LCCA).
4. IMT far wall of left internal carotid artery (LICA).

The corresponding mean values (Inclusive of right and left sides) of CCA and ICA were obtained separately. The data obtained in the cases & controls was compared & further correlated.

Following the data collection, statistical analysis was made with help of SPSS (Statistical Package for Social Science, Version.10.0.5) package.

RESULTS: The study population included 100 cases and 100 controls that were enrolled for evaluation of CIMT using Carotid B-Mode USG. In the present study the mean age of cases was 60.2 years & that of controls was 60.1 years.

The cases & controls were age matched & sex matched. Majority of the cases belonged to 60-69yrs age group & none in 30-39yrs age group. In both the cases and controls, males predominated over females.

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In cases approximately one fourth (26) had past history of previous MI.

The results of this study suggest a significant association between CIMT and cardiovascular events.

The IMT in CCA was significantly higher in the cases as compared to the controls. (Fig 3)

Similarly, the IMT in ICA was also higher in the cases as compared to the controls (Fig 4).

It was noted that mean IMT in both CCA is almost equal with only minimal difference with their respective sides (R>L) in both cases & controls.

Mean IMT in both ICA's was also almost equal with only minimal difference with their respective sides (R>L) in both cases & controls (Table 2).

The Chi-square test values helped in the prediction of the most significant risk factors. Hypertension is the most significant risk factor. Alcohol consumption, coconut oil used for cooking, Diabetes mellitus, history of smoking, hypertension are the significant risk factors for atherosclerosis (Table 3).

In summary, results of the study indicate that CIMT as detected by B mode USG can predict future cardiovascular events and can be used as a surrogate marker for prediction of the same. In this regard, CIMT has the potential to be used as an effective screening tool for identification of patients at risk for CAD and coronary events.

DISCUSSION: Cardiovascular disease has a major share in the incidence of non-communicable diseases. CVD is also one of the leading causes of morbidity and mortality in India. It is the first among top five causes of deaths in Indian population (Rural vs. urban, economically backward vs. developed states, men vs. women and at all stages vs. middle age). It has outgrown the boundaries of gender, location of dwelling etc. Recent trends indicate that the disease has escalated to younger age groups also. Apart from a high overall prevalence, there are regional variations in the prevalence of CVD.¹¹ The Chennai urban population study found out the overall prevalence of CAD in native South Indian population to be 11% while the age standardized prevalence was computed to be 9%.¹²

Regional variations in cardiovascular disease are mainly attributed to dietary factors. Coconut oil is the major cooking ingredient of the people of Dakshina Kannada district.⁴ The link between excessive consumption of dietary saturated fats and coronary heart disease (CHD) is now well established. Because of its high content of saturated fatty acids, the consumption of foods containing coconut oil may therefore be a risk factor for CHD.⁵ Epidemiological studies usually attribute an increased risk of CAD to elevated levels of serum cholesterol, which in turn is due to increased intake of saturated fats.⁶ The possible negative effects of the saturated fatty acids and the absence of the essential fatty acid like linolenic acid in coconut oil suggests that the coconut oil should not be used on a regular basis in adults.⁵ Our study stresses on the consumption of coconut oil as an additional important risk factor in this Dakshina kannada population.

CIMT is a valid marker of early atherosclerosis and thus has the potential to detect CVDs in its subclinical phase. It possibly reflects the cumulative deleterious effects of various cardiovascular risk factors over time. B-mode USG of the carotid system helps in sufficient visualization of the CIMT. Moreover this technique holds a better stand for predicting atherosclerotic lesions in coronary arteries as well.¹ CIMT measurement by USG is widely used in practice as an inexpensive, reliable, and reproducible method for detecting atherosclerosis in its pre-occlusive phase and thus is a non-invasive marker of coronary artery disease (CAD).

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Our cases consisted of patients with complaints of chest pain with either positive ECG findings or elevated serum enzyme levels.

In the current study the baseline characteristics of the 2 study groups are same to avoid confounding.

In Our Study Following are the Results:

1. CIMT is a marker of atherosclerosis as its value is raised in cases compared to age and gender matched controls and raised values of CIMT are strongly associated with CAD.
2. Risk factors for atherosclerosis like age, hypertension, DM, smoking, alcohol & coconut oil consumption increases value of CIMT.
3. Mean carotid intima-media thickness: As average CIMT goes above 1 mm, chances of having CAD increases.
4. In the present study if we consider CIMT as independent variable for atherosclerosis/CVD, it is well comparable with other conventional risk factors for CVD like age, DM & HTN. Our study is comparable with previous studies showing a significant association between raised IMT and the presence of significant atherosclerosis/CVD.
5. It was also noted in our study that people consuming coconut oil as cooking oil also had significant correlation with IMT. Carotid IMT is related not only to the presence of CAD, but also to the occurrence of coronary events.

Hodis H N, et al.,¹³ studied the role of CIMT in predicting clinical coronary events. The long-term follow-up study showed that for each 0.03 mm increase per year in CIMT, the relative risk for nonfatal MI or coronary death was 2.2 and the relative risk for coronary events was 3.1. Absolute thickness and progress in thickness predicted risk for a coronary event beyond that predicted by coronary arterial measures of atherosclerosis and serum lipid levels. The B-mode score is at least as useful as other well-known risk factors for identifying patients with CAD, and thus concluded that noninvasive B-mode USG measurement of progression of IMT in the distal CCA is a useful surrogate marker for clinical coronary events.

In India, Hansa G et al.,¹⁴ study was done in 2003 to determine whether CIMT is associated with CAD and cardiovascular risk factors in the Indian population. A total of 101 patients with CAD and 140 control subjects were assessed for CIMT and other conventional CVD risk factors. Results showed that the average IMT was significantly higher in the coronary disease group. The maximum CIMT was significantly higher in the CHD group compared to the controls (1.02 vs. 0.80mm). The average IMT was also significantly higher in the CHD group (0.82 vs. 0.67mm). On multivariate logistic regression analysis,

CIMT was the most important independent predictor of CAD. There was a significant association between number of CVD risk factors and the average IMT values in both control and CAD groups. Similar results are also seen with our study.

Among western studies, the Atherosclerosis Risk in Communities (ARIC) study,¹⁵ is worth mentioning. In this study CIMT was significantly higher in individuals with cardiovascular risk factors compared to normal controls. This is a population based cohort study in which large healthy controls without risk factors for atherosclerosis like family history of CVD, dyslipidemia, hypertension, DM were compared with people with risk factors for atherosclerosis and were followed up for at least 10 years. In our study we have compared controls with non-modifiable risk factors for atherosclerosis

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like age with CAD patients who have both modifiable and non-modifiable risk factors. We concluded similarly like ARIC study that CIMT increases linearly as number of risk factors for atherosclerosis increases.

According to Takashi W et al.,¹⁶ increased IMT and plaque development in the extracranial carotid arteries reportedly correlate well with the prevalence of CAD. In his study 40 patients with severe atherosclerosis of the coronary artery and 56 healthy control subjects with no risk factors for coronary atherosclerosis were included. The subjects were divided into a middle-age group (40-59yr) and an old-age group (60-79yr). In both groups, the IMT in the patients was significantly higher than that in the controls. IMT of at least 0.7mm in the middle-age group and at least 1.0mm in the old-age group was specific and positively predictive of CAD. The location of these atherosclerotic lesions in the carotid artery varies with age in patients with coronary artery atherosclerosis. Increased IMT thickness (>1.0mm) and calcification were more significant in patients than in controls.

Prati P et al.,¹⁷ did a study on 630 men and 718 women aged 18-99 years to assess the prevalence of asymptomatic carotid atherosclerotic lesions (Stroke and coronary atherosclerosis) and their relation to principal risk factors with the help of carotid gray scale USG. The global prevalence of carotid atherosclerosis was 25.4% in men and 26.4% in women. Intima-media thickening was found in 9.4% of men and 11.7% of women. Plaque prevalence was 13.3% in men and 13.4% in women; prevalence of stenotic plaques was 2.7% and 1.5%, respectively. Subjects aged < or = 39 years showed a very low prevalence of any asymptomatic carotid atherosclerotic lesions. In the multiple logistic regression, the analysis of subjects aged > or = 40 years showed a positive significant association between the severity of carotid atherosclerotic lesions (plaques and stenosis) and age ($p < 0.001$), systolic blood pressure ($p < 0.01$), cigarette smoking ($p < 0.0001$), and the protective effect of high density lipoprotein cholesterol ($p < 0.037$). It emphasizes the value of USG in the detection of early atherosclerotic lesions.

In the study done by Shetty S, et al.,¹⁸ in Dakshina Kannada district in year 2011, there were 70 cases with past history of CAD and with presentation of ACS and 30 matched controls. It was found that the mean carotid IMT in the study group was 0.923 ± 0.123 and in the control group was 0.689 ± 0.051 ($P=0.001$). The mean CIMT was significantly high in the case group as compared with the control, and the P-value was highly significant. Mean age in case group was 58.72 years & in controls was 62.73 years. In the study group, 77.1% ($n=54$) were males and 22.9% ($n=16$) were females. In the study group, 51.4% ($n=36$) were smokers compared with 13.3% ($n=4$) among the control group ($P=0.001$). In the study group, 20% ($n=14$) had diabetes while this was 13.3% ($n=4$) among the control group. In the study group, 52.96% ($n=37$) had hypertension while 16.7% ($n=5$) had hypertension in the control group ($P=0.001$). The mean total cholesterol among the study group was 197.4mg/dl while in the control group it was 175.9mg/dl. Thirty-two percent of the patients with CAD had anterior lateral wall ischemia, 21% had anterior wall, 21% lateral wall, 19% inferior wall and 7% unstable angina. The carotid IMT was found to be higher in patients with CAD, and there was a statistically significant difference between cases and controls.

Like many studies in the past have shown that carotid IMT can indicate the presence and extent of CAD, our study also suggests a significant association between IMT and the presence of CAD in the Indian population. However, more data are needed to establish carotid IMT as a noninvasive tool for the detection of CAD in symptomatic or asymptomatic individuals.

CIMT role in predicting the risk of future cardiovascular events in Western populations has already been established by several large-scale prospective studies. But CIMT role in India for

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prediction of future CVD has not been done on large randomized prospective studies. Our study was done on small number of patients with case-control nature, so it difficult to conclude on this aspect of CIMT role.

Finally it is said that the easy applicability and noninvasive nature of carotid B-mode ultrasonography makes it suitable for use as screening tool for atherosclerosis burden. Subsequently which group of people should undergo measurement of CIMT is a little controversial issue but those with multiple risk factors for CVD should undergo measurement for CIMT after physician recommendation.

CONCLUSION: The study showed that there is significant correlation between increased CIMT and cardiovascular events. However, as the cut off value of CIMT was increased the specificity dropped.

To conclude we found that IMT increases with advancing CAD and that patients with mean IMT over 01 mm have a high likelihood of CAD. CIMT can be used to assess atherosclerotic diseases burden.

CIMT is an independent variable for atherosclerosis/CVD. It is well documented tool to see the vascular age of the person. We also found that most important determinants for CIMT in our study are age, risk factors like smoking, alcohol consumption, coconut oil consumption for cooking, DM & hypertension , with hypertension being the most significant risk factor of all

So if a person with multiple conventional risk factors has normal CIMT we can say that he has less likelihood of having atherosclerotic diseases than a person without CVD risk factors but with increased CIMT. As CIMT depends on conventional and unknown atherosclerotic risk factors, it can replace other modes of assessment of conventional risk factors for atherosclerosis to know the risk of CAD.

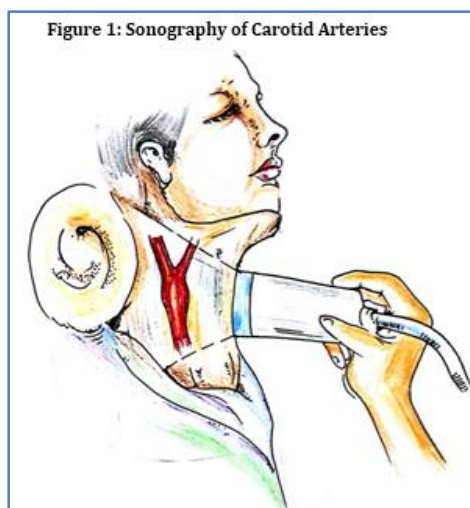
Large scale studies with randomization are required to establish a cut off value of average CIMT, according to age, gender and race, above which primary prevention of atherosclerosis can be started.

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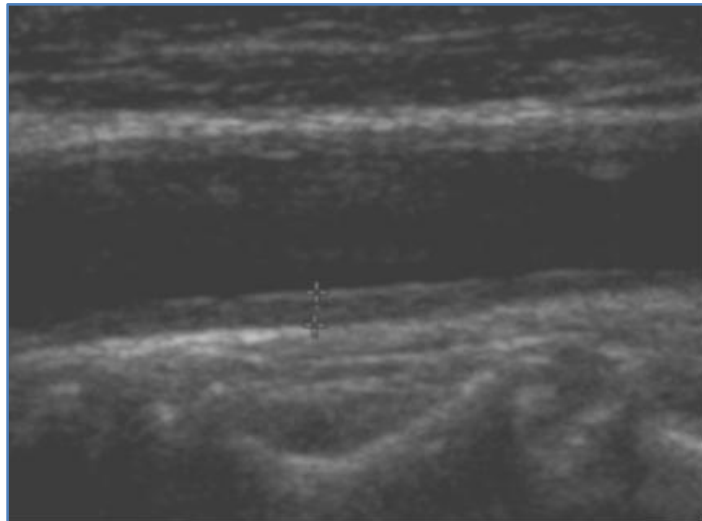


Figure 2: Gray Scale USG Image Showing the Method to Measure Intima-Medial Thickness

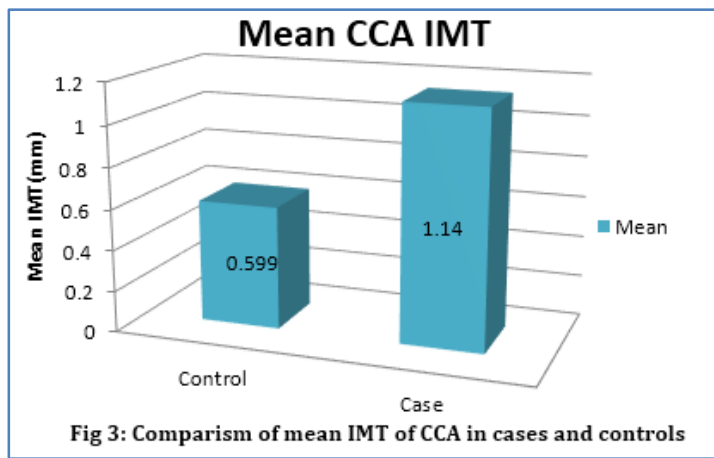


Fig 3: Comparison of mean IMT of CCA in cases and controls

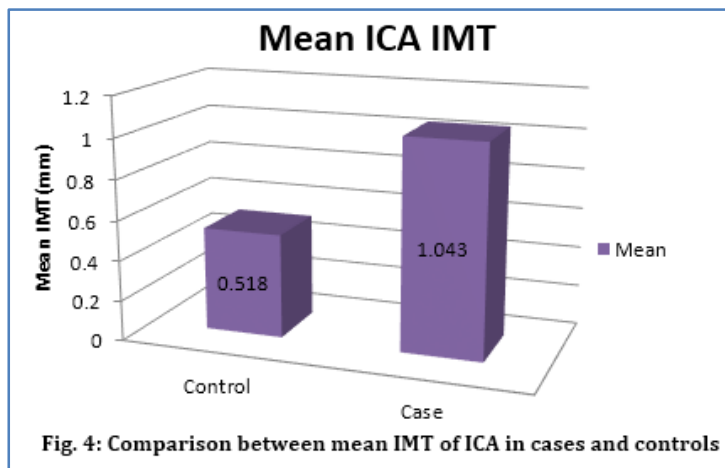


Fig. 4: Comparison between mean IMT of ICA in cases and controls

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Fig. 5: Image of a case showing increased IMT thickness in right CCA(1.4 mm). The adjacent image shows IMT thickness of right ICA(1.3mm).

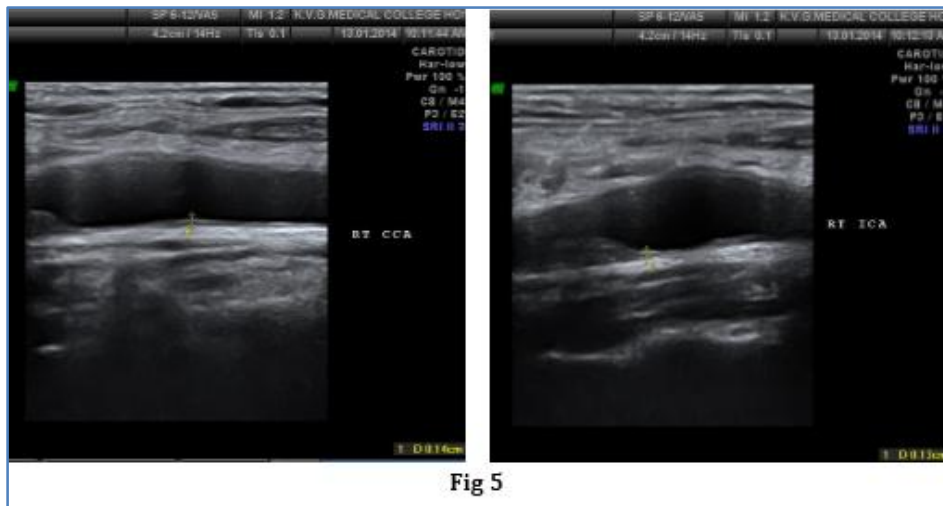


Fig. 6: Images of a case showing IMT in right CCA(0.5mm) & left CCA (0.7mm).

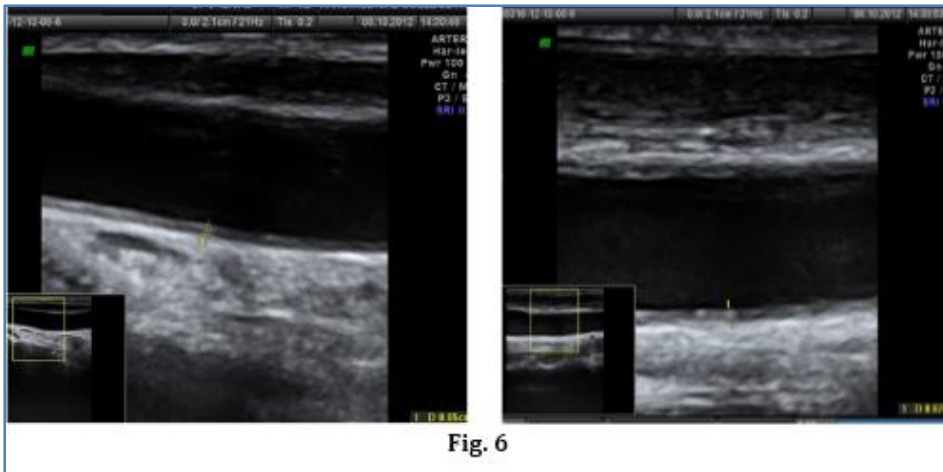
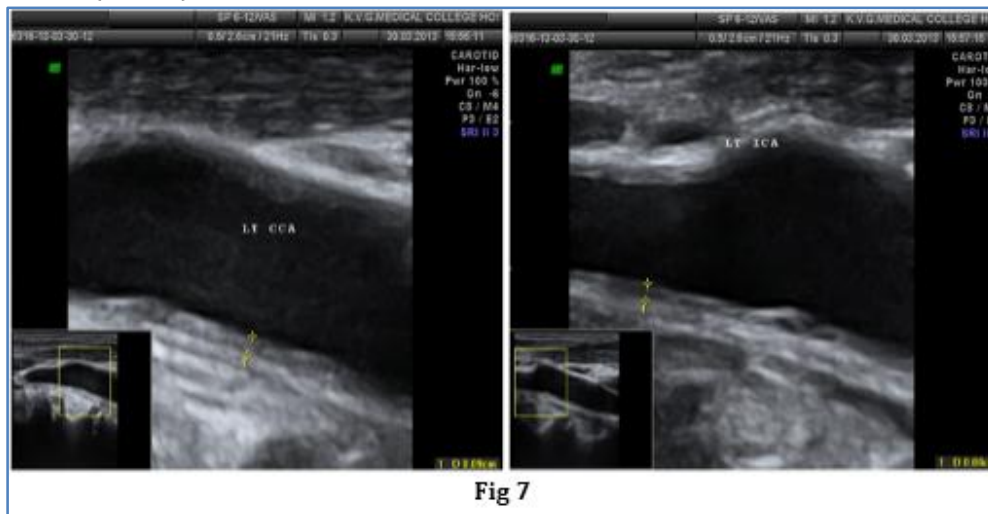


Fig. 7: Image of a case showing increased IMT thickness in left CCA(0.9 mm). The adjacent image shows IMT thickness of left ICA(0.8mm).



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Fig. 8: Images of a control showing slightly increased IMT thickness in right CCA(0.8 mm) & right ICA (0.7 mm).

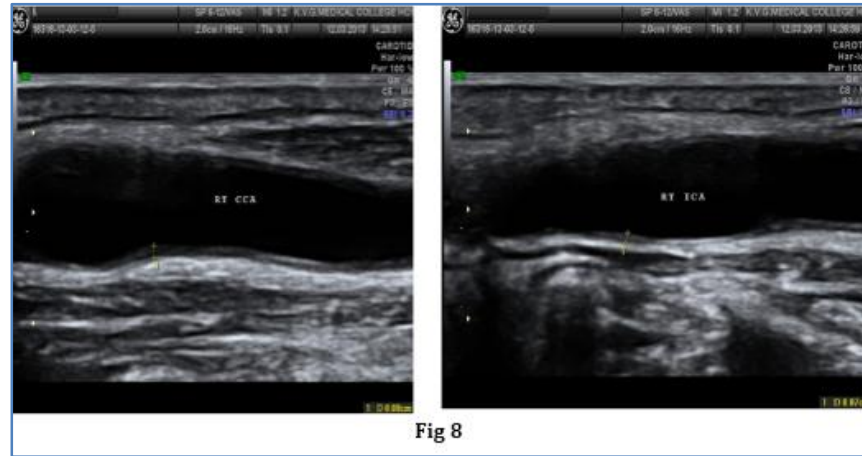


Fig 8

FEATURES	EXTERNAL CAROTID ARTERY	INTERNAL CAROTID ARTERY
Size	Small	Larger compared to ECA
Branches	Present	Absent
Position	Initially medial ,higher up takes lateral position	Initially lateral ,higher up becomes medial
Continuity with the carotid bulb	Not continuous	Continuous
Doppler spectral waveform	High resistance flow pattern	Low resistance flow pattern
Temporal tap	Waveform deflections	No deflections

Table 1: Differentiating features between external and internal carotid arteries

Group	Side		N	Mean (mm)	SD	Min.	Max.	't' value	'p' value
Case	Right	CCA	100	1.157	0.444	0.40	3.30	2.427	0.121
		ICA	100	1.060	0.436	0.50	3.50		
	Left	CCA	100	1.122	0.387	0.50	2.70	3.329	0.070
		ICA	100	1.026	0.356	0.50	2.10		

Table 2: Comparison between mean CCA IMT & mean ICA IMT values on both sides in cases

RISK FACTORS	P VALUE	SIGNIFICANCE
Gender	0.000	Not significant
Age	0.039	Not significant
H/o Alcohol consumption	<0.001	Significant
Coconut oil used for cooking	<0.001	Significant
Past h/o IHD	<0.001	Significant
Diabetes mellitus	<0.001	Significant
H/o Smoking	<0.001	Significant
Hypertension	<0.001	Significant

Table 3: Results of Chi-square test applied on risk factors in increasing order of significance

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	CCA	ICA
CASES	1.14 mm	1.043 mm
CONTROLS	0.599 mm	0.518 mm

Table 4: Intimo-medial thickening of CCA and ICA in cases and controls

AUTHORS:

1. Aishwarya K. C.
2. Shrunga Tejasvi
3. Rudresh Hiremath
4. Gowtham Gowda
5. Mahesh
6. Krishna Prashanti

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Radiodiagnosis, KVG Medical College.
2. Assistant Professor, Department of Radiodiagnosis, JSS Medical College.
3. Professor, Department of Radiodiagnosis, KVG Medical College.
4. Assistant Professor, Department of Radiodiagnosis, KVG Medical College.

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5. Junior Resident, Department of Radiodiagnosis, KVG Medical College.
6. Junior Resident, Department of Radiodiagnosis, KVG Medical College.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Aishwarya K. C,
Assistant Professor,
Department of Radiodiagnosis,
KVG Medical College,
Sullia-574327,
Dakshina Kannada.
E-mail: aishkc@gmail.com

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