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Carotid IMT and Haemodynamic Indices in Evaluation of Atherosclerosis in Hypertensives

Kenis Shedrack Felangu[1], Adams Ndako Baba[1] Saliu Abdulfatai[1], and Halilu Solomon D[2]

1. Department of Radiology, Ahmadu Bello University Teaching Hospita Zaria, Kaduna State Nigeria.

2. Department of Radiology, Abubakar Tafa-Bellewa University Teaching Hospital Bauchi, Bauchi State Nigeria.

Abstract: Purpose: To evaluate carotid haemodynamic indices and intima media thickness as sonographic markers of atherosclerosis for possible use in PHC clinics of resource limited countries. Methods and Materials: This was a cross-sectional study involving 130 hypertensive patients and 130 age-matched controls, all underwent carotid Doppler examination using Mindray DC-8 ultrasound machine. Blood sample was taken after an overnight fast for lipid profile and FBS. The Framingham Risk Score (FRS) was calculated from patients' information. The data were analysed using SPSS version 20.0. *T*-test was used to test the difference between variables. Pearson correlation was used to determine correlation between duplex finding and FRS. $p < 0.05$ was considered statistically significant. Results: The mean age of the hypertensive is 50.20 ± 10.30 and the mean age for control is 49.39 ± 9.89. The mean Carotid Intima-Media Thickness (CIMT) is significantly higher in hypertensives compared to control. Common Carotid Artery (CCA) Pulsatility Index (PI), CCA Resistive Index (RI), Internal Carotid (ICA) PI and ICARI were not significantly different between hypertensive and control. It was observed that the value of carotid haemodynamics indices increases with increasing age in the hypertensive but the relationship of increasing age and haemodynamic indices is less clearly demonstrated in the control. There is a strong correlation between CIMT and FRS in the hypertensives and only in ICA there was a correlation between haemodynamic parameters and FRS. Conclusion: CIMT appears to be the best sonographic marker of atherosclerosis. Though carotid haemodynamic indices correlate less clearly than CIMT, there appears to be a gradual increase in the carotid haemodynamics with age, particularly in the hypertensives.

Key words: Carotid intima-media thickness, haemodynamic indices, atherosclerosis and framingham risk score.

1. Introduction

Hypertension is a major health problem in both economically developing and developed countries in the world [1] and there is a confirmed link between hypertension and atherosclerosis [2, 3] making it a well-established risk factor for vascular disease. The burden of cardiovascular disease is considerable, An estimated 17.7 million people died from CVDs in 2015, representing 31 per cent of all global deaths worldwide of which over three quarters of the deaths took place in low and middle income countries [4]. There is therefore need for early recognition of atherosclerosis in patients with hypertension so that effective cardiovascular protection can be instituted in these countries, in order to prevent complication of atherosclerosis or its progression.

At present the burden of atherosclerotic disease is quantified using a variety of methods including but not limited to Coronary Artery Calcium Scoring (CACS) techniques, Framingham Risk Score (FRS), BHSS (British Heart Study Score) and SMART (Second Manifestations of ARTerial disease) score. The distribution of CACS and FRS has been studied in large population and in different ethnic groups [5, 6]. The application of CACS in developing countries is limited by availability and cost. FRS is relatively cheap and has been validated in multi-ethnic trial [7], but it is cumbersome to determine requiring knowledge of patient age, smoking history, blood pressure measurement and a number of ancillary investigations. Because of poor birth record in most low income

Corresponding author: Kenis Shedrack Felangu, MBBS, Consultant Radiology, Radiology

countries, in several instances patient may not know their exact age. Laboratory investigations of lipid profile are largely not available in Primary Health Care (PHC) clinics and where available it takes longer period for the result to be issued. These factors limit the application of FRS and make it unpopular among PHC physician. This then means that most PHC physicians do not have available data on atherosclerosis for patients to follow up, risk stratification with which future research will be designed.

On the other hand, carotid Intima-Media Thickness (IMT) can be determined in a single visit, with atherosclerosis manifesting as thickening of the intima-media complex. The carotid IMT has been studied as a reliable sonographic marker of early atherosclerosis [8, 9] capable of predicting subsequent cardiovascular event [10] and predicting the likelihood of having Coronary Heart Disease (CHD) [11]. It also evaluates the effectiveness of different treatment modalities for controlling morbidties that accelerate the development of atherosclerosis-based disease by identifying regression in IMT values after such intervention [12]. Local studies are basically concerned with distribution of carotid artherosclerosis among various risk groups. No local literature has looked at the relationship between carotid IMT and subsequent event. Although the best way to study this relationship is in a follow up study, this is expensive to design. In this study, carotid IMT was correlated with FRS which has been validated in several follow up study and correlated with subsequent clinical events.

Also carotid RI has been shown to correlate well with FRS [13]. It has been argued that ICA RI is comparable to well-known IMT in predicting atherosclerosis, as well as the ability to distinguish between low- and high-risk patients [14]. It is the purpose of this research to evaluate carotid haemodynamic indices with intima media thickness as early sonographic markers of atherosclerosis by correlating these parameters with well-known FRS.

2. Methods

One hundred and thirty patients with clinically established high blood pressure, aged 20 and above were recruited to form the hypertensive group, while 130 normotensive age and sex matched volunteers were recruited to form the control group in this study. Ethical and Research Committee of Ahmadu Bello University Teaching Hospital approved the study and written informed consent was obtained from all participants. Patient with diabetes mellitus, pregnancy, established cerebrovascular disease, chronic kidney disease, heart failure, sickle cell disease, carotid artery stenosis and those with complex anatomy of the carotid arterial system were excluded. Before Duplex examination, the blood pressure was measured using indirect technique. Venous blood was taken after an overnight fast and analyzed for fasting blood sugar FBS, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Normal sinus rhythm with a rate of 60–100 beats/min on a resting electrocardiogram (ECG) was also required.

2.1 Measurement of Carotid IMT and Hemodynamic Indices

The distal 1cm from the bulb of the far wall of the CCA was measured, as this site yields the most consistent data, best repeatability, least variability and provides a reasonably accurate estimation of generalized atherosclerosis [15, 16]. Avoiding plaques, the maximum IMT in the far wall of the CCA was measured on the right and left. Each measurement was taken two times and the final IMT was the average of all the measurements. Optimal B-mode settings of gain, depth, focal zone placement, and compression were individually adjusted for each vessel to enhance arterial wall structures and image quality. IMT was measured by manual technique using the electronic calipers of the equipment.

To obtain an optimal image, sound waves were beamed perpendicular to the arteries to show two parallel echogenic lines which correspond to the lumen-intima and media-adventitia [17]. The IMT is the distance between the leading edges of this line (fig. 1).

The Doppler volume was set in the middle region of the CCA and in the ICA region just distal to the bulb (or if the bulb is not detected 2 cm cranial to the start of the bifurcation) with a maximum angle of 60^o and a sampling volume of approximately three quarter of the vascular diameter. The systolic velocity, minimum diastolic velocity, RI and PI were determined automatically in two cardiac cycles (fig. 2). The measurement was repeated twice and performed on the contralateral side in the same way. The average of the measurements was recorded as the final measurement.

2.2 Quantification of Atherosclerosis

FRS is used to quantify the atherosclerotic burden of the participants, it is a sex-specific risk equations used to predict the risk of developing hard coronary disease events (MI or CHD-associated death) over the next 10 years. Risk was calculated for each individual using systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, age, current smoking status, and use of antihypertensive medications. Absolute FRS score was determined for each patient and they were subsequently divided into three groups according to their FRS: low (< 10%), and moderate risk (10–20%) groups.

2.3 Statistical Analysis

All data are expressed as mean ± s.d. For comparison between groups, an independent *t*-test was used. Pearson's correlation coefficient was used to assess the relationship between carotid RI, PI, and IMT with percentage FRS risk. Using receiver operating curve the performance of the duplex parameter in distinguishing low and moderate risk was determined. Data processing was performed with the software modules of statistical package for social science (SPSS) 20.00 (SPSS, Chicago, IL). A two-sided probability value of $p < 0.05$ was considered to be statistically significant.

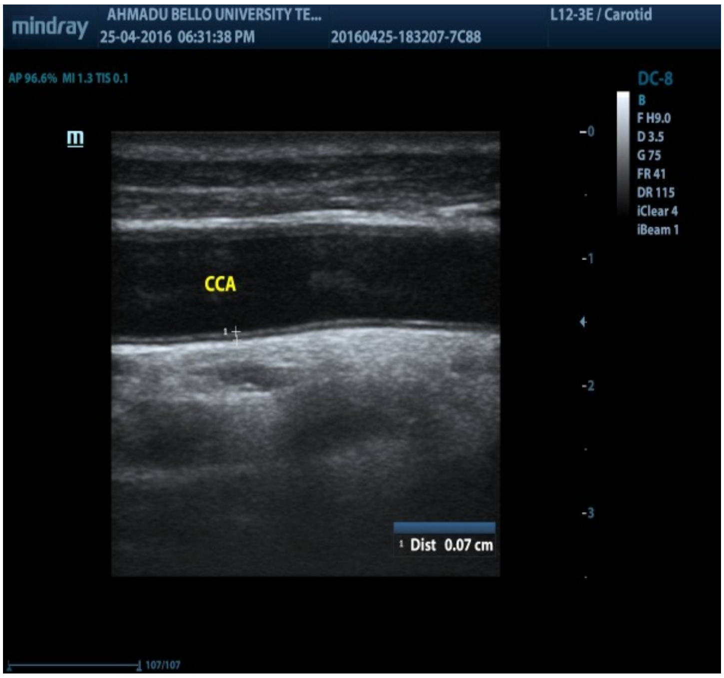

Fig. 1 B-mode scan image showing the placement of the calipers for measurement of IMT.

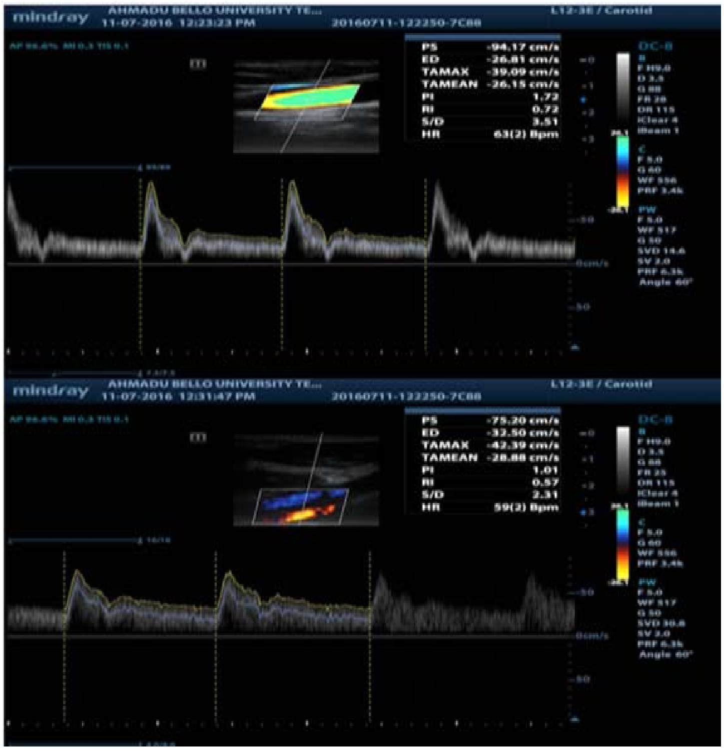

Fig. 2 Normal Duplex scan of CCA (upper panel) and ICA (lower panel).

3. Results

Of the 260 respondents 137 are males and 123 are females. There were 130 respondents in each of the hypertensive and control groups. These are 67 male and 63 female hypertensives and 70 male and 60 female controls. The mean age of the hypertensives is 50.20 ± 10.30 (range 25-75 years) and the mean age for controls is 49.39 ± 9.89 (range 25-72 years), $p = 0.52$. The mean CIMT value in the CCA was 0.82 ± 0.16mm which is statistically significantly higher than the control 0.77 ± 0.11, $p < 0.001$. The difference between the haemodynamic parameters between the hypertensive group and control did not attain statistical significance.

The main characteristics of the hypertensive population according to risk grouping are shown in Table 1. All the control subjects had a low risk FRS. The hypertensive with moderate risk FRS had higher means for age, IMT and haemodynamic parameters in the CCA and ICA. Table 2 shows that hypertensives have higher CIMT and haemodynamic indices than their control counterpart, although the haemodynamic indices did not attend scientific significance. There is a general tendency for a higher CIMT and haemodynamic indices with age in both hypertensives and controls, though this is more convincing so for CIMT after post hoc comparism (Tables 3 and 4).

3.1 Correlation between Atherosclerosis Score and IMT or Haemodynamic parameters

A highly significant correlation with the FRS score was found for CIMT; small and moderate significant correlation was observed in for ICA RI and ICA PI. Table 5 illustrates the relationship for all 5 parameters.

3.2 Categorizing Atherosclerotic Risk among Hypertensive Patients

The patients were divided into 2 groups on the basis of their atherosclerosis scores; Low risk group comprised scores of 0 to 10, moderate risk group comprised scores of 11 to 20. The area under the curve (AUC) in the low risk group was 0.91 for CIMT, 0.87 for PI ICA, and 0.71 for RI ICA. Fig. 3 and Table 6

Table 1 Comparison between low and medium of some parameters among hypertensive patients.

Parameter	Low (*n* = 113)	Medium (*n* = 17)	*t*-test	*p*
Age	47.96 ± 9.07	65.12 ± 6.77	7.482	0.001
CIMT	0.79 ± 0.11	1.06 ± 0.20	8.382	0.001
CCAPI	1.44 ± 0.21	1.56 ± 0.22	2.085	0.039
ICAPI	0.94 ± 0.17	1.17 ± 0.15	5.147	0.001
CCARI	0.69 ± 0.04	0.71 ± 0.06	1.946	0.054
ICARI	0.55 ± 0.06	0.61 ± 0.07	3.732	0.001

Table 2 Difference of the Age, CIMT, CCAPI, CCARI, ICAPI and ICARI between hypertensive and control groups.

Parameter	Control	Hypertensive	*t*-test	Df	*p*
Age	49.4 ± 9.89	50.2 ± 10.30	0.647	258	0.520
CIMT	0.77 ± 0.11	0.82 ± 0.16	3.457	258	0.001
CCAPI	1.49 ± 0.26	1.46 ± 0.21	0.973	258	0.332
CCARI	0.69 ± 0.04	0.69 ± 0.04	0.647	258	0.518
ICAPI	0.94 ± 0.16	0.97 ± 0.18	1.506	258	0.133
ICARI	0.55 ± 0.06	0.56 ± 0.06	0.776	258	0.439

Table 3 Difference of the CIMT, CCAPI, CCARI, ICAPI and ICARI with different age group among the hypertensive patients.

Age group	CIMT	CCAPI	CCARI	ICAPI	ICARI
21-30	0.68 ± 0.03[a]	1.44 ± 0.09[a,b,c]	0.65 ± 0.03[a]	0.83 ± 0.02[a]	0.46 ± 0.01[a]
31-40	0.71 ± 0.63[a,b]	1.35 ± 0.19[a]	0.67 ± 0.04[a,b]	0.90 ± 0.18[a,b]	0.56 ± 0.07[b]
41-50	0.81 ± 0.08[b,c]	1.56 ± 0.22[c,d]	0.70 ± 0.03[b,c]	0.98 ± 0.19[b]	0.54 ± 0.06[b]
51-60	0.86 ± 0.12[c]	1.38 ± 0.17[a,b]	0.68 ± 0.04[a,b,c]	0.99 ± 0.14[b]	0.56 ± 0.04[b]
61-70	0.90 ± 0.26[c]	1.53 ± 0.15[b,c]	0.71 ± 0.03[c]	1.00 ± 0.17[b]	0.58 ± 0.09[b]
71-80	1.22 ± 0.11[d]	1.72 ± 0.10[d]	0.76 ± 0.03[d]	1.30 ± 0.19[c]	0.66 ± 0.03[c]
F-test	18.350	7.911	8.314	5.897	6.448
p	0.001	0.001	0.001	0.001	0.001

Columns with different superscripts are statistically significantly different at $p < 0.05$.

Table 4 Difference of the CIMT, CCAPI, CCARI, ICAPI and ICARI with different age groups among the control respondents.

Age group	CIMT	CCAPI	CCARI	ICAPI	ICARI
21-30	0.56 ± 0.08[a]	1.67 ± 0.12[a]	0.69 ± 0.00[a]	0.75 ± 0.09[a]	0.46 ± 0.01[a]
31-40	0.68 ± 0.10[b]	1.38 ± 0.23[b]	0.66 ± 0.04[a]	0.85 ± 0.18[a,b]	0.52 ± 0.07[b]
41-50	0.81 ± 0.10[c,d]	1.60 ± 0.35[a]	0.69 ± 0.04[b]	0.99 ± 0.18[b]	0.56 ± 0.07[b,c]
51-60	0.81 ± 0.07[c,d]	1.47 ± 0.19[a,b]	0.69 ± 0.04[b]	0.98 ± 0.12[b]	0.57 ± 0.03[b,c]
61-70	0.74 ± 0.10[b,c]	1.39 ± 0.14[b]	0.68 ± 0.03[a]	0.94 ± 0.12[b]	0.53 ± 0.06[b]
71-80	0.90 ± 0.00[d]	1.68 ± 0.01[a]	0.71 ± 0.01[a]	1.01 ± 0.01[b]	0.62 ± 0.01[c]
F-test	15.850	3.520	2.925	5.251	6.046
p	0.001	0.005	0.016	0.001	0.001

Columns with different superscripts are statistically significantly different at $p < 0.05$.

Table 5 Correlation between % FRS risk and sonographic parameters among hypertensive.

Parameters	Corr. coefficient	*p*-value
CIMT	0.55	0.001
CCAPI	0.20	0.22
CCARI	0.19	0.27
ICAPI	0.31	0.001
ICARI	0.17	0.048

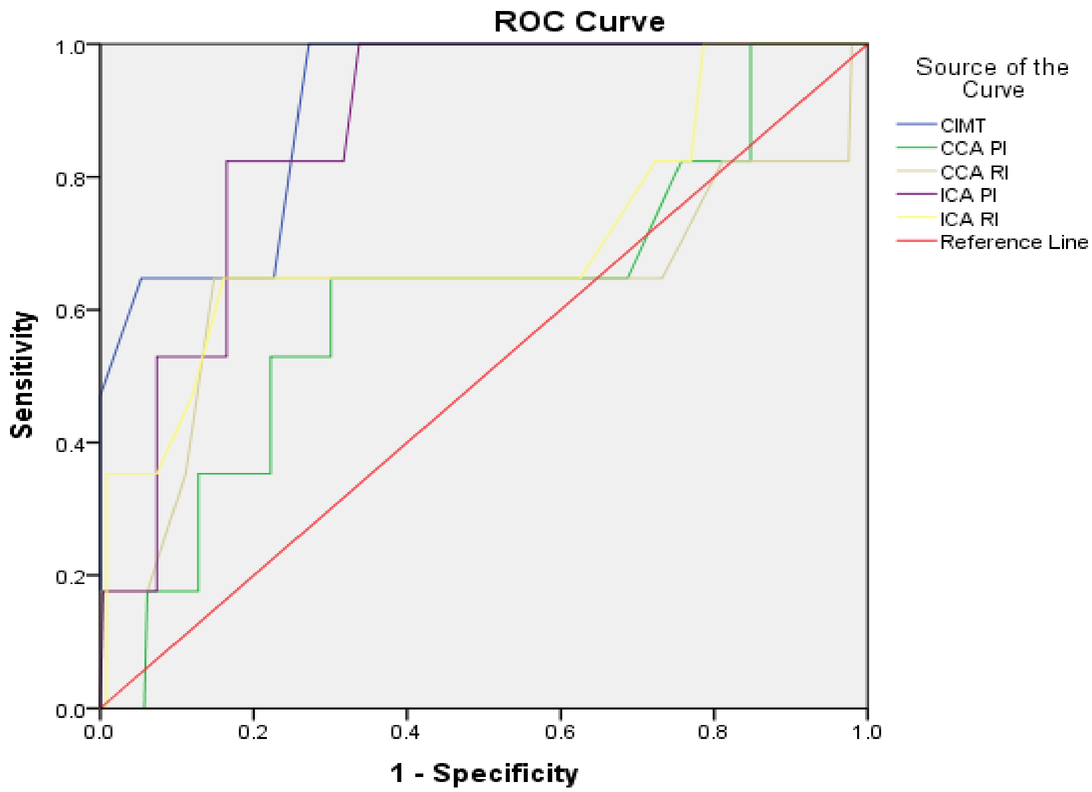

Fig. 3 AUC of receiver operating curves for CIMT, CCA PI, CCA RI, ICA PI and ICA RI to discriminate low-risk patients.

Table 6 Area under the curve.

Test result variable(s)	Area
CIMT	0.907
CCA PI	0.615
CCA RI	0.638
ICA PI	0.867
ICA RI	0.705

show the AUC values for the discrimination of low-risk patients relative to the Duplex parameters.

4. Discussion

The present study clearly demonstrates an increase in the CIMT with age in hypertensives and controls which is consistent with the findings of Lim et al. [18] where it was demonstrated that CIMT increases with age. The general outlook of the carotid haemodymic indices is that of lower indices in younger patient and higher indices in older hypertensives. It has been shown that vessel integrity reduces with age [19] giving rise to a higher resistance in the cerebral microvascular bed with age, irrespective of the blood pressure status. Increasing evidence is also suggesting that cardiovascular disease may be associated with cognitive impairment [20]. The mechanism that mediates this may be through compromises in the structural and functional integrity of the blood vessel over time [21]. These alterations may present as increase in haemodynamic indices with age, resulting in chronic hypoperfusion of the cerebrum with age. David et al. [22] had noted an increase in stroke risk with age even in those individuals without evidence of hypertension at the beginning of their follow-up. They observed that, while the risk of stroke rises with age in hypertensives, the risk rises more rapidly in normotensive subjects further establishing the role of age as a significant independent risk factor.

A significant strong correlation is seen between CIMT with FRS. Geroulakos et al. [23] also reported a similar correlation (r = 0.55) between CIMT with the British heart study score as seen in this study (r = 0.55) while Beat et al. [14] reported a comparable but slightly higher correlation (r = 0.62). A direct correlation between CIMT, myocardiac infarction and stroke in patients without prior history of vascular disease has been shown [24].

The study did not show a statistically significant correlation between CCA RI or CCA PI with FRS, this is in contrast to Beat et al. [14] which showed a moderate correlation between CCA RI with atherosclerosis (r = 0.35). Only in ICA haemodynamic indices there was a significant correlation with FRS, this was moderate with ICA PI (r = 0.31) and small with ICA RI (r = 0.17). These values are lower than those showed by Beat et al. [14] which demonstrated a strong correlation between ICA RI with atherosclerosis (r = 5.5). The lower correlation with atherosclerosis is most likely because of the different arteriosclerotic risk score used and the younger ages of our subjects.

In summary, CIMT appears to be the best sonographic marker of atherosclerosis; correlating strongly with the FRS and other clinical atherosclerotic score. CIMT in addition has the ability to better discriminate between low risk patient from moderate risk patient. Carotid haemodynamic indices correlate less clearly than CIMT, the effect of antihypertensive and a wide variation in heart rate may account for this and correction for these factors should be considered in feature research.

5. Limitation

Because we intend to test how useful CIMT and carotid haemodynamic indices will be in the follow up of hypertensive, we did not exclude patient on antihypertensive, even though this may likely affect the haemodynamic indices.

Also a varied heart rate of 60-100 which is normal in practice may technically affect the variation of the haemodynamic indices.

6. Recommendation

This study has clearly demonstrated a strong correlation of CIMT with FRS. This implies that a projected 10-year risk for cardiovascular disease can be made with a single measurement of CIMT. This can therefore be used in primary health care for assessing cardiovascular risk. To know whether this will impact the outcome of patient management, it is recommended that a follow up study be carried out.

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