Ischemic profile and cardiovascular function in African men: the SABPA study

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If any of you lack wisdom, let him ask of God, that gives to all men liberally, and it shall be given him.

James 1:5

OPSOMMING

AFRIKAANSE TITEL: DIE ISGEMIESE PROFIEL EN KARDIOVASKULÊRE FUNKSIE IN AFRIKAAN-MANS: DIE SABPA STUDIE

Motivering: Isgemiese hartsiektes is die agste veroorsakende faktor van sterftes in ‘n Afrika- populasie. Stille isgemie kan gedefinieer word as ‘n isgemiese episode sonder meegaande pyn. Die kliniese belangrikheid van stille isgemie is besig om te groei en kan gesien word as ‘n risikofaktor in die ontwikkeling van koronêre siektes. Hipertensie en verwante risikofaktore, hipercholesterolemie en diabetes mellitus word met stille miokardiale isgemie geassosieer. Ander faktore soos ‘n hoër polsdruk, dubbelproduk, harttempo en ‘n verhoogde karotis intima media dikte (merker van subkliniese aterosklerose) word ook met stille isgemie geassosieer.

Verstedeliking is besig om toe te neem in Suid-Afrika en dié nuwe leefstyl word geassosieer met verskeie risikofaktore, insluitend: swak diëte, laer aktiwiteitsvlakke, hipertensie en hoër rook- en alkoholmisbruik.

Die voorkomssyfer van beroertes is hoog in Afrikane en kan meestal toegeskryf word aan ‘n hoër voorkoms van hipertensie, diabetes en obesiteit.

Doelstelling: Die doelstelling van die studie is om die assosiasies tussen stille isgemie en verskeie kardiovaskulêre funksies in Afrikaan-mans te ondersoek. Die fokus val op hipertensie en geassosieerde risikofaktore, hoër totale cholesterol, polsdruk, harttempo en sub-kliniese aterosklerose.

Metodologie: Hierdie populasiestudie is in die Noordwes provinsie uitgevoer op Afrikaan manlike onderwysers, verstedelik en tussen die ouderdomme van 20-60 jaar. Ons SABPA (***S****ympathetic activity and* ***A****mbulatory* ***B****lood* ***P****ressure in* ***A****fricans*) sub-studie het ‘n totaal van 80 Afrikaan manlike vrywilligers gehad. Die *Cardiotens* apparaat, wat verantwoordelik is vir die neem van ambulatoriese bloeddruk en elektrokardiogram lesings, is die eerste oggend op die deelnemers geplaas. Die deelnemers het hierna met hul normale werksdag aangegaan tot 1700. Na oornag verblyf by die Metaboliese eenheid van die Noord-Wes Universiteit Potchefstroom kampus, is die apparaat ongeveer 0600 verwyder.

Gedurende statistiese analises is die Afrikaan-mans in twee groepe verdeel, naamlik, dié met stille isgemie (SI) en dié sonder stille isgemie (nSI) soos bepaal deur die ambulatoriese elektrokardiogram. Statistiese analises is uitgevoer met behulp van die sagteware program *Statistica* weergawe 10.

Resultate: In vergelyking met die nSI mans, het die SI mans die volgende aangedui: bo normale hoë sensitiewe C-reaktiewe proteïen en glukose, verhoogde ambulatoriese bloeddruk, harttempo, polsdruk, rustende ST-segment depressie en karotis intima-media dikte. Regressie analises het aangedui dat ambulatoriese stille isgemie met subkliniese aterosklerose geassosieer word en dat dit die risiko vir beroerte moontlik verhoog.

Gevolgtrekking: Ambulatoriese stille isgemie is ook met subkliniese aterosklerose geassosieer. Dis nie duidelik of hipertensie die stukrag in hierdie proses is nie.

Sleutelwoorde: stille isgemie, ambulatoriese bloeddruk, polsdruk, subkliniese aterosklerose, hoë-sensitiewe C-reaktiewe proteien, Afrikaan.

SUMMARY

ENGLISH TITLE: ISCHEMIC PROFILE AND CARDIOVASCULAR FUNCTION IN AFRICAN MEN: THE SABPA STUDY

Motivation: Ischemic heart disease is the eighth leading cause of death in an African population. Silent ischemia can be defined as an ischemic episode without associated pain. The clinical significance of silent ischemia is growing and can now be considered as a risk factor in the development of coronary disease. Hypertension and associated risk factors, hypercholesterolemia and diabetes are associated with silent ischemia. Other factors such as higher pulse pressure, double product, heart rate and higher carotid intima-media thickness are also associated with silent ischemia.

Urbanisation is rising in South-Africa. This new lifestyle is associated with several risk factors including: poor diets, lower physical activity levels, hypertension and increased smoking and alcohol abuse.

The prevalence of stroke is high among Africans, which can be due to a higher prevalence of hypertension, diabetes and obesity.

Purpose: The purpose of this study was to determine the associations between silent ischemia and cardiovascular function in African men. The focus fell on hypertension and associated risk factors, higher total cholesterol levels, and increased pulse pressure, heart rate and sub-clinical atherosclerosis.

Methodology: This study constituted a population study in the North-West province carried out on urbanized African male teachers aged between 20-60 years. The SABPA (***S****ympathetic activity and* ***A****mbulatory* ***B****lood* ***P****ressure in* ***A****fricans*) sub-study consisted of a total of 80 African male volunteers. The Cardiotens apparatus was placed on each participant on the first morning. This apparatus took ambulatory blood pressure measurements as well as Electrocardiogram measurements. Hereafter, participants continued with their normal work day until 1700. After an overnight stay at the Metabolic unit of the North-West University Potchefstroom campus, the apparatus was removed at 0600.

During statistical analyses, the African males were divided into groups of participants with silent ischemia (SI) and those without silent ischemia (nSI), as determined by the ambulatory electrocardiogram. Statistical analyses were performed by means of the *Statistica* version 10 software program.

Results: In comparison with the nSI men, the SI showed the following: above normal high sensitivity C-reactive protein and glucose, higher ambulatory blood pressure, heart rate, pulse pressure, resting ST-segment depression and carotid intima-media thickness. Multiple regression analyses indicated that ambulatory silent ischemia is associated with sub-clinical atherosclerosis, possibly increasing their stroke risk.

Conclusion: . Ambulatory silent ischemia was associated with sub-clinical atherosclerosis. It is however not clear whether hypertension is the driving force in this process.

Keywords: silent ischemia, ambulatory blood pressure, pulse pressure, subclinical atherosclerosis, high sensitive C-reactive protein, African.

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LIST OF ABBREVIATIONS

English:

ABPM:	Ambulatory Blood Pressure Measurement
beats/min:	beats per minute
BMI:	Body Mass Index
BP:	Blood Pressure
CAD:	Coronary Artery Disease
CIMT:	Carotid Intima-media Thickness
DBP:	Diastolic Blood Pressure
DP:	Double Product
ECG:	Electrocardiogram
ESH:	European Society of Hypertension
HART:	Hypertension in Africa Research Team
HR:	Heart rate
hs-CRP:	High Sensitivity C-reactive Protein
IDF:	International Diabetes Federation
Kcal/day:	Kilocalories per day
kg/m^2:	Kilogram per square meter
mg//:	Milligram per litre
mm:	Millimetre
mmHg:	Millimetre mercury
mmol//:	Millimol per litre
N:	Total participants
ng/ml:	Nanogram per millilitre
nSI:	No Silent Ischemia

PP:	Pulse Pressure
SABPA:	Sympathetic activity and Ambulatory Blood Pressure in Africans
SBP:	Systolic Blood Pressure
SI:	Silent Ischemia
U/*l*:	Units per litre
γ-GT:	Gamma Glutamyl Transferase

CHAPTER 1

PREFACE AND OUTLINE OF THE STUDY

1. PREFACE

For the purpose of this study the author decided to use the article format. Hence, Chapter 3 is in the form of a manuscript, which was submitted to the *Journal of Clinical and Experimental Hypertension* for peer review. A more elaborate survey of the literature is furnished in Chapter 2 together with relevant references at the end of Chapter 2 and Chapter 4, according to the prescribed format for referencing of the above mentioned journal selected for publication.

2. OUTLINE OF THE STUDY

The outline of the study is as follows:

Chapter 1: Preface and outline of the study.

Chapter 2: Introduction and literature overview.

Chapter 3: Manuscript: – Silent ischemia is associated with sub-clinical atherosclerosis in African men: the SABPA study.

Chapter 4: Summary of main findings.

3. AUTHORS' CONTRIBUTIONS

The contribution of each researcher involved in this study is stated in the following table:

Table 1.1 Authors' contribution list

Ms. Madelein E. Griffiths (B.Sc. Hons)	Responsible for literature research, statistical analyses, design and planning of manuscript, interpretation of results and writing of the manuscript.
Prof. Leoné Malan (Ph.D) (Physiologist)	Supervisor. Collection of data, initial planning and design of manuscript, supervision of the writing of the manuscript.
Prof. Johannes M. van Rooyen (D.Sc) (Physiologist)	Co-supervisor. Collection of data and supervision of the writing of the manuscript.

The following is a statement from the co-authors confirming their individual roles in this study, giving their permission for the manuscript to form part of this dissertation:

I declare that I have approved the above mentioned manuscript, that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of the M.Sc. dissertation of Madelein E. Griffiths.

_____ _____

Prof. L. Malan Prof. JM. van Rooyen

CHAPTER 2

INTRODUCTION AND LITERATURE OVERVIEW

1. INTRODUCTION

Ischemic heart disease ranks eighth among the leading causes of deaths in the African population, even though this has been considered rare in sub-Saharan Africa (1,2). The clinical significance of silent ischemia (SI) is rising and is nearly on the same level as that of symptomatic (painful) ischemia (3). SI can be considered as an independent risk factor for coronary artery disease (CAD) (4) and has been associated with other cardiovascular risk factors, such as, hypertension (5) and associated risk factors (6-9); hypercholesterolemia (10); diabetes mellitus (11); impaired glucose tolerance (12); higher pulse pressure (13); double product (14); heart rate (13) and an increased carotid intima-media thickness (CIMT) (15).

Urbanisation in Africa is increasing. This phenomenon is associated with numerous risks resulting in conditions such as obesity, malnutrition, dyslipidaemia and alcoholism (1,16). The prevalence of hypertension among Africans exceeds that of Caucasians and is associated with urbanisation, lower physical activity levels, higher smoking levels and higher levels of alcohol abuse (2,17).As urbanisation in the African population is rising, it raises the concern of a rising prevalence of silent ischemia in this population, its association with risk factors, and whether it is linked to sub-clinical atherosclerosis.

2. SILENT ISCHEMIA – A RAISED CONCERN

ST-segment and T-wave abnormalities indicate ischemia (18). SI can be defined as ischemic episodes without any associated symptoms (18,19), but is associated with transient ST-abnormalities during Holter monitoring or stress testing (5). These ‘silent’ ischemic events occur in 75–90% of the ST-depression episodes during Holter monitoring, according to Uen et al. (5); these events can also occur for a few minutes to over an hour (5,19).

During ambulatory ECG measurement, the criteria of the 1-1-1 rule (see Figure 1) is used to classify a silent ischemic event:

- Descending or horisontal ST-segment depression over 1 mm.
- The ST-segment depression lasted at least 1 minute.
- The interval between two successive ST-segment depression episodes has to be at least 1 minute and can thus be counted as separate episodes (5).

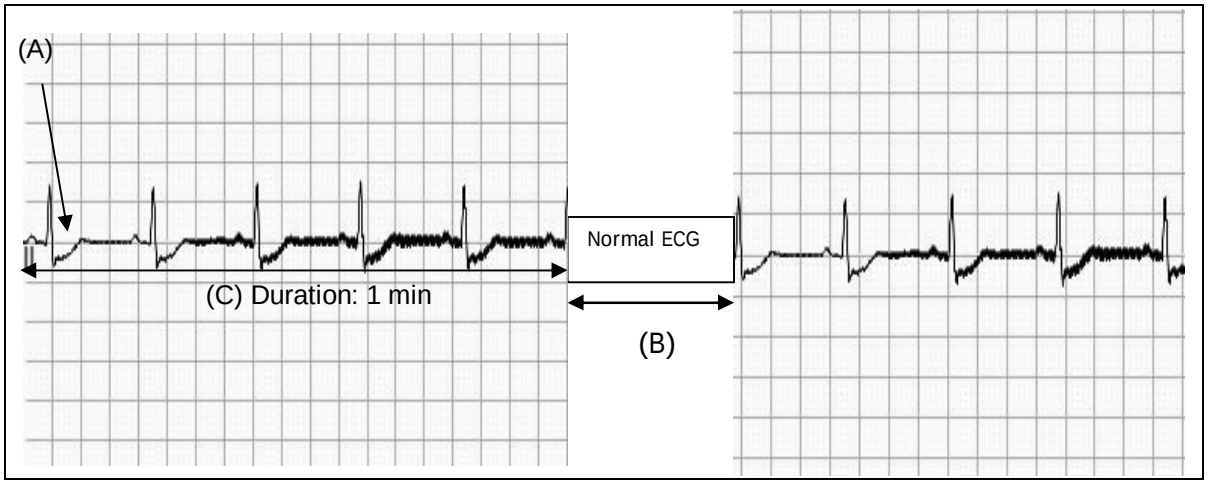

Figure 1: The 1-1-1 rule: (A) – ST-segment depression greater than 1 mm. (B) – There must be at least 1 minute of normal ECG readings between consecutive ST-segment depression episodes to be counted as separate episodes. (C) – The ST-segment depression episode must last at least 1 minute to be counted as an ischemic event (5).

Even though a few authors point out that ST-segment changes occur in several other occasions (20), the above mentioned-criteria (1-1-1 rule) are more than 95% specific for SI (21).

The understanding of the importance of the clinical significance of SI is rising and is currently on the same level as that of symptomatic (painful) ischemia (3). SI is still seen as a predisposing aspect for unexpected cardiac death due to ventricular arrhythmia (5). It is, however, not limited to participants with significant cardiovascular risk profiles or CAD and may also affect up to 10 % of the participants with asymptomatic CAD (22). SI also occurs in a broad spectrum of subjects with coronary disease, while in asymptomatic men it

occurs in 2 – 4% of the adult population (23). SI can be induced by mental or physical stress and can also occur without any trigger (3). Mansi et al. (24) further reported ethnic differences in the prevalence of silent ischemia among blacks and Caucasians.

Cohn et al. (25) classified SI into 3 categories:

Type 1: Participants with asymptomatic CAD, no history of myocardial infarction or angina pectoris, exhibit silent ischemic events detected by exercise testing.

Type 2: Participants with a history of single myocardial infarction, but have been asymptomatic since then. However, they indicated silent ischemic events detected by exercise testing.

Type 3: Participants with frequent angina events, who also experience silent ischemic events detected by exercise testing (25).

Whether these criteria hold true for ambulatory blood pressure measurement in everyday life in Africans is not clear.

The high prevalence of hypertension (26,27) as well as silent ischemia in Africans as cardiovascular risk markers and its relation to vascular dysfunction, needs to be addressed.

2.1. SILENT ISCHEMIA AND CORONARY ARTERY DISEASE (CAD)

The burden of cardiovascular disease among urban black Africans is increasing (28,29) and the incidence of SI is also high in stable CAD (30). In hypertensive participants, SI is an independent predictor of cardiovascular events (4). Kurl et

al. (31) found that exercise induced SI is a strong indicator of increased risk of stroke and cardiovascular disease, especially in men. SI in participants with known cases of CAD is 50 – 80% (13). More severe cases of CAD can also constitute as a risk factor for the occurrence of SI (10) — subjects with common risk factors for CAD have been noted to experience a greater incidence of SI (32). These risk factors include: hypercholesterolemia, hypertension, unstable angina, diabetes, age, smoking and family history of premature CAD (32). SI is common in subjects with stable symptoms of CAD, as detected by ambulatory measurement (33). It also increases the prevalence of new coronary events in older men with CAD (34).

Urbanisation appears to be a major contributing factor for the increase in the prevalence of myocardial infarction in Africans (9) and African Americans (35) and the subsequent lifestyle (lower physical activity, smoking, a high fat and low fibre diet) contributes to the development of atherosclerosis (9). The mortality rate of stroke in Africans is higher than their Caucasian counterparts due to a higher prevalence of hypertension, obesity and diabetes mellitus (36).

2.2. SILENT ISCHEMIA, HYPERTENSION AND CARDIOVASCULAR RISK FACTORS

2.2.1. Hypertension, ethnicity and lifestyle factors

Among Africans, hypertension is the most common cardiovascular disease risk factor (37). CAD is a key complication of hypertension and can manifest in the form of SI (38). Hypertensive subjects with SI, has a higher mean ambulatory

SBP than hypertensive subjects without SI (5,39). Boon et al. (40) contradicted above mentioned findings and found a lower prevalence of SI in hypertensive patients. SI is frequent in hypertensive patients with or without atherosclerotic disease (15) and is also more prominent in older hypertensive participants (41). The occurrence of SI is also higher in hypertensive men (4), although this was contradicted by Stramba-Badiale et al. (42), who demonstrated that SI is more common in women. SI, however, has also been related to inadequate blood pressure control (4).

A rise in blood pressure precedes and accompanies a silent ischemic event (5,30,38,43-45). As these rises in blood pressure are accompanied by a rise in heart rate, it indicates that the factors that establish oxygen consumption partake with the genesis of silent ischemia (30).

Hypertension appears to be more common among urban Africans (16,46). This was also true in African Americans who revealed a higher prevalence of hypertension than their Caucasian counterparts (47). He et al. (48) published a report that the incidence of hypertension in African Americans is similar to that of Caucasians. Obesity, dietary excess, alcohol consumption and lack of exercise, owing to urbanisation, contribute to the higher prevalence of hypertension in Africans (49-51). Obesity also constitutes a strong risk factor for acute myocardial infarction in Africans (52).

Alcohol intake is significantly associated with the risk of hypertension and light-to-moderate consumption increased the risk in men (53). This seems to be also

true for African men, who demonstrated higher alcohol abuse levels than Caucasians (17).A study by Fuchs et al. (6) found that alcohol consumption in low to moderate amounts is associated with an elevated risk of hypertension in black men. Smoking is a possible risk factor for hypertension (8,53) and in an urban black African population, higher smoking levels were observed (17), especially among men (2). Conversely, former smoking status was also associated with poor hypertension control (55). Most importantly, cigarette smoking is associated with ischemic heart disease (56).

However, the question arises as to whether these above-mentioned risk factors related to hypertension are also related to SI in African men. Further investigation into this is of importance.

2.2.2. Silent ischemia and cholesterol

Increased serum cholesterol concentration is one of the most prominent etiological factors for CAD (57). Higher total cholesterol levels have been associated with silent ischemia (11), while in another study, it was concluded that hypercholesterolemia is a major risk factor for the occurrence of silent ischemia in Mexicans (10). However, the prevalence of moderate and high-risk hypercholesterolemia was high in rural and urban younger aged Africans (58). As the prevalence of increased total cholesterol is rising (58), which may be due to urbanisation (59), the question arises as to whether SI is associated with higher total cholesterol levels in African men with SI in comparison to African men without SI.

2.2.3. Silent ischemia, heart rate, double product and pulse pressure

(a) Silent ischemia and heart rate

Silent ischemic events are accompanied and preceded by an increase in heart rate (5,38,44,45,60), which is an important factor in the determination of the onset of a SI event (43). While the increase in heart rate may be due to day-to-day variability of emotional and physical activities (43), Uen et al. (13) found that subjects with silent ischemia have a higher ambulatory heart rate mean value than subjects without silent ischemia. However, Solimene et al. (61) found that there is no relation between heart rate and silent ischemia.

(b) Silent ischemia and double product

A higher double product (heart rate (HR) x systolic blood pressure (SBP)) was linked to ischemic events in hypertensive subjects, according to Uen et al. (13). While this double product correlates with myocardial oxygen consumption, there is a significant increase in double product during a silent ischemic event (13,14). It also strongly correlates with the triggering of silent ischemic events (15). Double product, however, defines cardiac load better than HR or SBP alone (62).

(c) Silent ischemia and pulse pressure

Ambulatory pulse pressure, which is the difference between systolic and diastolic blood pressure, in hypertensive subjects, is another effective predictor of cardiovascular risk (13,63-65). A raised pulse pressure correlates with increased oxygen consumption and a raised left-ventricular afterload (66).

Hypertensive subjects with ischemic heart disease and silent ischemic events exhibit higher mean pulse pressure values than subjects without events (13). A pulse pressure of ≥60 is linked to a higher risk of the prevalence of SI (13). As far as the author could determine, no literature exists with regards to pulse pressure and the link with SI in Africans.

2.3. SILENT ISCHEMIA AND GLUCOSE

Cardiovascular disease is the leading cause of death among those with diabetes (67). Diabetes and associated cardiovascular complications are increasing and therefore gaining more interest in sub-Saharan Africans (68). Among the participants with diabetes, the prevalence of SI is extremely high (11,69). Huerta et al. (11) also concluded that other risk factors for CAD are also linked to SI. Falcone et al. (70), however, found that the incidence of SI is similar in diabetic and nondiabetic CAD participants, while a higher prevalence of angina pectoris was evident in diabetic CAD subjects. SI is a strong predictor of cardiac events in asymptomatic diabetics (71). Silent ischemic events are more often found in subjects with impaired glucose tolerance in comparison to those with normal glucose tolerance (12,72). SI was however not associated with fasting glucose (70,73). As diabetes is rising in sub-Saharan Africa, and the incidence of SI is high among diabetics, we therefore excluded clinically diagnosed diabetic patients in this investigation.

2.4. SILENT ISCHEMIA PROPOSED MECHANISM

Tabibiazar et al. (67) suspected that in diabetic participants, partial or complete autonomic denervation may be a contributing factor to SI. As SI occurs mostly in the morning and as the myocardial oxygen demand also increases during the morning hours (caused by an elevated heart rate, blood pressure, catecholamine concentrations, coronary vasomotor tone, platelet aggregation response and a dampened intrinsic fibrinolytic process), it is proposed that this mechanism also pertains to SI (70,74,75).

Vascular remodelling induced by hypertension is another mechanism proposed as being a cause of the incidence of SI (15). As pulse pressure is positively related to an increased IMT, and is also expressed as a determinant of myocardial oxygen demand, this indicates, to a certain extent, that vascular supply is a major determinant of the occurrence of SI (15).

Due to the absence of pain, it was suggested that subjects with SI have a defective warning system (3). It was also suggested that there is a decreased sensitivity to pain and this alteration or desensitization of the central nervous system could be the cause of SI (3).

Several researchers suggested that a possible mechanism for silent ischemic events constitutes an increase in myocardial oxygen demand due to reduced supply, which will increase heart rate and blood pressure preceding silent ischemic events (38,76,77). The burden of cardiovascular disease in urban

Africans is increasing (50,58,59). Recently, van Lill et al. (27) demonstrated the altered baroreceptor sensitivity in Africans during rest and exposure to stress. Furthermore, findings by Opie et al. (51) confirmed the possible role of higher sympathetic nervous system activity in urban Africans pertaining to hypertension. Therefore, it is recommended that the possible role of higher sympathetic activity be explored (46).

Silent ischemia and its relation to subclinical atherosclerosis

The burden of subclinical vascular disease among Africans is higher than for Caucasians and can be mostly explained by poor health behaviours, such as lower physical activity levels, alcohol abuse and higher smoking rates (17). Atherosclerosis as determined by carotid intima-media thickness is also linked to the prevalence of silent ischemia (15,78). Subjects with ambulatory silent ischemia are more prone to suffer multi-vessel coronary disease than their counterparts without ambulatory silent ischemia (3). Men are more prone to atherosclerosis than women (79-82) and the effect is higher in African Americans (79).

Carotid intima-media thickness is a reliable end-organ surrogate marker for atherosclerosis as well as vascular disease risk (79,83-86). Age, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol and an elevated BMI are long term predictors of CIMT (80-82,87,88). The prevalence and the severity of the stiffening of arteries increases with advancing age (80,82,89). Total cholesterol as well as cigarette smoking and the ratio of HDL to total

cholesterol are independently associated with carotid atherosclerosis (80). Another predictor of CIMT is high sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, which was associated with silent ischemia in diabetic Chinese subjects (7). Additionally, hs-CRP is also associated with sub-clinical atherosclerosis and the risk of coronary events (90,91). It appears that that SI could be associated with inflammation and endothelial dysfunction (46), while the latter is also an independent predictor of silent ischemia (92).

Therefore, the researchers took the opportunity to explore the ambulatory blood pressure, ECG and cardiovascular risk markers in an African cohort.

3. QUESTION ARISING FROM THE LITERATURE

The question arising from the literature was to determine the relationship between silent ischemia and several cardiovascular markers in African men. These included hypertension and its associated risk factors, total cholesterol levels, glucose, hs-CRP, pulse pressure, double product, heart rate and sub-clinical atherosclerosis.

4. HYPOTHESES

1. IMT and several conventional cardiovascular risk factors i.e. blood pressure, pulse pressure, heart rate, glucose, total cholesterol and hs-CRP are higher in African men with SI events compared with African men without events.
2. Silent ischemia in African men is associated with subclinical vascular disease, independent of conventional cardiovascular risk factors.

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CHAPTER 3

MANUSCRIPT: SILENT ISCHEMIA IS ASSOCIATED WITH SUB-CLINICAL ATHEROSCLEROSIS IN AFRICAN MEN: THE SABPA STUDY

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TITLE: Silent ischemia is associated with sub-clinical atherosclerosis in African men: the SABPA study

RUNNING HEAD: Silent ischemia, ethnicity, sub-clinical atherosclerosis

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DECISION LETTER FROM THE JOURNAL OF CLINICAL AND EXPERIMENTAL HYPERTENSION

28-Oct-2011

Dear Dr Malan:

Ref: Silent ischemia is associated with sub-clinical atherosclerosis in African males: The SABPA study.

Our referees have now considered your paper and have recommended publication in Clinical and Experimental Hypertension. We are pleased to accept your paper in its current form which will now be forwarded to the publisher for copy editing and typesetting. The reviewer comments are included at the bottom of this letter, along with those of the editor who coordinated the review of your paper.

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Thank you for your contribution to Clinical and Experimental Hypertension and we look forward to receiving further submissions from you.

Sincerely,

Mustafa F. Lokhandwala, Ph.D.

Editor in Chief, Clinical and Experimental Hypertension

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ABSTRACT

Silent myocardial ischemia is a predictor of sub-clinical atherosclerosis driven by increased cardiovascular risk markers, although still unknown in Africans. Our aim was to assess if silent ischemia are associated with cardiovascular risk markers. We stratified African men into a) 24h silent ischemia (SI, n = 38) and b) without (nSI, n = 40) groups. Ambulatory blood pressure (ABPM), silent ischemia, 12-lead resting ECG, ultrasound carotid intima media thickness (CIMT) measurements and fasting blood samples were obtained. SI men showed significant higher levels of BP, HR, pulse pressure and CIMT ($p \leq 0.05$). Hypertension prevalence was 89% in the African SI men opposed to 64% in the nSI men ($p=0.46$). Regression analyses revealed that CIMT in SI men explained 34% of the variance in silent ischemia events, whilst in all African men it explained 29%. In conclusion, silent ischemia was associated with sub-clinical atherosclerosis in African men. This could imply that silent ischemia is not necessarily driven by hypertension in African men, but through other possible mechanisms such as increased sympathetic nervous system activity.

Keywords: silent ischemia, ambulatory blood pressure, pulse pressure, sub-clinical atherosclerosis, Africans.

1. INTRODUCTION

ST-segment depression and T-wave abnormalities are indicators of myocardial ischemia (1,2), whereas silent myocardial ischemia is an objective documentation of myocardial ischemia in the absence of associated chest pain (3). Between 75-90% of all ST-segment episodes, as detected by Holter electrocardiogram (ECG), are not associated with chest pain and are classified as ‘silent’ (2).

Ambulatory silent ischemia has been linked to increased ambulatory blood pressure (BP), heart rate (HR) and pulse pressure (PP) in hypertensive Caucasians (4). Asmar et al. (2003) confirmed a higher prevalence of silent ischemia episodes in Caucasians with an increased BP (5).

Hypertension prevalence is escalating in Africans, particularly in males (6), but whether it is associated with silent ischemia, is unknown. Other studies have demonstrated an increased prevalence of ST-segment depression episodes in men from six different ethnic groups (7-9). These findings are debatable, as evidently confounding factors such as socio-economic, environmental, nutritional, and occupational confounders, were not controlled for. It has been well described that these confounding factors affect blood pressure and the electrocardiogram independently (7-9).

Anand et al. (10) suggested that a higher prevalence of silent ischemia was detected in patients with moderate coronary atherosclerosis. Whether silent

myocardial ischemia is associated with sub-clinical atherosclerosis, apparently driven by increased cardiovascular risk markers, is still unknown among Africans; this motivated our present study. Our aim was therefore to assess whether silent ischemia is associated with cardiovascular variables and sub-clinical atherosclerosis in African men.

2. METHOD

2.1. Study design

This sub-study forms part of the SABPA prospective cohort study (Sympathetic activity and Ambulatory Blood Pressure in Africans) conducted in 2008. The methodology is published elsewhere (11). We included a subsample of 101 African urban male teachers aged 25-60 years currently employed in the Dr Kenneth Kaunda Education district in the North West Province. This selection was performed in order to obtain a homogenous sample from a similar socio-economic class. The African males were stratified into a) a group with ambulatory silent ischemic events (N=46) (hereafter referred to as “SI”) and b) a group without ambulatory silent ischemic events (N=55) (hereafter referred to as “nSI”).

Participants with an ear temperature above 37.5°C, as well as those with psychotropic substance dependence or abuse, participants who were blood donors, or who had been vaccinated 3 months prior to this study, diabetic medication users (N=6), and those with renal impairment (N=1), HIV positive status (N=13) or insufficient data (N=1) were excluded. The final sample size for our sub-study constituted 80 males.

This study was approved by the Ethics Committee of the North-West University, Potchefstroom. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki for investigation of human participants (12). Each participant was fully informed about the objectives and procedures of the study

prior to recruitment and signed an informed consent form prior to the onset of the study. Participants received feedback regarding the results and were advised to seek medical advice if needed. Meals and overnight accommodation were provided.

2.2. Procedures

Each morning during the working week between 0700 – 0800, an ambulatory and 2-lead electrocardiogram apparatus, as well as an Actical® accelerometer were fitted to each of four teachers. At 1630, the participants were transported to the Metabolic Unit Research Facility of the North-West University, Potchefstroom campus for an overnight stay. This facility consists of 10 bedrooms, one kitchen, two bathrooms, a dining room and a living room. Participants were welcomed and introduced to the experimental setup. Pre-counselling for HIV/AIDS was conducted by a trained nurse. Dinner was provided at 1800 for each participant. They drank their last beverages (tea/coffee) at 2030 and were encouraged to go to bed at about 2200.

Participants were woken at 0545 the following morning and the ambulatory and ECG apparatus as well as the Actical® were removed after the last ambulatory blood pressure measurement (ABPM) at 0600. Subsequently, anthropometric measurements were taken; thereafter, participants were placed in a semi-recumbent position for a resting 12-lead ECG, blood sampling and ultrasound scanning.

2.3. Anthropometric measurements

The Actical® measured physical activity energy expenditure, taking the resting metabolic rate into account. Anthropometric measurements were taken in triplicate by qualified anthropometrists using calibrated instruments (Precision Health Scale; A&D Company, Tokyo, Japan; Invicta Stadiometer, IP 1465; Invicta, London, UK). These measurements included: weight, height and body mass index (BMI) calculated by means of the formula weight/height^2.

2.4. Cardiovascular measurements

ABPM and 5-lead ECG measurements were taken with the Cardiotens® (Meditech, CE0120, Budapest Hungary). The appropriate cuff size was fitted on the participant's non-dominant arm for the BP measurements. The successful inflation rate was 75.4% (±9.7%) in African men. The Cardiotens®, validated by the British Hypertension Society (13), was programmed to measure BP oscillometrically at 30 minute intervals during the day (0700 – 2200) and at hourly intervals during the night (2200 – 0600). Hypertension prevalence was identified according to the Europe Society of Hypertension guidelines (ESH) (SBP > 125 mmHg, DBP > 80 mmHg) (14). Participants were requested to continue with their normal activities and record any of the following symptoms on their ambulatory diary cards: chest pain, visual disturbances, headache, nausea, fainting, palpitations, physical activity and emotional stress.

The ECG unit of the Cardiotens® performed sequential ECG registrations according to a preset program. ECG recordings were made every 5 minutes for

20 seconds. Silent ischemia was automatically noted by the Cardiotens® apparatus by using the following criteria (also known as the 1-1-1 rule) (15), namely:

- horizontal or descending ST-segment depression by 1 mm;
- the duration of the ST-segment episode lasting for 1 minute; and
- there is at least a 1 minute interval from the preceding episodes.

Ambulatory BP and ECG data were analyzed by means of the CardioVisions® 1.19 Personal Edition. A standard 12-lead resting ECG was recorded for 6 cardiac cycles in order to determine resting ST segment depression (1 minute depression) using an electrocardiogram (NORAV, Medical Ltd PC 1200, Israel, Software version 5.030).

2.5. Target end-organ damage

The Sonosite Micromaxx ultrasound system (SonoSite, Bothell, WA) and a 6-13 MHz linear array transducer were employed for scanning the carotid intima-media thickness (CIMT). At least two optimal angle images of the left and right common carotid artery were imaged and measured. Previously prescribed protocols were followed (16,17). These images were imported into the Artery Measurement Systems automated software for dedicated analyses of the CIMT far wall. A good image quality with a maximal 10 mm segment was used for analytical purposes. Intra-observer variability for the far wall was 0.04 mm between two measurements taken four weeks apart on ten participants.

2.6. Biochemical analysis

A registered nurse obtained blood samples from the brachial vein branches by using a sterile winged infusion set. With the Beckman and Coulter time-end method (Unicel, DXC 800, Germany), sodium fluoride glucose and serum lipograms were determined. The enzyme rate method determined serum gamma glutamyl transferase (γ-GT) and high-sensitivity C-reactive protein (hs-CRP). Serum cotinine was determined by using a homogeneous immunoassay (Modular ROCHE Automized Switzerland). All the above biochemical analyses were performed in independent accredited laboratories.

2.7. Statistical analysis

Statistica version 10 (Tulsa OK, USA) was employed for all the statistical analyses. Shapiro Wilk's analyses evaluated the deviation from normality and hs-CRP values were normalized via logarithmic transformation. Chi-square statistics compared proportions. Independent T-tests compared differences between African SI and nSI groups. Single and multiple regression analyses were performed to determine associations between CIMT and several cardiovascular variables. Pearson correlations determined independent variables associated with a dependent marker CIMT to enter forward stepwise regression analysis models, which were executed for each group (SI = model 1; nSI = model 2; all African men = model 3). Independent variables included in the models were age, BMI, glucose, cholesterol, hs-CRP, systolic blood pressure (SBP), PP, ECG resting ST depression, and silent ischemia. The statistical significance was a two-sided α level of 0.05 or less.

3. RESULTS

Study population characteristics

The characteristics of SI and nSI African men are depicted in Table 1. Apart from having silent ischemia, the SI group had a significantly more vulnerable cardiovascular profile. They demonstrated a higher SBP, DBP, PP, HR and resting ST-segment depression compared to the nSI African men. Both the African SI and nSI groups revealed mean 24h BP reaching hypertensive status. In figure 1, both groups' fasting glucose and hs-CRP values exceeded the cut off points of 5.6 mmol// and 3.1 mg// set by the American Heart Association, respectively. However, mean glucose, cholesterol and hs-CRP did not differ between the groups. CIMT in African SI men was significantly increased compared to the nSI men.

Regression Analyses

The unadjusted regression analysis results (Table 2) demonstrated that positive associations existed between CIMT and age, hs-CRP, SBP, PP and silent ischemia for the SI group. In the African nSI group positive associations between CIMT and age, BMI, glucose, SBP and PP existed, but with no other risk factors. The total African group exhibited associations between CIMT and age, BMI, hs-CRP, glucose, cholesterol, SBP, DBP, PP, ECG resting ST-depression and 24h silent ischemia. Forward stepwise regression analyses in Table 3 revealed that only silent ischemia was associated with sub-clinical atherosclerosis independent of confounders, in the SI group.

DISCUSSION

The aim of this paper was to establish whether silent ischemia is associated with cardiovascular risk variables and sub-clinical atherosclerosis in African men. According to the ESH guidelines (14) age, BMI, PAI, γ-GT, cotinine, cholesterol and hs-CRP are strong predictors for cardiovascular disease. Whether these predictors are relevant for silent ischemia is not known.

Asmar et al. (5) indicated that the prevalence of silent ischemic episodes increases with aging in Caucasians. We, however, found no differences between our African groups (SI and nSI); however, the groups in this study were still relatively young.

In other studies on diabetic patients as well as in a Mexican population, the presence of higher total cholesterol has been linked to silent ischemia (18,19). This was however not the case in the SI and nSI African men as they exhibited normal values in terms of to the American Heart Association (<5.5 mmol/*l*) and levels did not differ between the groups.

Diabetes is a risk factor for silent ischemia (20). Although we excluded clinically diagnosed diabetics from this study, it is still apparent that fasting serum glucose levels for African SI and nSI groups were above normal, but not diabetic (<7.0 mmol/*l,* International Diabetes Federation (IDF)). The African SI group, although with a higher prevalence of silent ischemia, exhibited a tendency towards impaired fasting glycaemia (≥6.1 and < 7.0, mmol/*l,* IDF). Our

data supported other findings where silent ischemia was significantly more frequent in participants with impaired fasting glucose (21).

Additionally, high sensitivity CRP values were associated with silent myocardial ischemia in Chinese with type 2 diabetes mellitus (22). While our group was not diabetic, both groups (SI and nSI) had similar glucose levels demonstrated increased CRP values exceeding the cut off point of > 3 mg/*l*, thus increasing their risk for cardiac events.

Minagawa et al. (23) indicated that certain hypertensive medication lowers the incidence and duration of ST-segment episodes. If this holds true for Africans, the incidence of silent ischemia could further be masked. Silent ischemia has further been linked to higher ambulatory blood pressure values in hypertensive participants (4,5), which is supported in our study. Indeed, the African SI men indicated a higher 24h blood pressure, reaching hypertensive status . No significant differences existed between hypertension prevalence rates in the African SI (89%) and in the nSI (64%) groups. This could imply that silent ischemia is not necessarily driven by hypertension in African men, but rather through other possible mechanisms such as increased sympathetic nervous system activity (6, 24, 25). Van Lill et al. (26) recently revealed decreased baroreceptor sensitivity in this specific African population.

A rather interesting finding is that resting 12-lead ECG ST-depression was borderline significant in the SI group as well as the total group associated with

sub-clinical atherosclerosis. Clearly, further research is needed in larger sample groups in order to clarify these results.

It has been reported that hypertensive participants with ischemic heart disease and ischemic events have a higher mean 24h pulse pressure (27). Uen et al. (4) reported that in Caucasian hypertensive participants, an elevated 24h PP can also be considered as an effective predictor of cardiovascular risk. The mean PP for the SI group was higher compared to the nSI group supporting the findings of Uen et al. (4). Conversely though, it was not associated with sub-clinical atherosclerosis in African men.

Heart rate, which is normally higher during an ischemic event, was also found to be higher than normal heart rate in participants with intermittent claudication (28). A study conducted by Solimene et al. (29) suggested that there is no relationship between silent ischemia and heart rate after myocardial infarction. We found increased ambulatory heart rate values in the SI Africans, suggestive of the possible supportive role of an increased sympathetic nervous system (26,30).

Since the burden of cardiovascular disease in urban Africans is increasing, especially in males, it is suggested that the possible role of higher sympathetic activity be explored (11,30). The African SI group appears to be at risk with a profile of higher ABPM, above normal glucose and hs-CRP values, and silent ischemia. However, when accounting for these factors, only silent ischemia is

associated with sub-clinical atherosclerosis, possibly increasing stroke risk in this apparently vulnerable group (31,32).

The strength of the study lies in its well-controlled design in a group with a similar socio-economic status. Limitations include the small sample size and the nature of the prospective study design which cannot infer causality. A follow-up study is recommended to evaluate the progression of sub-clinical atherosclerosis in African men.

To conclude silent ischemia was associated with IMT and cardiovascular risk factors in Africans. Silent ischemia was associated with sub-clinical atherosclerosis independent of cardiovascular risk factors. It is, however, suggested that the role of sympathetic activity should be researched.

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Table 1 Characteristics of SI and nSI African male population (mean ± SD)

	Africans		
	SI (N=38)	nSI (N=42)	P-value
Age, years	44 (7.9)	41 (8.9)	0.12
Body Mass Index, kg/m^2	28.2 (6.3)	27.1 (5.6)	0.39
Lifestyle factors			
Physical activity, kcal/day	2774.5 (939.6)	2702.09 (708.1)	0.70
Cotinine, ng/ml	24.0 (41.3)	26.7 (54.2)	0.80
Gamma glutamyl transferase U/ℓ	92.2 (96.6)	63.0 (37.2)	0.07
Cardiovascular parameters			
24h SBP, mmHg	**145 (17.7)**	**132 (13.7)**	**<0.001**
24h DBP, mmHg	**91 (12.5)**	**85 (9.7)**	**0.02**
24h Pulse Pressure, mmHg	**53.5 (9.1)**	**46.9 (7.0)**	**<0.001**
24h Heart rate, beats/min	**82 (13.0)**	**76 (8.4)**	**0.01**
ECG resting ST depression, mm	**-0.53 (1.1)**	**0.49 (1.1)**	**0.01**
Mean 24h Silent ischemic events	**18.7 (26.4)**	**0**	**<0.001**
Hypertensive, N (%)	34 (89)	27 (64)	0.46
Hypertension medication, N (%)	6 (16)	6 (14)	0.53

N=number of participants. Abbreviations: SI – Africans with silent ischemia; nSI – Africans without silent ischemia; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; ECG – Electrocardiogram.

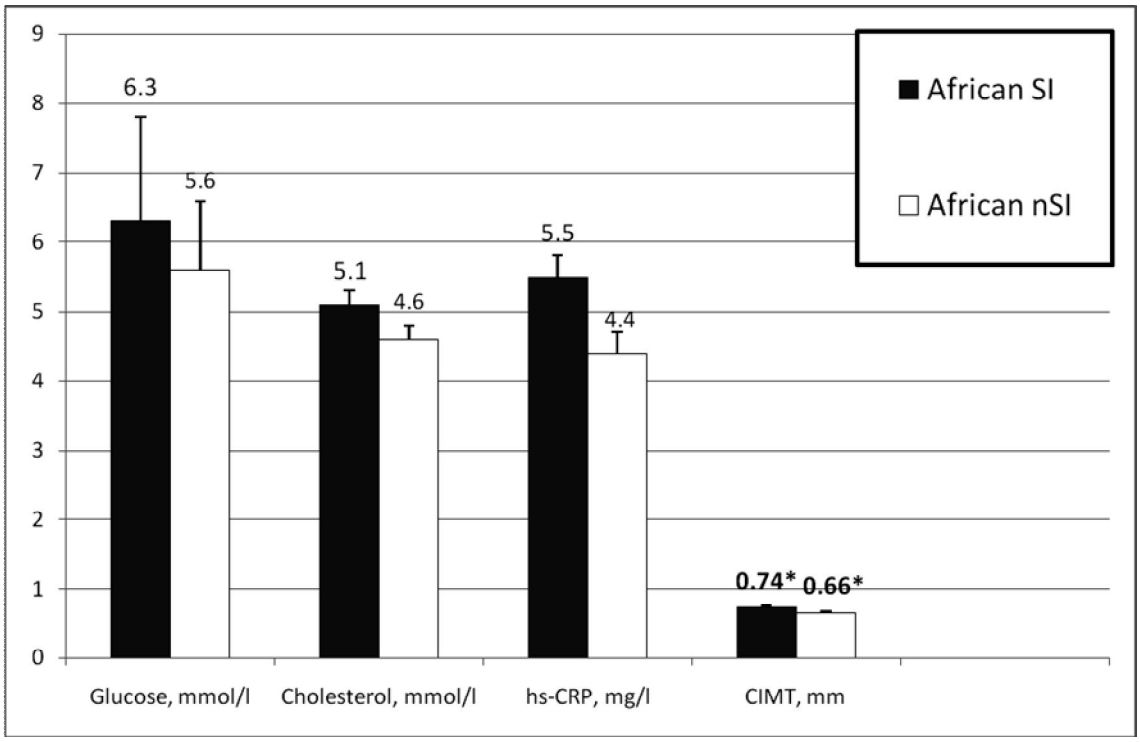

Figure 1. Independent T-test results comparing cardiovascular risk markers (mean ± SE) in SI and nSI African males, *P = 0.01.

Table 2 Unadjusted means revealing associations between CIMT and cardiovascular variables independent of confounders in African men with (SI) and without (nSI) silent ischemia

	SI		nSI		African men	
	CIMT		CIMT		CIMT	
Variable	r-value	P Value	r-Value	P-value	r-value	P-value
Age, years	**0.45**	**0.004**	**0.50**	**0.001**	**0.49**	**<0.001**
Body Mass Index, kg/m^2	0.09	0.61	**0.44**	**0.005**	**0.25**	**0.02**
Physical activity, kcal/day	0.06	0.72	-0.09	0.57	-0.08	0.48
Cotinine, ng/ml	0.10	0.54	0.09	0.57	-0.01	0.96
Gamma glutamyl transferase, U/ℓ	0.02	0.88	0.16	0.32	0.10	0.37
Log C-reactive protein	**0.44**	**0.006**	0.21	0.18	**0.34**	**0.002**
Fasting Serum Glucose mmol/ℓ	0.15	0.36	**0.31**	**0.05**	**0.25**	**0.02**
Cholesterol mmol/ℓ	0.28	0.09	0.17	0.29	**0.28**	**0.01**
24h SBP, mmHg	**0.34**	**0.04**	**0.36**	**0.02**	**0.40**	**<0.001**
24h DBP, mmHg	0.14	0.40	0.26	0.10	**0.24**	**0.03**

24h Pulse Pressure, mmHg	**0.46**	**0.004**	**0.35**	**0.02**	**0.47**	**<0.001**
24h Heart rate, beats/min	0.16	0.35	0.12	0.44	0.004	0.97
ECG resting ST depression, mm	-0.27	0.10	-0.17	0.30	**-0.30**	**0.007**
24h Silent ischemia	**0.53**	**0.001**	-	-	**0.47**	**<0.001**

Abbreviation: SI - Africans with silent ischemia; nSI - Africans without silent ischemia; CIMT – Carotid Intima-media Thickness; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; ECG – Electrocardiogram.

Table 3 Forward stepwise regression analyses indicating relationships between cardiovascular risk markers and a sub-clinical atherosclerosis marker

CAROTID INTIMA-MEDIA THICKNESS			
		African men	
	Model 1	Model 2	Model 3
	SI (N=38)	nSI (N=42)	
Adjusted R^2	0.34	-	0.35
	β (± 95%CI)	β (±95%CI)	β (±95%CI)
Independent co-variates			
Silent ischemia	0.35 (0.22;0.52)*	-	0.29 (0.19;0.39)*

β = standardized regression coefficient. Independent co-variables included:

Model 1(SI men): age, Log hs-CRP, SBP and PP.

Model 2 (nSI men): age, BMI, glucose, SBP and PP.

Model 3 (African men): age, BMI, Log hs-CRP, cholesterol, glucose, SBP, PP and ECG resting ST-depression. Abbreviations: SI – Africans with silent ischemia; nSI – Africans without silent ischemia;

*$P < 0.05$.

CHAPTER 4

SUMMARY OF MAIN FINDINGS

1. INTRODUCTION

A summary of the main findings reported in this dissertation, is presented in this chapter. The results will be discussed, interpreted and compared with relevant literature (Chapter 2). Subsequently, conclusions will be drawn and recommendations are made to researchers investigating silent ischemia and subclinical atherosclerosis in African men, with the purpose of ultimately elaborating an mechanism linking silent ischemia with sub-clinical atherosclerosis.

2. SUMMARY OF THE MAIN FINDINGS

The significant findings reported in the article of this dissertation were:

Silent ischemia is associated with sub-clinical atherosclerosis in African men

The main purpose of this study was to determine if silent ischemia is associated with cardiovascular variables and whether silent ischemia isassociated with sub-clinical atherosclerosis independent of cardiovascular risk markers in an urban African male population. In terms of the results, African men with silent ischemia exhibited a more vulnerable cardiovascular profile, that is, they demonstrated a higher ambulatory blood pressure, pulse pressure, and heart rate, compared to the African men without silent ischemia. It was evident, however, that the whole African male population under study had elevated levels of hs-CRP and fasting glucose. Mainly, carotid intima-media thickness

was significantly increased in African men with silent ischemia, which constituted the strongest marker associated with sub-clinical atherosclerosis.

3. COMPARISON TO RELEVANT LITERATURE

It is evident that certain findings are confirmed and others contradicted by those found in the literature (see Chapter 2).

Silent ischemia (SI) is associated with several cardiovascular risk factors, that is, hypertension (1), hypercholesterolemia (2), diabetes and impaired glucose tolerance (3-4), a higher pulse pressure (5) and heart rate (6) in Caucasians. Even though some of the findings in this study corroborated the findings reported in the literature, this study included on Africans only. Contradictory to the literature, however, is that no significant differences existed between hypertension prevalence, glucose, hs-CRP and cholesterol in African men with without silent ischemia. However, higher mean levels of SBP, DBP, pulse pressure and heart rate were more evident in Africans with silent ischemia.

Cardiovascular risk markers are elevated in Africans but only silent ischemia was strongly associated with a subclinical vascular disease marker. In terms of the above mentioned findings, both our hypotheses can be accepted.

4. CHANCE AND CONFOUNDING FACTORS

It is imperative that certain important factors are addressed before discussing the main findings in this study.

The possibility of chance should be taken into account. Forward stepwise regression analyses revealed that silent ischemia was the strongest marker associated with sub-clinical atherosclerosis in the SI group.

Several confounding factors such as physical well-being and diet could have influenced the results by causing over or underestimation of the associations. T-tests revealed that age, body mass index, physical activity, smoking and alcohol consumption were not different between African men with without silent ischemia. Unadjusted means revealed that in SI men age, log hs-CRP, SBP, PP and silent ischemia was associated with CIMT. In nSI men it revealed that age, BMI, glucose, SBP, and PP was associated with CIMT and in the total group it revealed that age, BMI, log hs_CRP, glucose, cholesterol, SBP, DBP, PP, resting ECG ST depression and silent ischemia was associated with CIMT, thus addressing the above mentioned confounding factors. When entering these factors into regression analyses it revealed that silent ischemia was associated with CIMT significantly.

All statistical results were interpreted from a physiological perspective, therefore, all statistical significance do not necessarily indicate physiological significance.

5. WEAKNESSES OF THIS STUDY

Several methodological issues may have caused weaknesses in the study and, therefore, might have influenced the different research outcomes:

a) The number of participants in this study could possibly have been inadequate to indicate trends correctly.
b) The participants were divided into groups of African men with silent ischemia and those without silent ischemia based on the ambulatory ECG recordings instead of exercise testing. This could have resulted in some participants being misclassified.
c) Statistical significance of various analyses could have been influenced by the exclusion of 13 HIV participants, those with insufficient data – 1, diabetic medication users – 6, and those with renal impairment – 1.

6. DISCUSSION OF MAIN FINDINGS

Silent ischemia is linked to higher ambulatory blood pressure values in hypertensive participants (7-9), which was supported by our study, with mean 24h SBP and DBP in the hypertensive range. . Even though the burden of cardiovascular disease in urban male Africans is increasing (10,11), no significant differences between hypertension prevalence existed in the SI an nSI groups. This might imply that hypertension is not necessarily the driving force behind silent ischemia in African men. The SI group however showed higher BP than the nSI group in the hypertensive range.

In hypertensive participants with ischemic heart disease, a higher 24h pulse pressure was demonstrated (12). Pulse pressure can be considered as an effective predictor of cardiovascular risk (12). Our results revealed that African men with silent ischemia showed a higher mean 24h pulse pressure value than the African men without silent ischemia, thus supporting the above-mentioned findings. Pulse pressure was however not associated with subclinical vascular disease in African men.

The results in the study indicated that African men with silent ischemia appear to be more vulnerable and at risk of developing subclinical vascular disease. Their profiles indicated higher ambulatory blood pressure, above normal glucose levels, high sensitive C-reactive protein levels. However, only silent ischemia was strongly associated with sub-clinical vascular disease possibly increasing stroke risk (13,14).

7. CONCLUSION

In conclusion, silent ischemia in African men was associated with several cardiovascular risk markers. These factors have been independently associated with subclinical atherosclerosis in other studies. Silent ischemia was also associated with sub-clinical atherosclerosis.It is however not clear by what silent ischemia is driven and the possibility of higher sympathetic nervous system activity should be considered.

8. RECOMMENDATIONS

The following recommendations are proposed for future studies.

- A larger sample size from different regions will constitute a more representative African male population.
- The measurement of silent ischemia during exercise is suggested as it could possibly indicate further pathology in these African men.

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