# Double product and end-organ damage in African and Caucasian men: The SABPA study

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Innovation through diversity

NORTH-WEST UNIVERSITY
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## TABLE OF CONTENTS

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***JESAJA 40:31***

*Maar dié wat op die Here vertrou kry nuwe krag. Hulle vlieg met arendsvlerke, hulle hardloop en word nie moeg nie, hulle loop en raak nie afgemat nie.*

**ENGLISH TITLE: Double product and end-organ damage in African and Caucasian men: The SABPA study**

## SUMMARY

**Motivation:** Recently, with urbanisation becoming an increasing trend, the African population have been introduced to the westernised lifestyle. This contributed to severe health implications and a rapid increase in cardiovascular morbidity and mortality in the African population. In South Africa and other sub-Saharan African countries, the prevalence of cardiovascular disease is increasing rapidly. The African population is thus regarded as a high risk group, and we deem it necessary and important to investigate additional possible cardiovascular risk markers in the attempt to improve the diagnosis of cardiovascular diseases and the treatment thereof. We investigate double product as a possible cardiovascular risk marker in African and Caucasian men from South Africa. Recent studies have suggested that increased double product values might be an independent predictor of cardiovascular morbidity and mortality. However, investigations on double product and end-organ damage are limited in this population group. The strength of associations between double product and various measurements of end-organ damage, including intima-media thickness, left ventricular hypertrophy and albumin-to-creatinine ratio, are compared with the associations between the more traditional risk factor, systolic blood pressure, and the measurements of end-organ damage.

**Aim:** The aim of this study is to investigate the usability of double product as a possible cardiovascular risk marker in African and Caucasian men from South Africa.

**Methodology:** The manuscript presented in Chapter 3 made use of the cross-sectional SABPA (**S**ympathetic **A**ctivity and Ambulatory **B**lood **P**ressure in **A**fricans) study, where 101 urbanised African and 101 Caucasian male school teachers from the North West Province of South Africa were recruited. Anthropometric measurements were taken in triplicate using standard methods. The cardiovascular measurements included 24-hour ambulatory blood pressure and electrocardiogram measurements. Double products were calculated as the product of 24-hour, daytime and night-time mean systolic blood pressure and mean heart rate values. The carotid intima-media thickness was also obtained following the prescribed protocols. A registered nurse collected blood samples and the biochemical measurements were performed by independent laboratories, blinded to the subject's cardiovascular profile. Means and proportions were compared by standard t-tests and the $\chi^2$ -tests, respectively. The association between markers of end-organ damage and double product were

investigated using single, partial and multiple regression analyses. All p-values ≤ 0.05 were deemed significant.

**Results and conclusions:** Results from this study showed that Africans displayed significantly higher systolic blood pressure values, heart rate values and subsequent double product values compared to the Caucasians. Despite these significant differences, double product only showed borderline significant correlations with the markers of end-organ damage in African men, while no correlations were evident in Caucasian men. In African men, systolic blood pressure displayed stronger and significant correlations with intima-media thickness, left ventricular hypertrophy, and albumin-to-creatinine ratio than double product. These findings suggest that double product may not be a good marker of increased risk for end-organ damage and subsequent cardiovascular-related mortality.

**KEY WORDS:** Africans, double product, end-organ damage, heart rate, systolic blood pressure

**AFRIKAANSE TITEL: Dubbelproduk en eind-orgaanskade in swart en wit mans: Die SABPA-studie**

## OPSOMMING

**Motivering:** Die onlangse toename in verstedeliking speel ‘n groot rol in die verwestering van die swart Suid-Afrikaanse populasie. Hierdie leefstylaanpassings het verskeie gesondheidsimplikasies en dra by tot die vinnige toename in kardiovaskulêre morbiditeit en mortaliteit onder dié populasiegroep. Volgens onlangse studies is daar ‘n skielike toename in die voorkoms van kardiovaskulêre siektes in Suid-Afrika en ander sub-Sahara Afrikalande. Die swart populasie word beskou as ‘n hoërisikogroep en daarom is dit noodsaaklik en van uiterste belang om addisionele kardiovaskulêre risikomerkers te ondersoek om sodoende die diagnose en behandeling van kardiovaskulêre siektes te bevorder. Ons wil dubbelproduk ondersoek as ‘n moontlike kardiovaskulêre risikomerker in swart en wit mans van Suid-Afrika. Onlangse studies het voorgestel dat verhoogde dubbelprodukwaardes ‘n onafhanklike voorspeller van kardiovaskulêre morbiditeit en mortaliteit kan wees. Navorsing rakende dubbelproduk en eind-orgaanskade in hierdie populasiegroep is uiters beperk. Dit is dus nodig om assosiasies tussen dubbelproduk en verskeie eind-orgaanskademetings, nl. intima-media dikte, linker ventrikulêre hipertrofie en albumien-tot-kreatinien ratio, te vergelyk met die assosiasies tussen die meer tradisionele risikofaktor, sistoliese bloeddruk, met eind-orgaanskademetings.

**Doelstelling:** Die doel van hierdie studie is om die bruikbaarheid van dubbelproduk as ‘n moontlike kardiovaskulêre risikomerker van eind-orgaanskade in swart en wit mans te ondersoek.

**Metodologie:** Die manuskrip wat in Hoofstuk 3 vervat is, het gebruik gemaak van die dwarsdeursnee SABPA (**S**ympathetic **A**ctivity and Ambulatory **B**lood **P**ressure in **A**fricans)-projek, waar 101 verstedelikte swart en 101 wit onderwysers van die Noordwes Provinsie van Suid-Afrika as proefpersone gekies is. Antropometriese metings is in drievoud geneem deur middel van standaardmetodes. Die kardiovaskulêre metings sluit 24-uur ambulatoriese bloeddruk en elektrokardiogram-metings in. Dubbelproduk is bereken as die produk van die gemiddelde sistoliese bloeddruk and gemiddelde harttempowaardes. Die karotis intima-media dikte is ook verkry volgens die voorgeskrewe protokol. ‘n Geregistreerde verpleegkundige het bloedmonsters by die proefpersone geneem en die biochemiese metings is uitgevoer deur onafhanklike laboratoriums, verblind tot die proefpersoon se kardiovaskulêre profiel. Gemiddeldes van die onderskeie populasiegroepe is deur middel

van standaard t-toetse en $\chi^2$ –toetse vergelyk. Die assosiasies tussen die merkers van eind-orgaanskade en dubbelproduk is ondersoek deur gebruik te maak van enkel-, parsiële en meervoudige regressie-analises. Alle p-waardes ≤ 0.05 is as betekenisvol beskou.

**Resultate en gevolgtrekkings:** Die resultate van hierdie studie toon dat die swart mans betekenisvol hoër sistoliese bloeddruk en harttempowaardes asook dubbelprodukte in vergelyking met die wit mans het. Ten spyte van hierdie betekenisvolle verskille het dubbelproduk slegs grenslyn- betekenisvolle korrelasies getoon met die merkers van eind-orgaanskade by die swart mans, terwyl geen korrelasies by die wit mans sigbaar was nie. By die swart mans het sistoliese bloeddruk sterker en betekenisvolle korrelasies getoon met die merkers van eind-orgaanskade, nl. intima-media dikte, linker ventrikulêre hipertrofie en albumien-tot-kreatinien ratio, as die van dubbelproduk. Hierdie bevindings suggereer dat dubbelproduk dus nie ‘n goeie merker van verhoogde risiko vir eind-orgaanskade en kardiovaskulêr-verwante morbiditeit is nie.

**SLEUTELWOORDE:** dubbelproduk, eind-orgaanskade, harttempo, sistoliese bloeddruk, Suid-Afrikaners

## PREFACE

This dissertation has the following format, as approved by the North-West University. It consists of four chapters, with Chapter 1 providing an introduction containing a short background, motivation, aim and hypotheses. Chapter 2 is a complete overview of the literature pertaining to the topic. Chapter 3 comprises of the article containing the methodology, results and interpretation of the study. Chapter 4 contains the general findings and conclusions. Appropriate references are presented at the end of each chapter, according to the instructions of the international, peer-reviewed journal, *Hypertension Research*.

## AUTHOR'S CONTRIBUTIONS

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

| NAME | ROLE IN THE STUDY |
|---|---|
| Mr. AJ Schultz | Involved during the SABPA study through supervising of the subject questionnaires and completing necessary procedures involved with serum and saliva sampling. Responsible for literature searches, processing of cardiovascular data, statistical analysis, design and planning of the manuscript, interpretation of results and writing of the manuscript. |
| Dr. R Schutte (Ph.D.) (Physiologist) | Supervisor. Supervised the writing of the manuscript, collection of cardiovascular data, as well as initial planning and design of the manuscript. |
| Prof. AE Schutte (Ph.D.) (Physiologist) | Co-supervisor. Supervised the writing of the manuscript, collection of cardiovascular data, as well as initial planning and design of the manuscript. |

This is a statement from the co-authors confirming their individual role in the study and giving their permission that the article may 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 Andreas Schultz.*

_____ _____

Dr. R Schutte Prof. AE Schutte

## LIST OF TABLES AND FIGURES

# CHAPTER 1

# INTRODUCTION

## GENERAL INTRODUCTION

In recent decades, urbanisation has become a global trend,[1] especially in developing countries like South Africa and other sub-Saharan African countries.[2,3] According to the World Developing Indicators Database, in 1990, 52.0% of the South African population resided in urban areas. This number has increased to 59.3% in the year 2005.[4,5] This increasing urbanisation mostly involves the African population.[2] Moving from the rural landscapes to the urban areas causes the African population to adopt a more westernised lifestyle. Lifestyle adaptation is often accompanied by changes in nutrition, daily activity,[3] and social environment causing increased levels of stress[1] and a higher prevalence of obesity.[6] Along with these lifestyle changes, there has been a rapid increase in cardiovascular diseases amongst the African population.[1,7] In comparison to Caucasians, Africans have a greater rise in, and prevalence of morbidity and mortality from renal disease, stroke and heart disease.[8-10] This is mainly ascribed to their higher blood pressure levels and increased prevalence of hypertension,[11] occurring at a younger age and leading to earlier damage to vital organs.[6] Therefore, cardiovascular risk prediction is essential. A point of departure to improve cardiovascular risk prediction is through the investigation of the associations between cardiovascular risk markers, such as double product and end-organ damage.

Double product is a determinant of the oxygen consumption and workload of the heart.[12,13] It is also known as the pressure-rate product, being the product of systolic blood pressure and heart rate.[14-16] These two hemodynamic variables have previously been reported to have strong associations with end-organ damage and are well-known cardiovascular risk markers.[17-20] However, the product of these two variables, hence double product, is a relatively new marker, with little information available about the strength of its association with end-organ damage. Previous studies involving double product investigated its prognostic significance in subjects having suffered myocardial infarctions during stressful situations such as physical activity.[14] This involved stressing the heart to its maximum workload, to achieve maximum double product levels. There are, however, some studies that have reported increased double product to be an independent predictor of cardiovascular morbidity and mortality,[12] leading to cardiovascular pathologies such as cerebrovascular disease, left ventricular hypertrophy, heart failure and nephropathy.[21,22] However, little is known about the prognostic power of double product as a cardiovascular risk marker compared to the more traditional risk markers such as systolic blood pressure and heart rate.

Double product values are determined using 24-hour ambulatory blood pressure measurements, which make it possible to retrieve accurate double product values for both daytime activity and nocturnal sleep. These values tend to change according to the circadian pattern, closely related with changes in systolic blood pressure.[23] Continuous fluctuations in systolic blood pressure leading to changes in double product values, are regarded as a cardiovascular risk factor.[15] Although less importance have been placed on heart rate in studies involving double product, it is believed that an increased heart rate, caused by over-activity of the sympathetic nervous system, can contribute towards end-organ damage such as left ventricular hypertrophy and carotid intima-media thickening.[15,24]

Double product has been investigated in Caucasian and African-American people.[12,15] In the study by Berenson et al., it was shown that double product was higher in African Americans compared to Caucasians.[15] It has, however, not been investigated amongst African people from South Africa.

## MOTIVATION

The SABPA (Sympathetic Activity and Ambulatory Blood Pressure in Africans) study was performed on African and Caucasian men and women from South Africa. The subjects participating in this study, consisting of school teachers, were classified as being in the same socio-economic group; however, their historical backgrounds differ immeasurably. The Caucasian population in South Africa have been exposed to the westernised lifestyle for centuries. In comparison, the African population have mostly been living a simple, rural lifestyle. This lifestyle is characterised by poverty, poor health and health care,[3] a low prevalence of obesity, and an increased level of daily activity.[6] Recently, the African population have been introduced to the western lifestyle, with urbanisation becoming an increasing trend.[2,4,5] Urbanisation is characterised by nutritional, economical and other lifestyle changes[3] with severe health implications. A rapid increase in cardiovascular morbidity and mortality among the African population has been reported in recent studies.[6,8,10] The SABPA study was performed to investigate and determine the influence of a westernised lifestyle on the cardiovascular system of Africans.

In South Africa and other sub-Saharan African countries, the prevalence of cardiovascular disease is increasing rapidly.[8-10] Therefore; we deem it necessary and important to investigate additional possible cardiovascular risk markers in the attempt to improve the diagnosis of cardiovascular diseases and the treatment thereof. Some of the more familiar cardiovascular risk factors include systolic blood pressure, heart rate, inflammation, glucose and cholesterol.[25]

We investigate double product, a measure of expressing the workload of the heart, as a possible cardiovascular risk marker. Double product has been investigated as a predicative index to evaluate the risk in patients performing physical exercise after suffering single or multiple myocardial infarctions.[14] The physical exercise causes the double product value to increase to maximum levels. However, recent studies[12,21] have suggested that increased double product values might also be an independent predictor of cardiovascular morbidity and mortality. This association is still a relatively controversial subject. We therefore focussed on testing the strength of associations between double product and certain markers of end-organ damage. In addition, we also compared the strength of these associations with the associations between systolic blood pressure and the markers of end-organ damage. Systolic blood pressure is a more familiar and traditional cardiovascular risk factor, and should therefore provide us with an adequate benchmark for comparison with the relatively unknown double product.

Renal disease, stroke and heart disease are some of the most common cardiovascular diseases caused by hypertension.[24,26] Therefore; the markers of end-organ damage we investigate in this study are cross-sectional wall area, left ventricular hypertrophy and albumin-to-creatinine ratio. Should double product have significant associations with the markers of end-organ damage, cardiovascular risk prediction may be improved. Increased risk prediction may thereby contribute to improved prevention of cardiovascular diseases, especially amongst the high risk groups like the African population.

In this study, we selected male subjects instead of their female counterparts. Men tend to have higher blood pressure levels and develop hypertension at an earlier age compared to women.[27] Heart rate levels are also higher in men younger than 50 years, compared to that of women.[28] This will subsequently lead to higher double products providing us with the opportunity to investigate the association of higher double product values with markers of end-organ damage.

## AIM

The aim of this study is to investigate the usability of double product as a possible cardiovascular risk marker in African and Caucasian men from South Africa.

## OBJECTIVES

- To compare the level of end-organ damage and double product between African and Caucasian men; and
- To evaluate the strength of the associations between end-organ damage and double product compared to the known risk factor, systolic blood pressure, in African and Caucasian men.

## HYPOTHESES

- Double product is higher in African men compared to Caucasian men.
- Intima-media thickness, left ventricular hypertrophy and albumin-to-creatinine ratio are higher in African men.
- Double product is more prominently associated with markers of end-organ damage compared to systolic blood pressure.

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# CHAPTER 2

# LITERATURE STUDY

# LITERATURE STUDY

## Population description

South Africa is a developing sub-Saharan country with a predominantly black population. It is a country known to have great social diversity, ranging from highly industrialised cities with advanced lifestyles, to remote rural regions with more traditional lifestyles.[1] However, since the early 1990's, South Africa has undergone a drastic economic, social and health transition, most notably among the traditional rural black tribes being introduced to the more western lifestyle. This has caused the black South African population to experience a change in socio-economic status, characterised by lifestyle changes, inevitable stress and acculturalisation, and dietary changes contributing towards obesity.[2] This phenomenon of urbanisation has contributed strongly towards the notion that South Africa is facing a situation of an emerging epidemic of cardiovascular disease.[3] This comes as no surprise, as many studies have suggested the influence of urbanisation on African Americans,[4,5] which is a population group much more familiar with the western lifestyle compared to black South Africans.[5]

Studies evidently suggests that since the onset of this transition, black South Africans are at greater risk of developing cardiovascular ailments, compared to their white counterparts. From data collected amongst rural black Africans between 1991 and 1994, it was evident that this population group was rarely affected by cardiovascular diseases.[6] However, studies performed a decade later suggest that rural Africa is severely influenced by an increased prevalence in cardiovascular disease,[2] despite already being challenged by the pandemic of HIV/AIDS and other infectious diseases such as tuberculosis.[3] Recent studies performed in Soweto, South Africa, also found that 33% of black urbanised South Africans suffer from hypertension.[7] Black South Africans have a higher prevalence of hypertension and a steeper slope of age-related blood pressure increases compared to white South Africans,[2-4] leading to increased cerebrovascular disease and stroke.[3,8] Hypertension, together with an increasing prevalence of diabetes mellitus amongst black South Africans, are prominent risk factors in the development of renal and cardiac damage.[2] It has been proven that black hypertensive individuals are more likely to have lower renin levels than white hypertensives, a sign of renal failure.[2] They are also more likely to be diagnosed with heart failure compared to their white counterparts.[1]

This mentioned black South Africans have greater levels of plasma HDL (high-density lipoproteins) -cholesterol, leading to a greater HDL-cholesterol to total-cholesterol ratio. A

ratio of higher than 20% is protective against coronary heart disease.[3] This is an important factor considering that traditionally black South Africans experience less coronary heart disease and myocardial infarction than white South Africans.[2,3] However, with increasing urbanisation and changing lifestyles in recent times, an increasing prevalence of coronary heart disease has been noted amongst black patients.[2]

Cardiovascular disease among black South Africans is a rising epidemic.[3] However, as a developing country, South Africa and other sub-Saharan countries are struggling to provide adequate treatment to its people. This is mainly the result of inadequate funds, lack of infrastructure, shortage of medical staff,[2,3] and poor management by health-care providers.[4] With the life expectancy in sub-Saharan countries projected to decline from 54.8 years to 44.7 years during the period 2006 to 2016,[9] it is of great importance that this situation be attended to. If not, the rate of occurring cardiovascular events will continue to rise, causing an increased prevalence of end-organ damage and cardiovascular mortality.[4]

## Double product

Double product, the product of systolic blood pressure and heart rate,[10,11] is a relatively new and accepted index of left ventricular oxygen consumption and a substantial measure of the workload of the heart.[12,13] Increases in either systolic blood pressure or heart rate contribute towards increases in the double product. Recently, elevated double product values were reported to be a strong independent predictor of cardiovascular morbidity and mortality[10] through its effects on target-organs such as the brain, heart and kidneys.[14] These cardiovascular pathologies include cerebrovascular disease, left ventricular hypertrophy, heart failure and nephropathy.[14,15] Not surprisingly, increased systolic blood pressure, and subsequent increased double product, also correlates well with several markers of end-organ damage such as the albumin-to-creatinine ratio and carotid intima-media thickness.[16]

Double product is determined using 24-hour ambulatory blood pressure measurements, known to be the best method for investigating cardiovascular risk factors related to hypertension.[17] This method makes it possible to retrieve accurate double product values for both daytime activity and nocturnal sleep. Double product tends to change according to the circadian pattern, as systolic blood pressure levels fluctuate during the day.[18,19] Hermida et al. found that double product tends to be the lowest during sleep (about 3 hours before awakening), and the highest in the afternoon (about 7 hours after awakening).[18] These fluctuations in double product, mainly due to fluctuations in systolic blood pressure, are well-known and have been well characterised as a cardiovascular risk factor. On the contrary, less importance has been placed on heart rate as a cardiovascular risk factor.[12] This raises

the question whether heart rate, and in effect double product, should be considered as a valuable predictor for cardiovascular events. Heart rate is controlled by the sympathetic nervous system.[12] Over-activity of the sympathetic nervous system is the main cause of increased heart rate and has been implicated in the pathogenesis of cardiovascular disease.[20]

Ethnic differences may play a role in double product variability and therefore contribute differently to the above-mentioned cardiovascular pathologies.[12] Interestingly, a study performed by Berenson et al., indicates that Caucasians tend to have a higher double product than African Americans during early childhood (mainly due to faster heart rates). This phenomenon is reversed at early adulthood (approximately at 25 years of age) due to greater blood pressure levels and sympathetic nervous system activation amongst the African American population.[12]

## Systolic blood pressure

Systolic blood pressure is defined as the maximum arterial pressure exerted by the left ventricle of the heart during contraction. Increased blood pressure is a well-known cardiovascular risk factor.[12,21] However, the Framingham study reported increased systolic blood pressure to be a better predictor of cardiovascular morbidity and mortality, than diastolic blood pressure.[21] Changes in systolic blood pressure may be caused by various physiological and structural determinants such as the stroke volume, rate of systolic ejection, and the arterial distensibility.[22] Over a period of time these blood pressure changes, and in particular increases in systolic blood pressure, usually reflects large artery stiffness and an elevation in total peripheral resistance, both contributing factors for cardiovascular morbidity and mortality.[21]

Despite these physiological factors, several environmental and lifestyle factors are associated with acute and chronic systolic blood pressure variability. These include age,[22] smoking,[23,24] nutrition,[25] obesity,[25,26] and the use of anti-hypertensive medication.[22] Systolic blood pressure as well as the associated cardiovascular risk increases with age and even more notably in persons aged over 55 years. The risk, as a result of aging, is mainly induced by dilation as well as stiffening of the aorta caused by thickening of the intima-media.[22] This risk is also known to be exaggerated in persons who smoke or used to smoke,[23,24] consequently leading towards increased systolic blood pressure and an increased prevalence of cardiovascular disease.[22] The importance of maintaining a healthy nutritional habit and associated lowered systolic blood pressure have also been reported in previous studies.[25] Unhealthy nutritional habits lead towards obesity and other illnesses like

diabetes mellitus. It has been proven that obese people are several times more likely to suffer from hypertension, compared to non-obese people.[25] There are however, means of lowering or even preventing increased systolic blood pressure and hypertensive-related diseases. Anti-hypertensive treatment, such as nitrates, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel antagonists, have shown favourable effects on the arterial wall through reduction in arterial stiffness and lowering of the peripheral resistance and consequently lowering systolic blood pressure.[22]

Increased systolic blood pressure is a known cardiovascular risk factor implicated in the development of cardiovascular pathologies such as hypertensive heart failure,[1] left ventricular hypertrophy,[26] cerebrovascular disease and renal failure.[27]

### Heart rate

Heart rate is an important, yet easily obtainable hemodynamic variable.[28] An elevated heart rate, also known as tachycardia, is considered to be an important independent risk factor for the development of cardiovascular diseases. Studies indicate that a resting heart rate exceeding 80 beats/min is associated with significant increases in the development of diseases[28] such as atherosclerosis,[29] vascular stiffening,[30] myocardial ischemia, left ventricular dysfunction and heart failure.[28] Tachycardia causes an increase in cardiac work and myocardial oxygen consumption while at the same time reducing the diastolic filling time,[29] exposing the arterial wall to chronic shear stress. Therefore, an elevated heart rate causes the development of atherosclerotic lesions in the carotid and the coronary arteries and has been shown to be associated with carotid stenosis as well as progression of coronary atherosclerosis.[30] Several epidemiological studies[31-33] showed that tachycardia is associated with increased cardiovascular morbidity and mortality[28] in patients with[29] or without coronary artery disease.[34]

The resting heart rate is determined by the sinus node activity, which is influenced by both parasympathetic and sympathetic nervous activation.[29,35] These separate nervous activations are responsible for decreasing and increasing the heart rate respectively.[35] Thus, tachycardia is caused by over-activation of the sympathetic nervous system.[20,30] Several modifiable and non-modifiable factors contribute towards sympathetic nervous system activation, and consequently an increased heart rate. Smoking, excessive alcohol and caffeine consumption, and an inactive lifestyle are all modifiable factors known to increase sympathetic nervous activity.[30]

The non-modifiable determinants of heart rate include age, sex and ethnicity as well as the circadian pattern.[35] The resting heart rate has been shown to progressively decline with aging, regardless of ethnicity.[35] However, Caucasians tend to have higher heart rates during childhood and adolescence, and Africans, higher heart rates during adulthood.[12] Heart rates also change according to the circadian pattern, with the heart rates decreasing by about 14 beats per minute during sleep, as compared to waking periods.[35]

Heart rate lowering has favourable effects on the cardiovascular system. This causes reduction of the myocardial oxygen demand and consequently a lower ischemic burden.[29] Heart rate lowering can be achieved by control of the modifiable determinants,[30] or the use of rate-limiting medication.[29] Although it is important to reduce the use of tobacco products and the intake of caffeinated and alcoholic beverages, studies have reported that physical activity is of utmost importance, for physically active people have a heart rate of 10 beats per minute lower than inactive people, regardless of age and ethnicity.[30]

## Cardiovascular pathologies

Nearly two-thirds of the world's population affected by hypertension, is living in developing regions such as African countries. The prevalence of hypertension in these regions is predicted to increase up to 80%, by the year 2025.[36] This is a major concern, knowing that hypertension is the major cause of damage to the heart, brain and kidneys.[16,20] Damage to these organs are usually reflected by markers indicating underlying injuries, characterized by the development of asymptomatic, structural and functional abnormalities.[37] These markers include hypertrophy of the left ventricle, intima-media thickening of the carotid artery, an increased urinary albumin excretion, arterial stiffening, cognitive decline and retinopathy.[14]

Arterial stiffness is a term used to describe the distensibility of the arterial wall.[38,39] Increased arterial stiffness causes the blood to travel at a higher velocity within the arteries, resulting in a greater proportion of stroke volume to be forwarded to the periphery. This contributes towards damage of the organs such as the brain and the kidneys and consequent deterioration of cognitive and renal function.[27] Dementia is a descriptive term used for a collection of symptoms that affect the brain, causing a progressive decline in a person's cognitive functions.[14] Vascular dementia and Alzheimer's disease are among others, the most common disorders associated with dementia.[40] Vascular dementia is progressive cognitive failure[14] resulting from a cerebrovascular disease in hypertensive patients.[40] Alzheimer's disease is a gradual decline of memory associated with people aged 65 years and older.[40] Retinopathy is a retinal disorder, characterised by signs of increased retinal capillary permeability. It is the leading cause of blindness in adults aged 20 – 74

years.[41] Retinopathy most often occurs in individuals with hypertension,[14] long-standing diabetes mellitus[42] and hyperglycemia.[43] It can however be prevented or delayed by control of blood pressure or blood glucose.[41] Retinopathy is strongly associated with increased risk of mortality amongst individuals with diabetes mellitus.[42]

All of the above-mentioned disorders are associated with hypertension,[14,44] and aging acting as a contributing risk factor.[27,40,41] Ethnic differences is also an important factor, with Africans known to be at greater risk of developing these cardiovascular disorders than Caucasians.[43,45] However, in the present study, particular reference will be made to three markers of subclinical organ damage. These are left ventricular hypertrophy, intima-media thickness and albumin-to-creatinine ratio.

## Left ventricular hypertrophy

Enlargement of the cardiac muscle, which is increased myocardial thickness, is a condition known as left ventricular hypertrophy.[46] It is one of the earlier signs of end-organ damage and an important predictor of cardiovascular events.[20] This condition is caused by chronic elevation of myocardial stress due to pressure overload such as hypertension[46] or aortic stenosis. Myocardial thickening occurs in order to compensate for continuous stress placed on the heart by an increased afterload.[14]

Left ventricular hypertrophy can be measured using echocardiography and 12-lead electrocardiography.[47,48] Echocardiography is currently the “gold standard” used to determine left ventricular hypertrophy. Echocardiography, made possible via the use of pulsed and continuous Doppler waves, is a two-dimensional (2D) or three-dimensional (3D) ultrasound imaging technique providing information concerning cardiovascular anatomy and function.[48] Another method is electrocardiography using the standard voltage criterion. This is measured in millivolts (mV), as reported by Sokolow and Lyon, 1949.[49] More recently, the Cornell product criterion was developed to determine left ventricular hypertrophy.[50] This criterion was reported to have higher detection sensitivity for the presence of left ventricular hypertrophy than the Sokolow-Lyon criterion. Left ventricular hypertrophy, as measured by both Sokolow-Lyon and Cornell-product criteria, are associated with stroke and other cardiovascular events in subjects with essential hypertension.[19,46]

With the exception of hypertension, several other conditions contribute to a greater prevalence of left ventricular hypertrophy. Patients with diabetes mellitus have a higher prevalence of left ventricular hypertrophy than non-diabetics.[46] Obesity has also been reported to be a strong determinant of this cardiovascular risk factor, indicating that the

metabolic syndrome may be an important contributor to left ventricular hypertrophy.[51] The prevalence of left ventricular hypertrophy is associated with ethnicity and sex. Africans, and in particular men, are more prominently affected by hypertensive heart diseases,[1] compared to Caucasians.[26]

## Intima-media thickness

Intima-media thickness is a measurement of the thickness of the arterial wall.[52] This measurement is mostly performed using non-invasive high resolution ultrasound scanning of the carotid artery, although other non-invasive techniques, i.e. magnetic resonance imaging[53] and invasive techniques involving an ultrasound catheter, do exist.[54,55] However, the non-invasive ultrasound technique is the preferred method used during epidemiological and intervention studies.[56]

The intima-media thickness is measured using the carotid artery far or near wall.[53,56,57] The carotid artery, rather than the femoral or other arteries, is the preferred position to measure the intima-media thickness. Not only is the carotid artery the more accessible and convenient option, the atherosclerotic burden in a carotid artery and a coronary artery is more or less the same.[58] Therefore, the carotid artery is considered an acceptable surrogate marker for coronary artery atherosclerosis.[53,56] Measuring the intima-media thickness is of great importance to determine the progression of the atherosclerotic process.[56] Atherosclerosis is the result of continuous progression of atherosclerotic plaque and is a chronic inflammatory disease[59] due to lipid deposits in the smooth muscle cells of the arteries.[60] This disease affects the general vascular tree, including the carotid artery.[56]

Carotid intima-media thickening, a result of the existence of atherosclerotic thickening, caused by excess plaque, is a well-known risk factor for cardiovascular disease.[54-56] Increased carotid intima-media thickness is associated with cardiovascular and cerebrovascular events[53,61] such as myocardial infarction,[38] transient ischemic attacks and stroke.[55] A high risk of recurrent stroke is associated with carotid intima-media thickening.[55] Hypertension, diabetes mellitus, hyperlipidemia, smoking,[62] and obesity[63] are the most important risk factors contributing towards increased carotid intima-media thickness.[62] Interestingly, moderate alcohol intake, together with normalisation of weight and physical activity, contribute towards a reduction in carotid intima-media thickness and subsequently the prevention of transient ischemic attacks and stroke.[62]

## Microalbuminuria

Albumin is a protein found in abundance in plasma which is produced by the liver. When a person suffers from nephropathy, a disease referring to damage of the kidney,[14] albumin leaks across the glomerular filtration barrier of the kidney into the urine, resulting in a condition known as microalbuminuria.[64] Increased urinary albumin excretion, results in a higher albumin-to-creatinine ratio, which is a well-known marker of renal damage and cardiovascular risk.[20,65]

Microalbuminuria is a complex disorder often accompanied by one or more of the markers associated with the metabolic syndrome. These include insulin resistance,[64] abdominal obesity, but also environmental factors such as smoking.[64,65] Previous studies show that there is an association between increases in body mass index and the progression of microalbuminuria.[65] Nevertheless, the major contributing factors towards the development and progression of microalbuminuria are hypertension and diabetes mellitus.[14,57,64,65] Previous studies indicate that microalbuminuria is a strong independent predictor of mortality amongst patients with diabetes mellitus, independent of hypertension treatment.[57] Nevertheless, hypertension remains the major risk factor contributing towards microalbuminuria, in both diabetic and non-diabetic patients. Additional risk factors in the development of microalbuminuria, and other renal diseases include ethnicity and gender. African Americans are several times more likely than Caucasians to develop hypertensive-related kidney diseases. Male individuals are also at greater risk of developing microalbuminuria than their female counterparts.[36]

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# CHAPTER 3

# DOUBLE PRODUCT AND END-ORGAN DAMAGE IN AFRICAN AND CAUCASIAN MEN: THE SABPA STUDY

**Andreas J Schultz, Rudolph Schutte, Aletta E Schutte**

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## ABSTRACT

Increasing urbanisation in sub-Saharan African countries is causing a rapid increase in cardiovascular disease. Evidence suggests that Africans have higher blood pressures and a higher prevalence of hypertension-related cardiovascular morbidity and mortality, compared to Caucasians. We investigated double product (systolic blood pressure x heart rate), a substantial measure of cardiac workload, as a possible cardiovascular risk factor in African and Caucasian men. The study consisted of 101 urbanised African and 101 Caucasian male school teachers. We measured 24-hour ambulatory blood pressure and carotid intima-media thickness, and determined left ventricular hypertrophy electrocardiographically by means of the Cornell product. Urinary albumin and creatinine were analysed to obtain the albumin-to-creatinine ratio. Results showed that Africans had higher blood pressures than the Caucasians. Their systolic blood pressure had stronger correlations with the markers of end-organ damage than double product, while heart rate showed no significant associations. 24-hour systolic blood pressure also correlated positively with markers of end-organ damage in multiple regression analyses (cross-sectional wall area: B=0.08, P=0.004; left ventricular hypertrophy: B=1.43, P<0.001; albumin-to-creatinine ratio: B=0.008, P=0.01). However, 24-hour double product showed only borderline significant associations. No associations were evident in Caucasian men. In conclusion, 24-hour double product may not be a good marker of increased cardiovascular risk when compared to 24-hour systolic blood pressure in African and Caucasian men.

**KEY WORDS:** Africans, double product, end-organ damage, heart rate, systolic blood pressure

## INTRODUCTION

Double product, a determinant of oxygen consumption and workload of the heart, is the product of systolic blood pressure and heart rate.[1-4] Double product values are determined using 24-hour ambulatory blood pressure measurements, which makes it possible to retrieve accurate double product values for both daytime activity and nocturnal sleep. These values tend to change according to the circadian pattern, closely related with changes in systolic blood pressure.[5]

Continuous fluctuations in systolic blood pressure leading to changes in double product values, is regarded as a cardiovascular risk factor.[3] Although less importance have been placed on heart rate in studies involving double product, it is believed that an increased heart rate, caused by over-activity of the sympathetic nervous system, can contribute towards end-organ damage such as left ventricular hypertrophy and carotid intima-media thickening.[3,6]

Double product is a relatively new marker, with little information available about its power as a predictor of end-organ damage. Some studies have demonstrated that double product is an independent predictor of cardiovascular morbidity and mortality,[1] leading to cardiovascular pathologies such as cerebrovascular disease, left ventricular hypertrophy, heart failure and nephropathy.[7,8] However, double product as a cardiovascular risk marker is still relatively unknown compared to the more traditional risk markers like systolic blood pressure.

Interestingly, an association exists between ethnicity and double product, being higher in African Americans compared to Caucasians.[3] In developing countries, such as South Africa and other African countries, cardiovascular diseases are increasing rapidly amongst the African population, particularly in urban areas as a result of urbanisation.[9,10] In comparison to Caucasians, Africans also have a greater prevalence of morbidity and mortality from renal disease, stroke and heart disease as a result of their higher blood pressure levels and increased prevalence of hypertension.[11] Although double product has been investigated in Caucasians[1] and African Americans,[3] it has not been investigated amongst African people from South Africa. The aims of this study are to investigate the usability of double product as a risk marker in African and Caucasian men, by comparing associations of double product and a more traditional risk factor, systolic blood pressure, with markers of end-organ damage.

# METHODS

## Study population

This study forms part of the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study conducted between February 2008 and April 2009. We recruited a total of 202 school teachers working for the Department of Education in the Dr Kenneth Kaunda district in the North West Province of South Africa. This included 101 urbanised African and 101 Caucasian men. The reason for this selection was to obtain a homogenous sample from a similar socio-economic class. We invited all eligible participants between the ages of 25 and 65 years to participate. Exclusion criteria were an elevated oral temperature, dependence or abuse of psychotropic substances, regular blood donors, and individuals vaccinated during the three months prior to testing.

Participants were fully informed about the objectives and procedures of the study prior to their inclusion. Assistance was available for any participant who requested the information to be conveyed in their preferred language. All participants signed an informed consent form. The study complied with all applicable international regulations, in particular the Helsinki declaration of 1975 (as revised in 2004) for investigation of human participants. The Ethics Review Board of the North-West University (Potchefstroom Campus) approved the study.

## Cardiovascular measurements

A 24-hour ambulatory blood pressure measurement (ABPM) and electrocardiogram measurement were conducted during the working week. At approximately 08:00, a 24-hour ambulatory blood pressure measurement apparatus and two-lead electrocardiogram apparatus (Meditech CE120® Cardiotens; Meditech, Budapest, Hungary) were attached to the participant's non-dominant arm at their workplace. The ambulatory blood pressure measurement apparatus was programmed to measure blood pressure at 30 minute intervals during the day (08:00 – 22:00) and every hour during the night (22:00 – 06:00). According to a preset program, the electrocardiogram recorded measurements every 5 minutes for 20 seconds. The participants continued with their daily activities and were asked to record any events such as nausea, headache, physical activity and stress on their ambulatory diary cards.

Participants reported to the Metabolic Research Unit of the North-West University at 16:30 where they were informed of the procedures for the following day. This facility consists of 10

bedrooms, 2 bathrooms, a living room and a kitchen. They received a standardised dinner and had their last beverages (tea/coffee) and two biscuits at 20:30. Thereafter, they relaxed by reading, watching television, or social interaction and refrained from consuming alcohol, caffeine, smoking and doing exercise. They were requested to go to bed at around 22:00. At 06:00, the ambulatory blood pressure measurement apparatus was removed and followed by anthropometry and blood sampling.

The 24-hour blood pressure and electrocardiogram data were downloaded onto a database using the CardioVisions 1.7.2 Personal Edition (Meditech, Budapest, Hungary). The 24-hour ambulatory blood pressure measurements had a successful inflation rate of 75.5% among African subjects and 84.7% among Caucasian subjects. In cases where less than 75.0% of the 24-hour ambulatory blood pressure measurement for a particular participant was successful, the measurement was repeated the next day. Participants were regarded as hypertensive if their mean daytime blood pressure exceeded 140 and/or 90 mmHg.[12] Double products were calculated as the product of mean systolic blood pressure and mean heart rate values.[1] Left ventricular hypertrophy was determined using data from the 12-lead ECG for the Cornell product: [RaVL + $Sv_3$) x QRS duration. A product greater than 2440 mV/ms indicates hypertrophy.[13-15]

The carotid intima-media thickness was obtained using a SonoSite Micromaxx ultrasound system (SonoSite, Bothell, WA) and a 6-13 MHz linear array transducer. Images from at least two optimal angles of the left and right common carotid artery were obtained. These segments were imaged and measured following the prescribed protocols.[16] The images were digitalised and imported into the Artery Measurement Systems automated software[17,18] for dedicated analyses of carotid intima-media thickness. A maximal 10 mm segment with good image quality was chosen for analysis. The software is programmed to automatically identify the borders of the intima-media of the near and far wall, and the inner diameter of the vessel, whereby it calculates the carotid intima-media thickness and diameter from around 100 discrete measurements within the 10 mm segment. Manual correction could be performed in events where the automated analysis was found not appropriate on visual inspection. For confirmation of structural and not functional changes in luminar diameter, we calculated the cross-sectional wall area (CSWA) as follows: $CSWA = \pi(d/2 + CIMT)^2 - \pi(d/2)^2$, where d denotes luminal diameter.

## Anthropometric measurements

Height and weight of participants were measured while being in their underwear using calibrated instruments (Precision Health Scale; A&D Company, Tokyo, Japan; Invicta

Stadiometer, IP 1465; Invicta, London, UK). Measurements were taken in triplicate using standard methods.[19]

## Biochemical measurements

After the anthropometric measurements were completed, a registered nurse collected blood samples with a sterile winged infusion set from the participants' antebrachial vein branches. Serum was stored at -80˚C. Fasting blood glucose samples were collected in sodium fluoride tubes and determined with a timed-end-point method (Unicel DXC800, Beckman and Coulter, Germany). Fasting serum samples for total cholesterol, and high-sensitivity C-reactive protein as well as urinary albumin and creatinine, were analysed using a sequential multiple analyser computer (Konelab 20i, Thermo Scientific, Vantaa, Finland). All biochemical measurements were performed by independent laboratories, blinded to the subjects' cardiovascular profile.

## Statistical analysis

For database management and statistical analysis, we used Statistica Version 9.0 software (Statsoft Inc., Tulsa, OK, 2009). The distribution of serum glucose, urinary albumin and creatinine, the albumin-to-creatinine ratio and high-sensitivity C-reactive protein were normalised by logarithmic transformation. The central tendency and spread of these variables were represented by the geometric mean, and the $5^{th}$ and $95^{th}$ percentile intervals. We compared means and proportions by a standard t-test and the $\chi^2$-test, respectively.

We investigated the association between markers of end-organ damage and double product using single, partial and multiple regression analyses. Covariates included in the model were age, body mass index, high-sensitivity C-reactive protein, serum glucose, high-density lipoprotein, smoking and alcohol. All p-values $\leq 0.05$ were deemed significant.

# RESULTS

## Characteristics of participants

Table 1 lists the characteristics of the African and Caucasian men. Both these groups were of the same age and stature. However, the African subjects smoked more (p=0.012), and used more antihypertensive medication (p=0.042). The 24-hour double product was significantly higher among African subjects compared to the Caucasians (Figure 1, p<0.001). As expected, 24-hour systolic blood pressure (p<0.001) as well as 24-hour heart rate (p<0.001) were also higher in the Africans (Table 1). The African men also displayed a significantly higher Cornell product (p<0.001) and albumin-creatinine ratio (p<0.001) than the Caucasian subjects (Figure 1).

## Unadjusted analysis

In Africans (Table 2), both double product and systolic blood pressure (24-hour, daytime and night-time) correlated with cross-sectional wall area. However, associations of cross-sectional wall area were stronger with the systolic blood pressures than double product. In addition, no associations existed between left ventricular hypertrophy and 24-hour, day and night double product, while associations with 24-hour, day and night systolic blood pressure were observed. Similarly, the albumin-to-creatinine ratio correlated stronger with the 24-hour, day and night systolic blood pressure than double product. Except for a correlation between night-time systolic blood pressure and cross-sectional wall area, no significant associations were observed in Caucasian men.

## Adjusted analysis

In Tables 3 and 4, markers of end-organ damage were compared across quartiles of 24-hour double product and 24-hour systolic blood pressure adjusted for age and body mass index. In African men, left ventricular hypertrophy (P-trend=0.065) and albumin-to-creatinine ratio (P-trend=0.082) tended to increase with increasing double product, while no associations were present in the Caucasians. However, cross-sectional wall area (P-trend<0.001), left ventricular hypertrophy (P-trend=0.012) and albumin-to-creatinine ratio (P-trend=0.004) increased significantly with an increase in systolic blood pressure. No associations were evident in Caucasian men.

**Table 1**: Subject characteristics of African men and Caucasian men.

| | African men (N = 101) | Caucasian Men (N = 101) | P |
|---|---|---|---|
| Age (yrs) | 43.18 ± 8.05 | 44.96 ± 11.08 | 0.55 |
| Body mass index (kg/m$^2$) | 27.57 ± 5.77 | 29.03 ± 5.20 | 0.33 |
| **Biochemical measurements** | | | |
| Glucose (mmol/L) | 5.75 (5.47 ; 6.05) | 5.89 (5.77 ; 6.07) | 0.74 |
| Urinary creatinine (mmol/L) | 9.12 (8.22 ; 10.26) | 15.13 (13.30 ; 16.98) | **<0.001** |
| Urinary albumin (mg/L) | 9.77 (8.38 ; 11.53) | 3.47 (3.03 ; 3.99) | **<0.001** |
| High-sensitivity C-reactive protein (mg/L) | 2.75 (2.19 ; 3.46) | 1.82 (1.57 ; 2.07) | **<0.001** |
| HDL-cholesterol (mmol/L) | 1.05 ± 0.37 | 1.00 ± 0.27 | 0.82 |
| HDL-to-total cholesterol ratio | 0.23 ± 0.09 | 0.18 ± 0.05 | **<0.001** |
| **Cardiovascular measurements** | | | |
| 24h systolic blood pressure (mmHg) | 136.61 ± 14.24 | 127.86 ± 10.37 | **<0.001** |
| 24h diastolic blood pressure (mmHg) | 87.24 ± 9.83 | 79.51 ± 7.44 | **<0.001** |
| 24h heart rate (bpm) | 78.51 ± 10.31 | 71.95 ± 11.12 | **<0.001** |
| Daytime systolic blood pressure (mmHg) | 141.80 ± 14.40 | 133.69 ± 10.65 | **<0.001** |
| Daytime diastolic blood pressure (mmHg) | 92.78 ± 10.10 | 84.98 ± 8.30 | **<0.001** |
| Daytime heart rate (bpm) | 83.81 ± 11.36 | 77.34 ± 12.02 | **<0.001** |
| Daytime double product (mmHg*bts/min) | 12017.50 ± 2233.53 | 10330.15 ± 2031.90 | **<0.001** |
| Night systolic blood pressure (mmHg) | 127.72 ± 15.85 | 116.89 ± 11.57 | **<0.001** |
| Night diastolic blood pressure (mmHg) | 77.15 ± 10.45 | 68.55 ± 8.28 | **<0.001** |
| Night heart rate (bpm) | 70.19 ± 10.73 | 63.08 ± 10.34 | **<0.001** |
| Night double product (mmHg*bts/min) | 8884.08 ± 1803.41 | 7353.08 ± 1604.50 | **<0.001** |
| Cross-sectional wall area (mm$^2$) | 15.39 ± 4.56 | 14.89 ± 3.82 | 0.79 |
| **Lifestyle** | | | |
| Smoking n (%) | 31 (30.69) | 16 (15.84) | **0.012** |
| Alcohol n (%) | 41 (40.59) | 55 (54.46) | **0.049** |
| Hypertensive n (%) | 64 (63.37) | 37 (36.63) | **<0.001** |
| HIV infected n (%) | 13 (12.87) | 0 (0) | **<0.001** |
| **Intake of medication** | | | |
| Anti-hypertensive treatment n (%) | 19 (18.81) | 9 (8.91) | **0.042** |

Values are arithmetic mean ± SD, geometric mean (5$^{th}$ to 95$^{th}$ percentile interval), or number of men (%).
HDL: High-density lipoproteins.

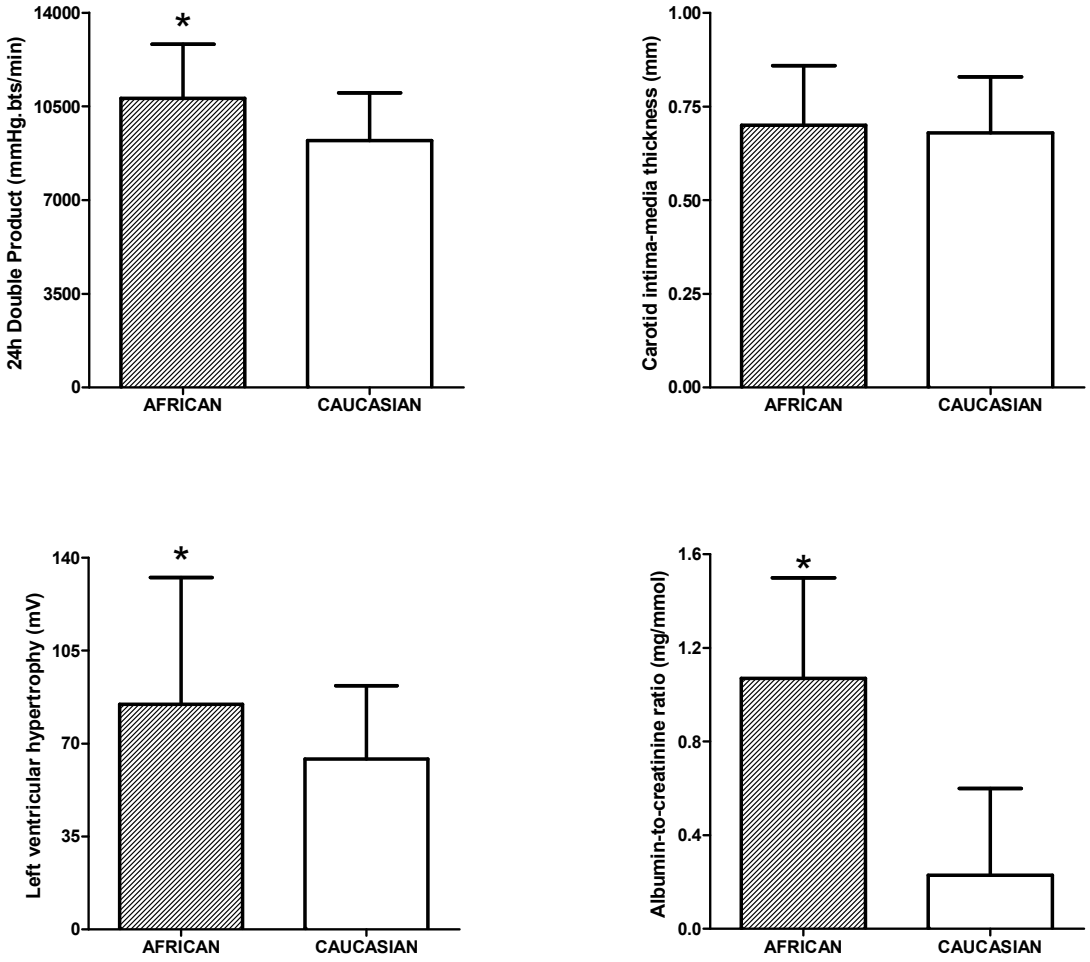


**Figure 1:** Ethnic differences in double product and markers of end-organ damage. Bars indicate means (SD); *, $p < 0.05$.

## Multivariate regression analysis

In multivariate regression analysis (Table 5), the above associations were confirmed. In African men, after adjusting for age, body mass index, high-sensitivity C-reactive protein, blood glucose, high-density lipoproteins, smoking, alcohol, and 24-hour mean arterial pressure, significant correlations were found between cross-sectional wall area and 24-hour systolic blood pressure (P=0.005), daytime systolic blood pressure (P=0.005), and night-time systolic blood pressure (P=0.026). The same trends were observed between left ventricular hypertrophy and 24-hour systolic blood pressure (P<0.001), daytime systolic blood pressure (P<0.001), and night-time systolic blood pressure (P<0.001), and albumin-to-creatinine ratio and 24-hour systolic blood pressure (P=0.01), daytime systolic blood pressure (P=0.12), and night-time systolic blood pressure (P<0.001). Double product, after adjusting for the same

covariates, showed only borderline significant associations with the markers of end-organ damage in African men, while no associations were evident in Caucasians with the exception of albumin-to-creatinine ratio which correlated significantly with night-time double product (P=0.003).

## Sensitivity analysis

Due to the influence of HIV/AIDS and the use of anti-retroviral therapy on the cardiovascular system,[20,21] we repeated the multiple regression analyses after excluding all infected subjects. By doing so, our results remained largely unchanged. (Data not shown)

**Table 2**: Correlation coefficients between markers of end-organ damage and double product, systolic blood pressure and heart rate.

| | Cross-sectional wall area | | Left ventricular hypertrophy | | Albumin-to-Creatinine Ratio | |
|---|---|---|---|---|---|---|
| | **African** | **Caucasian** | **African** | **Caucasian** | **African** | **Caucasian** |
| **24-HOUR** | | | | | | |
| Double product | **r=0.27; P=0.011** | r=0.12; P=0.22 | r=0.09; P=0.43 | r=-0.12; P=0.26 | **r=0.22; P=0.032** | r=0.03; P=0.80 |
| Systolic blood pressure | **r=0.44; P<0.001** | r=0.19; P=0.06 | **r=0.41; P<0.001** | r=-0.07; P=0.51 | **r=0.31; P=0.003** | r=0.09; P=0.37 |
| Heart rate | r=0.01; P=0.91 | r=0.58; P=0.57 | r=-0.10; P=0.35 | r=-0.11; P=0.28 | r=0.06; P=0.59 | r=-0.04; P=0.71 |
| **DAY** | | | | | | |
| Double product | **r=0.26; P=0.014** | r=0.11; P=0.27 | r=0.07; P=0.54 | r=-0.14; P=0.19 | r=0.17; P=0.10 | r=0.05; P=0.65 |
| Systolic blood pressure | **r=0.44; P<0.001** | r=0.18; P=0.079 | **r=0.39; P<0.001** | r=-0.07; P=0.49 | **r=0.23; P=0.032** | r=0.11; P=0.26 |
| Heart rate | r=0.002; P=0.99 | r=0.05; P=0.63 | r=-0.11; P=0.31 | r=-0.13; P=0.20 | r=0.06; P=0.58 | r=-0.02; P=0.82 |
| **NIGHT** | | | | | | |
| Double product | **r=0.29; P=0.005** | r=0.13; P=0.19 | r=0.09; P=0.39 | r=-0.12; P=0.26 | **r=0.31; P=0.003** | r=-0.009; P=0.93 |
| Systolic blood pressure | **r=0.39; P<0.001** | **r=0.21; P=0.039** | **r=0.37; P<0.001** | r=-0.11; P=0.30 | **r=0.41; P<0.001** | r=0.05; P=0.60 |
| Heart rate | r=0.07; P=0.48 | r=0.06; P=0.57 | r=-0.09; P=0.41 | r=-0.09; P=0.40 | r=0.08; P=0.44 | r=-0.06; P=0.57 |

**Table 3**: Markers of end-organ damage across quartiles of 24-hour double product for African and Caucasian men, adjusted for age and body mass index.

| | 24-hour Double product quartiles | | | | P | P |
|---|---|---|---|---|---|---|
| **African men** | **Q1 (N = 24)** | **Q2 (N = 25)** | **Q3 (N = 25)** | **Q4 (N = 25)** | **for trend** | **Q1 vs Q4** |
| Quartile borders | 6160 - 9112 | 9240 – 10578 | 10640 - 12246 | 12250 - 16326 | | |
| CSWA ($mm^2$) | 15.21 ± 0.19 | 15.12 ± 0.16 | 14.92 ± 0.17 | 15.94 ± 0.16 | 0.82 | 0.09 |
| LVH (mV) | 77.54 ± 3.05 | 75.90 ± 2.01 | 77.24 ± 2.17 | 108.86 ± 2.09 | 0.065 | 0.28 |
| A-C Ratio (mg/mmol) | 1.04 ± 0.05 | 0.78 ± 0.05 | 1.07 ± 0.05 | 1.62 ± 0.05 | 0.082 | 0.23 |
| **Caucasian men** | **Q1 (N = 25)** | **Q2 (N = 25)** | **Q3 (N = 25)** | **Q4 (N = 26)** | **P for trend** | **P Q1 vs Q4** |
| Quartile borders | 5232 - 7936 | 7938 – 9114 | 9177 - 10220 | 10286 - 13747 | | |
| CSWA ($mm^2$) | 14.40 ± 0.14 | 14.45 ± 0.13 | 15.35 ± 0.13 | 15.32 ± 0.13 | 0.64 | >0.99 |
| LVH (mV) | 63.54 ± 1.25 | 66.60 ± 1.18 | 65.82 ± 1.28 | 61.73 ± 1.17 | 0.94 | >0.99 |
| A-C Ratio (mg/mmol) | 0.26 ± 0.05 | 0.21 ± 0.05 | 0.18 ± 0.05 | 0.28 ± 0.05 | 0.23 | >0.99 |

CSWA, Cross-sectional wall area; LVH, Left ventricular hypertrophy; A-C, Albumin-creatinine; Q, quartile.
Values are mean ± SD.

**Table 4**: Markers of end-organ damage across quartiles of 24-hour systolic blood pressure for African and Caucasian men, adjusted for age and body mass index.

| | 24-hour Systolic blood pressure quartiles | | | | P | P |
|---|---|---|---|---|---|---|
| **African men** | **Q1 (N = 25)** | **Q2 (N = 24)** | **Q3 (N = 24)** | **Q4 (N = 28)** | **for trend** | **Q1 vs Q4** |
| Quartile borders | 111 - 124 | 124 – 136 | 136 - 146 | 147 - 199 | | |
| CSWA ($mm^2$) | 14.42 ± 0.15 | 12.88 ± 0.16 | 15.22 ± 0.15 | 18.33 ± 0.14 | **<0.001** | **<0.001** |
| LVH (mV) | 69.47 ± 2.65 | 75.49 ± 2.03 | 74.65 ± 2.00 | 114.38 ± 2.06 | **0.012** | **0.044** |
| A-C Ratio (mg/mmol) | 0.65 ± 0.05 | 1.07 ± 0.05 | 0.95 ± 0.05 | 1.86 ± 0.05 | **0.004** | **<0.001** |
| **Caucasian men** | **Q1 (N = 25)** | **Q2 (N = 23)** | **Q3 (N = 25)** | **Q4 (N = 28)** | **P for trend** | **P Q1 vs Q4** |
| Quartile borders | 109 - 121 | 122 – 125 | 126 - 131 | 132 - 158 | | |
| CSWA ($mm^2$) | 14.68 ± 0.14 | 14.78 ± 0.14 | 14.33 ± 0.13 | 15.86 ± 0.12 | 0.49 | 0.60 |
| LVH (mV) | 67.78 ± 1.22 | 55.00 ± 1.19 | 64.88 ± 1.20 | 68.38 ± 1.15 | 0.32 | >0.99 |
| A-C Ratio (mg/mmol) | 0.30 ± 0.05 | 0.20 ± 0.05 | 0.18 ± 0.03 | 0.25 ± 0.03 | 0.11 | >0.99 |

CSWA, Cross-sectional wall area; LVH, Left ventricular hypertrophy; A-C, Albumin-creatinine; Q, quartile.
Values are mean ± SD.

**Table 5**: Independent associations between markers of end-organ damage, double product, and systolic blood pressure.

| | Cross Sectional Wall Area * | | | | | |
|---|---|---|---|---|---|---|
| | African men (N = 101) | | | Caucasian men (N = 101) | | |
| | $R^2$ | β (95% CI) | P | $R^2$ | β (95% CI) | P |
| 24-hour DP | 0.326 | -0.011 [-0.248 ; 0.226] | 0.93 | 0.401 | 0.027 [-0.193 ; 0.247] | 0.81 |
| Daytime DP | 0.334 | 0.030 [-0.190 ; 0.250] | 0.79 | 0.401 | 0.015 [-0.203 ; 0.233] | 0.89 |
| Night DP | 0.323 | -0.034 [-0.291 ; 0.223] | 0.80 | 0.401 | 0.010 [-0.182 ; 0.202] | 0.92 |
| 24-hour SBP | 0.392 | **0.398 [0.126 ; 0.670]** | **0.005** | 0.405 | 0.093 [-0.146 ; 0.332] | 0.45 |
| Daytime SBP | 0.392 | **0.370 [0.117 ; 0.623]** | **0.005** | 0.402 | 0.057 [-0.178 ; 0.292] | 0.64 |
| Night SBP | 0.371 | **0.302 [0.039 ; 0.565]** | **0.026** | 0.410 | 0.130 [-0.082 ; 0.342] | 0.23 |

| | Left ventricular hypertrophy | | | | | |
|---|---|---|---|---|---|---|
| | African men (N = 101) | | | Caucasian men (N = 101) | | |
| | $R^2$ | β (95% CI) | P | $R^2$ | β (95% CI) | P |
| 24-hour DP | 0.073 | 0.250 [-0.012 ; 0.512] | 0.06 | 0.075 | -0.013 [-0.275 ; 0.249] | 0.92 |
| Daytime DP | 0.046 | 0.153 [-0.104 ; 0.410] | 0.25 | 0.077 | -0.058 [-0.318 ; 0.202] | 0.66 |
| Night DP | 0.065 | 0.252 [-0.017 ; 0.521] | 0.07 | 0.075 | -0.020 [-0.260 ; 0.220] | 0.87 |
| 24-hour SBP | 0.191 | **0.455 [0.231 ; 0.679]** | **<0.001** | 0.077 | 0.052 [-0.201 ; 0.305] | 0.69 |
| Daytime SBP | 0.177 | **0.434 [0.208 ; 0.660]** | **<0.001** | 0.075 | 0.019 [-0.231 ; 0.269] | 0.88 |
| Night SBP | 0.155 | **0.390 [0.167 ; 0.613]** | **<0.001** | 0.075 | 0.016 [-0.229 ; 0.261] | 0.90 |

| | Albumin-to-creatinine ratio | | | | | |
|---|---|---|---|---|---|---|
| | African men (N = 101) | | | Caucasian men (N = 101) | | |
| | $R^2$ | β (95% CI) | P | $R^2$ | β (95% CI) | P |
| 24-hour DP | 0.204 | 0.203 [-0.032 ; 0.438] | 0.09 | 0.122 | 0.0076 [-0.237 ; 0.253] | 0.95 |
| Daytime DP | 0.165 | 0.064 [-0.169 ; 0.297] | 0.59 | 0.124 | 0.053 [-0.190 ; 0.296] | 0.67 |
| Night DP | 0.267 | **0.364 [0.131 ; 0.597]** | **0.003** | 0.122 | -0.0087 [-0.234 ; 0.216] | 0.94 |
| 24-hour SBP | 0.218 | **0.280 [0.064 ; 0.496]** | **0.012** | 0.124 | 0.054 [-0.177 ; 0.285] | 0.65 |
| Daytime SBP | 0.185 | 0.178 [-0.042 ; 0.398] | 0.12 | 0.127 | 0.082 [-0.149 ; 0.314] | 0.49 |
| Night SBP | 0.265 | **0.364 [0.164 ; 0.564]** | **<0.001** | 0.122 | 0.010 [-0.211 ; 0.231] | 0.93 |

β, partial regression coefficient; 95% CI, 95% confidence interval; DP, double product; SBP, systolic blood pressure.

Covariates include age, body mass index, high-sensitivity C-reactive protein, blood glucose, high-density lipoprotein, smoking and alcohol.

* Additionally adjusted for 24-hour mean arterial pressure.

## DISCUSSION

This study investigated double product as a possible usable cardiovascular risk marker in African and Caucasian men. The main finding of this study was that although double product was higher in African men, systolic blood pressure correlated stronger with markers of end-organ damage compared to double product, suggesting that double product is not as strong a marker of increased cardiovascular risk as the traditionally used systolic blood pressure. In addition, in Caucasian men, neither double product nor systolic blood pressure showed any association with the markers for end-organ damage.

To date, relatively few studies determined the significance of double product as a cardiovascular risk marker. Studies performed were either irrespective of ethnicity[1] or were performed using African American participants.[3] Rafie et al. determined double product to be an independent predictor of cardiovascular mortality in healthy subjects and patients with ischemic heart disease,[1] while Berenson et al. indicated that African American adults have higher double product and an increased risk of cardiovascular disease, than Caucasian adults.[3] There is, however, no evidence confirming the association between double product and end-organ damage in the black population from South Africa, a population subjected to increasing urbanisation over the past few decades with concomitant increase in cardiovascular-related morbidity and mortality.[9,10]

The results from this study support the findings of Berenson et al. who reported a greater double product in African American adults compared to Caucasian adults.[3] However, the association of double product with end-organ damage can be deceptive. As the product of two hemodynamic variables, it is possible for a person with high systolic blood pressure and normal heart rate to have the same double product as a person with normal systolic blood pressure and an increased heart rate. Therefore, different mechanisms may be at work and therefore relate differently with markers of end-organ damage and cardiovascular diseases. Ethnic-specific associations between double product and end-organ damage are more explicable. Our results confirm previous reports[22-24] noting a higher blood pressure and prevalence of hypertension amongst Africans of South Africa.

This remarkable difference in blood pressure levels contribute towards the increased risk among Africans to develop end-organ damage, which ultimately results in end-points such as stroke, heart, and renal failure.[11,25,26]

Elevated heart rate, which forms one component of double product, is also independently associated with atherosclerosis and increased cardiovascular morbidity and mortality.[27]

Despite these reports, we found that the elevated heart rate in Africans was not associated with intima-media thickness or any of the other markers of end-organ damage. It is important to note that both ethnic groups investigated had mean heart rates well below 84 beats/min, which is the resting heart rate associated with cardiovascular morbidity and mortality in both African and Caucasian men.[28] This lends further support to the notion that, at least in this case, systolic blood pressure and not double product is a better marker of end-organ damage.

Importantly, our results correspond with previous studies,[22,23,25,29] indicating that African men are at increased risk of cardiovascular morbidity and mortality, compared to Caucasian men. This risk is mainly attributable to the higher systolic blood pressure levels and arterial dysfunction observed with the African men.[24] This mentioned, these studies[22,23,25] also reported that Africans have a lower prevalence of coronary heart disease and fewer myocardial infarctions, mainly due to a more favourable lipid profile. Our results support these studies, with a more favourable lipid profile observed in the African men. Still, despite our results showing both components of double product being higher in Africans, and literature stating their specific contributions towards cardiovascular risk,[30,31] our results do not suggest that double product is a stronger risk factor for increased end-organ damage than systolic blood pressure. Systolic blood pressure seems to be of greater importance and a more prominent contributor to the development of cardiovascular diseases, especially in high risk groups such as Africans, who are known to have elevated blood pressure.

The limitations and strengths of this study should be recognised. Our study groups were relatively small and larger groups may have provided more statistical power. Even though our results were consistent after multiple adjustments, we cannot exclude residual confounding effects. We applied a cross-sectional target population design to investigate the association between double product, systolic blood pressure and end-organ damage and therefore, cannot infer causality. However, both African and Caucasian study groups were matched for age and socio-economic status. This does not exclude the possibility that our groups may not be completely comparable. As mentioned, the literature[22,23,25] states that Africans are known to have higher blood pressure levels than Caucasians, and therefore less occurrence of end-organ damage would be expected in this Caucasian group. Left ventricular hypertrophy in this study was estimated by using electrocardiography. Although this is a validated method, echocardiography would have been a more accurate measure of left ventricular hypertrophy.[32] Besides, we conducted a well-designed study under controlled conditions. To our knowledge, this is the first study to investigate double product in African men from South Africa.

To conclude, in African men, systolic blood pressure displayed stronger correlations with markers of end-organ damage than double product. These findings suggest that double product may not be a good marker of increased risk for end-organ damage and subsequent cardiovascular-related mortality.

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# CHAPTER 4

# GENERAL FINDINGS AND CONCLUSIONS

## INTRODUCTION

In this chapter, a summary of the main findings from our manuscript reported in this dissertation will be given. The results from this manuscript will be discussed, interpreted, elucidated and compared to the relevant literature. Conclusions will be drawn and recommendations will be made to researchers investigating double product as a cardiovascular risk marker of end-organ damage.

## SUMMARY OF MAIN FINDINGS

The aim of this study was to investigate the usability of double product as a possible cardiovascular risk marker of end-organ damage. It was hypothesised that double product, and the level of end-organ damage is higher in African men compared to Caucasian men, and that double product is associated with intima-media thickness, left ventricular hypertrophy and albumin-to-creatinine ratio in both African and Caucasian men, however, more prominently in African men. We also hypothesised that double product is more prominently associated with markers of end-organ damage compared to the more traditional risk factor, systolic blood pressure.

Results indicated that double product is higher in Africans compared to the Caucasian men. The African subjects have significantly higher systolic blood pressure levels and heart rates than the Caucasians, hence the significantly higher double product. The first hypothesis, as mentioned in Chapter 1 (page 5), is thus accepted.

The African men also displayed higher levels of end-organ damage than the Caucasian men, with the markers indicating significantly higher levels of left ventricular hypertrophy and albumin-to-creatinine ratio. The second hypothesis is thus also accepted.

Results indicated that, despite the first and second hypotheses, double product only exhibited borderline significant associations with some of the markers of end-organ damage we investigated in African men, while no associations were observed in Caucasian men. Systolic blood pressure, a more traditional risk factor, had stronger significant correlations with the markers of end-organ damage in African men. However, systolic blood pressure also showed no significant correlations in Caucasian men. These findings suggest that double product may not be a good marker of increased cardiovascular risk, with systolic blood pressure serving as a better marker of increased risk of end-organ damage and subsequent cardiovascular-related mortality. The third hypothesis is therefore rejected.

## COMPARISON OF FINDINGS WITH THE LITERATURE

When the results from this study (Chapter 3) are compared with results found in the literature regarding previous studies, it is evident that our findings confirmed but also contradicted those found in the literature. Confirming findings were the cardiovascular profile of the African subjects.[1,2] The African subjects had significantly higher systolic blood pressure, heart rates and subsequent double products.[3] They also had a significantly higher number of hypertensive subjects compared to Caucasians of the same age.

The literature describes the African population as a high risk group compared to other ethnic groups.[4-6] This is confirmed in our study, with results indicating that the African subjects are at greater risk of developing heart and renal diseases due to significantly increased Cornell product values and albumin-to-creatinine ratio compared to the Caucasian subjects. Another confirming finding is the significantly higher HDL-to-total cholesterol ratio in African subjects. Thorogood et al. reports that Africans experience less coronary heart disease and myocardial infarctions as result of this increased HDL-to-total cholesterol ratio.[4]

Contradictory findings of this study were that double product was not significantly associated with any of the markers of end-organ damage, especially in Africans with higher double products, while Rafie et al. mentioned elevated double products to be a strong independent predictor of cardiovascular morbidity and mortality.[7] Viazzi et al. also reported that double product correlates with markers of end-organ damage such as the albumin-to-creatinine ratio and carotid intima-media thickness.[8]

Increased systolic blood pressure is a well-known and strong cardiovascular risk factor for the development of cardiovascular pathologies.[9] Our study both confirmed and contradicted these findings. The African subjects revealed strong associations, while the Caucasian subjects showed no associations between systolic blood pressure and end-organ damage. A possible reason for this could be merely the lower and normotensive blood pressure levels of the Caucasian men.

## CHANCE AND CONFOUNDING

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 may have caused weaknesses in this 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.

Several confounders could have influenced the results. These include age, body mass index, smoking, alcohol intake, level of physical activity, HIV-status, the use of anti-retroviral medication as well as their family history. These confounders, as extraneous factors, could have led to over- or underestimation of the association between double product and end-organ damage. Statistical adjustments were made to address the following confounders: Age, body mass index, smoking, alcohol intake and HIV-status. In addition, 24-hour mean arterial pressure was also included in the model when associations with cross-sectional wall area were investigated.

Electrocardiography was used to estimate left ventricular hypertrophy. The results might have been different if we used echocardiography instead, which is known to be the gold-standard measure for left ventricular hypertrophy.[10] Urinary albumin was assessed from 8-hour overnight urine specimens rather than multiple specimens or a timed collection. However, these collections correlate well with 24-hour collections.[11,12]

In the interpretation of the results in this dissertation, it was attempted to interpret statistical results from a physiological point of view at all times, while keeping in mind that a statistical significance does not necessarily mean physiological significance, and vice versa.

## DISCUSSION OF MAIN FINDINGS

Africans have previously been described as a high risk group for the development of end-organ damage and subsequent cardiovascular diseases[4-6] mainly as the result of increased urbanisation and the adoption of a more westernised lifestyle. We have found this description to be accurate as our results reveal Africans to have significantly higher systolic blood pressure levels and heart rates, in both day and night as well as 24-hour measurements compared to the Caucasians. This is contributory to the high prevalence of hypertension in this study, with more than 60% of the African subjects being hypertensive.

Our results indicate that contradictory to the more traditional risk factor, systolic blood pressure, the associations between double product and end-organ damage were mainly absent, suggesting that the prognostic power of double product is questionable. Previous studies reported double product to be a strong independent predictor of cardiovascular morbidity and mortality,[7] however, there are some factors that may contribute towards this

difference. We determined the associations between double product and end-organ damage using ambulatory measurements over a period of 24 hours. During this period, the subjects were exposed to various physical conditions that included periods of light physical activity (such as climbing a flight of stairs), rest and sleep, with few periods of strenuous physical activity. Importantly, during this time period the subjects had mean heart rates well below 84 beats/min, which is the resting heart rate associated with cardiovascular morbidity and mortality in both African and Caucasian men.[13] Consequently, this led to the double product values being much lower than in previous studies,[7,14] where maximum double product values were retrieved by exposing the subjects to strenuous physical activity. Although the African subjects had elevated double products compared to the Caucasian subjects, these values were obtained during normal daily activity and not maximum exposure to physical activity. Therefore, very high double product values usually found in people with extremely high blood pressures or who suffer from conditions such as of tachycardia, might be at increased risk of end-organ damage and cardiovascular pathologies. However, in this case where the double product was only slightly elevated, it is possible that the values were not high enough to be associated with end-organ damage at this stage.

A possible explanation for the weak associations between double product and end-organ damage may be the young age of our subjects. Despite the number of African hypertensive subjects being in excess of 60%, they are still relatively young compared to previous studies investigating the correlation between age and end-organ damage.[15,16] These studies reported that the levels of end-organ damage become more prominent with age. Due to the relatively young age of our subjects, the levels of end-organ damage are not so advanced compared to older subjects, thus possibly contributing towards the absence of associations between double product and end-organ damage.

Despite this, the association of double product with end-organ damage can also be deceptive. It is possible for a person with high systolic blood pressure and normal heart rate to have the same double product as a person with normal systolic blood pressure and an increased heart rate. As a result, different mechanisms may be at work and therefore relate differently with markers of end-organ damage and cardiovascular diseases.

## CONCLUSION

In African men, systolic blood pressure displayed stronger correlations with markers of end-organ damage than double product. These findings suggest that double product may not be

a good marker of increased risk for end-organ damage and subsequent cardiovascular-related mortality.

## RECOMMENDATIONS

From this study certain recommendations arise which justifies and would improve further research:

- This study was performed using data from a cross-sectional study. In order to make predictions about cause and effect of double product and end-organ damage, it is important to obtain data over an extended period by means of a longitudinal study in Africans.
- It is strongly recommended that the study include participants from various levels of the socio-economic class, in order to assess the influence of various lifestyles on double product and end-organ damage.
- Studying larger subject groups might improve the statistical power and deliver better results.
- The use of gold-standard measures throughout the study is strongly recommended. These measures include echocardiography and 24-hour urine samples, rather than electrocardiography and 8-hour urine samples.

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