CAROTID INTIMA-MEDIA THICKNESS – A SURROGATE MARKER FOR CORONARY ARTERY DISEASE IN THE SOUTH AFRICAN BLACK POPULATION?

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DECLARATION

I, Zaiboonnisa Holland, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science (Medicine) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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22nd Day of December, 2005.

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DEDICATION

To my husband, Errol Anthony Holland, for his unconditional support and encouragement, and most of all for his unwavering patience.

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ABSTRACT

B-mode ultrasound measurement of the carotid intima-media thickness (CIMT) has been convincingly shown to be a predictor of coronary artery disease (CAD) in several studies. To my knowledge such assessments have not been carried out in the Black South African population, which hitherto had a low prevalence of CAD. However, with the increases in prevalence of a cluster of risk factors categorised as the Metabolic Syndrome (MS), CAD is inevitably on the increase. The purpose of this study was to evaluate the role of CIMT in predicting CAD in Black South Africans, and to correlate CIMT with the known risk factors for CAD, including those of the MS.

My study has shown that CIMT predicts the extent of CAD as found at coronary angiography. Multiple regression analysis identified hypertension and fasting glucose as the most important determinants of CIMT. Age, obesity, smoking and LDL-Cholesterol also correlated positively with CIMT. The results suggest that in this population, hypertension and diabetes are crucial in the pathogenesis of thickening of the intima-media of carotid arteries, a surrogate marker of coronary artery disease.

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- The patients, for agreeing to participate in the project and also for their patience, co-operation and congenial attitude.

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TABLE OF TERMS AND ABBREVIATIONS

AUS	Arterial Ultrasound Score
BIF	Bifurcation of the Common Carotid Artery
BULB	Bulb of the Carotid Artery
CAD	Coronary Artery Disease
CCA	Common Carotid Artery
CIMT	Carotid Intima-Media Thickness
ECA	External Carotid Artery
HDL-C	High Density Lipoprotein Cholesterol
ICA	Internal Carotid Atery
IDF	International Diabetes Federation
IMT	Intima-media Thickness
LDL-C	Low Density Lipoprotein-Cholesterol
MI	Myocardial Infarction
MIMT	Mean Maximum Intima-Media Thickness
MS	Metabolic Syndrome
NCEP	National Cholesterol Education Programme
OAI	Optimal Angle of Interrogation
TG	Triglycerides

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1 INTRODUCTION

Historically, coronary artery disease (CAD) is uncommon in Black South Africans. However, increasing urbanisation and a change to a sedentary lifestyle amongst Black people in South Africa has led to a changing pattern of heart disease[1]. Isaacson investigated the autopsy results from cardiac deaths at the Baragwanath Hospital (the largest hospital where Black patients are being treated) during the period 1959 -1960 and compared this to those of 1976, noting that autopsy results are an approximation and may not be a true reflection of the incidence of cardiac deaths. Of the total number of autopsies performed, deaths from hypertension in 1959 were at 5.7%. The figure in 1976 had risen to 7.5%. Similarly, the incidence of myocardial infarction in 1959 was 0.9% and this increased to 11.7% in 1976. The increased incidence in cardiac deaths was largely due to an increase in myocardial infarction and hypertension.

Urbanisation appears to be the major factor contributing to the increased incidence of myocardial infarction in South African Blacks. With urbanisation comes a lifestyle that is conducive to developing atherosclerosis: smoking, a Westernised diet that has high fat content and is low in fibre and reduced exercise. All these are contributing factors to the increasing incidence of CAD[2].

Angiography and Doppler ultrasound were techniques used earlier as surrogate markers to assess atherosclerosis[3]. Although these techniques

[1] Isaacson C 1977.
[2] Gill GV and Ouwerkerk J. 1995.
[3] de Groot E, Hovingh GK, Wiegman A et al 2004.

have great clinical value, they are not adequate for detection of early atherosclerotic changes. Several papers attest to the fact that the measurement of the thickness of the intima and media layers of the carotid arteries by ultrasound is currently a widely accepted method to obtain reliable and reproducible evidence of early atherosclerosis[3] [4] [5].

There is insufficient research involving Black people in South Africa, where the incidence of CAD is increasing.

Two important studies that were done involving Blacks in sub-Saharan Africa are, the 'INTERHEART Africa' study[6], which looked at the association of risk factors in relation to acute MI and the other, 'Hypertension in Sub-Saharan African Populations', which looked at the prevalence and possible causes of hypertension in Blacks[7].

As far as I am aware of, no research has been done which included Black South Africans, in which B-mode ultrasound assessment of the carotid intima-media thickness (CIMT) as a risk factor, is compared to the presence and extent of CAD, and to the presence of known risk factors for CAD, in order to determine the value of CIMT as a predictor for CAD.

Hence research into whether carotid intima-media thickness could be a surrogate marker for coronary artery disease in the South African Black population is very relevant.

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[3] de Groot et al 2004.
[4] Knoflach M, Kiechl S, Kind M et al 2003.
[5] Weber F.2003.
[6] Steyn K, Sliwa K, Hawken S et al. 2005
[7] Opie LH, Seedat YK. 2005.

2 LITERATURE REVIEW

2.1 RISK FACTORS FOR CORONARY ARTERY DISEASE

Risk Factors Associated with Myocardial Infarction in Africa.

In more than 50% of all patients, myocardial infarction (MI) or other acute coronary syndromes are the first evidence of CAD. Therefore early detection of CAD allows for the introduction of effective treatment which may contribute to reducing mortality, through plaque stabilization and more aggressive control of atherosclerotic risk factors[8].

The increasing incidence of CAD in developing countries, and the fact that most of the published data around CAD comes from European countries, prompted the INTERHEART Africa Study (1999-2003)[6], which looked at acute MI in sub-Saharan Africa. The INTERHEART study was designed to assess the association of CAD risk factors and acute MI at an international level.

Nine countries participated in the INTERHEART Africa Study, with 80% of the participants coming from South Africa. Participants were divided into three groups in view of the diverse ethnic groups in South Africa, namely, Black Africans, Coloured Africans and European/other Africans.

Results from the INTERHEART Africa Study were compared to results from the INTERHEART global study. The mean age at which the African cases presented with a MI for the first time was 54.3 (SD±11.3 years), which was 3.8 years earlier than for the overall study cases. The degree of association for each of the major risk factors with acute MI in the African sample is consistent with that found in the global study. The risk factors with the strongest

[8] Kablak-Ziembicka A, Tracz W, Przewlocki T et al 2004.
[6] Steyn et al. 2005

relationship to acute MI in the African sample were previous histories of diabetes and hypertension. The prevalence of hypertension was significantly higher in the total African population than in the global INTERHEART population. Obesity was also a significantly stronger risk factor for acute MI in the African group.

The risk factors were generally consistent for all African groups, except for hypertension and smoking. In Black Africans hypertension was shown to have a stronger relationship to MI, whereas smoking showed a less striking relationship when compared to the other groups. Ironically, in Black Africans, rising affluence and higher education, important for transformation, was associated with an increase in the risk for MI, which is in contrast to other African groups. When compared to the overall INTERHEART group, a higher incidence of MI was found in the Black African group when there was a history of hypertension.

2.1.1 Hypertension

Hypertension in sub-Saharan Africa is a widespread problem and has a high prevalence in urban areas[7]. The exact data for South African Blacks is not known. A study was carried out in 1983, which included the adult population in Durban[9]. Results showed that hypertension was highest in urban Blacks (25%), intermediate in Whites (17%), lower in ethnic Indians (14%) and lowest in rural Blacks (9%). Another survey carried out in 1998, showed that of the

[7] Opie and Seedat, 2005
[9] Seedat YK. 1983

predominantly Black South African population over 60 years of age, 50-60% were hypertensive[10].

In Black patients, hypertension occurs at a very young age compared to Whites. No particular gender bias was found[1]. Deaths frequently occur from cerebral haemorrhage, uraemia or congestive cardiac failure. It was predicted that the incidence of hypertension would increase with the stress induced by urbanisation.

Opie and Seedat[7] refer to a study carried out in the USA (the National Health and Nutritional Survey – NHANES), where a similar pattern for hypertension was found. Hypertension was more common in Blacks (32%) than in Whites (23%). The factors contributing to hypertension in Black Americans were no different to those in Africa. Obesity was found to be a major contributing factor in both South African and American Blacks. South African Black females were found to outweigh males in their prevalence of obesity. With a population estimated at 650 million, increasing longevity and a Westernised lifestyle, hypertension and the severity of its complications, will impact greatly on the economy of sub-Saharan Africa. As was found in the INTERHEART Africa study, the incidence of MI in sub-Saharan Africa is rising, with hypertension as the strongest risk factor.

The effect of hypertension and smoking as single vascular risk factors on the CIMT was investigated by Csányi A, Egervári A and Nagy Z. (2001)[11]. They included participants that were hypertensive but with no other risk factors, and

[10] Steyn K, Gaziano TA, Bradshaw D, et al, 2001
[1] Isaacson, 1977
[7] Opie and Seedat YK. 2005
[11] Csányi A, Egervári A and Nagy Z. 2001

participants who were smokers with no other risk factors. CIMT was measured at both sides of the distal common carotid artery.

The largest increase in the CIMT was observed in the hypertensive group. Using multiple regression analysis they showed that only age, sex, smoking and hypertension correlated with CIMT significantly and independently ($r=0.518$, $p=<0.0001$).

It has been suggested that hypertension is one of the factors that can cause endothelial damage. This theory is based on the "Response-to-Injury" model of atherosclerosis[12]. According to this model, haemodynamic factors (particularly hypertension) and chemical factors in blood induce dysfunction of the endothelium. This injury may be followed by aggregation of blood platelets, oxidised lipids and smooth muscle cells in the intima, resulting in plaque formation. Thus hypertension and dyslipidaemias such as elevated low density lipoprotein serum cholesterol (LDL-C), established independent risk factors for increased CIMT[13] may act inter-dependently to cause atherosclerosis, manifesting as increased CIMT. The effect on CIMT of **hypertension** and **LDL-C** was studied by Sun P, Dwyer KM, Merz CNB et al[14]. They used B-mode ultrasound to measure the intima-media thickness of the common carotid artery. Subjects for the study (n= 511) were drawn from those participating in the Los Angeles Atherosclerosis Study. To depict the relations between CIMT with serum LDL-C and systolic blood pressure (SBP), covariate-adjusted mean CIMT was estimated within subgroups of LDL-C and SBP. Subjects were categorised in terms of tertiles of SBP and then quintiles

[12] Ross R, 1993
[13] Salonen R and Salonen JT, 1991
[14] Sun P, Dwyer KM, Merz CNB et al,2000.

of LDL-C within each blood pressure group. The results showed that CIMT is very strongly related to LDL-C under conditions of elevated SBP. CIMT was significantly related to LDL-C in the hypertensive (HYP) group. Results were similar for both sexes.

The findings of their study support the Response-to-Injury model of atherogenesis.

2.1.2 The Metabolic Syndrome (MS)

The MS is a cluster of key risk factors having a significant impact on the prevalence of CAD. Significant risk factors for the MS appear to be obesity, insulin resistance, aging and hormonal imbalance. It appears that in the United States, the increasing obesity contributes significantly to the prevalence of the MS and findings indicate that measurements, particularly of abdominal fat, is of significant value in defining the syndrome[15].

Atherosclerosis and cardiovascular disease are directly related to factors that constitute the MS. Of these factors hypertension, fasting plasma glucose and dyslipidaemia appear as the most significant risk factors. A prothrombotic state and a pro-inflammatory state are frequent findings in subjects with the above factors. Atherogenic dyslipidaemia, including increased Low Density Lipoproteins (LDL-C), reduced High Density Lipoprotein Cholesterol (HDL-C) and elevated Triglycerides (TG), creates an aggregation of lipid disturbances which contributes to these states[16].

[15] Domanski M and Proschan M, 2004
[16] Grundy SM, Cleeman JI, Daniels SR et al. 2005

Low HDL-C has been explored as an independent risk factor for CAD[17]. The study group consisted of 18 patients who had family history of low HDL-C. The control group of n=18 were pair-matched for gender, age and body mass index (BMI), to maximise statistical power. All the subjects were free of CAD symptoms.

The averages of the mean measurements of the CIMT were taken at the CCA, BULB and ICA, from three angles on either side.

CIMT in the group with low HDL (<0.77mmol/L) was higher than the control group (r=0.70, p=0.0009). As with previous studies, age was found to be a significant contributor to the increased CIMT in both groups. The increment of CIMT across the years was significantly larger in the low HDL-C group, implying an increased risk of developing plaque.

In this study, CIMT was found to be useful to detect early atherosclerotic changes in people with low HDL-C who are asymptomatic.

Some researchers believe that the MS is not sufficient as predictor of the 10-year risk for CAD. For those patients who are free of atherosclerotic cardiovascular disease or diabetes, the Framingham risk score (FRS) remains essential to estimate the10-year risk for CAD. In the FRS triglyceride levels, abdominal obesity and fasting glucose levels, important factors for the diagnosis of the MS, were not found to be significant in increasing the predictive value for CAD over and above the standard risk factors. These factors come into play in the longer term[16].

[17] Alagona C, Soro A, Westerbacka J et al. 2003.
[16] Grundy et al. 2005

2.1.2.1 Diagnosis of the Metabolic Syndrome

There are differing criteria for this syndrome. The two most important classifications are the National Cholesterol Education Program (NCEP)[18], which was proposed to provide criteria that are easily applicable in a clinical setting, and the recent International Diabetes Federation (IDF) classification[19], which is similar to the NECP, but places a greater emphasis on obesity as measured by the waist circumference. For this dissertation the IDF classification is used, as listed below.

NCEP III Criteria

Hypertension (>130/85 mmHg)

Obesity as defined by abdominal circumference (>102 cm in men; >88cm in women)

High TG level (>1.7 mmol/L)

Low HDL-C level (<1.0 mmol/L for men; <1.3mmol/L for women)

High fasting glucose level (>6.1 mmol/L)

IDF Criteria

A. Central Obesity: waist circumference >94 cm for men and > 80 cm for women

Plus any 2 of the 4 factors below

B. Raised TG level > 1.7 mmol/L

C. Reduced HDL-C <1.03 mmol/L in men, <1.29 mmol/L in women or specific treatment for these lipid abnormalities

D. Raised BP: systolic BP >130, or diastolic BP >85 mmHg or treatment of previously diagnosed hypertension

[18] Expert panel on detection, evaluation and treatment of high blood cholesterol in adults, 2001

[19] Segal P and Zimmet PZ. 2005

E. Raised fasting plasma glucose: >5.6 mmol/L or previously diagnosed Type 2 diabetes.

There is debate as to whether the NCEP or the IDF classifications provide the best possible estimate of the MS, in order to ascertain the best determinants for prevention and treatment. As indicated above, the increasing incidence of MS in the United States stems from the virtual epidemic of obesity and depicts a morbid scenario. The prevalence is 24% for those older than 20 years and rises to >40% in those over 60 years[15].

The exact prevalence of MS in South African Blacks and its predictive value for CAD is unknown.

2.1.3 Smoking

There is no clear understanding of the pathophysiological mechanism which makes smoking a major risk factor for CAD for both sexes. Research has been constrained, because smoking interacts with other classical cardiovascular risk factors, which in combination, affects the progression of atherosclerosis[20].

It was found that particularly in men, cigarette smoking is recognised as a major risk factor for atherosclerosis and CAD[21]. The imaging protocol in that study, which was designed to evaluate the effect of cigarette smoking on intima-media thickness, included the distal segment of the CCA and the common femoral artery bilaterally, using only the far wall segments. The study

[15] Domanski and Proschan, 2004
[20] v d Berkmortel FWPJ, Smilde TJ, Wollersheim H et al. 2000.
[21] Gariepy J, Denarie N, Chironi G et al. 2000

population consisted of 194 men and 330 women aged 17-65 years. The subjects were free from cardiovascular disease and had no other risk factors. Linear regressions were used to analyse the relationship between CIMT and age and CIMT and smoking. Multiple regression analysis was used for age and gender adjustment of the CIMT/smoking relationship.

The findings showed an increased CIMT in men smokers (both CCA and femoral arteries) and also in former smokers, compared to never-smokers. However, this was not so in the case of women.

Another study has also identified smoking as an independent risk factor[11]. Here the annual increase in CIMT was assessed in a healthy population without risk factors other than smoking and hypertension.

The study population consisted of three groups, n = 258 (randomised):

- a group of people who had hypertension (HYP) and no other risk factors (at least five years of treatment for hypertension);
- a group of people who were smokers (SMO) without other risk factors (current smokers with a five pack-cigarette-year);
- a group that was risk- and symptom free, healthy control subjects (HCS).

The mean age was significantly higher in the HYP ($p< 0.005$) and SMO groups ($p<0.001$) groups than in the HCS group.

Their results showed smoking as a single risk factor causing thickening of the intima-media layer of the CCA. The authors also indicate that their findings lend support to other studies where a similar trend was found and emphasise

[11] Csanyi, et al 2001

smoking as positively, significantly and independently related to CIMT[22]. It was also the explanation why the CIMT was different in twins that were not matched for smoking[23].

2.1.4 Age

Atherosclerosis progresses over a prolonged period. Over decades, this results in the gradual increase in width of the inner layers of arteries. It is the measurement of this phenomenon by ultrasound, the CIMT, which is the key aspect of the study discussed fully below. A healthy person reaches a CIMT of 0.78 mm at the age of 76 years[3]. The CIMT increases with advancing age in human as well as animal models of ageing[24].

The age-related increase in CIMT has always been thought to be due to atherosclerosis. However, there is now evidence that this may not be the case. One theory is that the increase in CIMT with age in healthy adults is an adaptive response of intrinsic compositional elements of the arterial wall to the chronic and progressive elevation in arterial blood pressure. The fact that resting brachial artery systolic and arterial pulse pressures increase with age in the general population and correlates with the age-associated increase in CIMT, is consistent with this concept. Findings in the study[25] indicate:

1. CIMT increases progressively with age in healthy normotensive men in the absence of elevations in peripheral SBP;

[22] Tell GS, Polak JF, Ward BJ, et al. 1994.
[23] Haapänen A, Koskenvuo M, Kapiro J, et al. 1998.
[3] de Groot et al 2004
[24] Nagai Y, Metter EJ, Early CJ et al. 1998.
[25] Tanaka H, Dinenno FA, Monahan KD et al 2001

2. Carotid SBP also increases with advancing age and is positively associated with an increase in CIMT;
3. The significant increase in CIMT with age is abolished after statistically accounting for the corresponding increase in carotid SBP. Carotid SBP was the only independent predictor of the age-associated increase in CIMT.

Thus the literature indicates that CIMT is strongly and positively related to elevations in carotid SBP. Chronic increases in local distending pressure may be an important mechanism in the wall thickening of central elastic arteries that occurs with human ageing.

2.2 ATHEROSCLEROSIS, CORONARY ARTERY DISEASE AND CAROTID INTIMA-MEDIA THICKNESS (CIMT)

2.2.1 Atherosclerosis and CIMT

The easy accessibility of the carotid arteries, due to their superficial location and size, makes them most suitable for study[26].

B-mode ultrasound assessment of CIMT provides measurements of arterial wall abnormalities and thus a non-invasive assessment of the degree of atherosclerotic change. Intense research has been done, and is ongoing, to assess the value of CIMT in complementing the established cardiovascular risk factors in predicting the outcome of cerebrovascular and coronary artery disease.

[26] Sinha AJ, Eigenbrodt M, Mehta JL et al. 2002.

In its early stages, atherosclerosis is restricted mainly to the intimal layer of the vessel wall. Ultrasound does not allow for the distinction between the intimal layer and the medial layer. CIMT measurements are done on B-mode ultrasound, when the two echogenic (bright) lines, representing the lumen-intima interface and the media-adventitia interface (intima-media complex), are visualized[27]. It is the thickness of the complex which constitutes the carotid intima-media thickness (CIMT).

2.2.2 Accuracy and Reproducibility of CIMT Measurements

Although studies have shown that ultrasound measurement of CIMT is a reliable surrogate marker for CAD, de Groot et al[3] emphasised the need for standardised and strictly implemented imaging protocols in observational studies and clinical research, in order to exploit the full potential of ultrasound imaging. Trials tend to be multi-centred and large numbers of images are generated. Standardised protocols would minimise inter-scanner differences and contribute to the accuracy of image analyses.

Earlier studies of the CIMT focused on the ultrasound measurement of the far wall of the common carotid artery intima-media complex only. It was found to be generally constant throughout the vessel and easily reproducible[28]. However, the most important objective of research in this field is the improvement of the accuracy and reproducibility of the measurements. This is particularly so for the precision required in assessing progression rates in

[27] Bots ML, Dijk MJ and Grobbee DE. 2002
[3] de Groot et al 2004
[28] Veller MG, Fisher CM, Nicolaides AN et al 1993.

intervention studies[29]. Design options and suitable ultrasound protocols are explored here. Questions raised include:

- Which arterial segments should be examined?
- Should measurements be taken at the near and far wall on the B-mode image?
- Should one optimal angle be used or several images?
- Should one use an automated measurement technique, or manual measurements the CIMT?

It was concluded that the use of the mean maximum CIMT, using images from all segments, including the common carotid (CCA), the carotid bulb (BULB) and the internal carotid artery (ICA), yields more information and is favoured over the mean common CIMT only. Multiple images were thought to reduce measurement errors and increase precision.

In terms of the measurements, automated edge detection systems work very well when there are clear interfaces on the ultrasound images. However, when there is an uneven margin created by focal plaque, manual measurements would be more advantageous.

In my study protocol multiple measurements (12) were recorded and CIMT was measured manually, as discussed in detail under technique.

[29] Bots ML, Evans GW, Riley WA et al .2003

2.2.3 Value of CIMT in Coronary Artery Disease

The impact of the known risk factors for CAD, namely hypertension, diabetes mellitus, hyperlipidaemia, cigarette smoking, age and gender on CIMT has been well established. However, the association between IMT and atherosclerosis of the coronary arteries, continues to be the subject of intense investigation[8]. The non-invasive, inexpensive, and reproducible features of ultrasound measurement of CIMT as a predictor of future cardiovascular events, makes it a valuable clinical tool[26].

O' Leary et al, highlights the value of the CIMT and the contribution it makes when added to known risk factors, to identify people at risk for CAD. Already in 1986 the value of B-mode ultrasound was recognised, where ultrasound assessment of atherosclerosis in the aorta was compared to the measurements of an excised segment of the aorta. The CIMT as measured by ultrasound was the same thickness as that measured by light microscopy. From then on CIMT was recognised as a surrogate marker of atherosclerosis[30].

However, the value of CIMT as an *independent* predictor of coronary artery events was questioned. In earlier studies of vascular wall changes, the CIMT was not widely accepted as a predictor for atherosclerosis in the sub-clinical phase. Veller et al[28] compared intima-media thickness (IMT) to the presence of risk factors and the arterial ultrasound score (AUS), a measure of large-scale qualitative changes in the vessel wall, a sensitive indicator of

[8] Kablak-Ziembicka et al 2004
[26] Sinha et al. 2002
[30] O' Leary D and Polak JF 2002
[28] Veller MG, et al 1993

asymptomatic coronary artery disease and good predictor for the subsequent development of cardiovascular symptoms. IMT was assessed bilaterally in 140 subjects who were symptom free, using the mean thickness of the common carotid artery (CCA) IMT. The mean IMT was linearly related to age, pack years of smoking, hypertension and to the arterial ultrasound score (AUS). The conclusion drawn from the study is that IMT, similar to AUS, is a predictor of risk for CAD. Smoking and hypertension were found to be significant contributors to increased IMT. However, limitations were experienced in the reproducibility of the IMT measurements, due to technical constraints, involving the resolution of the ultrasound beam.

Subsequently, with the improvements in the high-resolution equipment, reproducibility of B-mode ultrasound imaging of the IMT is greatly improved. It is now widely accepted as an accurate and reliable method to predict cardiovascular events[8] [31] [32], even with the use of different protocols. CIMT measurement errors have been minimised from 25-40% to 10-20%. Of importance, when compared with histology of arterial sections, measurement of far wall thickness by ultrasound was found to be a true measure of the arterial wall thickness[27].

Two publications arising from the Rotterdam study cohort, one of the largest studies to-date that used B-mode ultrasound to assess CIMT in a general population, are frequently sited in discussions around the evaluation of CIMT

[8] Kablak-Ziembicka et al 2004
[31] Oren A, Vos LE, Uiterwaal CSPM et al. 2003
[32] Takashi W, Tsutomu F and Kentaro F 2002.
[27] Bots el al 2002

as a tool to predict CAD outcomes and its relationship to the standard risk factors.

The first was a cross-sectional study by Bots, Hoes, Hofman et. al, where CIMT was measured to estimate the individual 10 -12 year absolute risk for stroke, coronary artery disease and death[33]. The risk function for stroke and CAD was calculated based on information from the Framingham Heart Study and the Framingham Heart Cohort. Risk factors included for CAD were age, systolic blood pressure, total- to HDL-C ratio, left ventricular hypertrophy (on ECG), smoking and Diabetes Mellitus. They found a strong positive correlation between CCA CIMT and risk score.

The authors conceded that increased CIMT may be of use to identify patients at high risk and therefore would be suitable to guide therapeutic decisions. However, they stated that the contribution CIMT makes in relation to other easily obtainable cardiovascular risk factors needs further evaluation.

In the second study, reservations were expressed around the value of the CIMT as an *independent* predictor of CAD[34]. The study focused on CIMT (mean maximum) and its relationship to established risk factors, to determine the predictive value of CIMT in coronary disease and cerebrovascular disease. The data was obtained from a nested case-control study in the area of Rotterdam in the Netherlands and included 374 subjects who were diagnosed with CAD or stroke and 1496 controls. Regression analyses and the area under the receiver operating characteristic curve (ROC area) were

[33] Bots ML, Hoes AW, Hofman A et al 1999
[34] del Sol AI, Moons KGM, Hollander M et al. 2001

used to quantify the predictive value of the established risk factors and the added value of CIMT.

The results showed a significant association between CIMT and risk of coronary artery disease and cerebrovascular disease. From their results, a single CIMT measurement (CCA in that study) does not add to the predictive value provided by the commonly used risk factors. The implication drawn was that CCA CIMT would not be more valuable as a screening method to identify patients at risk.

In the words of Bots et al. (1999) cited above, 'Quantitative information showing that increased intima-media thickness is related to long-term future cerebrovascular and cardiovascular disease is very limited but urgently needed'.

In a more recent publication by Bots et al.[29], the authors outline their planning for the use of CIMT in intervention studies. They favour the use of the mean maximum CIMT (from multiple sites) over the mean CCA CIMT (a single site). This was based on a review of several studies showing that the mean maximum CIMT measurements can be obtained in practically all subjects, in a reliable and reproducible manner.

Ward Riley presented a challenge to the medical community in an editorial[35], where he states that the use of CIMT has without doubt been shown to be a strong predictor of future cardiovascular events. He quotes the work of del

[29] Bots et al 2003
[35] Riley WA. 2002

Sol et al. cited above[34] where the authors found that CIMT (using only the common carotid artery measurements) is nearly as predictive for CAD as all the traditionally accepted risk factors such as age, sex, previous MI and stroke, diabetes mellitus, smoking, systolic blood pressure and total HDL-C levels.

Riley's concern is that researchers may assume that any measured segment of the carotid artery would have the same predictive value for CAD. Most of the studies that I have referred to used only the common carotid artery segment, probably because it is easier. The reason that has been given though, is that there is less missing data as compared to the use of the other segments of the carotid artery. What must be remembered though, is that, to quote Riley, "…atherosclerosis is a generalised disease that is circumferentially asymmetric..." The bulb tends to be the site where atherosclerosis begins. From a scientific perspective, all three segments would yield more information and should therefore be used in order to gain maximum value from using CIMT measurements to predict CAD. Riley's challenge to us is stated in the following quote, "We owe it to the potential of carotid intima-media thickness that it not go the way of other diagnostic tests due to a lack of resolve to do it the right way…"

In my dissertation the mean maximum CIMT is measured as the mean value measured at 12 sites.

[34] del Sol et al, 2001

2.2.4 CIMT and Angiographic Evidence of CAD

The following two studies are of particular relevance to the study I have done.

In the study of Geroulakos, Gorman, Kolodiki et al, the CIMT (CCA) was correlated with the extent of CAD found at angiography[36]. The study group consisted of 75 male subjects who had coronary angiography for assessment of angina, myocardial infarction or valvular disease. The control group consisted of 40 normal subjects who were matched for age and sex. Measurements of the CCA CIMT were done at the far wall, 2cm before the bulb. A total of six measurements were taken (three on each side) and a single observer took all the measurements.

No differences were found in the mean CIMT between controls and the group who had no coronary artery disease at angiography, CIMT for controls 0.71mm, and for subjects with no coronary disease 0.73mm. A progressive increase in the CIMT was shown for groups with single vessel (0.91mm, $p<0.05$), two-vessel (0.96mm, $p<0.01$) and three vessel disease (0.99mm, $p<0.01$), with a linear trend of $r=0.44$ ($p<0.00001$).

After correction for age, a cut-off point of .85mm was taken to predict severe CAD, with a high positive predictive and specificity value. The conclusion they drew was that a combination of high specificity and high negative predictive values, makes the CIMT a useful screening test in a population with a low prevalence of CAD.

In the second pertinent study, the relationship of CIMT and CAD was analysed in a large group of 558 subjects in Poland, with a mean age 58.8

[36] Geroulakos G, O'Gorman DJ, Kalodiki E et al 1994

(SD 9.2) years[8]. All subjects in the study group were suspected of having CAD on admission to the department: most of them had a positive treadmill test, segmental hypokinesis or akinesis on echocardiography, ischaemic changes on ECG, or symptoms suggesting angina of Functional Class II or more. Notwithstanding these clinical features, 17% of the subjects had no coronary artery lesions.

The coronary angiography results indicated the following:

1. 95 pts (17%) had normal coronary arteries;
2. 154 pts (27.6%) had one vessel CAD;
3. 104 pts (18.7%) had two vessel CAD;
4. 205 pts (36.7%) had three vessel CAD.

The changes in mean CIMT were correlated with known risk factors, including age, sex, hypertension, diabetes, hyperlipidaemia and cigarette smoking. These findings establish the value of CIMT as an independent risk factor for CAD.

Their results identified four independent predictors of CAD:

- Age ($p=0.0193$);
- Hyperlipidaemia ($p=0.0001$);
- Smoking ($p=0.0032$);
- CIMT ($p<0.0001$).

The theoretical distributions of CIMT showed that patients with a mean CIMT over 1.15mm had a 94% probability of having CAD, with a sensitivity of 65% and specificity of 80%.

[8] Kablak-Ziembicka et al, 2004

The conclusions they arrived at was that CIMT increases with advancing age, increases in the CIMT have a high and specific likelihood of CAD and that ultrasound examination of the carotid arteries can effectively predict atherosclerosis of the coronary arteries.

2.3 Conclusions from the Literature

Hypertension is the most significant risk factor for MI in Black South Africans. There is great enthusiasm amongst all researchers to find non-invasive methods for identifying people at risk for coronary artery disease, particularly where therapy can prevent adverse outcomes in atherosclerosis.

B-mode ultrasound has been accepted as safe and accurate and most of all, relatively inexpensive as a method for investigating atherosclerosis in its subclinical phase. Young people can now be included in multi-centred trials, because ultrasound is safe and non-invasive.

The use of standardised protocols for imaging and measuring CIMT will enhance the accuracy and thereby the predictive power of CIMT. This is particularly important in intervention studies, where accuracy and reproducibility of CIMT measurements would be critical, so that the efficacy of interventions could be more precisely assessed.

There is clear evidence of a positive correlation between CIMT and risk factors and CIMT and consequently CAD. There is growing support for CIMT as an independent predictor for CAD.

More research is needed, especially in South Africa, to support the use of B-mode ultrasound measurements of the CIMT as a surrogate marker for CAD, in view of the increasing incidence of CAD in the Black population.

3 THE STUDY

3.1 AIM OF THE STUDY

To determine the value of ultrasound measurements of carotid intima-media thickness – CIMT, as a surrogate marker for coronary artery disease, in the South African Black population.

3.2 OBJECTIVES OF THE STUDY

To compare Ultrasound measurements of CIMT in:

I. A study group of South African Black subjects with evidence of coronary artery disease on coronary angiography.

II. A control group of South African Black subjects with no evidence of coronary artery disease on coronary angiography.

A sub-group analysis was done in groups I and II to assess:

A. The presence of factors which constitute the Metabolic Syndrome as defined by the IDF:

a) Central Obesity: waist circumference >94 cm for men and > 80 cm for women; **Plus** any 2 of the 4 factors below

b) Raised TG level: > 1.7 mmol/L;

c) Reduced HDL-C: <1.03 mmol/L in men <1.29 mmol/L in women or specific treatment for these lipid abnormalities;

d) Raised BP: systolic BP >130, or diastolic BP >85 mmHg or treatment of previously diagnosed hypertension;

e) Raised fasting plasma glucose: >5.6 mmol/L or previously diagnosed Type 2

B. Other risk factors such as smoking, LDL-C and increasing age.

3.3 ETHICAL CLEARANCE:

University of the Witwatersrand Ethical Committee PRC 010 102 (See Appendix 1.)

3.4 INFORMED CONSENT

The attending physician obtained informed and written consent from every patient. The aims of the study, the rationale for all investigations and procedures and their voluntary participation was fully explained and formally agreed to.

3.5 HYPOTHESES

It was hypothesised that:

I. There will be a positive correlation between an abnormal CIMT measurement and the presence of coronary artery disease;

II. The factors which constitute the Metabolic Syndrome would have a positive correlation with an increase in CIMT;

III. The measurement of the CIMT would be a useful marker for CAD in the Black population of South Africa.

3.6 STUDY DESIGN, SETTING AND PROTOCOL

This was a prospective study in which the study population and the controls had undergone coronary angiography, and have had B-mode ultrasound to assess CIMT.

3.6.1 Study Population

3.6.1.1 Recruitment

Patients of both the study and control groups were recruited from the Cardiac Clinics of the Chris Hani Baragwanath, Helen Joseph and Johannesburg Hospitals.

The research population consisted of a total of 53 subjects of the age group 30-70 years including:

- Study group: 38
- Control group: 15

3.6.1.2 Criteria for Recruitment

The Study group were recruited on the basis of confirmed CAD at angiography - defined as lesions greater than 50% in one or more of the major coronary vessels. Subjects with a previous myocardial infarction had to be at least 3 months post-infarction before recruitment.

The Control group were patients who were suspected of having CAD, recruited on the basis of normal coronary arteries at angiography.

3.6.1.3 Exclusion Criteria

I. Subjects who were previously diagnosed with diabetes mellitus (DM) or genetic dyslipidaemia;
II. HIV-positive subjects;
III. Subjects who smoked >20 cigarettes per day;

IV. Subjects with overt renal, thyroid or liver disease;
V. Subjects where the imaging circumstances were very poor, with limited boundary visualization or where there were anatomical constraints, either a high carotid artery bifurcation or a short thick neck, where more than 2 segments were not visualized.

3.6.2 Ultrasound Setting

Ultrasound imaging was carried out at the Johannesburg Hospital by the candidate sonographer who holds a certificate in CIMT imaging from the Julius Centre in the Netherlands. This kind of training has vastly improved the technique and no doubt, the accuracy and reproducibility of the CIMT measurements.

To obtain certification, video recordings of the entire procedure of the designed protocol had to be regularly submitted to the Julius Centre for assessment, until certification. All certification scans were done on volunteers. Ongoing certification also requires the submission of monthly video recordings for the purposes of quality control.

The candidate sonographer was blinded to both the coronary angiography and clinical results until the end of the ultrasound studies on all the subjects.

3.6.3 Ultrasound Protocol

3.6.3.1 Imaging Instrumentation

I. High resolution B-mode ultrasonography was used;

II. All Scans were carried out using a single ultrasound machine: Toshiba System: Nemio Model SSA-550 A;

III. The transducer frequency was set at 11MHz for all patients (preset for the carotid programme).

3.6.3.2 Technique

I. Ultrasound imaging procedures were standardised for all subjects, using the same protocol;

II. The subject lies supine with the sonographer sitting at the head-end. The ultrasound machine is located to the left of both the patient and the sonographer. The head is slightly extended and turned 35 degrees to the contra-lateral side;

III. Scanning is commenced by holding the transducer in the transverse plane and then sliding it from above the clavicle, to the area of the bifurcation of the carotid artery. Identification of the thyroid gland medial to the vessels, and the internal jugular vein which is compressible, helps to identify the CCA;

IV. At the carotid bifurcation, the ECA and ICA are identified and depending on the position of these vessels in relation to each other, the optimal angle is selected, according to the technique taught at the Julius Centre. Selection at the optimum angle of interrogation (OAI), allows the visualization of the flow tip divider, which is the echogenic interface between the ICA and external carotid artery (ECA), the

CCA, BIF and ICA, in a single selected angle of the carotid arteries at the bifurcation;

V. The transducer is then placed longitudinally on the neck at the OAI where the CCA, BIF, ECA and ICA can be easily identified. Doppler is used to verify the identification of the ECA and ICA;

VI. The intima-medial thickness (IMT) was measured when the two echogenic lines, representing the lumen-intima interface and the media-adventitia interface, are visualized over a length of ≥1cm. The segment should be clear of calcified plaque, which obscures the lines and thereby obstruct the measurement of the IMT;

VII. Measurements of the IMT were done manually, using the calliper markers of the ultrasound unit (electronic measurement facilities are not available on the ultrasound machine used);

VIII. The IMT at the optimal angle of interrogation was measured, as the area of maximum thickness at the near and far walls of the CCA, BIF and ICA bilaterally (a total of 12 sites). In cases where calcific plaque obscured the IMT in the bulb, one wall was measured;

IX. The thickest measurement in each segment was imaged and recorded as the final measurement. The mean maximum IMT was recorded as the CIMT;

X. Images were stored on a magnetic optical disc as well as on thermal paper.

The following four figures depict the ultrasound images which were used when measuring the CIMT:

- Figure 3.1: Shows an image of the carotid artery selected at the optimal angle. All the segments included in the scanning protocol, namely, the CCA, BULB and ICA are demonstrated in a single view;
- Figure 3.2: Shows an image of the common carotid segment;
- Figure 3.3: Shows an image of the bulb or bifurcation;
- Figure 3.4: Shows an image of the bulb and the internal carotid artery.

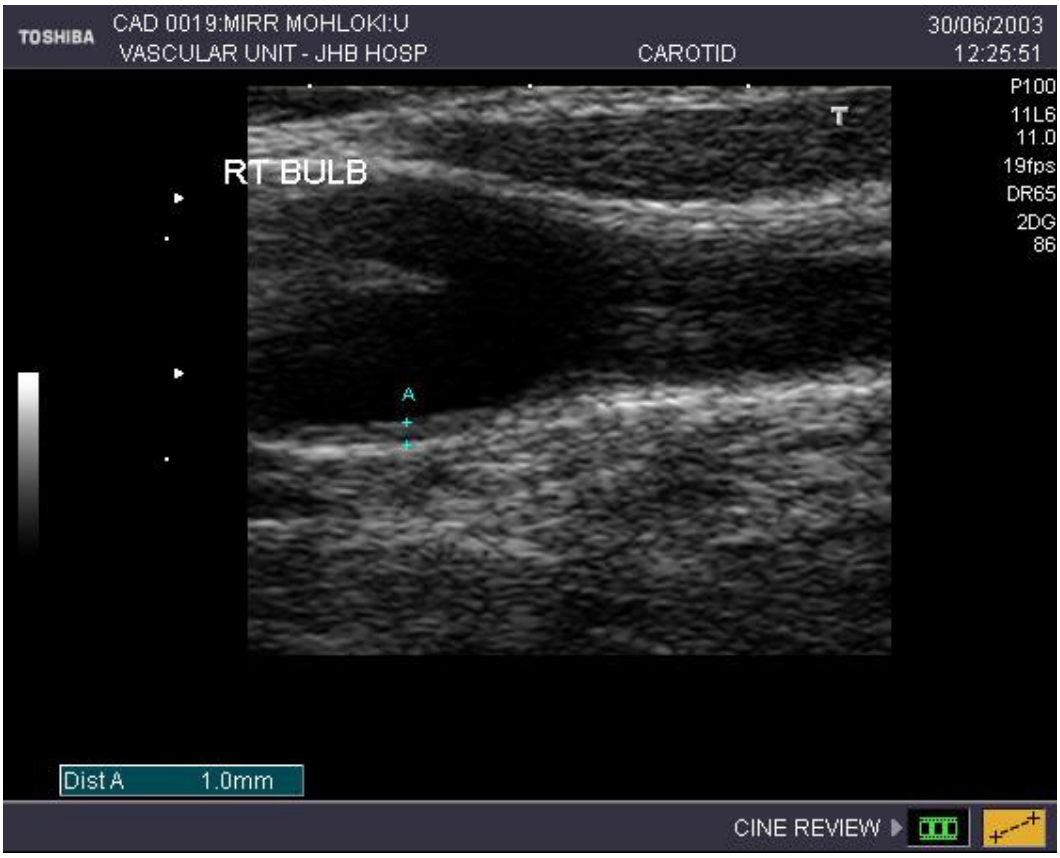
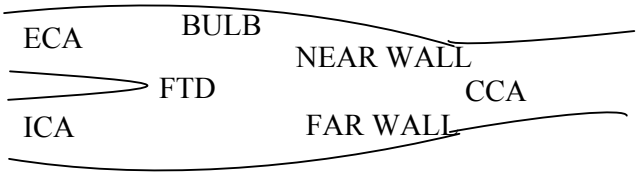


FIGURE 3.1 ULTRASOUND IMAGE OF THE CAROTID ARTERY SELECTED AT THE OPTIMAL ANGLE



The six segments that were measured are shown:
• CCA: Common Carotid Artery near and far wall
• Bulb or Bifurcation: Near and far wall
• ICA: Internal Carotid Artery near and far wall
Also seen are:
• FTD: Flow Tip Divider: Echogenic interface between the Internal and External
Carotid Arteries which is the landmark that identifies the Bulb
• ECA: External Carotid Artery (not used for measurements).

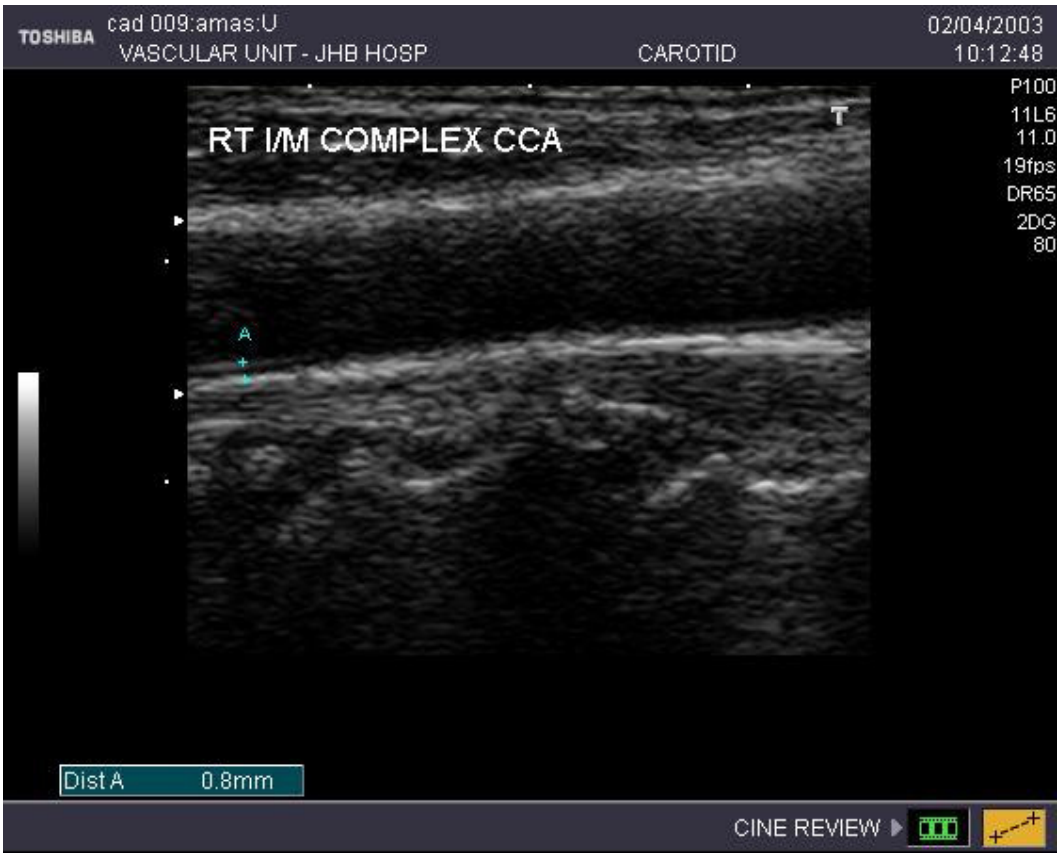
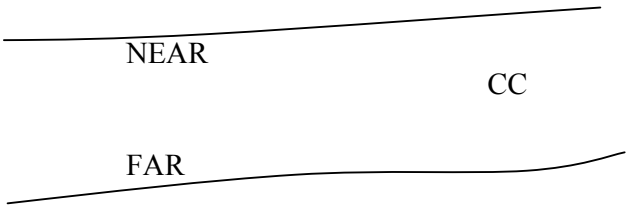


FIGURE 3.2 ULTRASOUND IMAGE OF THE COMMON CAROTID ARTERY



The caliper – A is positioned at the point where the distance between the parallel lines – the Intima-media of the far wall is measured

- The measurement of 0.8mm is the cut-off point for normal Intima-media width in my study.

33

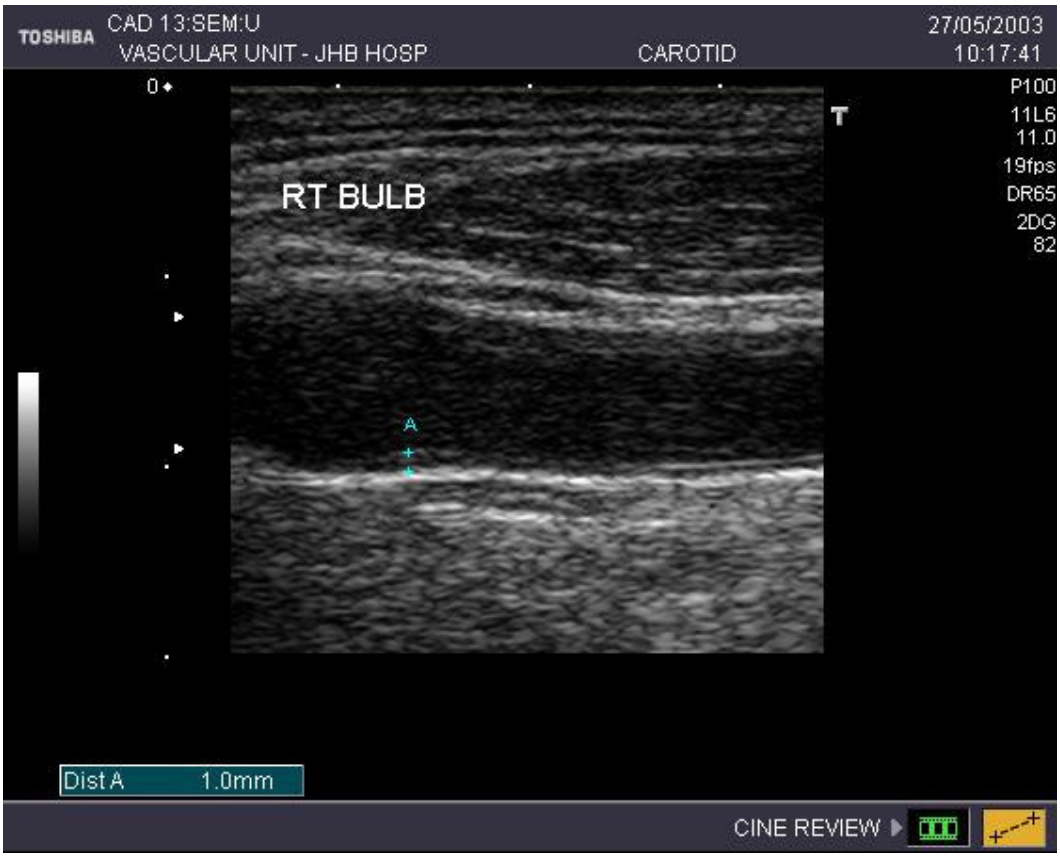
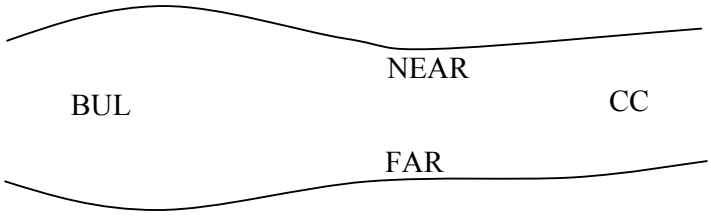


FIGURE 3.3 ULTRASOUND IMAGE OF THE COMMON CAROTID ARTERY AND THE BULB



The caliper – A is positioned at the point on the far wall where the width between the parallel lines - the Intima-Media is measured

- The measurement of 1.0mm is increased Intima-Media thickness in my study.

34

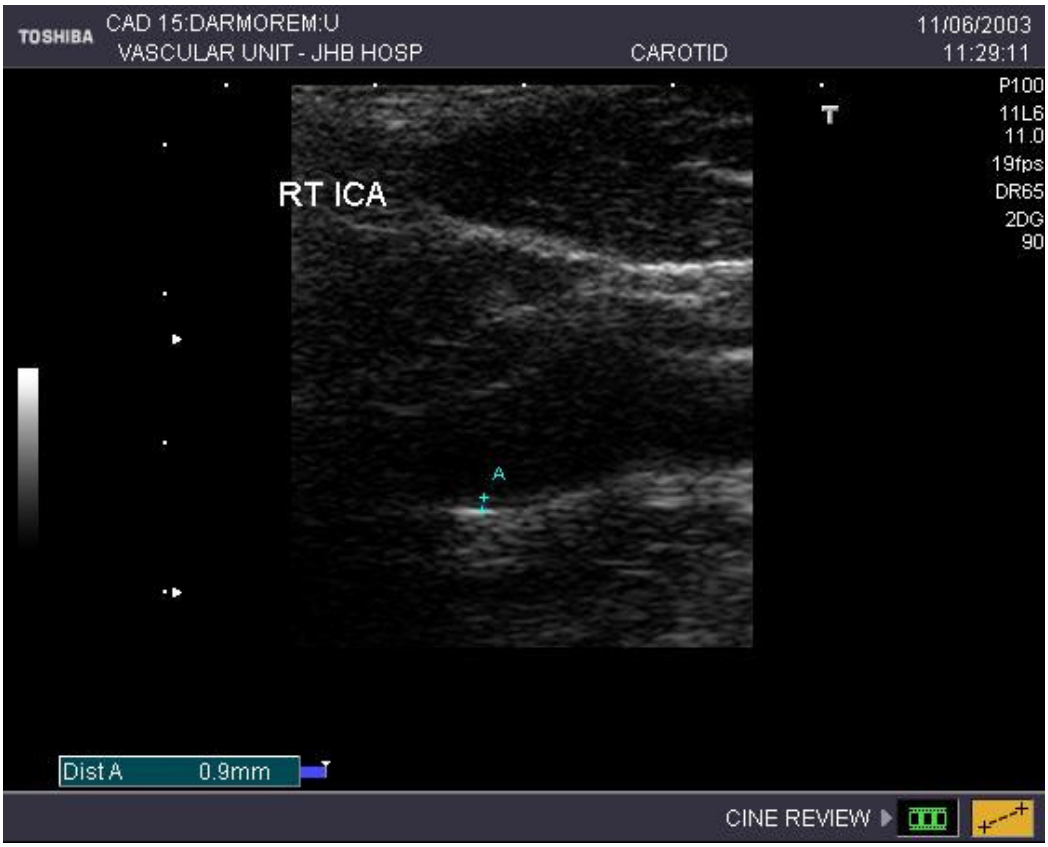
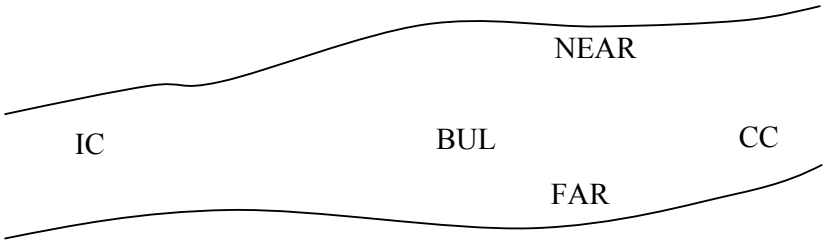


FIGURE 3.4 ULTRASOUND IMAGE OF THE BULB AND INTERNAL CAROTID ARTERY



The caliper – A is positioned at the point on the far wall of the Internal Carotid Artery where the distance between the parallel lines – the Intima-Media is measured

- The measurement of 0.9mm is increased Intima-Media thickness in my study.

3.7 DATA COLLECTION

Data on the clinical and biochemical risk factors, including those for the Metabolic Syndrome (MS) was provided from pooled patient information of a parallel study entitled “Coronary Artery Disease in Black South Africans”, using the same cohort[37].

After exclusion of known diabetics, all subjects were tested for fasting blood glucose and glucose tolerance tests were done to identify subjects with abnormal glucose metabolism.

3.8 THE DATA ANALYSIS

3.8.1 The Carotid Mean Maximum Intima-Media Thickness (CIMT) Measurements

The CIMT was calculated as the average for 12 sites for all subjects, using the Excel programme for Windows XP.

Mean values for the CIMT > 0.8mm were classified as increased thickness.

The work of de Groot et al[3] was used as the basis for the criterion for increased CIMT thickness in my study. They used a standard protocol for predicting progression rates for CIMT and concluded that the normal growth rate of CIMT is up to 0.78mm at the age 76 years. They also demonstrated that increases in the CIMT correlated with the known risk factors.

[37] Ntyintyane 2005 (PhD study in progress)
[3] de Groot et al 2004

3.8.2 Statistical Methods

Besides the control- and study populations based on the absence or presence of CAD at angiography, those with CAD were divided into three groups, in accordance to the number of coronary vessels involved at angiography: one-vessel, two-vessel or three-vessel involvement.

The Excel programme for Windows XP was used to calculate the mean maximum IMT (CIMT) of the carotid arteries. To assess the independent value of the CIMT as a predictor of CAD, linear and multiple regression analyses were done, using the GB –STAT for Windows, Version 10, Dynamic Microsystems Inc. 2004.

3.9 RESULTS

Among the 53 participants (41 men and 12 women) the coronary angiography results showed that 15 people had no evidence of CAD. This constitutes the Control group. The Study group was constituted of the 38 subjects with evidence of CAD.

The discussion of the results will firstly consider the Control group. Following on this, there will be comparisons between the Study and Control groups. The Study group will then be fully discussed in terms of all the risk factors. Selected graphs will be included.

NB Hypertension was the dominant feature in this study. The impact of hypertension on the development of atherosclerosis and thus on the CIMT, is well established. In addition, all the study subjects, except for one individual, were hypertensive and thus its effect separate from that of other risk factors affecting the CIMT could not be assessed.

3.9.1 THE CONTROL GROUP

Of the 15 subjects, there were ten males and five females, a ratio of 67% to 33% females. The mean age was 47 years, with an age-range of 30-65 years. 8 of the 15 (53%) had increased CIMT. The mean CIMT was calculated as 0.998.

The proportions of risk factors for the Metabolic Syndrome in the group were:

- Increased abdominal circumference: 33.3%;
- High blood glucose level: 13.3%;
- High Triglycerides : 26%;
- Low HDL-C: 33.3%;
- Hypertension: 60%;

Of the other risk factors:

- High LDL-C (defined as an LDL-C ≥ 3.4 mmol/L): 13.3%;
- Smokers and ex-smokers were categorised as smokers: 20%.

Of interest amongst the controls, is that three of the 5 females, aged 47, 52 and 64 years (none of them smokers), had evidence of the Metabolic Syndrome and correspondingly, increased CIMT:

- The CIMT for the 47 year old was 0.93 mm, for the 52 year old it was 1.03 mm and for the 64 year old it was 1.56;
- These subjects are all at risk for CAD. The outcome for the last subject having a very high value for CIMT is of particular concern, and close clinical follow-up is indicated.

3.9.2 COMPARISON OF PROFILES OF THE STUDY GROUP AND THE CONTROL GROUP

The comparison of the profiles of the control group with the study group are shown in Table 3.1

TABLE: 3.1 PROFILES OF CONTROL AND STUDY POPULATIONS

	CONTROLS	STUDY POPULATION
RATIO: % M:F	67M 33F	77M 23F
MEAN AGE (YEARS)	47.00	55.00
MEAN INTIMA-MEDIA THICKNESS (CIMT)	1.00	1.13
% OF SUBJECTS WITH INCREASED CIMT	53.00	76.00
MEAN LEVEL OF TG	1.38	1.88
% RAISED TG (> 1.7mmol/L)	26.70	50.00
% LOW HDL-C (M: <1.03; F: <1.29)	33.33	42.10
MEAN LEVEL OF LDL-C	2.65	3.28
% RAISED LDL-C (>3.4mmol/L)	13.33	42.11
MEAN LEVELS OF FASTING BLOOD GLUCOSE	4.33	5.23
% RAISED FASTING BLOOD GLUCOSE (> 5.6mmol/L)	13.33	15.79
% DOCUMENTED DIABETIC / IMPAIRED GLUCOSE METABOLISM	0	55.26
% OBESE (ABDOMINAL CIRCUMFERENCE BY EUROPEAN CRITERIA)	33.33	79.17
% HYPERTENSIVE	60.00	97.00
% SMOKERS OR EX-SMOKERS	20.00	62.50

The most pertinent difference was in terms of the CIMT. The average CIMT of the Study group was higher, 1.13 compared to 1.00 for the Control group and a higher percentage of the Study group had an increased CIMT (76%) than the Control group (53%). When examining for reasons for these differences, the data demonstrate that:

- The Study group mean age (55 yrs) was higher than the Control group (47 yrs);
- There were more males in the Study group than in the Control group (67% vs. 77%);
- In the Study group 79.17% of subjects were classified as obese, with 33.33% in the Control group;
- The Study group had a higher percentage diagnosed as hypertensive (97%) than the Control group (60%);
- The percentage of subjects with high fasting blood glucose was 15% for the study group and 13.33% for the controls;
- The proportion of subjects with high triglyceride levels were higher in the Study group (50%) compared to the Control group (26.7%);
- In the Study group the percentage of people with low HDL-C (42%) was higher than in the controls (33%);
- The proportion with raised LDL-C levels was higher in the Study group (42%) than for the controls (13.33%);
- Smokers in the Study group constituted 62.5% whereas only 20% were smokers or ex-smokers in the Control group.

Clearly, the Study group is characterised with a greater burden of all the known risk factors for CAD: the factors constituting the Metabolic Syndrome and the other two risk factors considered in my study, age and smoking. These features support the hypothesis that increased CIMT has a positive relationship with risk factors as well as with CAD as proven at angiography.

3.9.3 STUDY GROUP

In general, in the study population 29 of the 38 subjects had increased CIMT - 76%, with an average MIMT of 1.13mm. In the sections that follow, each of the specific risk factors for CAD are correlated with the changes in the CIMT.

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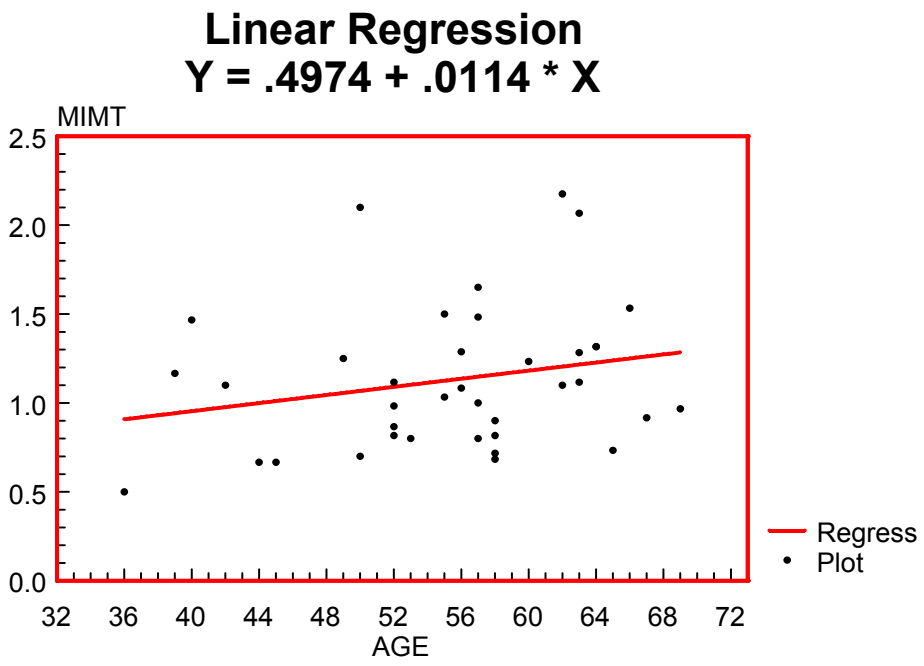
3.9.3.1 AGE

The mean age for the Study group was 55.4 years, with the ages ranging from 36 to 69 years. Linear regression analysis for CIMT against age (see Addendum) shows that increasing age is related to increased CIMT (Correlation Coefficient =.223, p= 0.17). The graph in Figure 3.5 depicts the linear regression trend. These findings support the findings in previous studies[8] [38] [39].

FIGURE 3.5 RELATIONSHIP OF CIMT WITH AGE



[8] Kablak-Zambicka et al 2004
[38] Scuteri A, Najjar SS, Muller DC et al 2004.
[39] Takami R, Takeda N, Hayashi M et al. 2001.

3.9.3.2 GENDER

The Study group consisted of many more males than females, 31 males and 7 females. The average CIMT for males (1.178) was higher than for the females (0.91).

The risk factor profile for CAD, other than age, where the women were older, (59 yrs vs. 55 yrs), was greater in males, both in terms of the IDF definition of the MS: obesity, hypertension, increased fasting glucose, high triglyceride levels and low HDL-C levels, as well as for the additional risk factors explored in this study, high LDL-C levels and smoking: none of the women smoked. Table 3.2 below depicts the differences in the two groups.

TABLE 3.2 COMPARISON OF FEMALES WITH MALES OF THE STUDY GROUP	FEMALES	MALES
NUMBERS	7	31
AVERAGE AGE	59	55
CIMT	0.91	1.18
NUMBER WITH INCREASED CIMT	5	24
%	71.43	77.42
NUMBER WITH INCREASED GLUCOSE	2	7
%	28.57	25.81
MEAN BLOOD GLUCOSE VALUE	5.6	5.17
NUMBER WITH ABNORMAL GLUCOSE METABOLISM	5	16
%	71.43	51.61
OBESITY	5	17
%	71.43	54.84
NUMBER WITH INCREASED TG	4	15
%	57.14	48.39
NUMBER WITH LOW BLOOD HDL-C	3	12
%	42.86	38.71
NUMBER WITH INCREASED BLOOD LDL-C	4	11
%	57.14	35.48
NUMBER WITH HYPERTENSION	7	30
%	100	96.77
NUMBER WITH THE METABOLIC SYNDROME (MS)	5	15
%	71.43	48.39
NUMBER WITH INCREASED CIMT	3	12
%	42.86	80
AVERAGE CIMT	1.00	1.244
SMOKERS	0	16
%		51.61

The risk profile for males is clearly higher in this study. These findings are similar to those of Oren et al[31]. However, the number of participants was much larger in their study. Future research on larger groups in the South African Black population needs to be done, for better evaluation of gender differences.

3.9.3.3 THE METABOLIC SYNDROME

Of the subjects with the MS, a higher percentage had increased CIMT when compared with the whole Study group (87.5% vs. 76%). These features are shown in Tables 3.1 and 3.3 and Figure 3.6. These findings support previous studies[38] [40] which showed a similar trend, where CIMT was shown to be higher in subjects with the MS as compared to controls and that the MS is independently associated with an increased CIMT.

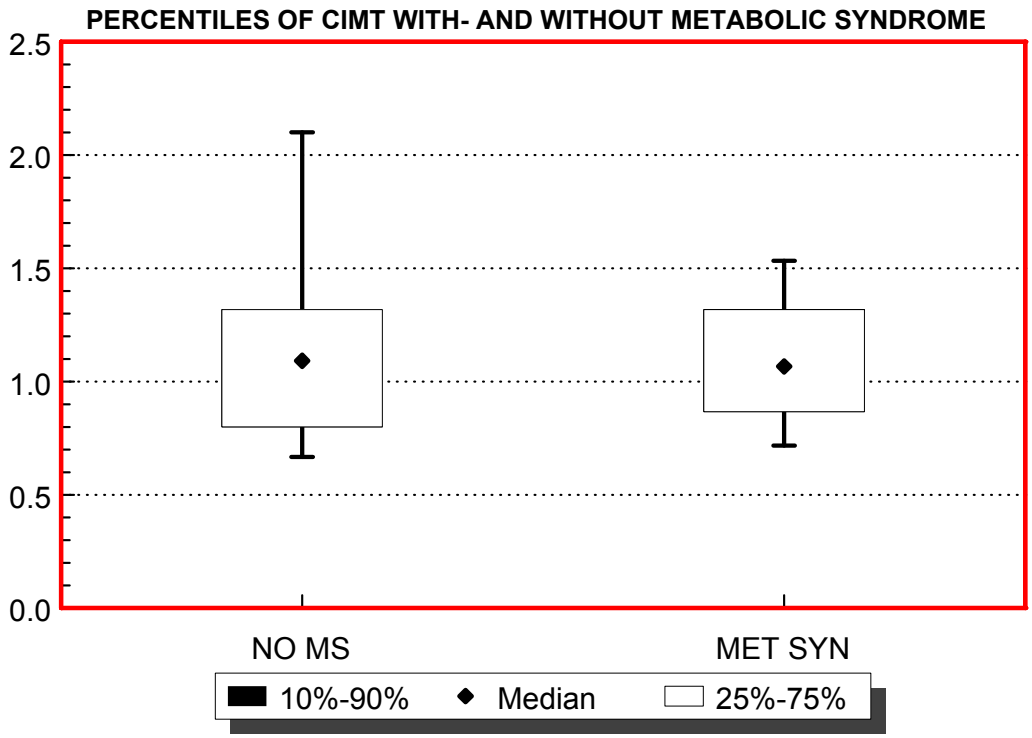
However, subjects **without** the MS also have a high percentage with an increased CIMT, 72.73%. As can be seen in Figure 3.6, the percentile scores for the CIMT values for those with the MS and those without the MS are virtually identical with median values of 1.07 and 1.09 respectively.

TABLE: 3.3 CORRELATION OF INCREASED CIMT IN THE PRESENCE OF THE METABOLIC SYNDROME ACCORDING TO THE INTERNATIONAL DIABETES FEDERATION DEFINITION

	NUMBER	%
NUMBER OF SUBJECTS WITH METABOLIC SYNDROME ACCORDING TO THE IDF DEFINITION	16	42.11
INCREASED CIMT	14	87.5

[31] Oren et al 2003
[38] Scuteri et al, 2004
[40] Czernichow S, Bertrais S, Blacher J et al. 2005

FIGURE 3.6 CIMT IN CAD WITH- AND WITHOUT THE METABOLIC SYNDROME



All of those who had increased CIMT without the MS (IDF classification) had hypertension. In four subjects hypertension was the only other risk factor. The remaining subjects had hypertension and one or two of the risk factors for the MS. These features are shown in Table 3.4. This supports the study' that hypertension is the most important risk factor for CAD in the South African Black population[6].

[6] Steyn et al. 2005

TABLE 3.4 CIMT VALUES FOR SUBJECTS WITH CAD WHO DO NOT FULFILL CRITERIA FOR THE METABOLIC SYNDROME		
ENTITIES	**NUMBER**	**AVERAGE CIMT** (IN DESCENDING ORDER)
HYPERTENSION, INCREASED FASTING GLUCOSE, LOW HDL-C	1	1.65
HYPERTENSION	4	1.43
HYPERTENSION, INCREASED TG	3	1.33
HYPERTENSION, OBESITY	8	1.11
HYPERTENSION, LOW HDL-C	2	0.96
HYPERTENSION, INCREASED TG, LOW HDL-C	3	0.77
INCREASED TG, LOW HDL-C	1	0.50

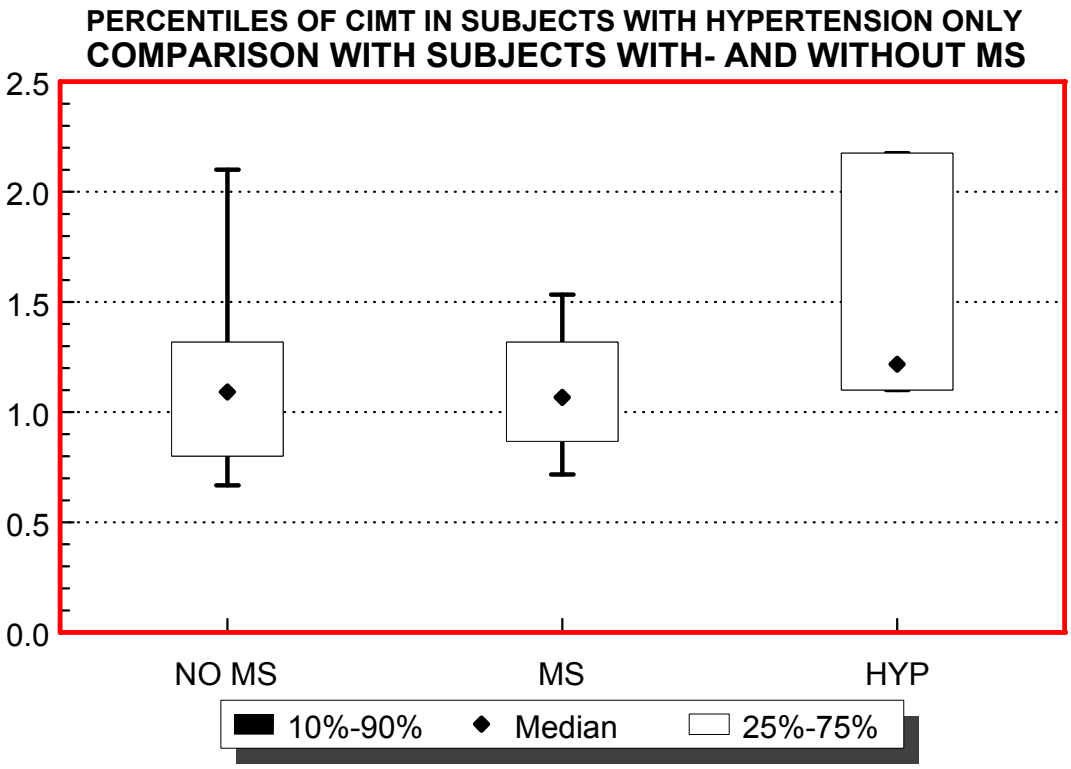
3.9.3.3.1 HYPERTENSION

The effect of hypertension on the incidence of coronary artery disease in the Black population as described[1] is evident in this study. As stated before, all the subjects (37) but one in the Study population had hypertension. The individual without hypertension had a very low CIMT of 0.5. He had raised TG and low HDL-C levels.

The effect of hypertension on CIMT has been shown in several papers[23] [40] and its dominant effect is demonstrated in Figure 3.7, where the graph of the values for CIMT of those patients of the group who had not fulfilled the criteria for the MS but had hypertension as the only risk factor, is superimposed on the graphic illustration of the CIMT values of subjects with- and without MS in Figure 3.6. The median percentile value of 1.22 is greater than that for both MS and non-MS groups (1.07 and 1.09 respectively).

[1] Isaacson 1977
[23] Haapänen et al 1989
[40] Czernichow et al. 2005

FIGURE 3.7 EFFECT OF HYPERTENSION ON CIMT



The figure above shows the effect of hypertension alone on the CIMT. The markedly increased range of percentile values in subjects with hypertension as the only risk factor for CAD indicates its profound effect on the CIMT. The major impact of hypertension on the structure and function on arteries has been documented in previous studies[40], and in this study it probably affects every CIMT measurement of the study subjects. A larger matched study of subjects with- and without hypertension is essential, in order to fully document its effect on the CIMT and to document the effects of the other risk factors free of the effects of hypertension on the CIMT.

[40] Czernichow et al. 2005

3.9.3.3.2 OBESITY

On analysis of the whole Study group, an increase in CIMT was found in 24 subjects, who were classified as obese, as indicated by their abdominal circumference. Of the obese patients, 79.17% had increased CIMT. However the non- obese subjects had a similar proportion with increased CIMT (78.57%). These features are shown in Table 3.5.

Linear regression analysis of CIMT against abdominal circumference of only the obese subjects shows a linear relationship of increasing abdominal circumference and increasing CIMT, with a Correlation Coefficient of 0.30, (p=0.15). This is demonstrated in Figure 3.8

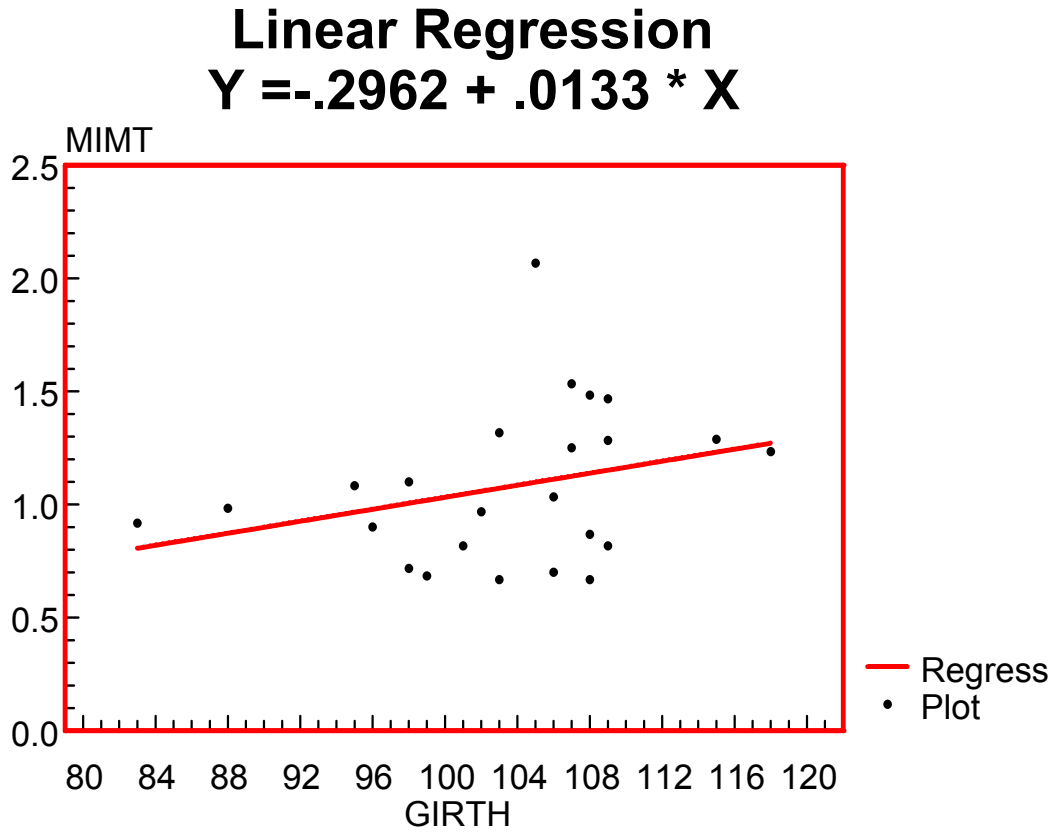
TABLE: 3.5 OBESITY AS INDICATED BY EUROPEAN CRITERIA USING ABDOMINAL CIRCUMFERENCE (M:>94 F: >80)

	NUMBER	%
NUMBER WITH INCREASED ABDOMINAL CIRCUMFERENCE	24	
% OBESE WITH INCREASED CIMT		79.17
NUMBER WITHOUT INCREASED ABDOMINAL CIRCUMFERENCE	14	
% NON-OBESE WITH INCREASED CIMT		78.57

From the results of my study, obese and non-obese subjects had similar percentages of increased CIMT. The findings were different in a study done within the population of the USA[15] where obesity was found to be the dominant factor affecting the CIMT. What Opie and Seedat[7] have pointed out, is that there is a clear relationship between the degree of obesity and blood pressure in South African Blacks.

The effect of hypertension on CIMT in non-obese patients needs to be clarified in future studies.

FIGURE 3.8 LINEAR REGRESSION ANALYSIS OF CIMT AGAINST ABDOMINAL GIRTH IN OBESE SUBJECTS



[15] Domanski et al. 2004
[7] Opie and Seedat, 2005

3.9.3.3.3 FASTING GLUCOSE

The most significant finding here, is that all the patients with a raised fasting glucose had increased CIMT (100%).

Of the patients who were found to have impaired glucose metabolism on glucose tolerance tests, 76.2% had increased CIMT. However, those with normal glucose metabolism (neither raised fasting blood glucose nor an abnormal glucose tolerance test) had a similar percentage of subjects with increased CIMT, 76.4%. These values are shown in Table 3.6 and the linear regression model for CIMT against fasting blood glucose levels in Figure 3.9

TABLE: 3.6 GLUCOSE METABOLISM OF STUDY POPULATION

	NUMBER	%
RAISED FASTING BLOOD GLUCOSE (> 5.6)	6.00	
% WITH INCREASED CIMT		100.00
DOCUMENTED DIABETIC / IMPAIRED GLUCOSE METABOLISM	21.00	
% WITH INCREASED CIMT		76.20
NORMAL GLUCOSE METABOLISM	17.00	
% WITH INCREASED CIMT		76.47

On simple linear regression analysis of the CIMT values against the fasting blood glucose levels, (see Addendum) there is good correlation of increased CIMT with raised fasting glucose levels (Correlation Coefficient of .35 and p = .03).

Thus in this study, high fasting glucose levels are an important factor in causing increased CIMT and an important component of the MS in the South African Black population.

What needs further study is the finding that subjects with impaired glucose metabolism as indicated by an abnormal glucose tolerance test have a proportion of subjects with increased CIMT which is no different to that for subjects with normal glucose metabolism. The possibility of a marked and overriding effect of hypertension in the subjects with normal glucose metabolism needs to be investigated.

A study done by Tropeano AI, Boutouyrie P, Katsahain S et al[41] showed that fasting glycaemia had a strong influence on CIMT in subjects who were hypertensive and had impaired fasting glucose (IFG). The aim of the study was to determine the influence of fasting glycaemia on CIMT in hypertensive subjects with either normal fasting glucose, impaired fasting glucose (IFG) or Type 2 diabetes (DM-2). The study population consisted of 158 subjects with essential hypertension, with either normal fasting glucose (n=74), IFG (n=24) or DM-2 (n=60). The CCA was used to assess the CIMT. The results showed that the CIMT of subjects with DM-2 were significantly higher than that of subjects with IFG and normal glucose. Using multivariate analysis, the results showed that in subjects with normal fasting glucose, blood pressure and age were the major determinants of CIMT and glycaemia was not. However in subjects with IFG or DM-2, **fasting hyperglycaemia** was strongly associated with increases in CIMT and blood pressure was not.

Their conclusion was that hyperglycaemia is the major determinant of increased CIMT in the presence of hypertension, already at the IFG stage (before the onset of frank diabetes), and in fact *overrides the effect of*

[41] Tropeano AI, Boutouyrie P Katsahia S et al 2004.

hypertension on the CIMT. They suggest that this indicates a need for early institution of anti-diabetic therapy.

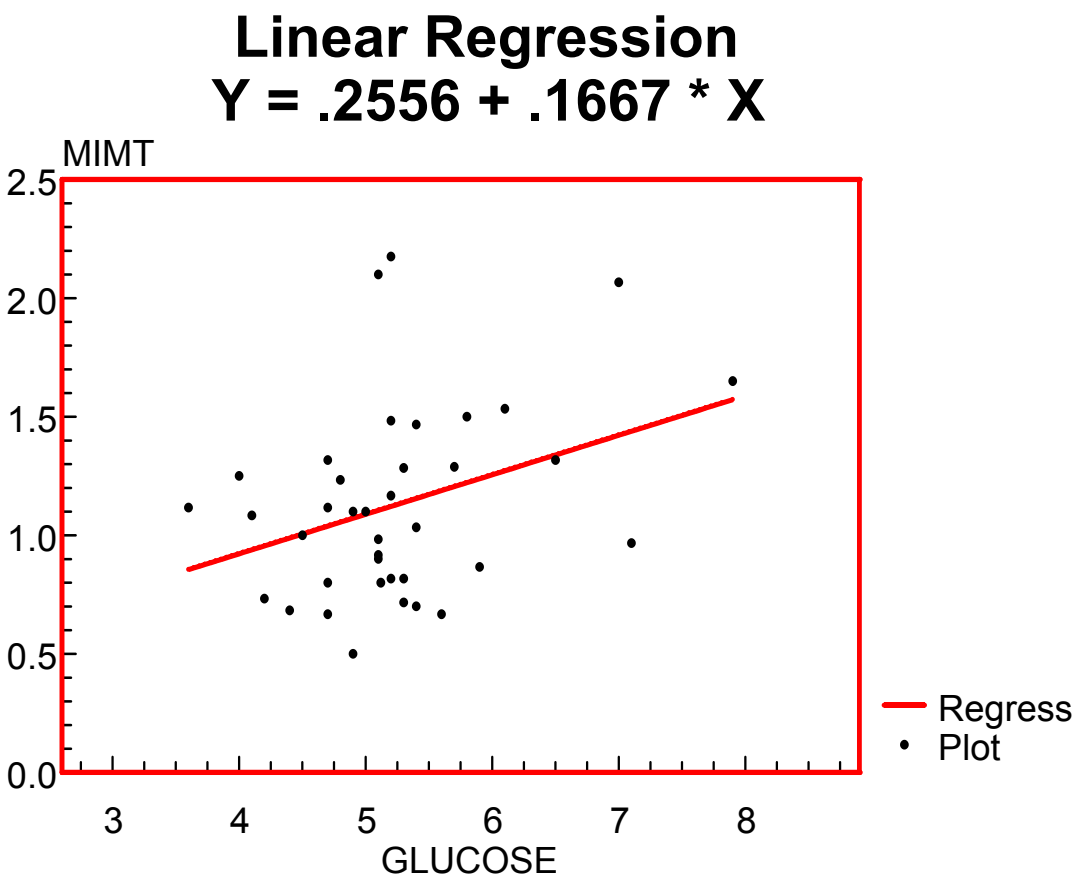
Some aspects of my study support their conclusions:

- Similarly to Tropeano et al, 100% of patients with high fasting glucose had increased CIMT, supporting the notion that high fasting glucose levels have an overriding effect on CIMT in patients with hypertension;
- The increased CIMT in 76.47% of subjects with normal fasting glucose and normal glucose tolerance tests is likely due to the dominant effect of hypertension on the CIMT.

However, my study has shown that the subjects with abnormal glucose metabolism (including those with high fasting blood glucose levels) as indicated by abnormal glucose tolerance tests, have a proportion (76.20%) with high CIMT, which is no different from those without this abnormality.

This suggests that in South African Blacks, *hypertension remains the dominant risk factor for CAD, even in the face of abnormal glucose metabolism, until the stage of high fasting blood glucose*. Clearly, a larger, carefully controlled study in this population is required to confirm this and to evaluate the proposal for early institution of anti-diabetic therapy for subjects with hypertension, as suggested by Tropeano et al.

FIGURE 3.9 RELATIONSHIP OF CIMT WITH FASTING BLOOD GLUCOSE LEVELS



3.9.3.3.4 BLOOD LIPIDS

The lipid components that form part of the Metabolic Syndrome are the blood triglycerides (TG) and HDL-C levels.

There were 19 patients who had raised TG levels and 78.95% had increased CIMT, which is expected. However the percentage with increased CIMT was similar in the 19 subjects with ***normal*** triglyceride levels (73.68%). The question of hypertension causing the increased CIMT needs to be investigated.

In the correlation with HDL-C levels, the CIMT values were ***higher*** in the subjects with normal to increased levels (81.81%), whereas only 68.75% of the 16 subjects with low HDL-C levels had increased CIMT. These findings cannot be fully explained. Further investigation on larger groups need to be carried out to determine the role of HDL-C in South African Blacks who are free of hypertension.

These results are shown in Table 3.7.

TABLE 3.7 LIPID PROFILE OF STUDY POPULATION

	NUMBER	%
NUMBER WITH TG >1.7	19	
% WITH INCREASED CIMT		78.95
NUMBER WITH NORMAL TG LEVELS	19	
% WITH INCREASED CIMT		73.68
NUMBER WITH LOW HDL-C (M: <1.03; F: <1.29)	16	
% WITH INCREASED CIMT		68.75
NUMBER WITH NORMAL / HIGH HDL-C	22	
% WITH INCREASED CIMT		81.81
NUMBER WITH LDL-C ≥ 3.4mmol/L	16	
% WITH INCREASED CIMT		93.75
NUMBER WITH NORMAL LDL-C	22	
% WITH INCREASED CIMT		63.64

Although LDL-C levels are not included in the classification of the MS, the correlates of CIMT with LDL-C in my study show findings more in keeping with the role of dyslipidaemia. Subjects with high LDL-C levels had increased CIMT in 93.75% of cases. Of the subjects who had normal LDL-C levels, 63.64% had increased CIMT. These findings support the “Response-to Injury”

theory[12] which was put to the test in the study of Sun et al, as cited in the literature review[14], which proposes that hypertension causes arterial wall damage, allowing high LDL-C levels to deposit in the intima-media, resulting in atherosclerotic changes.

3.9.3.4 SMOKING

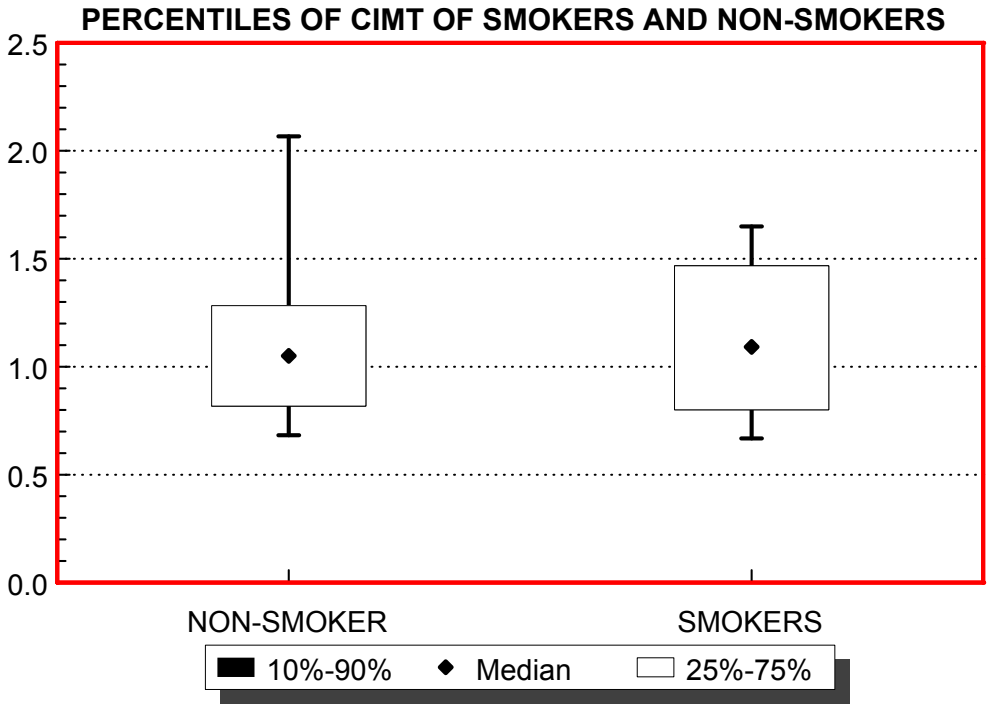
The percentage of subjects who were smokers and had increased CIMT and non-smokers who had increased CIMT were similar, 75% and 77.27% respectively. The CIMT percentile values were similar, with median percentile values of 1.09 and 1.05 respectively. These are shown in Table 3.8, with the graphs in Figure 3.10

TABLE 3.8 PERCENTILE CIMT VALUES OF SMOKERS AND EX-SMOKERS VS. NON-SMOKERS

	SMOKERS AND EX-SMOKERS	NON-SMOKERS
MEDIAN CIMT	1.14	1.12
25th PERCENTILE	0.8	0.82
75th PERCENTILE	1.48	1.28

[12] Ross, 1993
[14] Sun P et al, 2000

FIGURE 3.10 CIMT IN SMOKERS VS. NON-SMOKERS



These results are similar to studies which provide evidence for the increased CIMT[11] [21] associated with smoking as an independent risk factor for CAD. The limitation of my study was that it was not designed to test for smoking as an independent risk factor. Also, it needs to be restated that the overwhelming effect of hypertension is probably interfering with the demonstration of the full effect of smoking in this study.

[11] Csanyi et al 2002
[21] Gariepy et al. 2000

3.9.3.5 MOST SIGNIFICANT RISK FACTORS CONTRIBUTING TO INCREASED CIMT

The outcome of multi-variant analysis of CIMT against the individual risk factors is shown in Table 3.9.

TABLE 3.9 MULTIVARIANT REGRESSION ANALYSIS

		Dependent Variable: MIMT		
		Multiple R = .5524		
		Std Err Est = .3686		
		F = 2.2692		
Ind Var	**B Coef**	**Std Err(B)**	**t-Value**	**Prob**
AGE	.003387	.008029	.4219	.676
GLUCOSE	.213177	.085904	2.4816	.0187
GIRTH	-.009339	.006113	-1.5277	.1367
TRIGLYC	-.081728	.07444	-1.0979	.2807
HDL	.362041	.22524	1.6074	.1181
LDL	.057634	.063191	.9121	.3688
	Constant .272124			

Hypertension was not included in this table as its dominant effect was clearly evident in the data presented. Of the other risk factors, fasting glucose levels was the closest correlate with increased CIMT values (p=0.02). Age and LDL-C levels also showed a positive correlation. The positive HDL value is inconsistent with its protective role in the pathogenesis of atherosclorosis.

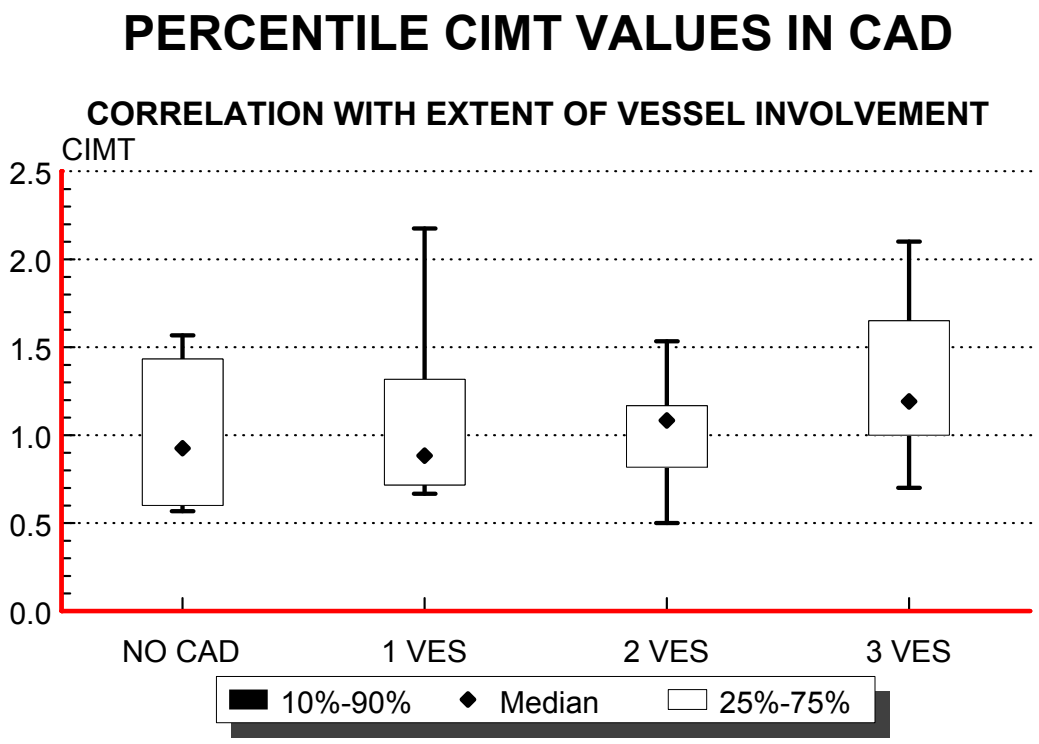
3.9.3.6 RELATIONSHIP OF CIMT WITH CORONARY ANGIOGRAPHIC FINDINGS

The angiographic findings within the Study population showed that 12 people had single-vessel, 11 people had two-vessel and 12 people had three-vessel CAD at angiography. Note that data regarding the number of vessels

involved for three of the patients who had confirmed CAD could not be located.

The CIMT values of the control (no CAD) and three study groups are depicted in Figure 3.11 below.

FIGURE 3.11 CIMT WITH EXTENT OF VESSEL INVOLVEMENT



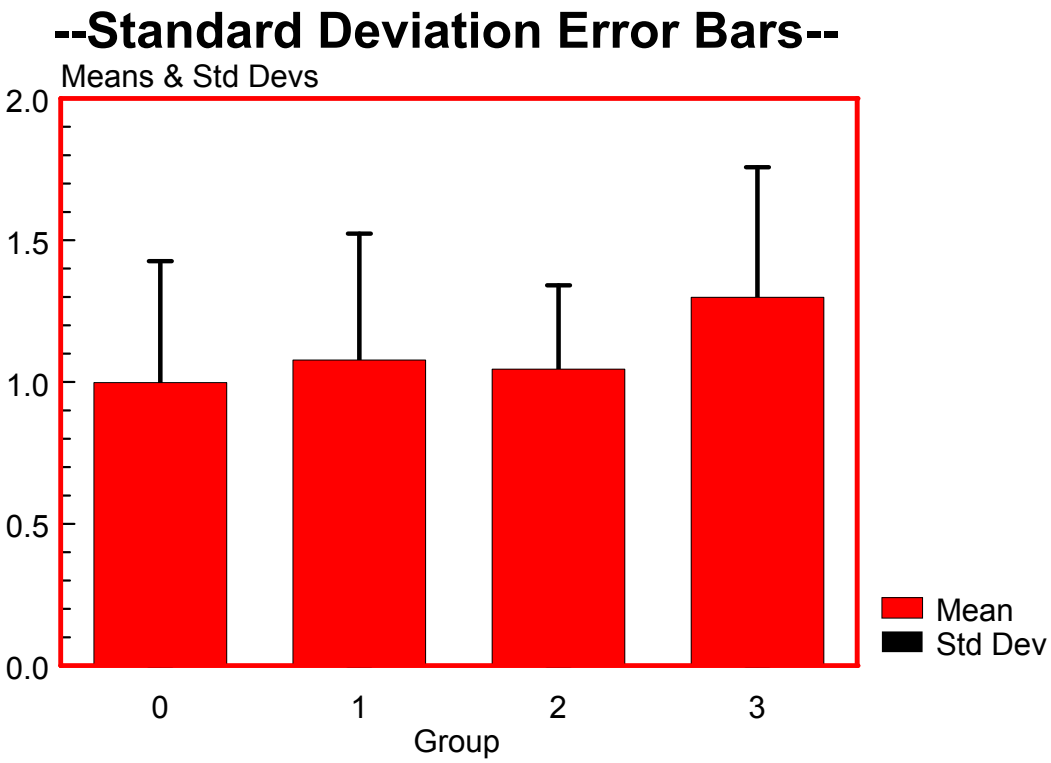
The above graph indicates a correlation of the CITM and the extent of CAD:

The median percentile scores show a progressive increase as the number of vessel involvement increases:

- No CAD (control subjects) Median = 0.93;
- Single coronary vessel involvement Median = 0.88;
- Two coronary vessel involvement Median = 1.08;
- Three coronary vessel involvement Median = 1.19.

The bar graph below, Figure 3.12, depicts the correlation of the mean CIMT of the control group (0 vessel involvement) and that of the groups with one- two- and three coronary vessel involvement in the study group.

FIGURE 3.12 MEANS AND STANDARD DEVIATIONS OF EXTENT OF VESSEL INVOLVEMENT



GROUP	NO CAD	1 VESSEL	2 VESSELS	3 VESSELS
AVE CIMT	1.00	1.08	1.04	1.29

The Correlation Coefficients for the groups above are as follows:

- No CAD (controls): 0.43;
- One-vessel CAD: 0.41;
- Two-vessel CAD: 0.28;
- Three-vessel CAD: 0.35;

Figure 3.12 shows that the average CIMT for the control group (no CAD), is much lower than the average CIMT of the study group, as was stated before. Of note is that average CIMT increases with the number of vessel involvement.

Thus increased CIMT was found to correlate well with the extent of vessel involvement in CAD.

The findings in my study support previous studies where increased CIMT was correlated with evidence of angiographically proven CAD[36] [8]. In the study by Geroulakos et al, 1994, they showed that there was a significant positive linear trend between CIMT and the number of involved vessels ($p<0.0001$, $r=0.44$) They demonstrated a high positive predictive value and specificity for the presence of CAD if a corrected-for-age CIMT >0.85 mm is used as a cut-off point for the prediction of severe CAD. They suggested that CIMT could be useful as a screening tool in a population with a low prevalence of CAD.

In the study by Kablak-Ziembicka et al, they also showed that increased CIMT was positively and linearly related to CIMT – subjects with a greater number of vessel involvement showed greater increases in CIMT. In addition they showed that a CIMT over 1.15mm was predictive of a 94% likelihood of having CAD. Four independent predictors of CAD were identified: age, hyperlipidaemia, smoking and increased CIMT. Hypertension does not seem to be as dominant as in my study.

[36] Geroulakos et al 1994
[8] Kablak-Ziembicka et al 2004

3.10 CONCLUSION

The paucity of research regarding CAD in the Black population of South Africa needs serious redress. Two important publications reviewed the situation in sub-Saharan Africa.

- The focus of Opie and Seedat[7] was on hypertension and its possible causes;
- Steyn et al[6] focused on MI and the risk factors contributing to MI.

These studies bear testimony to the following quote by Bradlow BA, Zion MM and Fleishman SL[42]:

> "*Africa provides a vast natural laboratory for the study of the aetiology and epidemiology of heart disease*".

From these publications, it is clear that hypertension occurs predominantly in Blacks. Together with diabetes, they constitute the major risk factors for MI in Blacks in Sub-Saharan Africa[6.] This is similar to the findings in the United States, where the prevalence of hypertension in Black Americans (32%) compared to Whites (23%) was demonstrated in the National Health and Nutritional Survey (NHANES)[43].

Although exact data concerning the incidence of hypertension in Black South Africans is not known, what has been reported, is that the prevalence of hypertension as well as MI is increasing and that "hypertension behaves in an

[7] Opie and Seedat, 2005
[6] Steyn et al, 2005
[42] Bradlow BA, Zion MM and Fleishman SL, 1964
[43] Burt VL, Cutler JA, Higgins M et al, 1995

explosive manner with deaths often occurring as a result of cerebral haemorrhage, uraemia or congestive heart failure"[1].

The INTERHEART Africa study found that hypertension as a risk factor for MI was most relevant in Black Africans, with the other known risk factors being generally consistent for the three ethnic groups of the study. The most likely reason for the increasing incidence of hypertension amongst Black Africans, has been attributed to the mass migration from rural to peri-urban and urban areas. The consequent acquisition of unhealthy lifestyles, including high-fat, low fibre diets and lack of physical exercise resulting in obesity, together with smoking, has parallels with the progressively developing situation seen over decades in the United States, where with extended exposure to the above risk factors, the CAD rates for African Americans has overtaken that for Whites[43]. Opie and Seedat suggest that obesity is a major factor contributing to hypertension in South African Blacks, as was found for both West African and American blacks[7].

Ward Riley, a leader in the field of CIMT in atherosclerosis, makes two important points in his editorial comment[35]. The value of CIMT as a risk factor for CAD is succinctly captured in the following statement: " Large population based studies in several countries have now convincingly demonstrated that carotid intima-media thickness is a strong predictor of future cardiovascular

[1] Isaacson, 1997
[43] Burt VL, Cutler JA, Higgins M et al, 1995
[7] Opie and Seedat, 2005
[35] Riley, 2002

events in adult men and women… and is nearly as predictive as all of the known risk factors combined."

My research shows support for CIMT as an independent predictor for CAD. Furthermore I have shown that increased CIMT correlates well with the known risk factors, including those constituting the Metabolic Syndrome. Using multiple regression analysis, the effects of the studied risk factors on the CIMT shows that the most significant factors affecting CIMT in my Study group were hypertension, high fasting glucose, age and smoking.

Limitations of my research in terms of generalising the findings to the larger population need to be stated. The limitations are inherent in the study design, which recruited subjects undergoing coronary angiography for a suspected clinical diagnosis of CAD. The study population, a total of 53 subjects, was thus highly selected, without the possibility of case-matching, particularly for the dominant risk factor, hypertension, which was present in every study subject but one. Future researchers will be faced with the challenge of recruiting a larger group of participants to allow for a controlled study within this population with a rising prevalence of CAD. Better definition of the impact of each of the risk factors on CIMT and consequently CAD should be the role of future studies.

Despite these impediments, a number of important perspectives have emerged from my study, which would be of value in planning future research in this important field:

1. The aim of my study was to explore whether ultrasound measurement of the CIMT could be used as a surrogate marker for coronary artery disease. The cardinal finding in this regard is the good correlation of the CIMT with the extent of the coronary vessel involvement in CAD (average CIMT values ranging from 1.0 for the control group with no CAD at angiography, to 1.29 for those with three vessels involved). Ultrasound has thus demonstrated its value as a tool to explore the pathogenesis of CAD, and to monitor its expected growth in prevalence in the South African Black population. CIMT could play a pivotal role in providing solutions, to prevent this population with a low prevalence of CAD, from gradually succumbing to the hazards of upward social and economic mobility, as was found within the Black population of the USA.

2. The principle risk factor, hypertension, has yet again demonstrated its physical effect on the intima-media of arteries as has been seen in other studies[25]. The effect of hypertension on CIMT in my study is evident from the following observations:

    - Four subjects had hypertension as the only risk factor for CAD, and the CIMT values of this group had a median CIMT percentile value (1.22) which was much greater than for subjects with multiple risk factors;

    - In subjects with normal and high HDL-C levels, the CIMT was increased in a higher proportion (81.8%) than for subjects with a low level of HDL-C (68.8%). This finding suggests that hypertension

[25] Tanaka et al, 2001

overrides the expected protective effect of normal to increased HDL-C levels against CAD in Black South Africans, suggested by Opie and Seedat[7];

- Bearing in mind that diabetics were excluded from my study at recruitment, the effect of high fasting blood glucose levels on the CIMT was significant. There was a good correlation of CIMT against fasting blood glucose levels of the whole group in simple linear regression analysis (Correlation Coefficient, 0.35; P=0.03). In addition, 100% of subjects with a high fasting blood glucose had an increased CIMT. Tropeano et al[41] found the same in their study where they looked at blood glucose levels and CIMT in subjects who were hypertensive and had hyperglycaemia. They concluded that hyperglycaemia was a major independent determinant of CIMT in hypertensive, hyperglycaemic subjects "***…offsetting the mechanical role of hypertension***".

  What is interesting in my study is the observation that the group of subjects with dysfunctional glucose metabolism, as indicated by an abnormal glucose tolerance test, have similar increases in CIMT values to the group with normal glucose metabolism (normal fasting glucose levels and normal glucose tolerance tests). An abnormal glucose tolerance test is the earliest manifestation of Type II diabetes, and ***my study did not show that this hyperglycaemic state offsets the effect of hypertension***. This indicates that

[7] Opie et al 2005
[41] Tropeano et al, 2004

hypertension remains the principle determinant of an increased CIMT in this population.

The profound effect of hypertension on the CIMT suggested by my findings supports the notion that every measurement, on every patient (except the single individual who was normotensive), had been markedly affected by hypertension. This would have a masking effect on the impact of the risk factors on the measurements of the intima-media in this study. Further studies are definitely required, which should incorporate large numbers of subjects, matched for all the critical risk factors, to verify this phenomenon.

Further studies are also needed to define the role of hypertension and a raised fasting glucose relative to the other risk factors of the Metabolic Syndrome. The effect of the Metabolic Syndrome on the CIMT is an important finding in my study, since it is similar to the trends in other studies where increased CIMT has been demonstrated in the presence of the Metabolic Syndrome[38] [40]. My results have shown that a higher percentage of subjects with the MS had increased CIMT as compared to the whole study group, 87.5% vs. 76% respectively.

The individual risk factors other than the dominant hypertension and fasting high blood glucose levels of the Metabolic Syndrome, demonstrate effects which require special consideration:

- Obesity does not appear to have the striking effect on the CIMT as found in other populations with an increasing incidence of CAD,

[38] Scuteri et al, 2004
[40] Czernichow S, Bertrais S, Blacher J et al. 2005

particularly in the African-American population of the United States[15]. Furthermore, in the study of Steyn et al[6] abdominal obesity was a significantly stronger risk factor for acute MI in the African group than the overall INTERHEART group (P<0.0001 for tests of heterogeneity of effects). In my study, the percentage of subjects with increased CIMT was similar for obese and non-obese subjects, 79.17% and 78.57% respectively. Once again the effect of hypertension on the CIMT in the non-obese subjects needs to be taken into account.

- The findings of the effects of the lipid components of the Metabolic Syndrome need careful consideration. Raised triglyceride levels were not strongly associated with increased CIMT, those with normal levels had similar associations with the CIMT (79% vs. 73.7%). In the case of HDL-cholesterol, as mentioned above, normal to raised levels did not protect against the development of dangerous degrees of intima-media thickness. In fact, the trends of the CIMT values were the reverse of the expected, with increasing HDL-C levels being associated with increasing rather than decreasing CIMT values in the linear regression module of intima-media thickness against HDL-C levels. Whilst once again the masking effect of hypertension needs to be considered, it begs the question whether the differences point to a unique situation in the Black South African population:
    - Are we witnessing a unique physiological response to dysfunctional internal lipid environments?

[15] Domanski et al. 2004
[6] Steyn et al, 2005

- Does this indicate that we are dealing with a genetically unique population?

OR

- Are we merely witnessing a society in social and economic transition as proposed for the Black population in the United States, where hypertension is considered to be due to changes in diets and lifestyles associated with a population shift from rural to urban?

These issues open up important research questions:

1. What should be the structure of research projects to establish the effects of rapid urbanisation, a growing economy, the drive for improved education and a more affluent lifestyle that is considered “better” but is clearly having a disastrous effect on the heath of the population?
2. Are there unique therapeutic interventions, individually and in combination that needs to be provided for a possibly unique population?

Research outcomes will provide the scientific support for Public Health and education programmes for the population:

- The irony of the negative consequences of development and upward social mobility, imperative for social transformation, needs to be brought to the attention of the society and policy decision-makers. In order to promote healthy lifestyles, the dangers of smoking and

obesity as a result of improper diet and lack of exercise in particular, need to be the focus of Public Health outreach programmes.

These are huge and important issues, which will require innovative approaches in order to provide scientifically sound solutions. Ultrasound measurement of the CIMT could be pivotal in providing the scientific basis for these solutions in that:

- It provides, with the correct training and quality control protocols, a precise, reproducible and direct measurement of the damage caused to arteries. This is important for scientifically defining the ‘Response to Injury ‘in the Black population of South Africa and the role of risk factors, independently and in combination, such as those of the Metabolic Syndrome.

Such data would provide direction for future fundamental molecular biology research into the pathogenesis of atherosclerosis in this population. This is of importance for the health of the Black population of South Africa in particular:

- With the rapidly growing pharmaceutical armamentarium against atherosclerosis, each potential agent needs careful documentation in terms of its efficacy, specifically in this population, where the economy may not allow everyone equal access to varieties of pharmaceuticals. Strategic combinations of agents may need to be explored for maximal additive effects.

For all the reasons stated above, CIMT measurement, properly done, is crucial:

- It is non-invasive and thus acceptable to individuals;
- It is an investigation which can be accurately done in a relatively short space of time, which would be appropriate for large studies;
- In view of the above it could be used in studies across all ages, including young children. As the vascular consequences of atherosclerosis starts in early childhood, the changes need to be studied across the age spectrum and repeated over time periods in order to adequately explore the possibility of a unique response to internal haemodynamic, rheological and biochemical assaults in this population. Accurate ultrasound measurements of the CIMT would be absolutely essential for such studies;
- It is very cost-effective relative to the scientific information it provides. In this regard, funds spent on procuring reliable and accurate equipment would be well spent;
- In a similar way, making available resources for the provision of high quality training of sonographers in the techniques and full certification of competence would be a sound investment. This will increase the accuracy of the CIMT measurements;
- Due to the importance of reproducibility in the technique, participation in efficient and continuous quality control systems

> is essential. The value provided will again be well worth the cost.

Ward Riley's second point in the editorial mentioned above[35] is tinged with caution. He refers to authors who found that measurement of the CIMT of the common carotid artery *only* is as predictive as all nine other risk factors. To quote del Sol et al[34], to whom he refers, "…a single carotid IMT measurement is of the same importance as commonly used risk factors in the prediction of coronary heart disease and cerebrovascular disease"

Clearly, the use of CIMT as the sole modality to identify people at risk for coronary and cerebrovascular events, without knowing their status in terms of the other risk factors, is a revolutionary notion, which perhaps is not fully appreciated by the medical community.

However, he makes a firm statement that the use of ***multiple*** sites to measure IMT, given the variation in the degree of arterial involvement in atherosclerosis, would yield more accurate information and should be the chosen protocol.

In conclusion, the use of B-mode ultrasound to measure CIMT should be strictly limited to trained and certified persons, in order to maintain its scientific validity as a surrogate marker for coronary artery disease, as demonstrated in this study.

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[35] Riley, 2002
[34] del Sol AI et al, 2001.

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ADDENDUM 1 ETHICAL CLEARANCE

Prof. F. J. Raal
Department of Medicine
JOHANNESBURG HOSPITAL

Dear Dr Raal

RE: PROTOCOL NO. NIL
PROTOCOL ENTITLED "Coronary Artery Disease in the emerging black population of South Africa – is there Ethnic Immunity?"

PRC REFERENCE NUMBER: 010102

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Please be advised that your trial application was:

APPROVED

The Expert Reviewers were: Prof B. J. Joffe
Dr A Woodiwiss

Also reviewed by: Dr M Joffe: Chairperson Protocol Review Committee
Dr J Moorman: Gauteng Department of Health
Dr S Kahn: Gauteng Department of Health
Dr W Sive: Superintendent – Johannesburg Hospital

Yours sincerely

Dr M Joffe PhD (Biochemistry)
Chairperson: Protocol Review Committee

Date: 19/02/2001

ADDENDUM 2 LINEAR REGRESSION: CIMT WITH AGE

Linear Y = A + B*X

Y = .4974 + .0114 * X

Parameter	Coefficient	Std Error	t-Value	Prob
Constant (A)	.497375	.452573	1.098995	.2791
AGE (B)	.011402	.008082	1.41079	.1669

Unadjusted r^2	= .05239	Regression ANOVA F	= 1.990327
Adjusted r^2	= .026068	2-Tailed Prob p	= .1669
Correlation Coef	= .228889	Degrees of Freedom	= 1 and 36
Std Err of Estimate	= .399485	Durbin-Watson Stat	= .145421
Variance of Estimate	= .159588	Dependent Var. Mean	= 1.129281
Mean Absolute Error	= .309714	Coeff. of Variation	= .353751

with X = AGE and Y = CIMT

ADDENDUM 3 LINEAR REGRESSION ANALYSIS: CIMT WITH FASTING BLOOD GLUCOSE LEVELS

Linear Y = A + B*X

Y = .2556 + .1667 * X

Parameter	Coefficient	Std Error	t-Value	Prob
Constant (A)	.255572	.39464	.647608	.5213
GLUCOSE (B)	.166655	.07433	2.242104	.0312

Unadjusted r^2	= .12253	Regression ANOVA F	= 5.027033
Adjusted r^2	= .098156	2-Tailed Prob p	= .0312
Correlation Coef	= .350043	Degrees of Freedom	= 1 and 36
Std Err of Estimate	= .384416	Durbin-Watson Stat	= .227331
Variance of Estimate	= .147776	Dependent Var. Mean	= 1.129281
Mean Absolute Error	= .292544	Coeff. of Variation	= .340408

with X = GLUCOSE and Y = CIMT