

The relationship between baroreflex sensitivity and cardiovascular function in Africans and Caucasians from South Africa: the SAfrEIC study

NADIA THERON B.Sc.Hons.

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Supervisor: Prof JM van Rooyen

Co-Supervisor: Dr R Schutte

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DECLARATION BY AUTHORS

The contribution of each of the researchers involved in this study is given in the following table:

<u>Name</u>	<u>Role in the study</u>
Miss N Theron (B.Sc Hons.) (Student)	Responsible for literature searches, statistical analysis, interpretation of results and writing of the manuscript.
Prof. JM van Rooyen (D.Sc.) (Physiologist)	Leader. Supervised the writing of the manuscript, collection of data, as well as initial planning and design of the manuscript.
Dr. R Schutte (Ph.D.) (Physiologist)	Co-leader. Supervised the writing of manuscript, statistical analysis, as well as initial planning and design of the manuscript.

The following is a statement from the co-authors confirming their individual role in each phase and giving their permission that the manuscript may be submitted in fulfilment of the requirements for the degree Magister Scientiae in Physiology at the School for Physiology, Nutrition and Consumer Sciences in the Faculty of Health Science of the North-West University.

I declare that I have approved the above-mentioned manuscript, that my role in this study, as indicated above, is representative of my actual contribution and that I hereby give my consent that the article may be published as part of the degree Magister Scientiae of Nadia Theron.

Prof. JM van Rooyen

Dr. R Schutte

AFRIKAANSE TITEL

Die verband tussen barorefleks sensitiviteit en kardiovaskulêre funksie by Afrikane en Koukasiërs van Suid-Afrika: die SAfrEIC studie.

OPSOMMING

Tydens die afgelope vier dekades, het Afrikane van sub-Sahara Afrika meer verwesters as gevolg van verhoogde verstedeliking. Dit is geassosieër met gepaardgaande veranderinge in lewenstyl en dieet, wat gevolglik gelei het tot die verhoogde voorkoms van nie-oordraagbare siektes, veral kardiovaskulêre siektes. Hierdie opwaartse tendens in die voorkoms van kardiovaskulêre siektes in sub-Sahara Afrika is waargeneem met hipertensie as die vernaamste. Koukasiër gebaseerde studies het getoon dat verlaagde barorefleks sensitiviteit, wat verwys na 'n versteuring in die outonome senuwee sisteem met 'n verskuiwing na die simpatiese tak, verwant is aan die aanvang van hipertensie. Dit is onduidelik of dit ook 'n bydraende rol speel in die verhoogde voorkoms van hipertensie onder Swartes.

Die studie is ingesluit by die SAfrEIC (South African study regarding the influences of Sex, Age and Ethnicity on Insulin Sensitivity) studie wat 747 swart en Koukasiër mans en vroue van die Potchefstroom area van die Noordwes Provinsie van Suid-Afrika ingesluit het. Die insluitingskriteria was skynbaar gesonde deelnemers 20 – 70 jaar. Die uitsluitingskriteria was swangerskap, laktering en diabetes (tipe 1 of 2 sowel as die gebruik van diabetiese medikasie). Deelnemers is verdeel in vier groepe. Swart vrouens (n = 192); swart mans (n = 181); Koukasiese vrouens (n = 211) en Koukasiese mans (n = 163). Massa, lengte en middelomtrek is gemeet met 'n pressiesie Gesondheidskaal, A & D Company, Japan; Invicta Stadiometer, IP 1465, VK; Holtain nie-rekbare metaal maatband). Bloeddruk van die deelnemers is gemeet met 'n Finometer apparaat (FMS, Finapres Measurement Systems, Arnhem, Holland). Die Beatscope 1.1 sagteware program het die data van elke deelnemer geïntegreer (ouderdom, geslag en lengte). Bloeddruk van die deelnemers is ook gemeet met die geldig verklaarde OMRON Model HEM-757. Polsgolf snelheid, as 'n indikator van arteriële styfheid is gemeet met die Complior SP apparaat. Barorefleks sensitiviteit is bepaal deur die geldig verklaarde kruis-korrelasie barorefleks sensitiviteit (xBRS) metode, verkry vanaf kontinue bloeddruk meting met die Finometer apparaat. Serum totale cholesterol en gamma glutamietransferase is geanaliseer met die Konelab TM outo-analiseerder (Thermo Fisher scientific Oy, Vantaa, Finland) en lae-digtheidslipoproteïen is bereken volgens die Friedewald formule.

Die hoof bevinding van die studie is dat barorefleks sensitiwiteit afneem met verhoogde polsgolf snelheid, wat aanduidend is van die bydraende rol van arteriële styfheid tot verlaagde barorefleks sensitiwiteit. Alhoewel sistoliese bloeddruk en polsgolf snelheid die hoogste is by die swart mans, het geen betekenisvolle verskille bestaan vir barorefleks sensitiwiteit tussen die groepe nie. Nadat daar egter gekorrigeer is vir betekenisvolle veranderlikes, het barorefleks sensitiwiteit geneig om te verlaag met verhoogde polsgolf snelheid by slegs die swart mans. Tot op hede is daar geen studies wat hierdie spesifieke verhouding in swartes van Suid-Afrika ondersoek het nie.

Die gevolgtrekking is dat verhoogde arteriële styfheid moontlik bydrae tot verlaagde barorefleks sensitiwiteit in swart Suid-Afrikaners.

ABSTRACT

In the past four decades Africans from Sub-Saharan Africa has become more westernised due to increasing urbanisation. Along with this came changes in lifestyle and diet, which consequently led to the increased prevalence of non-communicable diseases, especially cardiovascular disease. This upward trend in the prevalence of cardiovascular diseases in Sub-Saharan Africa is observed with hypertension being the most prominent. Caucasian-based studies indicate that reduced baroreflex sensitivity, which is an imbalance in the autonomic nervous system with a shift to the sympathetic side, is linked to the onset of hypertension. It is unclear whether this also has a contributing role in the increased hypertension prevalence observed in Africans.

The study was embedded in the SAfrEIC (South African study regarding the influence of Sex, Age and Ethnicity on Insulin sensitivity) study that included 747 African and Caucasian men and women living in the Potchefstroom region of the North West Province of South Africa. The inclusion criteria were apparently healthy participants aged 20–70 years. The exclusion criteria were pregnancy, lactation and diabetes (type 1 or 2 as well as the use of diabetic medication). Participants were divided into four groups: African women (n = 192); African men (n = 181); Caucasian women (n = 211) and Caucasian men (n = 163). Weight, height and waist circumference were measured with a precision Health Scale, A & D Company, Japan; Invicta Stadiometer, IP 1465, UK; Holtain unstretchable metal tape, respectively. Blood pressure was measured with a Finometer device (FMS, Finapres Measurement Systems, Arnhem, The Netherlands). The Beatscope 1.1 software programme integrated the data of each participant (age, gender and height). Blood pressure of the participants was also measured with the validated OMRON Model HEM-757. Pulse wave velocity, as an indicator of arterial stiffness was measured with the Complior SP apparatus. Baroreflex sensitivity was determined by the validated cross-correlation baroreflex sensitivity (xBRS) method, derived from the continuous blood pressure measurement using the Finometer apparatus. Serum total cholesterol and gamma glutamyltransferase were analyzed with the Konelab TM auto analyzer (Thermo Fisher Scientific Oy, Vantaa, Finland), while low-density lipoprotein was computed according to the Friedewald-formula.

The main finding of the study was that baroreflex sensitivity decreased with increasing pulse wave velocity, indicating a contributing role of arterial stiffness to decreasing baroreflex sensitivity. Although systolic blood pressure and pulse wave velocity was the highest in African men, no significant differences existed for baroreflex sensitivity between the groups. However, after adjusting for significant covariates, baroreflex sensitivity tended to decrease with increasing pulse wave velocity in African men only. To date, there are no studies that explored this specific

relationship in Africans from South Africa. In conclusion, increased arterial stiffness possibly contributes to reduced baroreflex sensitivity in black South Africans.

ABBREVIATIONS

ANOVA	Analysis of variance
BMI	Body mass index
BRS	Baroreflex sensitivity
C _w	Arterial compliance
DBP	Diastolic blood pressure
DMPA	Depot medroxyprogesterone acetate
GGT	Gamma glutamyltransferase
HR	Heart rate
LDL	Low-density lipoprotein
MAP	Mean arterial pressure
PWV	Pulse wave velocity
SAfrEIC	South African study regarding the influences of Sex, Age and Ethnicity on Insulin Sensitivity
SBP	Systolic blood pressure
TC	Total cholesterol
xBRS	Cross-correlation baroreflex sensitivity

CHAPTER 1

INTRODUCTION AND LITERATURE STUDY

1.1 GENERAL INTRODUCTION

In the previous four decades, Africans from Sub-Saharan Africa were subjected to increasing urbanisation. This process was associated with changes in lifestyle and diet, factors that consequently led to the increased prevalence of non-communicable diseases, particularly cardiovascular disease.¹ The vast majority of Sub-Saharan Africa's population can be defined as black.² Due to increasing longevity and westernisation in Sub-Saharan Africa, hypertension has changed from a rare condition to a major problem.² The prevalence of hypertension and stroke is a general phenomenon among the adult black population.³ According to Kluger, ten million to twenty million people may be hypertensive in Sub-Saharan Africa; the African Union has called hypertension one of the continent's greatest health challenges after AIDS.⁴ In recent years there has been growing interest in the increased prevalence of hypertension among black South Africans.⁵ Studies have shown that black South Africans are more prone to developing hypertension than their Caucasian counterparts.⁶ In addition, the highest prevalence of hypertension is among, older, black South African males in urban areas.⁷ There has been considerable speculation about why black South Africans are more prone to develop hypertension. One hypothesis is that reduced baroreflex sensitivity, which is an imbalance of the autonomic nervous system to the sympathetic side, is linked to the onset of hypertension.⁸ To the best of our knowledge, studies describing the relationship between baroreflex sensitivity and cardiovascular function among African populations are unavailable. Research on factors which contribute to increased blood pressure, such as baroreflex sensitivity may aid in counter-acting the increased cardiovascular morbidity and mortality observed in Africans.

1.2. AIM

The aim of the study was to investigate the relationship between baroreflex sensitivity and cardiovascular function in African and Caucasian men and women.

1.3. HYPOTHESES

- Baroreflex sensitivity is the lowest and blood pressure and pulse wave velocity the highest in Africans compared to Caucasians.
- Reduced baroreflex sensitivity contributes to increased blood pressure in Africans.

1.4. PREFACE

For the purpose of this study, the article format is followed. Although the appropriate and relevant literature background is discussed in the manuscript, Chapter 1 also gives an additional, more elaborate literature survey. In the manuscript, the promoter and co-promoter are named as co-authors. However, the main and first author initiated and was responsible for most stages of the manuscript, including literature searches, collection of data, statistical analysis, interpretation of results and the writing of the article. The co-authors, therefore, acted in their roles as promoter and co-promoter. All co-authors gave consent that the articles could be used in this manuscript. Therefore, Chapter 2 is a manuscript, submitted to the Journal of Human Hypertension. Chapter 3 provides a summary of all the results, recommendations are made and conclusions are drawn. The relevant references are provided at the end of each chapter according to the Vancouver style. For the purpose of uniformity, a similar style was used throughout this dissertation.

1.5. LITERATURE STUDY

1.5.1 Cardiovascular disease

Specific ethnic populations suffer from a disproportionately greater burden of cardiovascular diseases including coronary heart disease and stroke.⁹ Adapting to a westernised lifestyle has marked effects across racial and ethnically different populations in disease risk.⁹ During the past four decades in Africa an increasing rate of urbanisation and lifestyle associated changes occurred that subsequently increased the prevalence of non-communicable chronic diseases, in particular, cardiovascular diseases.¹ Stroke and hypertension are global causes of death and disability.¹⁰ An upward trend in the prevalence of cardiovascular diseases in Sub-Saharan Africa is observed with hypertension as the most prevalent cardiovascular disease.¹¹ It is unclear whether this increase in prevalence is due to improved diagnostic ability and technology,¹¹ or because of a true natural increase in cardiovascular diseases, which is consistent with the nutritional and epidemiological transition.¹⁰ Rural Sub-Saharan Africa is at an early stage of economic and health transition.³ In South Africa today, blacks have better access to healthcare which previously, along with the initial consultation of traditional healers, resulted in the late presentation of disease.¹² There are limited data available before 1990 reporting the prevalence of hypertension in rural black South Africans. In a study published in 1972 on black South African rural women, five (1%) hypertensives were diagnosed out of 485 women studied.¹³ Today, the prevalence of hypertension is the highest in this population group.¹⁴

1.5.2 Hypertension

Hypertension is the clinical term used when blood pressure is constantly raised.¹⁵ High blood pressure is defined as systolic blood pressure of 140 mmHg or higher and diastolic blood pressure of 90 mmHg or higher, or the taking of antihypertensive medication. Hypertension is regarded as a silent killer due to the absence of visible symptoms when blood pressure levels are raised.¹⁵ High blood pressure is one of the primary causes of heart attack, stroke, kidney failure and premature mortality.¹⁵ The adverse environmental and lifestyle changes associated with mass migration from rural to urban areas are related to the increased prevalence of hypertension in urban black Africans.² Urban African societies have an increased risk for hypertension in comparison to rural populations.² This is a major public health concern, including in the North West Province of South Africa where the prevalence in urbanised black populations, living in informal settlements in the North West Province of South Africa are: systolic blood pressure = 34.9% , diastolic blood pressure = 22.7%; (men) and systolic blood pressure = 31.4%, diastolic blood pressure = 26.9% (females).¹⁶ It is believed that the rapid process of urbanisation causes increased levels of stress due to social

and cultural disruption, which may lead to decreased baroreflex sensitivity.^{17,18} On the other hand, increased arterial stiffness can also contribute to reduced baroreflex sensitivity.

1.5.3 Hypertension in Africans, and its comparability to African Americans

The increased prevalence and severity of hypertension in African Americans have multifactorial origins¹⁹, and seem to be related to those suggested for blacks living in Africa.² With a population of 650 million people in Sub-Saharan Africa, along with an increased lifespan and urbanisation, hypertension has evolved from a scarcity to a foremost health problem.² Suggestions about the origins of hypertension in African Americans may not directly apply to Africans living in Africa, even though African Americans or other black populations may be more susceptible to hypertension and may even have diverse contributing factors or diverse degrees of the similar contributing factors.² According to Saunders, their genetic predisposition may be permissive rather than determinative.²⁰ Apart from the recognized contributions of the epithelial sodium channel and defects in angiotensinogen and aldosterone synthase genes found in African but not Caucasian hypertensive patients, there are, in general, no key genetic disparities to explain these observations. Environmental disparities may justify this to a great extent. Thus, both environmental risk factors and genes play a role in the problem.² However, there is a shifting of the emphasis towards environmental instead of genetic disparities to account for the increased prevalence of hypertension in Africans.² Studies on African Americans can provide important evidence in efforts to limit the increased prevalence of hypertension in black South Africans. In contrast to Caucasians, African Americans develop hypertension earlier in life and their average blood pressures are greatly increased.²¹ Therefore, in comparison to Caucasians, African Americans have a 1.3-times higher chance of nonfatal stroke, a 1.8-times higher chance of fatal stroke, a 1.5-times greater chance of heart disease mortality, and a 4.2-times higher chance of developing end-stage kidney disease.²¹

1.5.4 Environmental factors and lifestyle

The pathogenesis of hypertension in black populations is influenced by environmental factors and lifestyle changes.²² This theory is supported by the fact that hypertension is more prevalent among urban than rural black populations.¹¹ The comparison of migrant populations to traditional populations still living in deep rural areas may provide some clues as to how significant the contribution of environmental and lifestyle factors are in the development of hypertension.²³ In the Kenyan Luo migration study, blood pressure of black rural Africans who migrated to urban areas increased significantly with longer duration of urbanisation, which seems to be associated with increased weight and disturbances of urinary electrolyte balance.²⁴ Blacks experience chronic sympathetic nervous system activity related to recurrent exposure to social and environmental

stressors.²⁵ Constant stress-induced sympathetic nervous system activity instigates increased vascular reactivity that leads to the pathogenesis of hypertension.²⁶ Thus, environmental stressors like urbanisation increase sympathetic nervous system activity which plays a role in the pathogenesis of hypertension in black populations.²⁶

Salt sensitivity can be described as an increase in blood pressure in response to an increase in sodium intake.²⁶ Black populations are more salt sensitive than Caucasian populations.²⁷ In addition, salt sensitivity enhances sympathetic nervous system-induced vascular reactivity.²⁶ During hypertension, increased vascular reactivity and increased salt sensitivity takes place.²⁶ Black people from Africa have an abnormal transport mechanism of sodium and decreased renin activity.² In South Africa, a high sodium intake is common, especially in poor settings where salt is used to preserve food or enhance the flavour of food.²⁸ Large amounts of salt are added to food while cooking and monosodium glutamate-based flavouring cubes or salts are commonly used to enhance taste.²⁸ In addition, people in Sub-Saharan Africa often eat little fruit and vegetables leading to decreased potassium intake.²⁸ For many people in South Africa, bread is a staple food and contains high salt levels which facilitates the baking process.²⁸ According to Hoosen, a potassium deficient diet may play a role in the aetiology of hypertension in South Africans.²⁹ Black hypertensive patients exhibit an increased sensitivity to the pressure effects of noradrenaline which is enhanced by a high-sodium diet.³⁰

1.5.4.1 Stress

Mental stress is part of everyday life. Higher stress levels may cause impairment of arterial function.³¹ Changes in arterial stiffness are mainly dependent on the level of perceived stress.³¹ Transition of black populations from rural to urban lifestyles increases levels of psychosocial stress and is consistent with the increased prevalence of hypertension in such populations.³² Results from the THUSA and THUSA BANA studies in South Africa sketch a picture of a mainly Setswana-speaking black population migrating from traditional rural to urban areas while adapting to a new lifestyle to which their ancestors were not accustomed to.³³ This new lifestyle includes numerous risks factors such as malnutrition, availability of tobacco and alcohol use, as well as psychological stresses in informal settlements with extremely high crime rates.³³ When African men are exposed to stressful situations, as during urbanisation, they exhibit exaggerated vascular responsiveness with an increased blood pressure.^{34,35} Environmental stressors, including mental and emotional stressors³⁶ may change blood pressure control and, therefore, the baroreflex sensitivity.³⁷ Consequently, stresses initiate vasoconstriction and increased heart rate via increased sympathetic outflow resulting in higher blood pressure.³⁸ The increased sympathetic nerve activity may, therefore, predispose blacks to the occurrence of hypertension as a result of stress.³⁹ Interestingly,

blacks display a more pronounced increase in sympathetic nerve activity compared to Caucasians during stress.³⁹

1.5.5 Baroreflex

Reduced baroreflex sensitivity denotes a shift of balance of the autonomic sympathetic and parasympathetic nervous system towards the sympathetic side.⁸ Arterial blood pressure is usually regulated within a narrow range, with a mean arterial pressure usually ranging from 85 to 100 mmHg in adults.⁴⁰ Control of this pressure is essential in order to guarantee sufficient blood flow to organs right through the body.⁴⁰ This is achieved by negative feedback systems including baroreceptors (pressure receptors) that perceive the arterial pressure.⁴⁰ The arterial baroreceptors are mainly located in the carotid sinus and in the aortic arch and act in response to distension of the arterial wall so that when the arterial pressure unexpectedly increases, the arterial walls distend which, in turn stimulates firing of these receptors. Conversely, if arterial blood pressure decreases, the decreased distension of the arterial wall causes a decrease in receptor firing.⁴⁰ The baroreflex response to sustain arterial pressure forms an afferent connection to the vasomotor and cardioinhibitory areas, and the efferent pathways from these areas compose a reflex feedback mechanism that stabilises blood pressure and heart rate.⁴¹ When arterial stiffness increases, it results in a non-stop stretching of the baroreceptors, leading to downregulation (reduced in baroreflex sensitivity), which in turn alters autonomic nervous system activity, by a decrease in parasympathetic activity and an increase in sympathetic activity.⁴¹

1.5.5.1 Baroreflex heart rate control in hypertension

Baroreflex mechanisms play an important role in short term control of heart rate, sympathetic activity and accordingly, blood pressure.⁴² The arterial baroreflex usually acts to counter increases in blood pressure by restraining sympathetic activity, leading to vasodilatation and decreasing heart rate.⁴² It is generally accepted that the arterial baroreflex is abnormal in hypertensive patients,^{43,44} with an increased threshold of activation and a decrease in sensitivity. In addition, these alterations are a consequence of increases in arterial blood pressure.⁴² Baroreflex resetting is a crucial mechanism that permits sympathetic activity and arterial blood pressure to increase.⁴⁴ According to Narkiewicz & Grassi, baroreflex resetting refers to a shift in the relationship between blood pressure changes and efferent autonomic response (e.g. sympathetic nerve activity or heart rate).⁴² Continuous increases in arterial pressure initiate resetting of the operational point of the reflex to an increased level of pressure. In other words, the baroreflex loses much of its ability to offset the increased pressure and in fact operates to sustain pressure at an increased level.⁴² Hypertension-initiated resetting of the baroreflex may be evoked by both baroreceptor resetting and central nervous system resetting which leads to altered autonomic outflow.^{45,46} The arterial baroreflex may

be more crucial in long-term blood pressure regulation than generally believed.⁴⁷ Alterations in arterial baroreflexes in hypertensive patients may denote a genetic component in the pathogenesis of essential hypertension and could lead to increased arterial pressure.^{48,49} Abnormalities in baroreflex control of parasympathetic activity do not automatically predict alterations in baroreflex control of sympathetic activity and vascular resistance.⁵⁰

The baroreflex is a division of the autonomic nervous system that controls the sympathetic along with the parasympathetic activity via the integration centres of the central nervous and cardiovascular centres.⁵¹ Hypertensive individuals are subjected to changes in the baroreflex during the onset of the disease which may play a role in the development of hypertension.⁵¹ A decrease in baroreflex sensitivity is related to an increased risk of adverse cardiovascular events and cardiovascular mortality in patients with postmyocardial infarction,⁵² heart failure,⁵³ stroke,⁵⁴ as well as patients with renal failure.⁵⁵ Baroreflex sensitivity is linked to several other cardiovascular risk factors such as age, blood pressure, heart rate and dyslipidemia in hypertensive individuals.⁵¹ It has even been implied that baroreflex is a general cardiovascular risk marker.^{56,57} A decrease in baroreflex sensitivity could have direct effects on pathophysiological mechanisms, leading to adverse prognosis.⁵¹ Cardiovascular incidences such as myocardial infarction, cerebral stroke and unexpected death happen most often towards the end of the night and early morning hours⁵⁸ and occur with a period when sympathetic activity, blood pressure and heart rate can change quickly.⁵⁹ The baroreflex restricts this occurrence, but a change in its sensitivity can merely worsen these unexpected hemodynamic changes⁶⁰ and add to an overkill of incidents during this period.⁵¹

1.5.6 Sympathetic modulation

Exaggerated vascular reactivity has been a hypothesised mechanism for the increased prevalence of hypertension in African men.³⁴ This may be due to genetic disparities related to polymorphic variations in α -adrenergic receptors, leading to exaggerated peripheral vascular sensitivity to norepinephrine.^{61,62} Thus, a decrease in parasympathetic activity and an increase in sympathetic activity shifts the balance of the autonomic nervous system, which is a common denominator in future development of hypertension.^{63,44} Increased psychosocial stress during urbanisation is believed to increase sympathetic outflow which causes an increase in the prevalence of hypertension among urban black South Africans.³⁴ Increased sympathetic reaction leads to morphological changes of blood vessels and consequently hypertension.

1.5.7 Parasympathetic modulation

Changes in the autonomic balance, like increased parasympathetic activity, increase the baroreflex sensitivity which means a shift of the autonomic control to the parasympathetic side. Baroreflex sensitivity alters the efferent autonomic signals that are consecutively linked to the elastic properties of the arterial wall.⁴¹ African Americans exhibited decreased parasympathetic activity in comparison to the non-African Americans.⁴¹ The decrease in parasympathetic activity at rest may be a physiological consequence of the associated changes in arterial stiffness and baroreflex sensitivity.⁴¹

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CHAPTER 2

THE RELATIONSHIP BETWEEN BAROREFLEX SENSITIVITY AND CARDIOVASCULAR FUNCTION IN AFRICANS AND CAUCASIANS FROM SOUTH AFRICA: the SAfrEIC STUDY

2.1 INSTRUCTIONS TO AUTHORS: Journal of Human Hypertension

- The article must be divided into major sections, each to start on a fresh page. These are, (a) Title; (b) Abstract; (c) Introduction; (d) Materials and Methods; (e) Results; (f) Discussion followed immediately by Acknowledgements; (g) References; (h) Tables with their footnotes (which must have page numbers); (i) Figures with their legends (which need not have a page number but if so must have a statement of figure number, i.e. fig1, fig 2 etc. There is to be no separate Conclusion – this is what the Summary table is for.
- Must include a Summary table with two parts: firstly, the heading 'What is known about the topic', and then secondly: 'What this study adds'. This should be two or three bullet points for each, with one short sentence for each bullet point. The Summary table is given the last number in the series of tables.
- Abbreviations and symbols must be standard and SI units used throughout. Acronyms must be fully explained when first used.
- References must appear as numbers starting at 1. At the end of the paper they should be listed (double spaced) in numerical order corresponding to the order of citation in the text.
- Figures and images should be labelled sequentially, numbered and cited in the text. Figure legends should be printed, double spaced, on a separate sheet titled 'Titles and legends to figures'. Figures should be referred to specifically in the text of the paper but should not be embedded within the text.
- Tables should be labelled sequentially as Table 1, Table 2, etc. Each table should be typed on a separate page, numbered and titled, and cited in the text. Reference to table footnotes should be made by means of Arabic numerals.

2.2 ABSTRACT

Objective: Increased sympathetic nervous system activity may predispose blacks to the development of hypertension. Seeing that the arterial baroreceptor reflex is the key mechanism for short-term control of blood pressure, it appears feasible to presume that it also plays a central role in altering blood pressure responses to stress. This study was conducted to investigate the relationship between baroreflex sensitivity and cardiovascular function in Africans and Caucasians from South Africa. **Design:** The study included 747 African and Caucasian participants from both genders living in the Potchefstroom region of the North West Province of South Africa. The overall sample was divided into four groups, African women (n = 192), African men (n = 181), Caucasian women (n = 211) and Caucasian men (n = 163). **Methods:** The Finapres apparatus was used to obtain arterial compliance. Arterial stiffness was measured by means of pulse wave velocity using the Complior SP apparatus. OMRON sitting blood pressure was used in the analyses. Baroreflex sensitivity was determined by the validated cross-correlation baroreflex sensitivity method, derived from the continuous blood pressure measurement using the Finometer apparatus. **Results:** Systolic blood pressure increased significantly with reduced baroreflex sensitivity in African men ($r = -0.40$; $p < 0.001$) and Caucasian men ($r = -0.42$; $p < 0.001$) and women ($r = -0.47$; $p < 0.001$). Diastolic blood pressure also increased significantly with reduced baroreflex sensitivity in African ($r = -0.39$; $p < 0.001$) and Caucasian men ($r = -0.51$; $p < 0.001$) and Caucasian women ($r = -0.40$; $p < 0.001$), while pulse wave velocity increased significantly with a reduced in baroreflex sensitivity in African men ($r = -0.45$; $p < 0.001$) only. After adjusting for significant covariates, the negative correlation between pulse wave velocity and baroreflex sensitivity in African men became borderline significant ($r = -0.122$; $p = 0.090$), while the absence of this association in African women and Caucasian men and women was confirmed. **Conclusions:** A significant increase in pulse wave velocity was apparent among African men. Associations indicate that increased arterial stiffness possibly contributes to decreased baroreflex sensitivity in African men. This could perhaps contribute to the increased prevalence of hypertension among black South Africans.

2.3 INTRODUCTION

Hypertension in Sub-Saharan Africa is a general problem of great economic significance because of its increased prevalence in urban areas, its recurrent underdiagnosis, and the gravity of its complications.¹ Stroke is the third most general cause of death worldwide and an increasingly important cause of death in South Africa². Risk factors for stroke and cardiovascular disease are common among the South African population, however, distributed differently between the various population groups.² Hypertension is a key risk factor for stroke and is the most threatening risk factor in all the population groups. However, it stands out most prominently in blacks.² The rates for hypertension as measured during the THUSA study (1996 - 1998) for urbanised blacks, living in informal settlements in the North West Province of South Africa were: Systolic blood pressure = 34.8%, diastolic blood pressure = 22.7% (men); and systolic blood pressure = 31.4%, diastolic blood pressure = 26.9% (women).³ The arterial baroreflex plays an important role in the short-term regulation of blood pressure.⁴ A decrease in baroreflex sensitivity indicates an increase in sympathetic nervous system activity. Abnormal arterial baroreflex function has been associated with adverse cardiovascular outcomes⁴ and there is increasing evidence that the baroreflex is implicated in the pathogenesis of essential hypertension.⁵ Baroreflex sensitivity can be defined as the magnitude of response in heart beat interval to a change in blood pressure expressed in ms/mmHg.⁶ Not surprisingly, reduced baroreflex sensitivity is an independent predictor of total mortality and cardiovascular morbidity in hypertensive patients.⁷

Many studies have focused on hypertension in black South Africans in an attempt to understand the increased prevalence of hypertension among this population group. Studies linking baroreflex sensitivity and hypertension in South Africans have not been published to date. The aim of this study was, therefore, to investigate the relationship between baroreflex sensitivity and cardiovascular function in Africans and Caucasians from South Africa.

2.4 METHODS

Study population

The study was embedded in the SAfrEIC (South African study regarding the influence of Sex, Age and Ethnicity on Insulin sensitivity) study that included 747 African and Caucasian men and women living in the Potchefstroom region of the North West Province of South Africa. The inclusion criteria were apparently healthy participants aged 20–70 years. The exclusion criteria were pregnancy, lactation and diabetes (type 1 or 2 as well as the use of diabetic medication). Participants were divided into four groups: African women ($n = 192$); African men ($n = 181$); Caucasian women ($n = 211$) and Caucasian men ($n = 163$). This study was approved by the Ethics Committee of the North-West University, Potchefstroom Campus and conforms to the ethical guidelines of the 2004 Declaration of Helsinki.⁸ Participation was voluntary and could have been discontinued at any time. The opportunity was given to ask questions and assistance was available to provide information in their home language. All subjects signed informed consent documents.

Experimental procedure

All participants reported at 07:00 at the Metabolic Unit facility of the North-West University, Potchefstroom Campus. The participants were introduced to the experimental set-up while the objectives and procedures as well as the requirements of the study were explained. Each participant completed a demographic and lifestyle questionnaire, as well as the Beacke physical activity questionnaire, while the women were asked to complete an additional hormone and menopausal assessment form.

Anthropometric measurements

Weight, height and waist circumference were measured by trained anthropometrists (Precision Health Scale, A & D Company, Japan; Invicta Stadiometer, IP 1465, UK; Holtain unstretchable metal tape). Measurements were taken in triplicate using standard methods.⁹

Cardiovascular measurements

The participants rested for 10 minutes prior to cardiovascular measurements. Blood pressure of the participants was measured for seven minutes by a cardiovascular physiologist on the finger and the left upper arm with a Finometer device (FMS, Finapres Measurement Systems, Arnhem, The Netherlands). The FinometerTM computed all cardiovascular variables and stored the data in computer files. The Beatscope 1.1 software programme integrated the data of each participant (age, gender and height). The data were further analysed to obtain systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and arterial compliance (C_w) of each participant.

Blood pressure of the participants was also measured twice at a five minute interval with the validated OMRON Model HEM-757. Arterial stiffness by means of pulse wave velocity (PWV) was measured between the carotid and dorsalis-pedis artery (Complior SP). OMRON sitting blood pressure was used in the analyses. Baroreflex sensitivity (BRS) was determined by the validated cross-correlation baroreflex sensitivity (xBRS) method, derived from the continuous blood pressure measurement using the Finometer apparatus. xBRS computes the correlation between beat-to-beat SBP and R-R interval, resampled at 1 Hz, over 10 second sliding windows – a time-span sufficient to accommodate fully 10 second variability in rhythm, or several cycles at ventilatory frequencies. It has been suggested that this method be used in clinical and experimental settings because of its lower within-patient variance compared to other BRS methods.⁶

Biochemical measurements

Serum total cholesterol (TC) and gamma glutamyltransferase (GGT) were analyzed with the Konelab TM auto analyzer (Thermo Fisher Scientific Oy, Vantaa, Finland). Low-density lipoprotein (LDL) was computed with the Friedewald-formula, $LDL = TC - HDL \text{ cholesterol} - (0.45 \times \text{triglycerides})$.¹⁰

Statistical analysis

For database management and statistical analyses, the Statistica v.8 software (Statsoft, Inc., 2008) was used. Variables with a non-Gaussian distribution were logarithmically transformed and the central tendency and spread represented by the geometric mean and the 5th and 95th percentile intervals. Means and proportions were compared by analyses of variance (ANOVA) and the chi-square (χ^2) test, respectively. Correlations between cardiovascular function and BRS using single, partial and multiple linear regressions were investigated. A forward stepwise multiple regression analysis was executed for each group with SBP, DBP and PWV* as dependent variable and BRS, age, body mass index (BMI), physical activity, GGT, TC, smoking, alcohol and antihypertensive treatment as independent variables. *PWV was additionally adjusted for mean arterial pressure (MAP).

2.5 RESULTS

Study population

The overall sample of 747 participants consisted of African women (25.70%), African men (24.23%), Caucasian women (28.25%) and Caucasian men (21.82%). Table 1 describes the baseline characteristics of the participants stratified by ethnicity and gender.

Table 1 Baseline characteristics of participants stratified by ethnicity and gender

Variables	African women (n = 192)	African men (n = 181)	Caucasian women (n = 211)	Caucasian men (n = 163)
Age (years)	41 ± 0.8	40.8 ± 1.0	40.8 ± 0.9	40.0 ± 1.0
BMI (kg/m ²)	27.1 ± 0.5 ^a	20.6 ± 0.3 ^{abc}	27.3 ± 0.4 ^b	28.4 ± 0.4 ^c
Waist circumference (cm)	82 ± 1.01 ^{ab}	75 ± 0.8 ^{acd}	82 ± 0.9 ^{ce}	95 ± 1.1 ^{bde}
Cardiovascular measurements:				
SBP (mmHg)	126 ± 1.7 ^{ab}	132 ± 1.5 ^{ac}	118 ± 1.1 ^{bcd}	127 ± 1.0 ^d
DBP (mmHg)	86 ± 1.0 ^{ab}	85 ± 1.0 ^{cd}	78 ± 0.7 ^{ac}	80 ± 0.7 ^{bd}
MAP (mmHg)	99 ± 1.15 ^a	100 ± 1.1 ^{bc}	91 ± 0.8 ^{abd}	96 ± 0.8 ^{cd}
C _w (ml/mmHg)	1.7 ± 0.04 ^{ab}	1.6 ± 0.03 ^{cd}	2.0 ± 0.04 ^{ace}	2.2 ± 0.04 ^{bde}
HR (bpm)	74 ± 0.9 ^{abc}	68 ± 1.1 ^a	68 ± 0.6 ^b	65 ± 0.7 ^c
PWV (m/s)	7.8 ± 0.1 ^a	8.6 ± 0.1 ^{abc}	7.6 ± 0.1 ^{bd}	8.1 ± 0.1 ^{cd}
BRS (ms/mmHg)	9.4 (3.1 – 29.7)	10.7 (3.5 – 33.6)	9.8 (3.8 – 34.8)	10.04 (3.4 – 29.1)
Biochemical measurements:				
GGT (U/L)	56 (17 – 349)	81 (21 – 486)	26 (13.4 – 80.3)	38 (18.1 – 103.9)
TC (mmol/l)	4.4 ± 1.1 ^{ab}	4.3 ± 0.1 ^{cd}	5.9 ± 0.1 ^{ac}	5.8 ± 0.1 ^{bd}
LDL (mmol/l)	2.4 ± 0.1 ^{ab}	2.2 ± 0.1 ^d	3.7 ± 0.1 ^{ac}	3.8 ± 0.1 ^{bd}
Lifestyle:				
Physical activity (MJ/h)	7.4 ± 0.1 ^{ab}	8.2 ± 0.1 ^{ac}	7.2 ± 0.1 ^{cd}	7.9 ± 0.1 ^{bd}
Smoking, n (%)	91 (47.4) ^{bc}	134 (74.4) ^{ace}	20 (9.5) ^{bde}	35 (21.5) ^{cd}
Alcohol, n (%)	103 (53.7) ^a	151 (83.4) ^a	122 (57.6) ^b	123 (75.5) ^b
Antihypertensive treatment, n (%)	1 (0.5) ^b	0 (0)	37 (17.5) ^b	36 (22.4)
Contraception – pill, n (%)	5 (2.6)	–	44 (20.9)	–
Contraception – injection, n (%)	26 (13.6)	–	6 (2.8)	–
Hypertensives, n (%)	53 (27.9) ^{ac}	67 (36.8) ^{ac}	12 (5.7) ^a	14 (8.5) ^c

Data are arithmetic ± SE, geometric mean (5th and 95th percentile intervals), or number of women (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; C_w, arterial compliance; HR, heart rate; PWV, pulse wave velocity; BRS, baroreflex sensitivity; GGT, gamma glutamyltransferase; TC, total cholesterol; LDL, low-density lipoprotein. Means with the same superscript letter are statistically significant (p ≤ 0.05).

BMI and waist circumference were significantly lower in African men compared to African women, Caucasian women and Caucasian men. SBP was significantly higher in African men compared to African and Caucasian women and DBP significantly higher compared to Caucasian women and men. PWV was the highest in African men compared to the other three groups. No significant difference in BRS existed between the groups. TC was the lowest in African men in comparison to Caucasian men and women. LDL was also lower among African men compared to Caucasian

men. African men were more physically active than African and Caucasian women. There were more African men who smoked compared to the other groups, while alcohol consumption was higher in African men compared to African women. The prevalence of hypertension was also the highest in African men.

Table 2 Pearson correlations of BRS with measures of cardiovascular function

	African women (n = 192)	African men (n = 181)	Caucasian women (n = 211)	Caucasian men (n = 163)
SBP (mmHg)	$r = -0.45; p < 0.001$	$r = -0.40; p < 0.001$	$r = -0.47; p < 0.001$	$r = -0.42; p < 0.001$
DBP (mmHg)	$r = -0.40; p < 0.001$	$r = -0.39; p < 0.001$	$r = -0.40; p < 0.001$	$r = -0.51; p < 0.001$
PWV (m/s)	$r = -0.43; p < 0.001$	$r = -0.45; p < 0.001$	$r = -0.38; p < 0.001$	$r = -0.31; p < 0.001$

BRS, baroreflex sensitivity; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity.

Unadjusted analysis

In single regression analysis, SBP ($r = -0.40$ to -0.47 ; $p < 0.0001$), DBP ($r = -0.39$ to -0.51 ; $p < 0.0001$) and PWV ($r = -0.31$ to -0.45 ; $p < 0.0001$) correlated negatively with BRS in all groups (Table 2).

Adjusted analysis

After partially adjusting for age, BMI and C_w , SBP increased significantly with decreased BRS in African men (p for trend = 0.038), Caucasian women (p for trend = 0.008) and Caucasian men (p for trend = 0.001) (Fig.1a). Similarly, DBP increased with decreased BRS in African men (p for trend = 0.081), Caucasian men (p for trend = 0.0003) and Caucasian women (p for trend = 0.002). However, BRS decreased significantly with an increase in PWV in African men (p for trend = 0.025) only. After full adjustment (age, BMI, C_w , physical activity, current smoking, current alcohol consumption, antihypertensive treatment, GGT, TC, HIV and the use of contraception (oral / DMPA) (Table 3 and 4), the previously obtained associations with SBP, DBP and PWV were confirmed. SBP and DBP correlated negatively with BRS in all four groups. However, a negative correlation between PWV and BRS was evident in the African men only.

Sensitivity analyses

Due to significantly higher use of the Depot medroxyprogesterone acetate (DMPA) contraceptive injection among the African women (18.6% vs. 2.8%, $p < 0.0001$) and conversely, significantly higher use of oral contraception among the Caucasian women (29.9% vs. 2.6%, $p < 0.0001$), the data were additionally adjusted for these variables. After doing so, the result remained unchanged. In addition, due to the significantly higher incidence of HIV among the African participants (43.1% vs. 0.3%, $p < 0.0001$), there was also an additional adjustment for HIV-status in African women and men. Again, by doing so did not appreciably alter the findings.

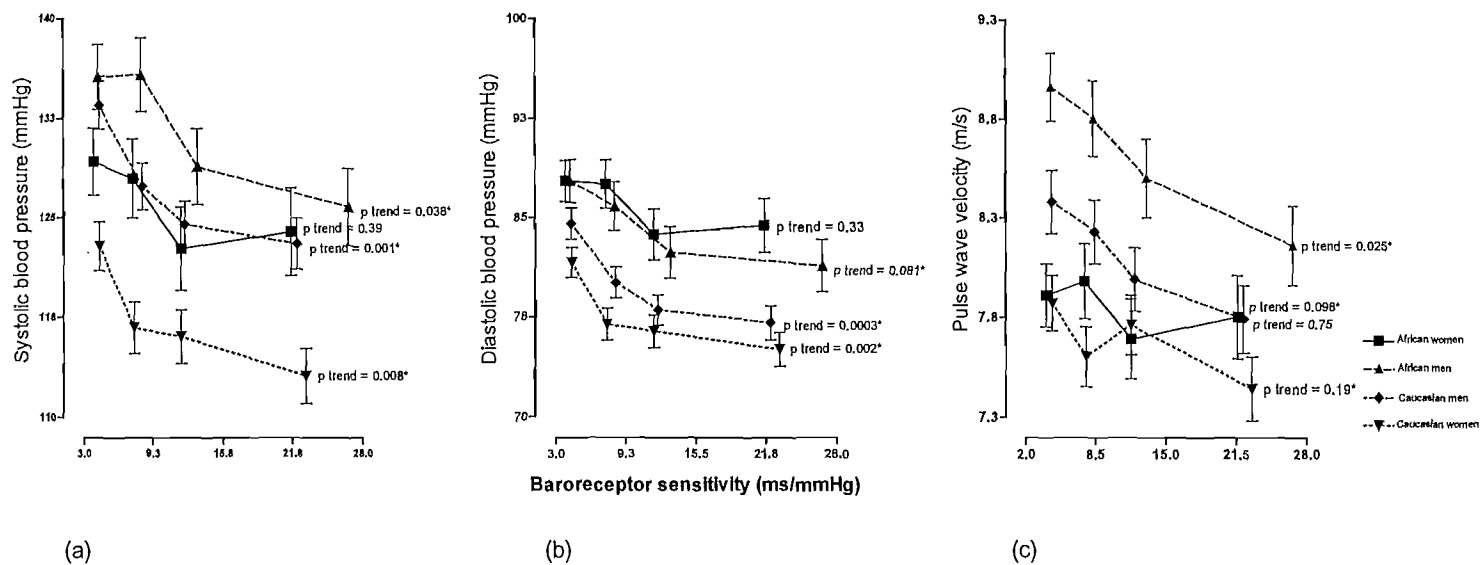


Fig. 1: SBP, DBP and PWV by quartiles of BRS. Plotted values are least squares means (SE) adjusted for age, BMI and C_w . p denotes significance for trend; $p < 0.05$.

Table 3 Independent associations of blood pressure and pulse wave velocity with baroreceptor sensitivity

African women (n = 192)						
R ²	SBP (mmHg)		DBP (mmHg)		PWV (m/s)	
	0.380		0.304		0.400	
	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
BRS (ms/mmHg)	-0.235 (-0.390 to -0.080)	0.003	-0.237 (-0.400 to -0.073)	0.005	NS	
Age (years)	0.306 (0.134 to 0.477)	0.0006	0.177 (0.003 to 0.351)	0.048	0.312 (0.191 to 0.432)	<0.0001
BMI (kg/m ²)	0.10 (-0.03 to 0.23)	0.138	0.236 (0.101 to 0.372)	0.0008	-0.123 (-0.231 to -0.016)	0.026
Physical activity (MJ/h)	NS		NS		NS	
Smoke (0,1)	-0.118 (-0.264 to 0.028)	0.114	NS		NS	
Alcohol (0,1)	0.172 (0.037 to 0.307)	0.013	0.181 (0.042 to 0.320)	0.012	NS	
MAP (mmHg)	–		–		0.542 (0.420 to 0.663)	<0.0001
GGT (U/L)	NS		NS		NS	
TC (mmol/l)	0.141 (-0.003 to 0.285)	0.057	0.119 (-0.033 to 0.271)	0.127	NS	
C _w (ml/mmHg)	NS		NS		NS	
Antihypertensive treatment (0,1)	0.171 (0.041 to 0.301)	0.011	NS		NS	
African men (n = 181)						
R ²	SBP (mmHg)		DBP (mmHg)		PWV (m/s)	
	0.273		0.311		0.367	
	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
BRS (ms/mmHg)	-0.287 (-0.444 to -0.130)	0.0005	-0.252 (-0.416 to -0.087)	0.003	-0.122 (-0.262 to 0.018)	0.090
Age (years)	0.155 (-0.006 to 0.315)	0.061	NS		0.198 (0.068 to 0.327)	0.003
BMI (kg/m ²)	0.254 (0.113 to 0.394)	0.0005	0.303 (0.165 to 0.442)	<0.0001	-0.153 (-0.018 to -0.288)	0.027
Physical activity (MJ/h)	NS		-0.107 (-0.251 to 0.038)	0.149	NS	
Smoke (0,1)	NS		NS		NS	
Alcohol (0,1)	NS		NS		NS	
MAP (mmHg)	–		–		0.484 (0.351 to 0.617)	<0.0001
GGT (U/L)	NS		NS		0.184 (0.057 to 0.311)	0.005
TC (mmol/l)	0.119 (-0.026 to 0.264)	0.109	NS		NS	
C _w (ml/mmHg)	NS		NS		NS	
Antihypertensive treatment (0,1)	NS		NS		NS	

BRS, baroreflex sensitivity; BMI, body mass index; MAP, mean arterial pressure ; GGT, gamma glutamyltransferase; TC, total cholesterol; C_w, arterial compliance.

Table 4 Independent associations of blood pressure and pulse wave velocity with baroreceptor sensitivity

Caucasian women (n = 211)						
R ²	SBP (mmHg)		DBP (mmHg)		PWV (m/s)	
	0.432		0.382		0.324	
	<u>Beta (95% CI)</u>	<u>p</u>	<u>Beta (95% CI)</u>	<u>p</u>	<u>Beta (95% CI)</u>	<u>p</u>
BRS (ms/mmHg)	-0.311 (-0.448 to -0.174)	<0.0001	-0.282 (-0.408 to -0.156)	<0.0001	NS	
Age (years)	NS		NS		0.373 (0.229 to 0.517)	<0.0001
BMI (kg/m ²)	0.209 (0.081 to 0.337)	0.002	0.345 (0.221 to 0.468)	<0.0001	NS	
Physical activity (MJ/h)	NS		NS		NS	
Smoke (0,1)	NS		NS		NS	
Alcohol (0,1)	NS		NS		NS	
MAP (mmHg)	–		–		0.312 (0.163 to 0.459)	<0.0001
GGT (U/L)	NS		NS		NS	
TC (mmol/l)	0.131 (0.009 to 0.253)	0.037	0.154 (0.033 to 0.276)	0.014	NS	
C _w (ml/mmHg)	NS		NS		NS	
Antihypertensive treatment (0,1)	0.339 (0.204 to 0.474)	<0.0001	0.211 (0.084 – 0.337)	0.001	0.125 (-0.023 to 0.272)	0.100
Caucasian men (n = 163)						
R ²	SBP (mmHg)		DBP (mmHg)		PWV (m/s)	
	0.328		0.455		0.244	
	<u>Beta (95% CI)</u>	<u>p</u>	<u>Beta (95% CI)</u>	<u>p</u>	<u>Beta (95% CI)</u>	<u>p</u>
BRS (ms/mmHg)	-0.341 (-0.482 to -0.200)	<0.0001	-0.30 (-0.439 to -0.152)	<0.0001	NS	
Age (years)	NS		0.221 (0.070 to 0.372)	0.005	0.446 (0.280 to 0.612)	<0.0001
BMI (kg/m ²)	NS		0.337 (0.199 to 0.475)	<0.0001	NS	
Physical activity (MJ/h)	0.158 (0.018 to 0.300)	0.028	NS		NS	
Smoke (0,1)	NS		NS		0.117 (-0.030 to 0.264)	0.121
Alcohol (0,1)	NS		NS		NS	
MAP (mmHg)	–		–		NS	
GGT (U/L)	NS		NS		NS	
TC (mmol/l)	NS		NS		-0.134 (-0.282 to 0.015)	0.081
C _w (ml/mmHg)	NS		NS		NS	
Antihypertensive treatment, (0,1)	0.407 (0.266 to 0.548)	<0.0001	0.169 (0.028 to 0.310)	0.020	NS	

BRS, baroreflex sensitivity; BMI, body mass index; MAP, mean arterial pressure; GGT, gamma glutamyltransferase; TC, total cholesterol and C_w, arterial compliance..

2.6 DISCUSSION

A population based sample of African and Caucasian men and women was examined to investigate the relationship between BRS and cardiovascular function in African and Caucasian men and women. Although, SBP and PWV was the highest in African men, no significant differences existed for BRS between the groups. After adjusting for significant covariates, associations indicated that blood pressure increased with a decrease in BRS in all four groups. In addition, in African men with stiffer arteries, associations indicate that increased arterial stiffness could possibly contribute to reduced BRS and increased blood pressure in black South Africans.

Zion et al.¹¹ investigated the differences in arterial stiffness and autonomic modulation between young, healthy African-American men with no signs of hypertension, and age and gender-matched non-African American men. The findings of the study revealed that these African-American men have stiffer arteries and an augmentation in sympathovagal balance.¹¹ The increased arterial stiffness and changes in autonomic modulation observed were independently and in combination related to increased risk of hypertension.¹¹ Due to the shift in autonomic balance to the sympathetic side (reduced BRS), as shown in this study, the higher sympathetic outflow may alter vascular reactivity and has been a suggested mechanism for the increased prevalence of hypertension in black men.¹² The negative correlation with arterial stiffness indicates a contributory role of arterial stiffness in attenuating BRS. The increased arterial stiffness in African men could be due to the higher prevalence of smoking and drinking, and hypertension prevalence observed in the African men. Cigarette smoking, via its vasoconstrictive effects, increases blood pressure, and possibly promotes endothelial injury and dysfunction and thereby the hypertensive state.¹³ Excess alcohol consumption provokes hypertension, possibly acting through release of aldehydes that stimulate the adrenergic system.¹³ This may be clarified by genetic differences related to polymorphic differences in α -adrenergic receptors possessing peripheral vascular sensitivity to norepinephrine. As the measure of PWV includes both muscular and elastic arteries, the results could indeed also reflect this enhanced vascular reactivity in Africans. Previous studies¹² in this population group found an enhanced vascular reactivity, which, as this study shows, could be due to reduced BRS (enhanced sympathetic activity).

To date, no studies explored this relationship in Africans from South Africa, although a few related studies are available. Urbanised black populations are more vulnerable to increases in blood pressure during everyday life.¹² Exaggerated cardiovascular reactivity during mental and emotional stress in urbanised blacks may lead to the development of hypertension.¹² In the present study however, associations indicate that the effect of increased arterial stiffness on decreasing BRS is

more prominent in African men. This study may have important implications for the cardiovascular health of Africans from South Africa, since Caucasians are 44% less prone to develop hypertension compared to blacks.² In a house-to-house study of 994 urban Zulus conducted in Durban in 1982, the prevalence of hypertension was 25%.¹⁴ In a multicentre, observational study of patients attending general practice in South Africa, the prevalence of stroke risk factors was evaluated through the return of 9731 questionnaires. The survey showed that hypertension was the highest in black patients (59%).² Data from a registry of 4162 patients admitted to Baragwanath Hospital in Soweto in 2006 showed that 31% had advanced heart failure and 87% of people living in Soweto had one or more risk factor(s) for coronary heart disease.¹⁵ The changes in BRS may contribute to the higher prevalence of hypertension found in Black South Africans.

This current study must be interpreted within the context of its limitations and strengths. Although the results were consistent after multiple adjustments, one cannot exclude residual confounding. A cross-sectional design was applied to investigate the relationship between BRS and cardiovascular function and cannot infer causality. The carotid-dorsalis pedis PWV and not the carotid-femoral PWV was used. However, this measure of PWV was used in all groups and, therefore, comparable.

It seems feasible to conclude that increased arterial stiffness could possibly contribute to a decrease in BRS and increased SBP in black South Africans. This may contribute to the increased risk of cardiovascular diseases and higher incidence of hypertension in the black population of South Africa.

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CHAPTER 3

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

3.1 INTRODUCTION

In this chapter, a summary of the main findings from the manuscript reported in this dissertation will be given. The results from the manuscript will be discussed, interpreted, elucidated and compared to the relevant literature. Conclusions will be drawn and recommendations will be made to researchers investigating baroreflex sensitivity and cardiovascular function in Africans and Caucasians from South Africa.

3.2 SUMMARY OF MAIN FINDINGS

The aim of the study was to investigate the relationship between baroreflex sensitivity and cardiovascular function in African and Caucasian men and women from the Potchefstroom area in South Africa, using data from the SAfrEIC study. It was hypothesised that baroreflex sensitivity is the lowest and blood pressure and pulse wave velocity the highest in Africans compared to Caucasians from South Africa. In addition, it was hypothesised that the reduced baroreflex sensitivity contributes to increased blood pressure in Africans.

Associations indicated that as baroreflex sensitivity decreases, blood pressure increases in African men and Caucasian men and women. In addition, the stiffer arteries as reflected by increased pulse wave velocity observed in the African men, also seem to have the most prominent attenuating effect on baroreflex sensitivity. Increased sympathetic nervous system activity is a possible mechanism that may lead to reduced baroreflex sensitivity.¹ Due to the shift in the autonomic balance to the sympathetic side, the increased sympathetic outflow may alter vascular reactivity in Black men or enhance arterial stiffness (increased pulse wave velocity) and thereby reduce baroreflex sensitivity. Conversely, stiffer arteries may contribute to decreased baroreflex sensitivity due to environmental and genetic factors.² Arterial stiffness increases pulse pressure, pulse wave velocity and baroreflex load, and thus reduces baroreflex sensitivity.¹ A further reduction in baroreflex sensitivity reduces buffering even more, and results in larger increases in blood pressure.² Systolic blood pressure was significantly higher in African men compared to African and Caucasian women, indirectly reflecting stiffer arteries. Furthermore, pulse wave velocity was also significantly higher in African men in comparison to African women and Caucasian men and women. However, baroreflex sensitivity did not differ significantly. The first hypothesis is, therefore, partly accepted. The association between baroreflex sensitivity and pulse wave velocity was the most prominent in the black men. Therefore, the increased arterial stiffness could possibly contribute to the reduced baroreflex sensitivity and higher hypertension prevalence observed in the black South African men. The second hypothesis is also accepted. Numerous lifestyle factors, for example smoking and alcohol consumption influence arterial properties and baroreflex sensitivity.¹

Because smoking and drinking were the highest in black African men, these factors may contribute to endothelial damage and higher arterial stiffness, and eventually decrease baroreflex sensitivity.³ This decrease in baroreflex sensitivity is brought about by a reduction in mechanical stretching and relaxation of the arterial wall during changes in blood pressure⁴ and hampers the functioning of the baroreceptors.

3.3 Chance and Confounding

Chance

Before the main findings of this study are discussed, it is important to reflect critically on some important factors that may have affected the results. There are some methodological issues that could have weakened the study and, therefore, might have influenced the different outcomes.

Concerning the results, the possibility of chance should be taken into account. By using partial correlations and forward stepwise regression analysis, statistics indicated that one out of twenty significant correlations may be because of chance.

Confounders

Confounders such as smoking, alcohol intake, level of physical activity and antihypertensive treatment could have influenced the results by causing over or under-estimation of the associations between baroreflex sensitivity and the various variables of cardiovascular function investigated in this study. Age, arterial compliance and body mass index, as possible confounders, were addressed by statistically adjusting for them. Sex, as a possible confounder in this study, was addressed by the classification of male and female groups. Although the explanation of procedures was done in the participants' home language, the understanding of the procedures by the participants could not be guaranteed and could, therefore, have had confounding effects on the outcome of the study. Although the results were consistent, after multiple adjustments, one cannot exclude residual confounding.

Confounders can also mask a real association. In the interpretation of the results in this manuscript, it was attempted to interpret statistical results from a physiological viewpoint at all times, while keeping in mind that a statistical significance does not necessarily mean physiological significance, and vice versa.

3.4 CONCLUSIONS

It seems feasible to conclude that:

- Increased arterial stiffness could possibly contribute to reduced baroreflex sensitivity and increased blood pressure in black South Africans.
- Reduced baroreflex sensitivity shifts the autonomic balance to the sympathetic side which may contribute to the increased risk of cardiovascular disease and high prevalence of hypertension in the black South African population.
- Increased sympathetic nervous system activity may be aggravated by chronic stressors associated with urbanisation.

The results of this study are valuable in contributing to the current knowledge regarding the black South African population. Since only associations of baroreflex sensitivity and cardiovascular parameters were investigated, it could also give direction for future clinical research concerning cause and effect relationships that could be used for recommendations to health professionals.

3.5 RECOMMENDATIONS

After the interpretation of the results, it became clear that the following recommendations need to be made to obtain a complete picture of the relationship between baroreflex sensitivity and cardiovascular function in Africans and Caucasians from South Africa:

- The S AfrEIC study consisted of a total of 757 participants, which included 32% black hypertensives and 7% Caucasian hypertensives. Also 60% of blacks smoked compared to 15% of Caucasians and 68% of blacks consumed alcohol in comparison to 66% of Caucasians. If healthier black subject groups were available, it could have led to more plausible, reliable and comparable results. This could indeed be a weakness and the use of healthy participants is recommended.
- Certain participants were more restless or afraid because of unfamiliar procedures – despite the fact that they were informed about the procedures – while their cardiovascular measurements were taken, which could have led to false high values. It is recommended to take more than one measurement to ensure true values are reflected as in the case of pulse wave velocity.
- Although it was attempted to draw representative samples from the population in the North West Province, it is possible that the participants did not represent the population from which they were selected. It is recommended to draw population samples from different geographical areas to ensure a true representation of the whole population group.

- Due to the cross-sectional design, this study cannot establish cause and effect. By the application of an appropriate prospective design, a clearer picture may be obtained regarding the underlying mechanisms at work.
- Salt sensitivity and sympathetic activity have been reported to play a significant role in the development and/or maintenance of hypertension in Africans⁵ and should, therefore, always be assessed when studying this population group.

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