Prehypertension and target organ changes in an African population

Mokwena Caroline Motheo

(1895614)

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the Degree of **Master of Science in Medicine**.

Johannesburg, 2021

Declaration

I, Caroline Motheo Mokwena, declare that this dissertation is my own unaided work, except where stated. It is being submitted for the degree of Master of Science in Medicine in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been previously submitted for any degree or examination to the current or any other institution.

_____

(Signature of candidate)

On this _____day of_____ in_____

I certify that the studies contained in this dissertation have the approval of the Committee for Research in Human Participants of the University of the Witwatersrand, Johannesburg. The ethics approval number is **M190646**.

_____

(Signature of candidate)

On this _____day of_____ in_____

Prof. Muzi J. Maseko	Dr Busisani Lembede
(Supervisor)	(co-supervisor)

Dedications

This dissertation is dedicated to my late mother Nthabiseng Sarah Mokwena and my brother Mahlogonolo Mokwena.

My contributions to data collection and data analysis

I declare that I collected Most of the data myself. I collected the Blood pressure, anthropometric, sphygmocor, intima media thickness and 24-hour urinary excretion data. I conducted the questionnaires with the help of my colleagues, Nolwazi Mndebele and Kgothatso Nkoana. Blood samples were collected with the help of a qualified nurse. Urine samples were sent to an accredited laboratory for analysis. I analysed the data with the assistance of my main supervisor, Professor Muzi J. Maseko.

Abstract

Hypertension (HT) remains the leading risk factor for cardiovascular diseases (CVDs) and a leading cause of death globally. It is estimated that HT causes 10.4 million deaths annually. Studies showed that even individuals who are in the normotensive (NT) range show indications of target organ damage. This gave rise to a new category of HT called pre-hypertension (pre-HT). Prior 2017, HT was defined as a blood pressure (BP) ≥ 140/90 mm Hg and pre-HT was defined as a BP of 120 mm Hg to 139 mm Hg. In 2017 these guidelines were revised by the American College of Cardiology (ACC) and the American Heart Association (AHA). According to these new guidelines, HT is defined as BP ≥ 130 mm Hg and pre-HT as BP of 120 mm Hg to 129 mm Hg. However, both the South African Hypertension Society (SAHA) and European Society of Cardiology/European Society of Hypertension (ESC/ESH) do not recommend these new guidelines. Both organisations still recommend the definition of HT as a BP ≥ 140/90. Even though the ESC/ESH guidelines are accepted by the SAHA, there is no evidence to indicate which of the guidelines are more appropriate for African communities since all the studies were conducted in western countries like the United States of America (USA) and the United Kingdom (UK). Therefore, in this study we recruited South African people from South Africa, determined the prevalence of HT and pre-HT assessed cardiovascular target organ changes.

We recruited 1211 participants of African ancestry and measured both conventional and ambulatory blood pressure (ABP). To asses cardiac changes we used echocardiography to measure early-to-late diastolic filling and left ventricular wall thickness. To measure vascular changes we used the SphygmoCor to measure pulse wave velocity (PWV). Blood samples were collected to measure plasma hormone concentrations and 24-hour urine samples were collected to measure urinary electrolyte excretion. Anthropometric measurements were taken and body mass index (BMI) was calculated as weight divided by height squared. A standardised questionnaire was administered to determine intake of medication and lifestyle habits like alcohol intake and cigarette smoking.

Our results indicate that the average age of the population was 44.05±18.29 years. There were more female (65%) participants than male (5%). The overall population was overweight with a BMI of 29.47±8 kg/m^2. Fifteen percent (15%) of the sample population were smokers. Participants who consumed alcohol were 21%. When the AHA guidelines were used, more participants were hypertensive (41.5%) compared to those who were pre-hypertensive (18.6%). On the other hand when the ESC/ESH guidelines were used, more participants were pre-hypertensive (34.2%) compared to those who were hypertensive (25.9%). The night-time BP of the pre-hypertensives and grade-1 (HT1) was within normal range while the night-time BP of the grade 2 (HT2) and grade 3 (HT3) was elevated. The pre-hypertensives and the three HT groups had an attenuated decline in nocturnal BP. Compared to the NT, the PWV and left ventricular mass index (LVMI) of all the HT groups, including the pre-HT were significantly higher. As the HT stages progressed there was a reduction in diastolic function observed.

In conclusion our results indicate that according to the SAHS/ESH that are currently applied in SA, pre-HT is overestimated while HT is underestimated. Furthermore, using the AHA guidelines, our findings indicate that cardiovascular target organ changes increase significantly from the pre-HT to the HT1 stage. Since both stages (pre-HT and HT1) are considered NT according to the SAHS/ESC/ESH guidelines, by the time they reach HT2 stage which is the first stage considered as hypertensive, target organ damage may have progressed significantly. Therefore, these results indicate that the AHA/ACC guidelines are more appropriate for the SA population. If these guidelines can be adopted for HT treatment, CVD target organ damage can be significantly reduced.

Acknowledgement

First and foremost I would like thank the Lord Almighty, for the strength to carry on through these rough seas. I would like to thank my main supervisor Professor Muzi J. Maseko for the resolute support throughout this project. It has been an honour and privilege to be cultivated by such enthusiastic advisor. I am exceptionally grateful for your supervision, patience and strength of character. This milestone would not have been possible without your guidance. I would also like to thank my co-supervisor Dr Businani Lembede for his financial support. Additionally, I would like to thank Mrs Nkele Maseko and Delene Nciweni for assisting me with techniques for data collection. To colleagues at the South African Hypertension and Diet Study (SAHDS), thank you for the guidance, support and motivation. To my friend Lerato Mokwana, thank you for challenging me and inspiring me to always do better. I would like to extend my gratitude to the constant encouragement and inspiration received from Makgomo Mogashoa. Finally, a BIG thank you and a lot of appreciation go to the participants of SAHDS study for your voluntary participation in my study, your participation made this project a success.

Table of Contents

Declaration ii
Dedications iv
My contributions to data collection and data analysis iv
Abstract v
Acknowledgement viii
List of abbreviations xi
List of Tables xiv
List of figures xv
Preface xvi
CHAPTER 1 1
1.1 Introduction 2
1.2 Classification of hypertension 3
1.2.1 European Society of Hypertension guidelines 3
1.2.2 American Heart Association guidelines 5
1.2.3 South African Hypertension Society guidelines 6
1.3 Hypertension and target organ damage 7
1.3.1 Arterial stiffness 7
1.3.2 Left ventricular hypertrophy 9
1.3.3 Diastolic dysfunction 10
1.4 Aim of the study 12
1.4.1 Objectives 12
CHAPTER 2 13
2.1 Study Population 14
2.2 Clinical, demographic and anthropometric measurements 15
2.3 Urine collections 16
2.3.1 Fresh urine samples 16
2.3.2 Twenty-four-hour urine assessment 17
2.4 Conventional blood pressure 17
2.5 Carotid intima media thickness 18
2.6 Measurements of arterial stiffening 19
2.7 Ambulatory blood pressure measurements 20

2.8 Blood sampling 21
2.9 Echocardiography 22
2.10 Inclusion and exclusion criteria 22
2.11 Data analysis 22
CHAPTER 3 24
RESULTS 24
CHAPTER 4 43
DISCUSSION 43
CHAPTER 5 52
REFERENCES 52
Appendix 1: Ethical clearance 66
Appendix 2: Change of title 67
Appendix 3: Consent form 68
Appendix 4: Questionnaire 64

List of abbreviations

ABP	Ambulatory Blood Pressure
ABPM	Ambulatory Blood Pressure Monitoring
ACC	American College of Cardiology
AHA	American Heart Association
AI	Augmentation Index
AIC	Central Augmentation Index
AIP	Peripheral Augmentation Index
BMI	Body Mass Index
BP	Blood pressure
Ca^{2+}	Calcium
CAD	Coronary artery disease
CBP	Conventional Blood Pressure
CIMT	Carotid Intima-Media Thickness
CLS	Clinical Laboratory Services
CVDs	Cardiovascular diseases
DBP	Diastolic Blood Pressure
DBPC	Conventional Diastolic Blood Pressure
DBPD	Day-time Diastolic Blood Pressure
DBPN	Night-time Diastolic Blood Pressure
DM	Diabetes Mellitus

ECG	Electrocardiogram
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HDL	High-density lipoprotein
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HIV/AIDS	Human Immunodeficiency Virus Acquired Immunodeficiency Syndrome
HSFSA	Heart and Stroke Foundation South Africa
HT	Hypertension
HT1	Stage 1 Hypertension
IMT	Intima-media thickness
JNC7	the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
K^+	Potassium
LDL	Low density lipoprotein
LV	Left Ventricular
LVDD	Left Ventricular Diastolic Dysfunction
MAP	Mean Arterial Pressure
Mg^{2+}	Magnesium
mm Hg	Millimetre mercury
MUAC	Mid Upper Arm Circumference
Na^+	Sodium
NHANES	National Health and Nutrition Examination Survey

NHLBI	National Heart, Lung, and Blood Institute
NT	Normotensives
Pre-HT	Prehypertension
PWV	Pulse Wave Velocity
RDA	Recommended Dietary Allowance
RDBP	Night-time to Daytime Diastolic Blood Pressure Ratio
RSBP	Night-time to Daytime Systolic Blood Pressure Ratio
SA	South Africa
SAHA	South African Hypertension Society
SAHDS	South African Hypertension and Diet Study
SAHS	South African Hypertension Society
SBP	Systolic Blood Pressure
SBP24	24-hour Systolic Blood Pressure
SBPC	Conventional Systolic Blood Pressure
SBPD	Day-time Systolic Blood Pressure
SBPN	Night time Systolic Blood Pressure
SD	Standard Deviation
SOWETO	South West Township
TP	Total Population
UK	United Kingdom
USA	United State of America
WHO	World Health Organisation

List of Tables

Page numbers

Table1. 1: Classification of office blood pressure and definitions of hypertension grade according to the ESH/ESC guideline..... 4

Table1. 2: Classification of hypertension according to the AHA/ACC hypertension guideline..... 6

Table1. 3: The current SAHS definition of hypertension..... 7

Table 3. 1: General characteristics of the study population..... 26

Table 3. 2: The relationship between body mass index (BMI) and blood pressure (BP)..... 31
Table 3. 3: Haemodynamic parameters of the study population 33

Table 3. 4: Plasma hormone concentrations..... 35

Table 3. 5: Urine electrolytes..... 37

Table 3. 6: The relationship between pulse wave velocity and early-to-late diastolic filling..... 39

List of figures

Page numbers

Figure1. 1: Major risk factors for diastolic dysfunction, which can lead to asymptomatic or symptomatic diastolic dysfunction. Adapted from Jeong and Dudley, 2014. 12

Figure 2. 1: An example of residential area where participants were recruited. 14

Figure 2. 2Positioning of the head in the Frankfort plane (Marfell-Jones *et al.,* 2012). 16

Figure 2. 3: Example of intima media complex of the common carotid artery and the specific site where the CIMT is measured (Gaarder and Seierstad, 2015). 18

Figure 2. 4: Devices used in determining arterial stiffness. 20

Figure 3. 1: Pulse wave velocity obtained from participants under the current study 40

Figure 3. 2: The impact of hypertension status on early-to-late diastolic filling of the population under the study. 41

Figure 3. 3: Effects of hypertensive status on left ventricular mass of the population under study. 42

Preface

Cardiovascular diseases (CVDs) are a cluster of conditions affecting the heart and blood vessels that includes stroke, heart failure, and peripheral vascular disease, often share similar risk factors, and are currently a leading cause of death in sub-Saharan region. According to the World Health Organization (WHO), CVDs are the number one cause of preventable mortality and morbidity accounting for about 30% of all deaths world-wide with 80% of the total deaths occurring in developing countries. The Sub-Saharan region is currently affected most by urbanisation, westernisation and modernisation. As a result, these changes in lifestyle habits in Sub- Saharan regions cause an increased burden for CVDs. The increased burden of CVDs in this population results from an increased incidence of elevated blood pressure (BP). The progression of elevated BP to Hypertension (HT) increases mortality and morbidity rates.

The pathophysiological mechanisms behind HT have not been explained definitively; however, ageing of populations and behavioural factors like an unhealthy diet, excessive alcohol intake, lack of physical activity, increased body weight hugely contribute to its manifestation. More importantly, members of African descent are reported to be salt-sensitive; therefore, the combination of increased risk for HT development and salt-sensitivity predisposes them to severe end organ damage due to salt retention. In addition, socioeconomic inequalities and noncompliance with pharmacological treatment within South Africa (SA) have further been shown to be barriers to effective HT control.

Generally, cardiovascular events occur more frequently in salt sensitive individuals with HT. Therefore the question arises, if cardiovascular event are prominent in salt sensitive HT then are pre-HT salt sensitive individuals at a higher

risk class of developing cardiovascular implication? Hence the focus of the study is aimed to investigate the association between pre-HT and cardiovascular target organ changes. The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines used aim at understanding the pathophysiology, epidemiology and risk factors that are associated with HT. The ESC/ESH guidelines provide wealth evidence that demonstrate that lowering BP can significantly lessen premature mortality and morbidity along with updated threshold values. On the other hand AHA guidelines focus is on medical practice in the USA. Although guidelines may be used to inform guiding decisions, they are intended to improve patients' quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment. Lastly South African Hypertension Society (SAHS) guidelines aim at providing accessible and comprehensive management of HT by healthcare professionals in the public and private sectors. Moreover, South African SAHS reviews HT and CVD treatment and prevention guidelines as well as HT trials reporting clinical end-points, including those with individuals with important co-morbidities such as diabetes mellitus and chronic kidney disease. This dissertation consists of 5 chapters namely: Chapter 1 which introduces the general mechanisms responsible for the development of HT, BP monitoring methods and end organ damage. Chapter 2 discusses the detailed methodology used to collect data for the current study. Chapter three presents the results obtained. Chapter four discusses these results in context to existing literature and the conclusion and limitations of the current study.

CHAPTER 1
INTRODUCTION

1.1 Introduction

In recent years, non-communicable diseases including CVDs and diabetes have become a leading cause of mortality globally. Studies propose that CVDs are an ongoing crisis in Africa and other countries worldwide (Cuppuccio and Miller, 2016; Keates *et al*., 2017). Cardiovascular diseases are responsible for almost a third of total deaths worldwide (WHO, 2013). According to the Heart and Stroke Foundation South Africa (HSFSA), CVDs are the leading cause of deaths and disabilities worldwide, accounting for 17 million deaths every year (31% of total global deaths). In SA, CVDs remains the leading cause of death after HIV/AIDS and more people die of CVDs than all cancers combined (Bradshaw *et al*., 2003; Norman *et al*., 2007; WHO, 2009; WHO, 2011; WHO, 2004; HSFSA, 2016).

Over half of the 17 million deaths due to CVDs annually arise from complications of elevated BP, a condition known as HT (WHO, 2013). In 2010 a systematic analysis conducted for the Global Burden of Disease report and the findings revealed that HT was the leading risk factor for mortality worldwide, accounts for 7% of deaths globally (Lim *et al*., 2012). Often hypertension goes undetected as it is asymptomatic; hence hypertensive individuals often become aware of their condition only after developing complications (Mungati *et al*., 2014).

According to a study by Cooper *et al*. (2015), members of African descent have the highest prevalence of HT compared to other ethnicities. Globally, the highest prevalence of HT has been recorded in Africa, where 46 % of the adult population is hypertensive (WHO, 2013). In a recent study carried out in four Sub-Saharan African countries, Soweto had the highest prevalence (54.1%) out of the six locations studied (Gómez-Olivé *et al*., 2017). The six locations span the African continent. In West Africa, the rural areas of Nanoro and Navrongo; in East Africa an urban informal settlement in Nairobi; and in South Africa, the rural areas of Agincourt in the province of Mpumalanga and Dikgale in the province of Limpopo, and the suburban township of Soweto that lies on the outskirts of Johannesburg.

The risk of developing CVD is directly proportional to the rise in BP and this trend is observed even in individuals with BP values that are considered to be within the normal range (Grotto *et al*., 2006). Studies have shown that individuals with

systolic and diastolic blood pressure as low as 115 mmHg/ 70 mmHg respectively, have an increased risk of developing CVD when compared to individuals with lower BP values (Lewington *et al*., 2002; Grotto *et al*., 2006).

In 2003, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) categorized individuals with systolic blood pressure between 120 and 139 mmHg or diastolic pressure between 80 and 89 mmHg as having pre-HT (JNC7, 2003). In the years 1999 to 2000, the National Health and Nutrition Examination Survey (NHANES) suggested that the prevalence of pre-HT was 40% for men and 23% for women (Wang and Wang, 2004). Russell *et al* (2004), reported that pre-HT accounted for 3.4% of hospitalizations and 9.1% of deaths, including elevated rates of left ventricular hypertrophy and increased carotid intima media thickness. Similarly, Kim *et al* (2011), observed impairments in cardiovascular function and structure in prehypertensive individuals. In addition, the cardiovascular alterations were independent of the prehypertensive state of the individuals. In contrast, Norton *et al* (2008), demonstrated that pre-HT is not a predictor of organ damage in young-to middle-age persons of African ethnic descent. Due to the findings, the association between pre-HT and target organ changes is not well understood.

1.2 Classification of hypertension

1.2.1 European Society of Hypertension guidelines

The 2018 ESC/ESH guidelines for the management of arterial HT are intended for adults aged ≥18 years with HT. The specific aims of these Guidelines were to produce pragmatic recommendations to improve the detection and treatment of HT, and to improve the poor rates of BP control by promoting simple and effective treatment strategies. The 2018 ESC/ESH guidelines follow the same principles upon which a series of HT Guidelines were jointly issued by these two societies in 2003, 2007, and 2013.

The association between BP and renal and cardiovascular events is constant, which then makes the distinction between NT and HT , based on cut-off BP values, somewhat subjective (Lewington *et al*.,2002; Thomopoulos *et al*., 2e014; Ettehad *et al*., 2016). Nonetheless, cut-off BP values are used for practical reasons in order to make the diagnosis and treatment decision less complicated in practice. Epidemiological associations between BP and CV risk extend from very low BP levels systolic BP (SBP) >115 mmHg. However, HT is defined as the level of BP at which the benefits of treatment undeniably outweigh the risks of treatment, as documented by clinical trials. The evidence that support the later serves as the basis for the recommendation the classification of BP and definition of HT remain unchanged from previous ESH/ESC Guidelines (Table 1.1) (ESH/ESC. 2003; ESH/ESC, 2013)

Hypertension is defined as office SBP values ≥140 mmHg and/or diastolic BP (DBP) values ≥90 mmHg. Similar classifications are used in middle-aged, younger, and older people.

Table 1. 1: Classification of office blood pressure and definitions of hypertension grade according to the ESH/ESC guideline.

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 Hypertension	140–159	and/	90–99
Grade 2 Hypertension	160–179	and/or	100–109
Grade 3 Hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Adopted from Williams *et al*, 2018: 2018 ESC/ESH guidelines for the management of arterial HT.

1.2.2 American Heart Association guidelines

The American College of Cardiology and American Heart Association have been translating scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health, since early 1980. In 2013, the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council recommended that the NHLBI focus specifically on reviewing the highest-quality evidence and partner with other organizations to develop recommendations. Accordingly, the AHA and ACC collaborated with the NHLBI and other organizations to complete and publish guidelines on assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults. In 2014, the AHA and ACC, in partnership with several other professional societies, initiated a guideline on the prevention, detection, evaluation, and management of high BP in adults. These guidelines are based on systematic methods to classify and evaluate evidence, provide basis for quality cardiovascular care.

In the current guidelines, BP is categorised into: normal, elevated, and stage 1 or 2 HT (Table 1.2). This categorisation is different from the previous recommendation in the JNC 7 report, with stage 1 hypertension defined as an SBP of 130–139 or a DBP of 80–89 mm Hg, and stage 2 HT in the current guideline corresponding to stages 1 and 2 in the JNC 7 report (Beckett *et al*., 2008). The motivation for this categorisation was based on randomised controlled trial (RCT) of lifestyle modification to lower BP, observational data related to the association between SBP/DBP and CVD risk, as well as RCTs of treatment with antihypertensive medication to prevent CVD. The increased risk of CVD among adults with stage 2 hypertension is well established (Whelton *et al*., 2018).

Table 1. 2: Classification of hypertension according to the AHA/ACC hypertension guideline

Category	SBP		DBP
Normal	< 120	And	< 80
Elevated	120–129	And	< 80
Hypertension			
Stage 1	130–139	Or	80–89
Stage 2	≥140	Or	≥ 90

Adopted from Whelton *et al*., 2018; AHA/ACC Hypertension guidelines.

1.2.3 South African Hypertension Society guidelines

In 2014 SAHS released the sixth HT guideline where the target BP for antihypertensive management was systolic < 140 mmHg and diastolic < 90 mmHg. Hypertension was categorized into: high normal BP 130–139 mmHg systolic and 85–89 mmHg diastolic; grade 1 HT 140-159 mmHg systolic and 90-99 mmHg diastolic; grade 2 HT 160-179 mmHg systolic and 100-109 mmHg diastolic; grade 3 HT ≥180 mmHg systolic ≥90 mmHg diastolic. Moreover the high normal group was sought to be at a higher CV risk and the development of HT (Seedat *et al*., 2014)

In late 2017, the new ACC/AHA HT guidelines created considerable controversy. Hypertension threshold was redefined as > 130/80 mmHg and target blood pressure < 130/80 mmHg. As a result SAHS released a commentary to give clarity on their position of the new ACC/AHA. More than 90% hypertensives in SA are not controlled at < 140/90 mmHg. Furthermore, by redefining HT to a level of 130/80 mmHg will significantly increase the prevalence of HT by 43%. Moreover, newly published threshold will necessitate increased use of laboratories, the use of health care services as well as greater use of anti-hypertensive medication. It is the position of SAHS that the new definition and targets are not relevant to low- and middle-income countries such as South Africa, the threshold for hypertension remains at 140/90 mmHg, and a universal target is < 140/90 mmHg for all categories of HT (Rayner *et al*., 2019). However, the current SAHS guidelines may be

contributing significantly to the under diagnosis of hypertension in South Africa which may be the main cause of the rising incidence of cardiovascular diseases in this community. To date there is no evidence of whether cardiovascular target organ damage is significantly higher when SAHS guidelines are used compared to AHA guidelines.

Table 1. 3: The current SAHS definition of hypertension

Category	SBP		DBP
Normal	< 120	And	< 80
Optimal	120–129	And	< 80
High normal	130–139	Or	80–89
Hypertension			
Grade 1	140–159	Or	90–99
Grade 2	160–179	Or	100–109
Grade 3	≥180	Or	≥ 110
Isolated systolic	≥140	And	< 90

Adopted from Seedat *et al*., 2014; South African hypertension practice guideline 2014

1.3 Hypertension and target organ damage

1.3.1 Arterial stiffness

The measurement of PWV is a well-known method that quantifies arterial stiffness non-invasively and is considered the gold standard of arterial stiffness due to its simplicity, accuracy, reproducibility, and predictive value (Hansen *et al*., 2006). The arterial stiffness is an index of vascular health and has been shown to present additional independent predictive value for adverse cardiovascular outcomes in patients and the general population (Mitchell *et al*., 2010; van Bortel *et al*., 2012).

Several studies conducted among hypertensive individuals and the general population demonstrated aortic PWV as an important independent determinant of

cardiovascular events (Laurent *et al*., 2001; Sutton-Tyrrell *et al*., 2005; Mitchell *et al*., 2010). These observations were supported by two meta-analyses conducted in 17635 individuals across the world. From these meta-analyses the association between aortic PWV and cardiovascular events was strong in young individuals suggesting that clinical value of aortic stiffness measurements might be in younger populations (Vlachopoulos *et al*., 2010; Ben-Shlomo *et al*., 2014). Although HT and arterial stiffness present with aging (Ferreira *et al*., 2011), they are progressively becoming more prevalent in young individuals (Sun, 2015).

Arterial stiffness is increasingly recognized as an important prognostic indicator of cardiovascular events and a potential therapeutic target in patients with HT (Payne *et al*., 2010). Moreover, it is considered as an independent risk factor for CVDs because increased risk of HT development is associated with elevated augmentation index and decreased arterial distensibility (Karras *et al*., 2012). There have been controversies as to whether the stiffening of arteries precedes the development of increased BP (Yu and McEniery, 2020). Galis *et al*. (2013) reported an increase in aortic PWV within one to two months in their animal study and at six months BP was elevated; thus, indicating that aortic stiffness precedes an increase in mean arterial pressure (MAP) and pulse pressure (PP). The purpose of their study was to elucidate the importance of arterial stiffness in the pathogenesis and development of HT (Galis *et al*., 2013; Mitchell, 2014).

In a longitudinal community-based cohort study conducted in Framingham, Massachusetts, Kaess *et al*. (2012) observed an association between increased aortic stiffness and augmentation with high risk of HT. Conversely, BP was not independently associated with the risk of aortic stiffness. Therefore, arterial stiffness precedes an elevated SBP and incident HT (Kaess *et al*., 2012; Sun, 2015). These observations show a close relationship between the development of HT and aortic stiffness.

Laurent *et al*. (2003) showed that arterial stiffening could be an early marker of vascular degeneration and that it could result in increased BP and the eventual progression and development of HT. Arterial stiffness is undeniably influenced by aging and BP in long term (Cecelja and Chowienczyk, 2009). Arterial stiffening co existing with HT shows characteristics that aggravate degeneration of the arterial

wall which demonstrate further arterial damage (Safar *et al*., 2006). The American Heart Association recommends that BP and Arterial stiffness should be measured and implications thereof should be considered (Townsend *et al*., 2015)

1.3.2 Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) can be defined as abnormal growth in the left ventricular mass and is commonly measured by echocardiography, magnetic resonance imaging and electrocardiography (Armstrong *et al*., 2012; Brady, 2015; Aronow, 2017). In addition, LVH contributes to and is a marker for heart failure, coronary events, stoke, peripheral arterial disease, and cardiovascular mortality in patients with hypertension (Gerdts *et al*., 2012:Desai *et al*., 2016;Okin *et al*., 2017).

Hypertension induced LVH usually exhibits increased wall thickness (concentric hypertrophy), without an increase in cavity size (eccentric hypertrophy) (de Simone *et al*., 2005). Induced concentric LVH by HT with time it leads to LV dilation, which then results in a decrease in the LV ejection fraction and in dilated cardiac failure (Frohlich et al., 1992; Schillaci *et al*., 2000). Moreover, the widening of the LV chamber results in circulatory complications and the metabolic vicious cycle to the cardiac muscle (ACC/ESC, 2003; Opie, 2004).

The left ventricle generally adapts to sustained arterial HT by developing concentric hypertrophy (de Simone *et al*., 2005). According to the model of compensatory ventricular response to a chronic pressure overload, ventricular wall thickness should increase proportionally to blood pressure level to maintain normal wall stress (Frohlich *et al*., 2011) and the left ventricular dilation represent a late transition toward myocardial failure (Messerli *et al*., 2017).

Left ventricular geometry in individual presenting HT is affected by several factors that includes: comorbidities (diabetes mellitus, obesity, coronary artery disease), age, sex, genetic factors, alterations in the cellular matrix, volume load, severity, the neurohormonal milieu, and the rapid increase of onset pressure load (Heckbert *et al*., 2006; Bluemke *et al*., 2008; Lønnebakken *et al*., 2017).

1.3.3 Diastolic dysfunction

Left ventricular (LV) diastolic dysfunction (LVDD) is characterised by alterations in LV diastolic filling, which may include abnormal distensibility of the myocardium and impairments in myocardial relaxation (Verma and Solomon, 2009; Wan *et al*., 2014). Left ventricular diastolic dysfunction is common among the elderly, and is sought to be a strong predictor of incident heart failure (HF) and cardiovascular events (Wan *et al*., 2014). Figure 1.1 illustrates major risk factors for the diastolic dysfunction, which can lead to asymptomatic or symptomatic diastolic dysfunction. Hypertension and other several risk factors including, obesity, age, coronary artery disease (CAD), and diabetes mellitus (DM), are implicated in the development of LVDD (Wan *et al*., 2014; Nadruz *et al*., 2017). Hypertension has been reported as a major risk factor for LVDD and contribute to the development of HF (Redfield *et al*., 2003; Chobanian *et al*.,2003). Moreover, LVDD is considered a critical link between hypertension and HF, particularly in individuals with HF with preserved ejection fraction (HFpEF), and is associated with significant morbidity and mortality (Verma and Solomon, 2009; Shah *et al*., 2003; Nadruz *et al*., 2017).

In LVDD, the LV does not fill with sufficient blood at low pressure and in the absence of increased left atrial pressure, there is slow or incomplete chamber filling. Subsequently, LV filling becomes more dependent on high atrial pressure and left atrial contraction (Gaasch and Zile, 2004). Any mechanism that may affect the removal of calcium (Ca^{2+}) from the cytosol and actin–myosin cross-bridge detachment, results in Impairments in myocardial relaxation (Kass *et al*.,2004) Recently, diastolic dysfunction has been associated with cardiac oxidative stress. Some changes in the increased Ca^{2+} sensitivity of myofilaments and Ca^{2+} handling proteins may be explained by the elevated levels of cardiac reactive oxygen species (ROS) (Kass *et al*., 2004; Jeong and Dudley, 2014;Jeong *et al*., 2015). Here are some of the proposed mechanisms: Increased diastolic Ca^{2+} delayed Ca^{2+} extrusion from the cytoplasm, or increased myofilament Ca^{2+} sensitivity could theoretically cause diastolic dysfunction. A prolonged Ca^{2+} transient results in elevation of intracellular Ca^{2+} during diastole, leading to abnormalities in both active relaxation and passive stiffness (Jeong and Dudley, 2014) Calcium homeostasis is regulated by a number of Ca^{2+} handling proteins, including the sarcoplasmic reticulum (SR)

Ca^{2+} release channel (the ryanodine receptor, RyR), the SR Ca^{2+} pump, the sarcolemmal L-type Ca^{2+} channel, and the sodium-calcium exchanger (NCX). Increased diastolic intracellular Ca^{2+} may be a result of three possible mechanisms: decreased SR Ca^{2+} pump activity; SR Ca^{2+} leakage; abnormalities in the ionic channels responsible for calcium transport (Kass *et al*., 2004)

The notion that pressure overload plays an important role in the development of LVDD is supported by the strong association between LVDD and HT (Redfield *et al*., 2003; Santos *et al*., 2016). Markers of impaired diastolic function are consistently associated with casual BP measurements (Oe *et al*., 2013). Additionally, 24-hour BP measurements show a strong association with LVDD as opposed to casual BP, since 24-hour BP measurements are more representative of the hemodynamic load imposed by hypertension (Galderisi *et al*., 1996; Zhang *et al*., 2015).

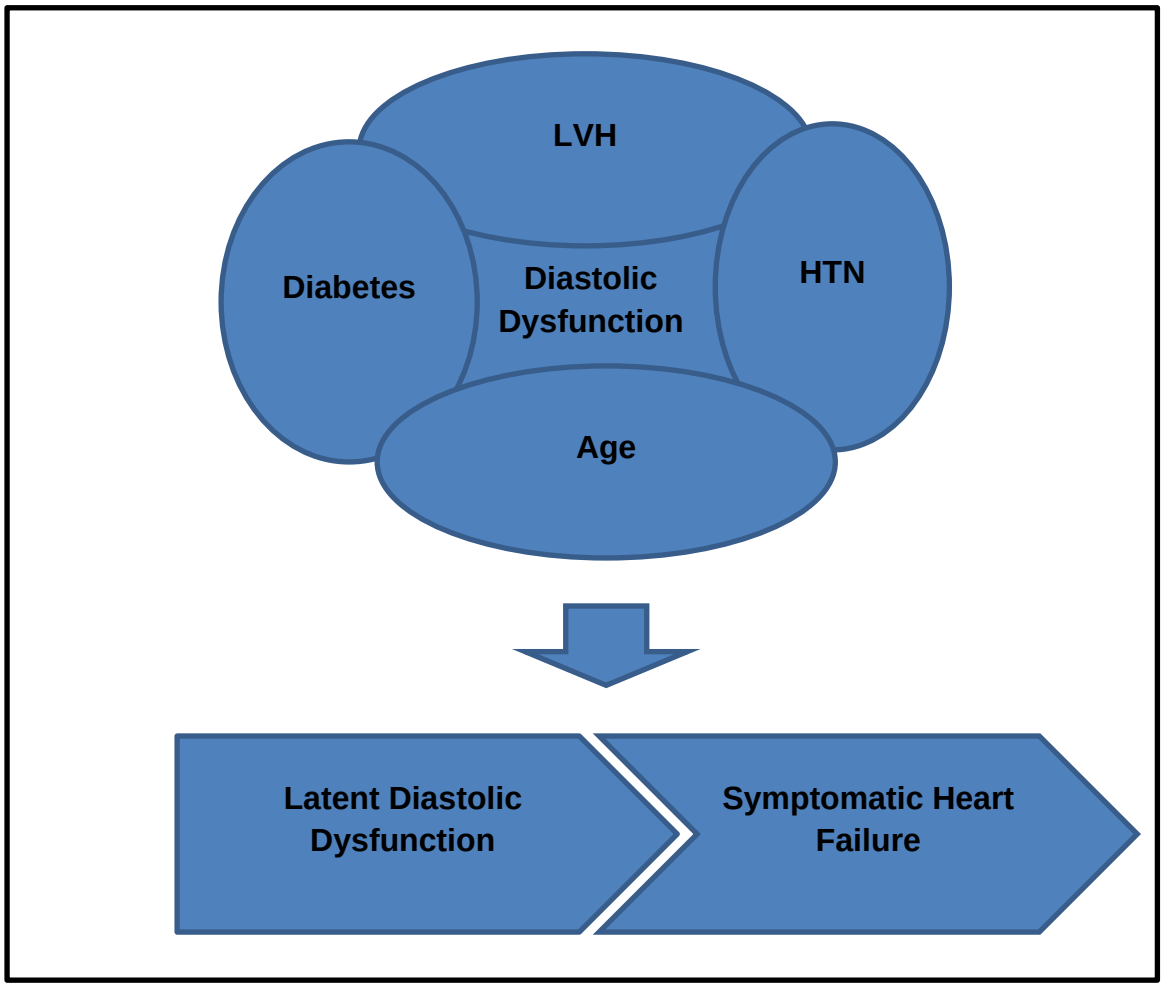

Figure 1. 1: Major risk factors for diastolic dysfunction, which can lead to asymptomatic or symptomatic diastolic dysfunction. Adapted from Jeong and Dudley, 2014.

1.4 Aim of the study

The aim of the study is to investigate the impact of hypertension stages on cardiovascular target organ changes.

1.4.1 Objectives

1) To determine the prevalence of pre-hypertension, stage-1 hypertension, stage-2 hypertension and stage-3 hypertension using both the ESC/ESH and AHA/ACC guidelines.

2) To determine the impact of the four hypertension stages (Pre-HT, HT-1, HT-3 and HT-3) on arterial stiffness and left ventricular hypertrophy.

3) To determine the impact of the four stages of hypertension on diastolic heart function.

4) To determine the relationship between general adiposity and the four stages of hypertension.

5) To investigate the role of four plasma hormones (renin, aldosterone, leptin and insulin) on the development of the four stages of hypertension.

6) To determine the relationship between arterial stiffness and diastolic dysfunction.

CHAPTER 2
METHODOLOGY

2.1 Study Population

The research project was conducted at the University of the Witwatersrand Medical School Johannesburg, South Africa and was approved by the University of Witwatersrand Human (Medical) Research Ethics Committee, approval number: **M190646**. One thousand two hundred and eleven South Africans of black African ancestry were randomly recruited by word of mouth from Johannesburg, Soweto a township in the south west of Johannesburg (Figure 2.1). The minimum age of the participants was 18 years and there was no upper age limit.

Figure 2. 1: An example of residential area (Soweto) where participants were recruited.

2.2 Clinical, demographic and anthropometric measurements

The purpose of the study was explained to the participants following which they gave informed written consent and a standardised questionnaire was administered (Appendix 3-4). The standard questionnaire was explained in a language of their understanding. To avoid a translation errors a study assistant familiar with language spoken by the participant helped in instances where language barriers were present as well as to answer any question that may rise.

The questionnaire (appendix 4) collected information with regards to date of birth, gender, previous medical history, the presence of hypertension, diabetes mellitus and kidney disease, prior and current drug therapy (analgesic use included), prior and current occupation, level of education, smoking status (including the number of cigarettes smoked in the past and at the present time), daily alcohol consumption (beer, traditional beer or other forms of alcohol and the daily quantity), caffeine consumption (number of cups of tea or coffee and whether they are decaffeinated and the number of fizzy or cola drinks a day), exercise frequency and family history of hypertension and cardiovascular events. For females, menstrual history, history of pregnancies and oral contraceptive use was evaluated. Most of the questions simply required a “Yes” or “No” answer.

Participants were requested to remove their clothing and shoes, and a medical gown to wear. This was done to allow access to measurement areas with no interference. Anthropometric measurements were taken using the International standards for anthropometric assessments (Marfell-Jones *et al*., 2012). Height and body weight were measured to the nearest 0.1 m and 0.1 kg respectively. Height was measured using a stadiometer with the head of the subject placed in the Frankfort plane and the body standing upright and then a sliding head board was lowered to the vertex of the head (refer to Figure 2.2). Weight was measured using a flat scale (Healthometer Professional, McCook, IL, USA). Body Mass Index (BMI) was calculated as weight in kilogrammes divided by the square of the height in meters (kg/m^2). The findings were used to categorise the participants as underweight, normal, overweight or obese using the cut-off values adapted from and WHO, (2000).

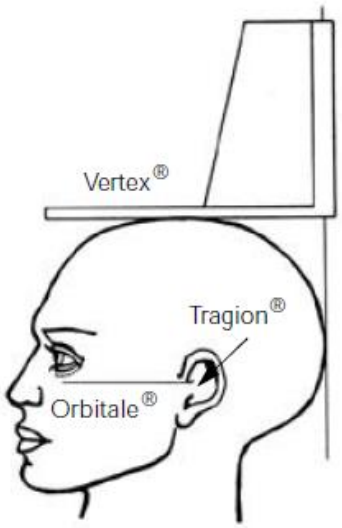

Figure 2. 2Positioning of the head in the Frankfort plane (Marfell-Jones *et al.,* 2012).

2.3 Urine collections

2.3.1 Fresh urine samples

Participants were asked for fresh urine samples upon arrival at the clinic, prior to the, commencement of other measurements. Standard urinalysis was done using routine urine test strips (Siemens Multistix® 10 SG, Siemens Healthcare (Pty) Ltd, Midrand, South Africa). The participants' pH, specific gravity and the presence or absence of protein and blood were determined to screen for renal pathology and any clinical conditions. Further electrolyte concentration and excretion rates analysis rates was done at clinical laboratory services (CLS).

2.3.2 Twenty-four-hour urine assessment

When all measurements were completed, participants were given two urine collection bottles, labelled “day time” and “night time”. Participants were advised to add each consecutive urine sample into the appropriate bottle, in order to allow separate determination of the electrolyte excretion rates and ratios between daytime and night-time. Participants were given careful instruction on how to differentiate between the times daytime – from breakfast to supper (after having breakfast to before having supper) and night time – from supper to before breakfast (after having supper to before breakfast). Twenty-four-hour urine samples with a volume of ≥400 ml/day were considered an acceptable volume from each participant, and the evaluable urinary creatinine (mmol) was between 3.5 and 35 for males and 3.5 and 30 for females. The urine samples were taken to CLS for determination of 24-hour, daytime and night-time urinary excretion rates of Ca^{2+}, K^{+}, Na^{+}, magnesium (Mg^{2+}) and creatinine. Sample with urine <500 ml/day were assumed to be incomplete urine collections.

2.4 Conventional blood pressure

Brachial blood pressure of the participants was measured using an automated sphygmomanometer (Omron, Kyoto, Japan) with the participants seated on a chair with a back and arm rest. Participants were advised not to cross their legs and they rested the arm at which the BP was measured on a table that was set beside the chair at an elevation close to the level of the heart. Caution was taken by using a cuff suitable to the arm circumference of each participant when the BP measurements were taken. A standard cuff with inflatable bladder measuring at 22 x 12 cm was used, and participants with slightly bigger arm circumferences were measured using bigger cuff sizes with bladders at 31 x 14 cm and higher. Without interruptions, participants rested for five minutes before taking the first BP measurement. Five consecutive measurements were taken at one-minute intervals. The five measurements were averaged to determine the participants’ systolic and diastolic BP in mm Hg and resting heart rate.

2.5 Carotid intima media thickness

Measurements of carotid intima media thickness (CIMT) were used to assess the risk of stroke and CVD by checking for the presence of plaques in the carotid artery. Carotid intima media thickness was measured using a high resolution B-mode ultrasound (SonoCalc IMT SonoSite inc. Bothell, WA) using a linear array 7.5Hz probe. Measurements were done according to the method described by Brand *et al*. (2013). Measurements were done on the right and left common carotid arteries. Images of ≥1cm length of the far wall of the distal portion of the right and left common carotid artery from an optimal angle of incidence were obtained. Figure 2.3 shows the site of measurement of intima media complex of the common carotid artery and the specific site where the CIMT is measured. Five consecutive measurements were done on both right and left sides and an average was calculated. These measurements were done using semi-automated border detection and quality control software. Intima media thickness of more than 0.9 mm was considered abnormal.

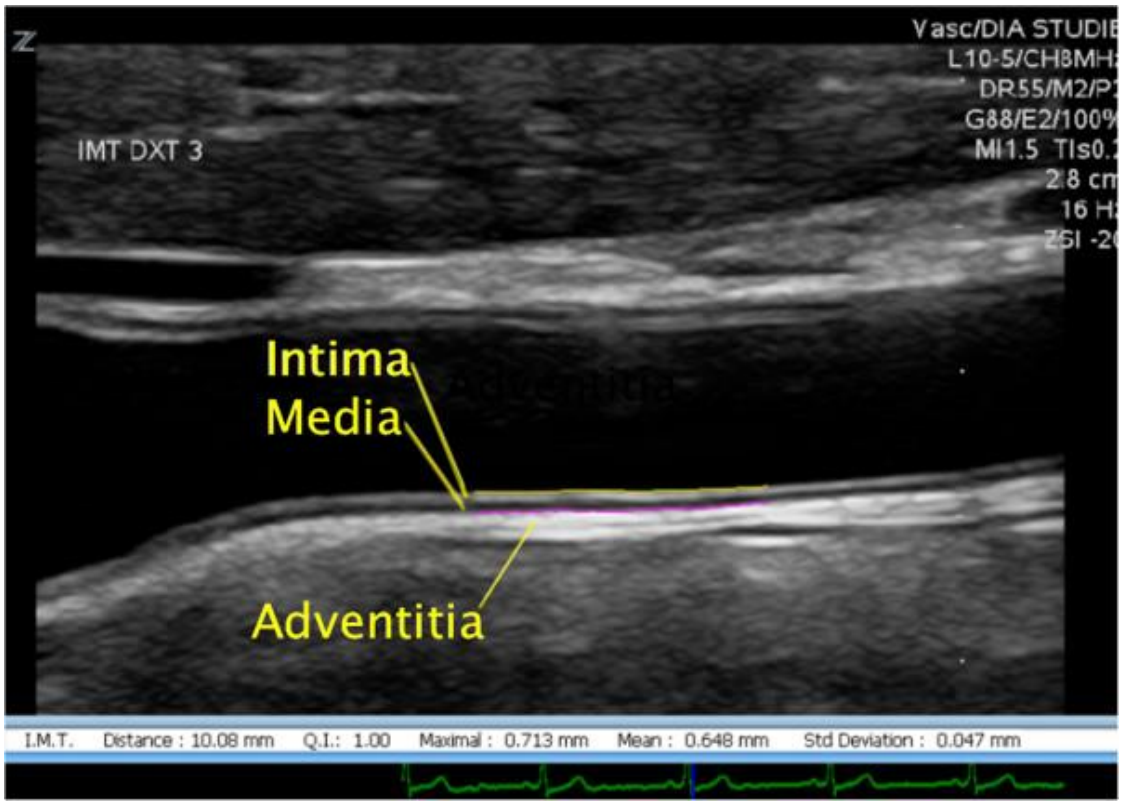

Figure 2. 3: Example of intima media complex of the common carotid artery and the specific site where the CIMT is measured (Gaarder and Seierstad, 2015).

2.6 Measurements of arterial stiffening

Arterial stiffness was determined by recording carotid and femoral PWV using augmentation indexes (AI) including central Al (Alc) and peripheral Al (Alp). The method has been previously described by Shiburi *et al*., 2006. The pulse wave was calibrated (using auscultation) by measuring BP immediately before the recordings. Participants were allowed to rest for 15 minutes in the supine position. The carotid and femoral waveforms were recorded by applanation tonometry at the participants' dominant arm. A high-fidelity SPC-301 micro manometer (Millar Instrument, Inc., Houston, Texas), interfaced with a SphygmoCor software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia); version 9.0. was used. The aortic pulse wave was calculated using a validated generalised transfer function. The radial AIp was defined as the ratio of the second to the first peak of the pressure wave expressed in percentage. Distances from the suprasternal notch to the carotid sampling site (labeled as distance A), and from the suprasternal notch to the femoral artery (Distance B) were measured. The pulse transmit time was determined from the average of 10 consecutive beats (the mean time difference between sites A and B). Lastly, aortic pulse wave velocity was determined as the ratio of the distance in meters to the transit time in seconds. Arterial stiffness was determined using the augmentation index. Data with consecutive waveforms that exceed 5% due to variability in systolic or diastolic BP or the pulse wave signal with amplitude of less than 80mV were discarded.

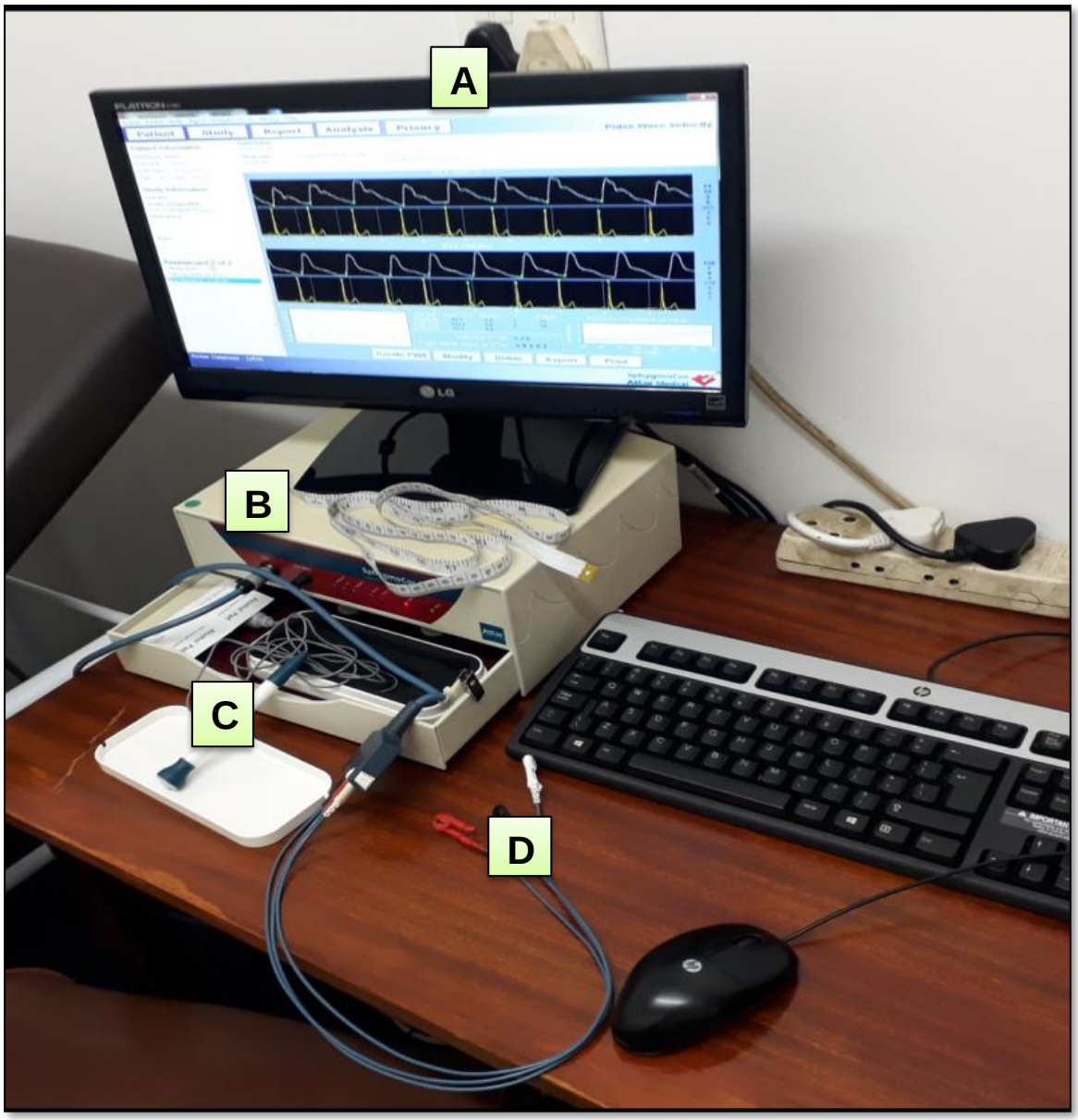

Figure2. 4: Devices used in determining arterial stiffness.

A Computer showing PWV analysis; B SphygmoCor device used to amplify pulse waves; C Applanation tonometer used to detect PWV; D ECG electrodes to determine timing of pulse waves.

2.7 Ambulatory blood pressure measurements

After all the assessments were done, participants were given a monitor to assess 24- hour ambulatory BP. The non-dominant arm was used for

measurements. The monitors were calibrated against a mercury manometer. Cuff sizes were the same dimension as explained in conventional BP measurements. Monitors were programmed to measure BP at thirty-minute intervals from 06:00–22:00 and then one hour intervals from 22:00–06:00. Participants kept a diary card to record times for going to bed in the evening and getting up in the morning. Ambulatory BP was expressed as 24-hour, daytime and night time systolic and diastolic BP. The ABPM, which was connected to a cuff around the participant's upper arm, was attached to a belt around the participant's waist. The ABPM was small enough that the participant could go about their normal daily life and even sleep with it on. Participants were asked to continue with their normal daily activities and to keep the cuff arm steady during measurements. On completion of the recording, the data were transferred to a computer for analysis. Participants enrolled in the study whose ABP measurements did not meet the pre-specified quality criteria (more than 20 hours of recordings and more than 10 and 5 readings for the computation of daytime and night-time means respectively) were discarded from the analysis. Ambulatory BP data were expressed as 24-hour average SBP and DBP, the percentage decrease in BP at night (mean day-mean night/ mean day x 100), the difference between day and night BP and the ratio of day-to-night BP. Definitions for pre-HT from ABP (120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic) values were based on published guidelines (The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, 2003; Grotto *et al*., 2006).

2.8 Blood sampling

Participants were asked to fast overnight prior to the clinical visit. Following an overnight fast, venous blood of about 18 ml was drawn from the median cubital vein of the participants' arm with the help of a professional nurse. The samples were taken to Central Laboratory Services (CLS) for analysis which included: serum concentrations of renin, aldosterone, insulin, leptin, and aldosterone.

2.9 Echocardiography

Echocardiographic measurements were used to assess the size of the left ventricle to detect left ventricular hypertrophy, to assess diastolic function and Left ventricular filling pressure. The measurements were performed according to the method described by Sliwa *et al*. (2002), and analysed according to the American Society of Echocardiographic convention (Sahn *et al*., 1978). Prior Participants were required to be in a supine position. A pulse colour Doppler Hewlett Packard model 5500 recorder coupled to a 2.5 MHz transducer was used to conduct a two-dimensional guided M-mode echocardiography. The transducer was placed on the chest perpendicular to the chest wall or pointed inferiorly and laterally at the end 34 of the long axis (Sahn *et al*., 1978). Data obtained in the short-axis view allowed for measurements of the septal wall thickness, posterior wall thickness, and the left ventricle diameter during late diastole and systole. Left ventricular mass was derived from an anatomically validated formula and indexed to height 2.7 (Devereux *et al*., 1986). Left ventricular wall thickness, left ventricular mean wall thickness, left ventricular hypertrophy and left ventricular concentricity were defined as described by Nunez *et al*. (2005).

2.10 Inclusion and exclusion criteria

Participants who had all measurements taken and had completed 24-hour urine collections and the 24-hour ambulatory BP measurement were included for analysis. Participants who had missing data were excluded for analysis. A 24-hour urine sample was considered acceptable if urine volume was <500ml/day.

2.11 Data analysis

Data management and statistical analysis was performed using SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA). Continuous data and characteristics of the participants were expressed as mean ± standard deviation (SD) or as frequencies (%). Waist circumference and BMI

assessed in separate. Data was analysed according to HT status to determine effects on stages of HT. Means were corrected for confounding variables where necessary. Confounders included: age, gender, BMI, diabetes status, hypertension status, alcohol intake, sex and smoking. The distribution of data was tested for normality using histograms. ANOVA test used to compare the means of the different HT groups and the NT. Data distributed normally was presented as mean ± SD and skewed data was presented as median and interquartile range (IQR). A multivariate regression analysis was used to determine the relationship between BMI and SBP; the effect of HT status on early-to-late diastolic filling; the relationship between PWV and early-to-late diastolic filling. Pearson's correlation was used to determine left ventricular mass index and indices of overweight/obesity. P-value <0.05 was considered statistically significant.

CHAPTER 3

RESULTS

Table3.1 gives a description of the demographic, general and clinical characteristics of the participants of the present study. Characteristics include age, body mass index (BMI), blood pressure (BP), alcohol intake, diabetic and smoking status. The average age of the population was 44.05±18.29 years. The Stage 3 Hypertension (HT3) group was older (62.22±14.55 years) than the other four groups; normotensive (NT) (33.74±17.41), pre-hypertensive (Pre-HT) (40.26±16.24), stage 1 hypertension (HT!) (49.55±17.05) and stage 2 hypertension (HT2) (57.23±13.35). There were more female participants than male participants in the study 65%. The overall population was overweight with a body mass index (BMI) of 29.47±8 kg/m^2, and stage 3 hypertension (HT3) group exhibited the highest body mass index (BMI) (32.63±7.52 kg/m^2). Fifteen percent (15%) of the sample population were smokers, stage 2 hypertension (HT2) group being the lowest with 13%, followed by the normotensive (NT) 14% then pre-hypertensive (Pre-HT) and stage 1 hypertension (HT1) at 16% the highest recorded was stage 3 hypertension (HT3) at 18%. Nine percent (9%) of participants were diabetic; normotensives (NT) had the lowest percentage (4%) as compared to stage 1 hypertension (HT1) group with the highest at 14%. Participants who consumed alcohol were 21%.

Table 3. 1: General characteristics of the study population

	TP	NT	Pre-HT	HT1	HT2	HT3
Number	1211	483	225	189	182	132
Age (years)	44.05±18.29	33.74±17.41	40.26±16.24[a]	49.55±17.05[ab]	57.23±13.35[abc]	62.22±14.55[abcd]
BMI (kg/m^2)	29.47±8.07	26.78±7.29	30.05±8.55[a]	30.82±7.66[a]	32.63±7.52[a]	31.95±7.89[a]
Female (%)	65	68	62	61	65	63
Smokers (%)	15	14	16	16	13	18
Alcohol intake (%)	21	19	21	24	24	17
Diabetic (%)	9	4	9	14	12	13

TP, total population; NT, normotensives; pre- HT, pre hypertensive; HT1, stage 1 hypertension; HT2, stage 2 hypertension; HT3, stage 3 hypertension; BMI, body mass index; Age and BMI data expressed as mean ± standard deviation; [a], significantly different from the normotensives; [b], significantly different from the pre-hypertensives; [c], significantly different from HT1; [d], significantly different from HT2.

Table 3.1. 1Prevalence of hypertension according to AHA/ACC and ESH/ESC guidelines

Guideline	NT	Pre-HT	HT1	HT2	HT3	Total hypertensives	
AHA/ACC	39.9 %		18.6%	14.5%	25.9%	-	40.5%
ESH/ESC	58.5%		14.5%	14.8%	7.3%	3.6%	25.7%

NT, normotensive; Pre-HT, prehypertension; HT1, stage 1 hypertension; HT2, stage 2 hypertension; HT3, stage 3 hypertension; ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension

Table 3.1.2 shows the relationship between body mass index (BMI), age and Normotension (NT), pre-hypertension (Pre-HT), stage 1 Hypertension (HT1), stage 2 Hypertension (HT2) and stage 3 Hypertension (HT3). There was a significant difference observed in all the hypertension stages vs normotensive (NT) and body mass index (BMI) ($p<0.0001$). In prehypertension (Pre-HT) vs the other stages significant difference was observed only in the age column.

Table 3.1. 2 Shows relationship between age and body mass index (BMI)

		Age	**BMI**
NT vs		P value	P value
	Pre-HT	0.0217	<0.0001
	HT1	0.0053	<0.0001
	HT2	<0.0001	<0.0001
	HT3	<0.0001	<0.0001
Pre-HT vs			
	HT1	0.0316	0.3574
	HT2	<0.0001	0.4021
	HT3	<0.0001	0.1033
HT2 vs			
	HT3	0.0182	0.8215
	HT!	0.0293	0.7714

BMI, body mass index; NT, normotensive; Pre-HT, pre-hypertensive; HT!, stage 1 hypertension, HT2, stage 2 hypertension; HT3, stage 3 hypertension; ; P value < 0.05 considered significant.

Table 3.2 shows the multivariate regression analysis of the relationship between body mass index (BMI) and systolic blood pressure (SBP). Adjustments were made for age, gender, presence of diabetes, cigarette smoking and alcohol intake. There was significant relationship between body mass index (BMI) and blood pressure (BP) in the total population (TP), the normotensives (NT) and the pre-hypertensives (Pre-HT). However, no relationship was found between body mass index (BMI) and systolic blood pressure (SBP) in the grade-1, grade-2 and grade-3 hypertensives. There was a moderate positive relationship between body mass index (BMI) and blood pressure (BP) in the total population (TP), normotensives (NT), pre-hypertensives (Pre-HT) and grade-1 hypertension (HT1). A weak negative relationship was observed in grade-2 (HT2) and grade-3 hypertension (HT3).

Table 3. 2: The relationship between body mass index (BMI) and blood pressure (BP)

	R^2	CI	P value
BMI vs BP			
Total population	0.10	0.02 to 0.14	0.0078*
Normotensives	0.12	0.03 to 0.21	0.0087*
Pre-hypertensive	0.14	0.01 to 0.27	0.0486*
Grade-1 hypertension	0.02	-0.03 to 0.17	0.7975
Grade-2 hypertension	-0.01	-0.15 to 0.15	0.9565
Grade-3 hypertension	-0.04	-0.22 to 0.14	0.6889

The regression analysis corrections were made for age, gender, alcohol intake and cigarette smoking. BMI, body mass index; BP, blood pressure; R^2, adjusted coefficient of determination; CI, confidence interval; BP range: Normotensive, < 120 mmHg systolic and < 80 mmHg diastolic; Pre-HT, 130–139 mmHg systolic and 85–89 mmHg diastolic; stage-1 HT, 140-159 mmHg systolic and 90-99 mmHg diastolic; stage-2 HT, 160-179 mmHg systolic and 100-109 mmHg diastolic; stage-3 HT, ≥180 mmHg systolic ≥90 mmHg diastolic

Table 3.3 gives the haemodynamic characters of the participants. The mean and standard deviation is recorded for all the clinical blood pressure parameters and blood pressure parameter from the ambulatory blood pressure monitor (ABPM). The only significant difference was observed between the normotensive vs pre-hypertensive group for both systolic and diastolic 24-hour BP ($p<0.0001$). The average conventional blood pressure was higher (129.31±22.28 and 83.84±12.57) than the average 24-hour BP (118.30±14.98 B and 72.64±10.18) and night time BP (111.33±17.19 and 64.92±11.72). The ambulatory systolic and dipping ratio was recorded at 0.91±0.08 and diastolic at 0.84±0.10 for the total population. Both the systolic and diastolic dipping ratio remained constant throughout the hypertensive stages.

Table 3. 3: Haemodynamic parameters of the study population

Variables	TP	NT	Pre-HT	HT1	HT2	HT3
SBP24 (mmHg)	118.30±14.98	109.41±8.71	116.57±10.21[a]	120.68±12.39	127.63±12.11	141.19±19.07
DBP24 (mmHg)	72.64±10.18	67.53±6.79	71.26±7.32 [a]	74.48±9.35	78.63±9.39	84.65±14.05
SBPN (mmHg)	111.33±17.19	102.13±10.11	109.31±12.76	113.33±15.28	121.35±16.16	135.45±21.83
DBPN (mmHg)	64.92±11.72	59.73±8.27	62.99±9.37	66.96±10.39	71.37±11.75	77.52±15.69
SBPC (mmHg)	129.31±22.28	109.66±7.17	124.82±2.91	134.99±2.86	147.74±5.68	175.62±14.38
DBPC (mmHg)	83.84±12.57	74.86±7.74	82.92±6.84	87.69±8.66	91.95±8.64	101.82±14.77
RSBP	0.91±0.08	0.90±0.07	0.91±0.07	0.91±0.09	0.93±0.10	0.93±0.08
RDBP	0.84±0.10	0.82±0.10	0.82±0.09	0.85±0.11	0.86±0.71	0.86±0.09

NT, normotensives; pre- HT, pre hypertensive; HT1, stage 1 hypertension; SBP24, 24-hour systolic blood pressure; DBP24, 24-hour diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, night-time diastolic blood pressure; SBPC, conventional systolic blood pressure; DBPC, conventional diastolic blood pressure; RSBP, night-to-daytime systolic blood pressure ratio; RDBP, night-to-daytime diastolic ratio; [a], significantly different from the normotensives; ± values are the standard deviations

Table 3.4 gives plasma hormone concentration levels of participants under the current study. The hormones studied were aldosterone, Renin, Leptin and Insulin. The average aldosterone level was 195.78±164.35 pg/mL and stage 3 hypertension group exhibited highest levels of aldosterone and no statistical difference was noted. The average renin level for the total population was recorded at 40.95±89.65 ng/mL, stage 1, 2, 3 hypertension groups were significantly different from the normotensives (P=0.411; 0.0343; 0.0359). Leptin levels increased as the hypertensive stages progress. The average leptin levels were recorded at 25.34±26.26 ng/mL, there was a significant difference noted between pre-hypertension and the normotensive (P=0.0212), grade 1 hypertension and the normotensive (P=0.0342), grade 2 hypertension and normotensive (P=0.0069) and stage 3 hypertension group was significantly different from the normotensive (P=0.0014). The total population had high levels of insulin (13.19±16.24 mmol/l), there was no significant difference observed between grade 2 hypertension and the normotensive group (P=0.1461). Furthermore, the average ratio between aldosterone and renin was 26.81±49.58. The ratio increased significantly with the hypertension stages. Grade 1, 2, 3 hypertension group was significantly different from the normotensives and the prehypertensive group (P<0.0001).

Table 3. 4: Plasma hormone concentrations

	TP	NT	Pre-HT	HT1	HT2	HT3
Aldosterone (pg/mL)	195.78±164.35	189.16±163.35	192.78±172.13	183.08±142.96	205.28±168.06	232.38±175.14
Renin (ng/mL)	40.95±89.65	48.68±95.18	43.59±91.19	33.93±106.89[a]	30.89±63.31[ab]	31.12±64.23[a]
Leptin (ng/mL)	25.34±26.26	19.86±22.37	27.37±27.84[a]	26.85±25.41[a]	27.99±27.94[a]	36.68±31.87[a]
Insulin (mmol/l)	13.19±16.24	11.72±15.55	13.02±14.19	14.67±17.35	15.23±19.41[a]	13.91±15.20
Aldoren	26.81±49.58	17.36±29.48	17.26±25.56	30.32±40.80[ab]	40.92±77.30[ab]	54.11±79.56[abc]

TP, total population; NT, normotensives; Pre- HT, pre-hypertensive; HT1, stage 1 hypertension; HT2, stage 2 hypertension; HT3, stage 3 hypertension; Aldoren, aldosterone-to-renin ratio; [a], significantly different from the normotensives; [b], significantly different from the pre-hypertensives; c, significantly different from HT1; ± values are the standard deviation

Table 3.5 gives urine electrolytes excretion of participants. Urinary Na^+ excretion of this population was higher than the recommended Na^+ value of 100 mmol/d (110.10 ± 83067). The average urinary Ca^+ excretion was within normal limits at <6.2 mmol/d (1.60±1.90). Urinary Mg^+ excretion was lower than the recommended range of 3.0-3.43 (2.27±1.90). The average urinary K^+ was lower than the recommended concentration 120mmol/d (28.73±22.24). Sodium potassium ratio was recorded at 4.45±2.99.

Table 3. 5: Urine electrolytes

	TP	NT	Pre-HT	HT1	HT2	HT3
Na^+ (mmol/d)	110.10±83067	117.71±89.61	111.52±82.95	106.38±91.17	97.76±67.13	105.09±73.75
Ca^{2+}(mmol/d)	1.60±1.90	1.67±1.77	1.80±2.19	1.62±2.18	1.29±1.64	1.45±1.60
Mg^{2+}(mmol/d)	2.27±1.90	2.49±2.20	2.34±1.81	2.22±1.92	1.94±1.27	1.95±1.64
K^+(mmol/d)	28.73±22.24	31.23±26.49	30.0619.26	27.11±21.87	25.23±16.67	25.80±18.44
Na^+/K^+	4.45±2.99	4.61±3.85	4.19±2.19	4.40±2.87	4.32±2.13	4.59±2.23

TP, total population; NT, normotensives; pre- HT, pre hypertensive; HT1, stage 1 hypertension; HT2, stage 2 hypertension; HT3, stage 3 hypertension; Na^+, sodium; Ca^{2+}, calcium; Mg^{2+}, magnesium; K^+, potassium; Na^+/K^+, sodium potassium ratio; ± values are the standard deviation

Table3.6 shows the regression analysis between pulse wave velocity and early-to-late diastolic filling. There was a significant difference observed in all the models (p=0.0001 for all the four models). The coefficient interval decreased as the data was adjusted with more covariates. A negative relationship was observed in model 1 (r2= -0.48), model 2 (r2= -0.43), model 3 (r2=-0.33) and model 4 (r2=-0.23) and the proportion of the variance was moderate.

Table 3. 6: The relationship between pulse wave velocity and early-to-late diastolic filling

	R^2	CI			P value
Model 1	-0.48	-0.54	to	-0.43	<0.0001
Model 2	-0.43	-0.49	to	-0.37	<0.0001
Model 3	-0.33	-0.39	to	-0.26	<0.0001
Model 4	-0.23	-0.30	to	-0.16	<0.0001

R^2, adjusted coefficient of determination; CI, confidence interval; P<0.0005 considered significantly different; Model 1, uncorrected; Model 2, corrected for sex and BMI; Model 3, corrected for the Model 2 covariates plus diabetes status, hypertension status, smoking and drinking; Model 4, corrected for all the Model 3 covariates plus systolic blood pressure.

Figure 3.1 shows the association between pulse wave velocity (PWV) and hypertensive status of the population under the study. The average pulse wave velocity (PWV) of the total population was 6.41± 2.6. The pulse wave velocity increased as the condition progressed. Normotensive group was the lowest at 5.03±1.35, followed by the pre-hypertension group at 6.14 ±2.22, then grade-1 hypertension at 7.02±2.44, grade 2 hypertension at 7.63±2.77 and the highest was grade 3 hypertension at 9.78±3.32. Pre-hypertensives, grade 1, grade 2 and grade 3 hypertensive groups pulse wave velocity (PWV) was significantly different from the normotensives (P=0.0303; 0.0110; 0.0048 and P<0.0001). Other significant difference is observed between grade-3 hypertension group and grade 2 (P=0.0109), pre-hypertensives and grade 3 hypertension group (P<0.0001). Lastly, normotensive were significantly different from the grade-3 hypertension group (P<0.0001).

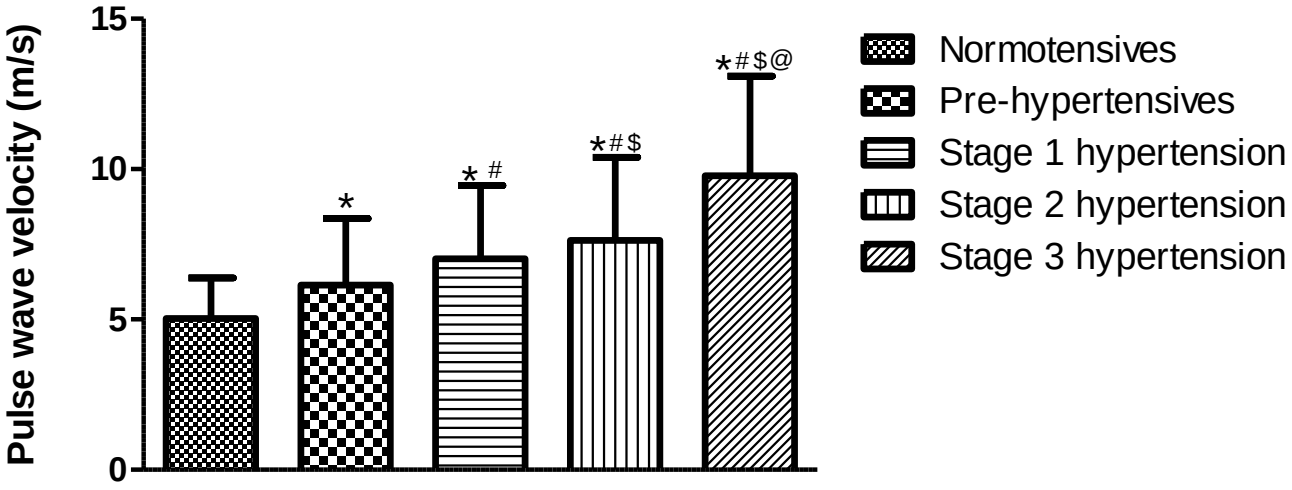

Figure 3. 1: Pulse wave velocity obtained from participants under the current study.

Means corrected for age, gender, BMI, smoking and alcohol intake. ***** Significantly different from the normotensives; # significantly different from the pre-hypertensives; **$**significantly different from the stage 1 hypertensives; @significantly different from the stage 2 hypertensives.

Figure 3.2 shows the effect of hypertensive status on early-to-late diastolic filling of the population under study. The means were adjusted for age, gender, body mass index (BMI), smoking and alcohol intake. The total population average early-to-late diastolic filling rate was 1.28±0.49. As the condition progresses the values decreased. The normotensive group had the highest value at 1.53±0.48, followed by the pre-hypertensive group at 1.33±0.45, then grade-1, grade-2 and grade-3 hypertension (1.14±0.4, 0.98±0.34, 0.93±0.36 respectively). There was a significant difference observed between the Pre-hypertensive, grade 1, grade 2, grade 3 hypertensive group's rate and the normotensives (P=0.022; 0.0103; <0.0001; <0.0001). Other significant difference is observed between grade1, 2, 3 hypertension group and Pre-hypertensive group (P=0.0401; 0.0171; P<0.0001). Grade 2 and grade 3 hypertensive groups are significantly different from the grade1hypertension group (P=0.0440; 0.0109).

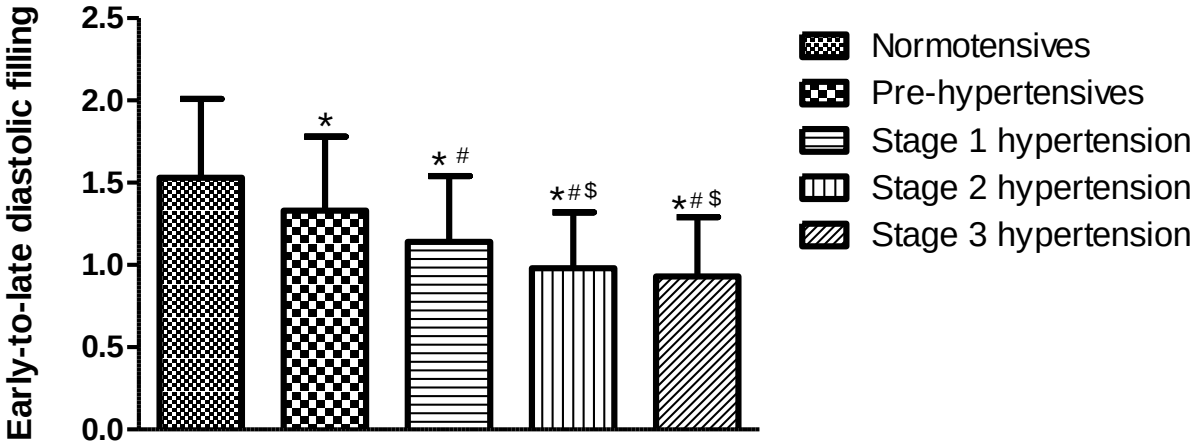

Figure 3. 2: The impact of hypertension status on early-to-late diastolic filling of the population under the study.

Means corrected for age, gender, BMI, smoking and alcohol intake. ***** Significantly different from the normotensives; # significantly different from the pre-hypertensives; **$**significantly different from the stage 1 hypertensives

Figure 3.3 illustrates the left ventricular mass index (LVMI) values of the population under study. The total population left ventricular mass index (LVMI) was 67.28±24.04. Grade 3 hypertension group had the highest left ventricular mass index at 79.79±27.84, grade 2 hypertension was the second highest at 75.08±23.71, third highest was grade 1 hypertension at 69.66±23.59, followed by pre-hypertension at 67.25±21.84 and the lowest group was the normotensive group at 59.67±20.42. Statistical difference was observed between Normotensive vs pre-hypertension, grade-1, 2, 3 (P=0.0400; 0.0391; 0.0272; 0.0051). In pre-hypertensive vs grade-1 hypertension there was no statistical difference noted (P=0.2013). Whereas, in pre-hypertension vs grade-2 and grade- 3 statistical difference was noted at P=0.0397 and P=0.0005 respectively. Grade-2 hypertension vs grade-1 hypertension no statistical difference noted (P=0.1175), grade-2 vs grade-3 statistical difference was observed at P=0.0416.

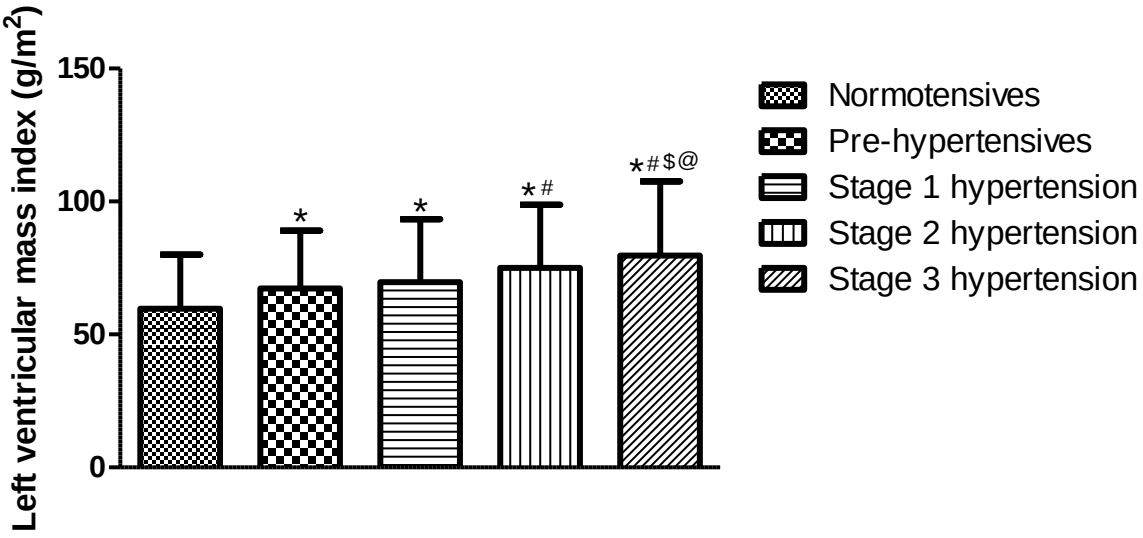

Figure3. 3: Effects of hypertensive status on left ventricular mass of the population under study.

Means corrected for age, gender, BMI, smoking and alcohol intake. ***** Significantly different from the normotensives; # significantly different from the pre-hypertensives; **$**significantly different from the stage 1 hypertensives; @significantly different from the stage 2 hypertensives.

CHAPTER 4

DISCUSSION

Our results show that there is a discrepancy between the two guidelines. According to the ESC/ESH guidelines that are used in South Africa, 25.7% of population sample is hypertensive, however, according to the more stringent AHA/ACC, the prevalence of hypertension is 40.5 %. Whether this indicates an under estimation of hypertension by or an overestimation of hypertension by the AHA/CC guidelines can only be determined by assessing if there is any significant target organ damage in the group where the discrepancy exists i.e. people that are normotensive according to the ESC/ESH guidelines yet hypertensive according to the AHA/ACC guidelines. However before assessing target organ damage, let us first look at the determinants of hypertension. Our results show that the HT stages progresses with age. The average age of our study population were 44.05±18.29 years with the normotensive individuals being the youngest at age 33.74±17.41 years, followed by the pre-HT at the age of 40.26±16.24 years, then the HT1 at 49.55±17.05 years and HT2 at 57.23±13.35 years. The oldest were the HT3 at 62.22±14.55 years. The ages between all the groups were significantly different. These results confirm what has been shown by previous studies that age is associated with BP (Dua *et al* 2014), however our findings go a step further by showing that age is not just associated with BP but it also determines the HT stage of an individual. So, the uniqueness of the current study is that it shows age specific changes in HT stage.

The mechanisms responsible for these age specific changes in HT status need further clarification. Our results show that none of the groups have normal BMI. This is an indication that adiposity is a serious problem in this population. The BMI of the pre-HT is in the overweight range while the BMI of all the other groups (HT1, HT2 and HT3) are in the obese range. Furthermore, there is no significant difference in the BMI values of all the groups in the obese range even though the ages are significantly different. This implies that as age increases from the early thirties to the forties, BMI also increases and that is translated to an increase in BP from the normotensive range to the pre-HT range. However, as age increases from the pre-HT to HT1 and the subsequent stages, BMI remains unchanged even though BP increases. Table 3.1 shows that the relationship between BMI and BP is limited to the transition from NT to pre-HT, and that it does not contribute to age related

changes in BP from the pre-HT stage to the HT3 stage. This is confirmed by our regression analysis (Table 3.2) which shows a relationship between BMI and BP which remains significant even after correcting for age. Furthermore, table 3.2 shows that the relationship between BMI and BP is independent of age in the NT and pre-HT groups. However, the regression analysis shows no significant relationship between BMI and BP from HT1 to HT3, confirming that BMI does not play a significant role in the age related increases in BP from pre-HT to HT3. These results are not consistent with findings from other studies. Findings by Hosseini *et al*. (2005) show that BP percentiles are steadily increased by age and BMI. Besides the racial differences, the degree of adiposity could account for the different results of the two studies. The average BMI of the Iranian population in Hosseini's study was in the overweight range while all the HT subtypes of the Black SA population were in the obese range. Furthermore, the age groups of the two studies are slightly different. In the Iranian study the participants were aged 25 to 69 years while in the SA study it was from 18 years with no upper age limit.

Importantly these findings show that an increase in body fat as indicated by BMI plays a significant role in the increase in BP from the NT range to the pre-HT stage, which represents an increase in age from the early thirties to the forties. Therefore, prevention of the development of obesity in young adults through exercise and dietary intervention, may prevent the progression of BP from the NT to pre-HT. The mechanisms that govern the relationship between BP and BMI are well understood. Leptin plays a major role in this relationship. As the BMI remain significantly different to that of NT, but then unchanged for pre-HT, HTl, HT2 and HT3, the leptin concentrations also are significantly different from the NT, but stay constant in pre-HT,HT2, HT2 and HT3, as it can be seen in Table 3.4.. The relationship between BP and BMI is mediated by leptin. Leptin is synthesised by adipose tissue, therefore it would be reasonable to assume that an increase in adipose tissue mass would result in increased plasma leptin concentrations (Harris, 2014). There are two mechanisms that account for the leptin induced changes in BP. Firstly, increased plasma leptin concentration result in increased sympathetic nervous system activation (Rahmouni, 2010). This will result in stimulation of the α and β adrenergic receptors. Stimulation the β1 receptors will activate the pace maker of the heart, the sinoatrial node, resulting in increased heart rate (Gorre and

Vandekerckhove, 2010). Furthermore, increased sympathetic nervous system activation will result in stimulation β1 receptors in the ventricles which would then result in increased force of contraction of the ventricular muscle (Gordan *et al*., 2015). The combined effects of an increased heart rate and increased force of contraction result in increased BP. Secondly, leptin acts on the kidneys causing salt retention (Beltowski *et al*., 2004; Hall, 2010). Reduced sodium excretion will cause an increase in plasma sodium concentration resulting in increased BP. However, the salt induced change in BP was not seen in the current study as there was no significant difference in the urinary sodium excretion rate between all the groups. Hence the leptin induced increase in sympathetic activity may be the main cause of the increase in BP which leads to the progression from NT to Pre-HT.

Now the question remains, if BMI does not account for an increase in BP from age 40, what physiological mechanisms can account for the observed increases in BP. Our results show that BP increases with increasing age from Pre-HT to HT3 even though BMI remains unchanged. As stated in table 3.2, BMI does not contribute to these changes, tables 3.4 shows that the aldosterone-to-renin ratio (ARR) changes consistently as BP progresses from the Pre-HT stage to HT3. The ARR of the NT and pre-HT is similar, demonstrating that ARR does not play a role in this transition, and we have already shown that BMI is the main contributor to this change. However, the ARR of the HT1 and HT2 groups is significantly higher than that of the pre-HT and NT groups; it is almost two times higher. This ratio further increases as BP progresses from HT2 to HT3. The ARR of HT3 is significantly higher than all the other groups (NT, Pre-HT, HT1 and HT2). So the younger NT and pre-HT groups have the lowest aldosterone-to-renin ratio while the older stage-2 and stage-3 HT have the highest ratio. The role of the renin-angiotensin-aldosterone system in the control of BP is well understood. This system is stimulated by a decrease in BP and when it is over activated the result is HT. Renin has always been thought to be to be the initiator of the cascade of reactions that leads to an increase in BP. Renin cleaves angiotensinogen to form angiotensin I which is converted to angiotensin II by angiotensin converting enzyme. Angiotensin II stimulates aldosterone secretion. However, research has shown that plasma aldosterone concentration can increase despite decreasing renin secretion (Egan *et al*., 1994; Goodfriend *et al*., 1999; Colussi *et al*., 2007; Rossi *et al*., 2008; Ku and Campese,

2009; Kidambi *et al*., 2009;). This is exactly what the findings of this study show. Table 3.4 shows that as age increases, plasma renin decreases while aldosterone increases. Even though there is no statistical difference in the aldosterone concentrations between the different groups. The ultimate result is an increase in the ARR. The relationship between BP and aldosterone-to-renin ration has been described in a number of studies. Kidambi and others reported that BP is associated with plasma aldosterone, insulin resistance and waist circumference, which raise the possibility that aldosterone plays a role in obesity-related HT (Kidambi *et al*., 2009). In a study conducted among African Americans, Kidambi *et al*. (2009) demonstrated that plasma aldosterone independently contributes to BP variance and to HT prevalence among normal weight, overweight and obese individuals. Furthermore, the relationship between aldosterone-to-renin ratio and BP was largely attributed to the strong negative relationship between plasma renin and BP. Similarly, there are previous reports that suggest the positive association between aldosterone and obesity which is not related to plasma renin activity (Egan et al., 1994; Goodfriend et al., 1999; Rossi et al., 2008). This association between obesity and aldosterone that is independent of renin may account to the increases in HT stages (from pre-HT to HT3) in this population. Since BMI does not directly influence BP as shown previously, the increased BMI indirectly influences though aldosterone. Literature, further demonstrates that excess aldosterone, reflected by the aldosterone to active renin ratio, may contribute to high blood pressure (Gekle and Grossmann, 2009; Shatat *et al*., 2009). This is in line with the observation that elevated aldosterone levels at baseline play a significant role in the future incidence of HT in NT individuals who are obese (Table 3.3). The renin-angiotensin system (RAS) plays a central role in blood pressure regulation and fluid-electrolyte homeostasis, and its dysregulation contributes to the development of HT (Kim and Iwao, 2000). Studies have demonstrated that rat and human adipose tissue possess all of the components necessary for production of angiotensin II (Ang II), including angiotensinogen renin-like activity angiotensin-converting enzyme, and angiotensin type 1 receptor (Engeli et al., 1999). Adipose-derived angiotensinogen is also released into the circulation where it serves as substrate for conversion to bioactive Ang II, contributes to plasma Ang II levels (Shenoy and Cassis, 1997; Schling *et al*., 1999; Ye *et al*., 2009). Underlying mechanisms seem to be changes in vascular smooth muscle cells and fluid homoeostasis and increased profibrotic and

proinflammatory activity (Tomaschitz *et al*., 2010) as well as sympathetic drive which translates into a rise in BP (Geerling and Loewy, 2009; Huang *et al*., 2005).

Having established the mechanisms that determine the age related changes in HT status, we went on to investigate if the different stages of HT are associated with any target organ changes. Previous studies have shown that increasing age is associated with higher odds for all stages of HT (Rampal *et al*., 2008; Gebreselassie and Padyab, 2015; Abebe *et al*., 2015). Figure 3.1 shows that PWV which is an index of arterial stiffness, increases with each subsequent stage of HT (Pre-HT to HT3). Arterial stiffness is significantly different in all the stages of HT ($p<0.0001$). The mechanisms that govern the increase in arterial stiffness with increasing age are well established. These age-related vascular alterations may vary in different vessels and differ from one species to another. Throughout aging, the aortic diameter as well as the luminal diameter progressively enlarges. Chesnutt and Han, 2011 reported that the thickness of the media does not show a significant difference between adults and young participants whereas the tunica intima thickens with age and results in the increasing aortic diameter. Thus the increase in diameter implies an irregular shaped aortic lumen, which then contributes to reduced elasticity of the aorta, subsequently resulting in an increased BP (Benetos *et al*., 1993). The peripheral arterial system in younger individuals is stiffer as compared to the central arterial system. However, with time that reverses, older individuals have greater central artery stiffness compared to peripheral arteries (Shikai and Carmel, 2020). Amongst other causes that lead to the change in arterial structure and function, changes in structural components, increased reactive oxygen species, inflammatory changes, and endothelial dysfunction are observed with aging. An increase in the levels of inflammatory mediators seen with aging, leads to the production of reactive oxygen species that then lead to endothelial damage predisposing the vascular system to atherosclerosis (Dai *et al*., 2015).

Our results further indicate that as the HT stages progress from pre-HT to HT3, there is a reduction in early-to-late diastolic filling. With increasing HT status, diastolic filling is redistributed to late diastole. This means the filling of the ventricle is

more dependent on atrial contraction than on passive filling, indicating reduced relaxation during diastole. This condition eventually leads to diastolic heart failure, which is heart failure with preserved ejection fraction. In a multivariate regression analysis (figure 3.2), our results show that arterial stiffness is the main contributor to this age related diastolic dysfunction.

From our results, the regression model shows that there is a significant negative relationship between PWV and early-to-late diastolic filling. The p-value remained constant ($p<0.0001$), even when the models were corrected for more covariates there was still significant negative relationship between PWV and early-to-late diastolic filling. The NT and the pre-HT have a higher early-to-late diastolic filling rate while stage1, stage 2 and stage 3 HT group have the lowest rate. This relationship shows that as the PWV of the population sample increases the early-to-late diastolic filling rate decreases. An increased PWV means increased arterial stiffness, a sign of aging. Now as it is demonstrated in our results (Figure 3.1) PWV increases with the progression of HT stages and age. Several studies have reported that arterial stiffening is a hallmark of aging-related HT, and associated with elevated SBP and PP in longitudinal and cross-sectional settings (Safar *et al*., 1987; O'Rourke and Hashimoto, 2007; Kaess *et al*., 2012). However, other studies propose that arterial stiffness, measured by carotid-femoral PWV does not only correlate with BP but also an independent predictor of cardiovascular myocardial infarction and stroke (Laurent *et al*., 2001; Mattace-Raso *et al*., 2006;Willum-Hansen *et al*., 2006; Mitchell *et al*., 2010). In addition to arterial stiffening acting as a risk factor, it may also promote disease by different mechanisms. Increased SBP leads to ventricular stiffening and LVH, ultimately leading to diastolic dysfunction and heart failure (Lakatta and Levy, 2003). It is generally accepted that an elevated arterial stiffness influences the development of LV diastolic dysfunction. In addition to that an increased afterload by stiffened arteries leads to a decrease in diastolic pressure and LVH (Lakatta and Levy, 2003; Dao *et al*., 2005).

Left ventricular hypertrophy and HT-induced increase in left ventricular mass is known as a pediatric surrogate marker for HT- induced mortality and morbidity in

adults (Woroniecki *et al*., 2017). The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing longitudinal, multicentre study of a diverse, population-based sample with no known heart disease. Furthermore, they observed that the risk of cardiovascular outcomes only became visible after five years of follow up (Kawel-Boehm *et al*., 2019). From our results (Figure3.3) we observed an increase in the left ventricular mass index as the HT stage increases. This implies that with increasing age and increased PWV, LVMI increase. The mechanisms of the consequence of aging have been explained above. Based on our results this population under study have demonstrated to be overweight and not young. There was a significant difference noted between all the HT stages and the NT group. Even after correcting for age, gender, BMI, smoking and alcohol intake, figure 3.3 shows that the LVMI is higher in all the HT groups. Grade 3 HT exhibited the highest LVMI as compared to the other groups (NT, pre-HT, stage 1and stage 2) and the difference significant. In a study conducted by Kartal *et al*. (2008), they found a relationship between serum leptin and LVH. Furthermore, LVH was significantly related to leptin independent of BMI and BP. This could be explained by the sympathetic activation role of leptin. The findings of this study are similar to the present study in such a way that our results showed a significant increase in leptin as HT stage progresses, and also we observed a steady BMI.

Conclusion

In conclusion our results show that age specific changes, age is associated with BP and that it determines the HT stage of an individual. Since both stages (pre-HT and HT1) are considered NT according to the SAHS/ESC/ESH guidelines, by the time they reach HT2 stage which is the first stage considered as hypertensive, target organ damage may have progressed significantly. Therefore, these results indicate that the AHA/ACC guidelines are more appropriate for the SA population. If these guidelines can be adopted for HT treatment, CVD target organ damage can be significantly reduced.

Limitations of the study

There were several limitations noted in the currents study. As observed with most of studies, the current study consisted of more females than males. This could be because males are more influenced by socio-economic status and they do not have a positive outlook on human medical research as compared to females. In future studies, more participants could be encouraged to participate. Having a large number of participants could be useful in stratifying the importance of BP monitoring to prevent adverse cardiovascular effects in a population based study. Furthermore, due to the cross sectional nature of the study the relationship between cause and effect could not be firmly established. The findings of this study need further confirmation in a longitudinal study.

CHAPTER 5

REFERENCES

References

American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. 2003. *Journal of the American College of Cardiology*, **42**: 1687—1713.

Abebe, S.M., Berhane, Y., Worku, A. and Getachew, A. 2015. Prevalence and Associated Factors of Hypertension: A Crossectional Community Based Study in Northwest Ethiopia. *PLOS ONE*, **10**: doi.org/10.1371/journal.pone.0125210

Armstrong, A., Gidding, S., Gjesdal, J., Wu, C., Bluemke, D. and Lima, J. 2012. LVM assessed by echocardiography and cardiac magnetic resonance, cardiovascular outcomes, and medical practice. *Cardiovascular Imaging*, **5**: 837—848.

Aronow, W.S. 2017. Hypertension and left ventricular hypertrophy. Ann Transl Med, 5: 310—313.

Beckett, N.S., Peters. R., Fletcher, A.E., Staessen, J.A., Lui, L., Durnitrascu, D., Stoyanovsky, V., Antikainen, R.L., Nikitin, Y., Anderson, C., Belhani, A., Forette, F., Rajkumar, C., Thijs, L., Banya, W. and Bulpitt, C.J. 2008. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine*, **358**: 1887—1898.

Bełtowski, J.,GrażynaWójcicka, G.,AndrzejMarciniak, A. and Jamroz, A. 2004. Oxidative stress, nitric oxide production, and renal sodium handling in leptin-induced hypertension. *Life Science*, **74**: 2987—3000.

Benetos, A., Laurent, S., Hoeks, A.P., Boutouyrie, P.H. and Safar, M.E. 1993. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arteriosclerosis, Thrombosis and Vascular Biology*,**13**: 90—97.

Ben-Shlomo, Y., Spears, M., Boustred, C., May, M., Anderson, S.G., Benjamin, E.J., Boutouyrie, P., Cameron, J., Chen, C.H., Cruickshank, J.K., Hwang, S.J., Lakatta, E.G., Laurent, S., Maldonado, J., Mitchell, G.F., Najjar, S.S., Newman, A.B., Ohishi, M., Pannier, B., Pereira, T., Vasan, R.S., Shokawa, T.,Stton-Tyrell, K., Verbeke, F., Wang, K.L., Webb, D.J., Hansen, T.W., Zoungas, S., McEniery, C.M., Cockcroft, J.R. and Wilkinson, I.B. 2014. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of American College Cardiology*, **63**: 636—646.

Bluemke, D.A., Kronmal, R.A., Lima, J.A.C., Liu, K., Olson, J., Burke, G.L. and Folsom, A.R. 2008. The relationship of left ventricular mass and geometry to

incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) Study. *Journal of American College of Cardiology*, **52**: 2148—2155.

Bradshaw, D., Groenewald, P., Laubscher, R., Nannan, N., Nojilana, B., Norman, R., Pieterse, D., Schneider, M., Bourne, D.E., Timaeus, I.M., Dorrington, R. and Johnson, L. 2003. Initial burden of disease estimates for South Africa 2000. *South African Medical Journal*, **92**: 682—688.

Brady, T.M. 2015. The Role of Obesity in the Development of Left Ventricular Hypertrophy Among Children and Adolescents. *Current Hypertension Reports*, DOI 10.1007/s11906-015-0608-3.

Cecelja, M. and Chowienczyk, P. 2009. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension*, **54**: 1328—1336.

Chesnutt, J.K. and Han, H.C. 2011. Tortuosity triggers platelet activation and thrombus formation in microvessels. *Journal of Biomechanical Engineering*, **133**: 121004, Doi: 10.1115/1.4005478.

Colussi, G., Catena, C., Lapenna, R., Nadalini, E., Chiuch, A. and Sechi, L.A. 2007. Insulin resistance and hyperinsulinemia are related to plasma aldosterone levels in hypertensive patients. *Diabetes Care*, **30**: 2349—2354.

Cooper, R.S., Forrester, T.E., Plange-Rhule, J., Bovet, P., Lambert, E.V., Dugas, L.R., Cargill, K.E., Durazo-Arvizu, R.A., Shoham, D.A., Tong, L. and Cao, G., 2015. Elevated hypertension risk for African-origin populations in biracial 78 societies: Modelling the epidemiologic transition study. *Journal of hypertension*, **33**: 473—481.

Cuppuccio, F.P. and Miller, M.A. 2016. Cardiovascular disease and hypertension in sub—Saharan Africa: burden, risk and interventions. *Internal and Emergency Medicine*, **11**: 299—305.

Dai, X., Hummel, S.L., Salazar, J.B., Taffet, G.E., Zieman, S. and Schwartz, J.B. 2015. Cardiovascular physiology in the older adults. *Journal of Geriatric Cardiology*, **3**: 196—201.

Dao, H.H., Essalihi, R., Bouvet, C. and Moreau, P. 2005. Evolution and modulation of age-related medial elastocalcinosis: Impact on large artery stiffness and isolated systolic hypertension. *Cardiovascular Research*, **66**: 307—317.

de Simone, G., Daniels, S.R., Kimball, T.R., Roman, M.J., Romano, C., Chinali, M., Gelderisi, M. and Devereux, R.B. 2005. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension*, **45**: 64—68.

Desai, C.S., Bartz, T.M., Gottdiener, J.S.,Lloyd-Jones, D.M. and Gardin, J.M. 2016. Usefulness of left ventricular mass and geometry for determining 10- year prediction of cardiovascular disease in adults aged >65 years (from the Cardiovascular Health Study). *American Journal of Cardiology*, **118**: 684—690.

Devereux, R.B., Alonso, D.R., Lutas, E.M., Gottlieb, G.J., Campo, E., Sachs, I. and Reichek, N. 1986. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *The American Journal of Cardiology*, **57**: 450—458.

Dua, S., Bhuker, M., Sharma, P., Dhall, M. and Kapoor, S. 2014. Body Mass Index Relates to Blood Pressure Among Adults. *North American Journal of Medicine*, **2**: 89—95.

Egan, B.M., Stepniakowski, K. and Goodfriend, T.L. 1994. Renin and aldosterone are higher and the hyperinsulinemic effect of salt restriction greater in subjects with risk factors clustering. *American Journal of Hypertension*, **7**: 886—893.

Engeli, S., Gorzelniak, K., Kreutz, R., Runkel, N., Distler, A. and Sharma, A.M. 1999 Coexpression of renin-angiotensin system genes in human adipose tissue. *Journal of Hypertension*, **17**: 555—560.

ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013. *Journal of Hypertension*, **31**: 1281—357.

ESH/ESC Practice Guidelines for Primary Care Physicians: 2003 ESH/ ESC Hypertension Guidelines. 2003. *Journal of Hypertension*, **10**: 1779—1786.

Ettehad, D., Emdin, C.A., Kiran, A., Anderson, S.G., Callender, T., Emberson, J., Chalmers, J., Rodgers, A. and Rahimi, K. 2016. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*, **387**: 957—967.

Frohlich, E.D., Apstein, C., Chobanian, A.V., Devereux, R.B., Dustan, H.P., Dzau, V., Fauad-Tarazi, F., Horan, M.J., Marcus, M., Massie, B., Pfeffer, M.A., Re, R.N., Roccella, E.J., Savage, D. and Shub, C. 1992. The heart in hypertension. *New England Journal of Medicine*, **327**: 998—1008.

Frohlich, E.D., González, A. and Díez, J. 2011. Hypertensive left ventricular hypertrophy risk: beyond adaptive cardiomyocytic hypertrophy. *Journal of Hypertension*, **29**: 17—26.

Gaarder, M. and Seierstad, T. 2015. Measurements of carotid intima media thickness in non-invasive high-frequency ultrasound images: the effect of dynamic range setting. *Cardiovascular Ultrasound*, 13: 1—5.

Gaasch, W.H. and Zile, M.R. 2004. Left ventricular diastolic dysfunction and diastolic heart failure. *Annual Review of Medicine*, **55**: 373—394.

Galderisi, M., Petrocelli, A., Alfieri, A., Garofalo, M. and de Divitiis, O. 1996. Impact of ambulatory blood pressure on left ventricular diastolic dysfunction in uncomplicated arterial systemic hypertension. *American Journal of Cardiology*, **77**: 597—601.

Galis, Z.S., Thrasher, T., Reid, D.M., Stanley, D.V. and Oh, Y.S., 2013. Investing in high blood pressure research: A national institutes of health perspective. *Hypertension*, **61**: 757—761.

Gebreselassie, K.Z. and Mojgan Padyab, M. 2015. Epidemiology of Hypertension Stages in Two Countries in Sub-Sahara Africa: Factors Associated with Hypertension Stages. *International Journal of Hypertension*, doi.org/10.1155/2015/959256.

Geerling, J.C. and Loewy, A.D. 2009. Aldosterone in the brain. *American Journal of Physiology-Renal Physiology*, **297**: 559—576.

Gekle, M. and Grossmann C. 2009. Actions of aldosterone in the cardiovascular system: the good, the bad, and the ugly. *European Journal of Physiology*, **458**: 231—246.

Gerdts, E., Okin, P.M., Boman, K., et al2012. Association of heart failure hospitalizations with combined electrocardiography and echocardiography criteria for left ventricular hypertrophy. *American Journal of Hypertension*, **25**: 678—683.

Gómez-Olivé, F.X., Stuart, A.A., Made, F., Kyobutungi, C., Engelbert Nonterah, E., Micklesfield, L., Alberts, M., Boua, R., Hazelhurst, S., Debpuur, C., Mashinya, F., Dikotope, S., Sorgho, H., Cook, I., Muthuri, S., Soo, C., Mukomana, F., Agongo, G., Wandabwa, C., Afolabi, S., Oduro, A., Tinto, H., Wagner, R.G., Haregu, T., Wade, A., Kahn, K., Norris, S.A., Crowther, N.J., Tollman, S., Sankoh, O., Ramsay, M. and as members of AWI-Gen and the H3Africa Consortium. 2017. Regional and sex differences in the prevalence and awareness of hypertension across six sites in sub-Saharan Africa: an H3Africa AWI-Gen study. *Global Heart Journal*, **12**: 81—90.

Goodfriend, T.L., Kelley, D.E., Goodpaster, B.H. and Winters, S.J. 1999. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. *Obesity Research*, **7**: 355—362.

Gordan, R., Gwathmey, J.K. and Xie, L. 2015. Autonomic and endocrine control of cardiovascular function. *World Journal of Cardiology*, **7**: 204—214.

Gorre, F. and Vandekerckhove, H. 2010. Beta-blokkers: focus on mechanism of action. Which bwta-blocker, when and why? *Acta Cardiologica*, **5**: 565—570.

Grotto, I., Grossman, E., Huerta, M. and Sharabi, Y. 2006. Prevalence of Prehypertension and Associated Cardiovascular Risk Profiles Among Young Israeli Adults. *Hypertension*, **48**: 254—259.

Hall, J.E., Da Silva, A.A., Do Carmo, J.M., Dubinion, J., Hamza, S., Munusamy, S., Smith, G. and Stec, D.E. 2010. Obesity-induced hypertension: Role of sympathetic nervous system, leptin, and melanocortins. *Journal of Biological Chemistry*, **285**: 17271—17276.

Hansen, T.W., Staessen, J.A. and Torp—Pedersen, C. 2006. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*, **113**: 664—670.

Harris, R.B.S. 2014. Direct and indirect effects of leptin on adipocyte metabolism. *Biochimica et Biophysica Acta – Molecular Basis of Disease*, **1842**: 414—423.

Heckbert, S.R., Post, W., Pearson, G.D., Arnett, D.K., Gomes, A.S., Jerosch-Herold, M., Hundley, W.G., Lima, J.A. and Bluemke, D.A. 2006. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging. *Journal of American College of Cardiology*, **48**: 2285—2292.

Heyward, V.H. and Wagner, D.R., 2004. Applied body composition assessment 2nd Edition. *Human Kinetics*. pp 280.

Hosseini, M., Baikpour, M., Yousefifard, M., Fayaz, M., Jalil Koohpayehzadeh, J., Ghelichkhani, P., Asady, H., Asgari, F., Etemad, K., Rafei, A. and Gouya, M.M. 2005. Blood pressure percentiles by age and body mass index for adults. *EXCLI Journal*, **14**: 465—477.

Huang, B.S., Wang, H. and Leenen, F.H.H. 2005. Chronic central infusion of aldosterone leads to sympathetic hyperreactivity and hypertension in Dahl S but not Dahl R rats. *American Journal Physiology-Heart and Circulatory Physiology*, **288**: 517—524.

Jeong, E.M. and Dudley, S.C. Jr. 2014. New diagnostic and therapeutic possibilities for diastolic heart failure. *Rhode Island Medical Journal*, **97**: 35—37.

Jeong, E.M. and Dudley, S.C. Jr. 2015. Diastolic Dysfunction – Potential New Diagnostics and Therapies. *Circulation Journal*, **79**: 470—477.

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. 1997. The Sixth Report of the Joint National

Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), *Archives of Internal Medicine*, **157**: 2413—2446.

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. 2003. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *Hypertension*, **42**: 1206—1252.

Kaess, B.M., Rong, J., Larson, M.G., Hamburg, N.M., Vita, J.A., Levy, D., Benjamin, E.J., Vasan, R.S. and Mitchell, G.F. 2012. Aortic stiffness, blood pressure progression, and incident hypertension. *Journal of American Association*, **308**: 875—881.

Karras, A., Haymann, J.P., Bozec, E., Metzger, M., Jacquot, C., Maruani, G., Houillier, P., Froissart, M., Stengel, B., Guardiola, P., Laurent, S., Boutouyrie, P. and Briet, M. 2012. Large artery stiffening and remodelling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease: Nephro Test Study Group. *Hypertension*, **60**:1451—1457.

Kass, D.A., Bronzwaer, J.G. and Paulus, W.J. 2004. What mechanisms underlie diastolic dysfunction in heart failure? *Cirulculation Research*, **94**:1533—1542.

Kawel-Boehm, N., Kronmal, R., Eng, J., Folsom, A., Burke, G., Carr, J.J. Shea, S., Lima, J.A.C. and Bluemke, D.A. 2019.Left Ventricular Mass at MRI and Long-term Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis (MESA). *Radiology*, **293**: 107—114.

Keates, A.K., Mocumbi, A.O., Ntsekhe, M., Sliwa, K. and Stewart, S. 2017. Reviews: Cardiovascular disease in Africa: epidemiological profile and challenges. *Nature Reviews Cardiology*, **14**: 273—293.

Kidambi, S., Kotchen, J.M., Krishnaswami, S., Grim, C.E. and Kotchen, T.M. 2009. Aldosterone contributes to blood pressure variance and to likelihood of hypertension in normal-weight and overweight African Americans. *American Journal of Hypertension*, **22**: 1303—1308.

Kim, S. and Iwao, H. 2000. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacological Reviews*, **52**: 11—34.

Kim, S.H., Cho, G.Y., Baik, I., Lim, S.Y., Choi, C.U., Lim, H.E., Kim, E.J., Park, C.G., Park, J., Kim, J. and Shin, C. 2011. Early Abnormalities of Cardiovascular Structure and Function in Middle—Aged Korean Adults with Prehypertension: The Korean Genome Epidemiology Study. *American Journal of Hypertension*, **24**: 218—224.

Ku, E. and Campese, V.M. 2009. Aldosterone and Hypertension in African Americans. *American Journal of Hypertension*, **22**: 1234.

Lakatta, E.G. and Levy, D. 2003. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part I. Aging arteries: A 'set up' for vascular disease. *Circulation*, **107**: 139—146.

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., Ducimetiere, P. and Benetos, A. 2001. Aortic stiffness is an independent predictor of all—cause and cardiovascular mortality in hypertensive patients. *Hypertension*, **37**: 1236—1241.

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., Ducimetiere, P. and Benetos, A. 2001. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*, **37**: 1236—1241.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R. and Collins, R. 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, **360**: 1903—1913.

Lim, S., Vos, T., Flaxman, A., Danaei, G., Shibuya, K. and Adair—Rohani, H. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, **380**: 2224—2260.

Lønnebakken, M.T., Izzo, R., Mancusi, C., Gerdts, E., Losi, M.A., Canciello, G., Giugliano, G., De Luca, N., Trimarco, B. and de Simone, G. 2017. Left ventricular hypertrophy regression during antihypertensive treatment in an outpatient clinic (the Campania Salute Network). *Journal of American Heart Association*, DOI: 10.1161/JAHA.116.004152.

Marfell-Jones, M.J., Stewart, A.D. and De Ridder, J.H., 2012. International standards for anthropometric assessment. Wellington, New Zealand: *International Society for the Advancement of Kinanthropometry*, [ISBN- 9780620362078].

Maseko, M.J., Majane, H.O., Milne, J., Norton, G.R. and Woodiwiss, A.J. 2006. Salt intake in an urban, developing South African community: cardiovascular topics. *Cardiovascular Journal of South Africa,* **17**: 186–191.

Maseko, M.J., Majane, H.O., Milne, J., Norton, G.R. and Woodiwiss, A.J. 2006. Salt intake in an urban, developing South African community. *Cardiovascular Journal of South Africa*, **17**: 186—191.

Mattace-Raso, F.U.S., van der Cammen, T.J.M., Hofman, A., van Popele, N.M., Bos, M.L., Maarten

A.D.H. Schalekamp, M.A.D.H., Asmar, R., Robert S. Reneman, R.S., Hoeks, A.P.G., Monique M.B. Breteler, M.M.B. and Witteman, J.C.M. 2006. Arterial Stiffness and Risk of Coronary Heart Disease and Stroke: The Rotterdam Study. *Circulation*, **113**: 657—663.

Messerli, F.H., Rimoldi, S.F. and Bangalore, S. 2017. The Transition From Hypertension to Heart Failure: Contemporary Update. *Heart Failure*, 5: 543—551

Mitchell, G.F., 2014. Arterial stiffness and hypertension. *Hypertension*, **64**: 13—18.

Mitchell, G.F., Hwang, S.J. and Vasan, R.S. 2010. Arterial stiffness and cardiovascular events: the framingham heart study. *Circulation*, **121**: 505—511.

Mitchell, G.F., Hwang, S.J., Vasan, R.S., Larson, M.G., Pencina, M.J., Hamburg, N.M., Vita, J.A., Levy, D. and Benjamin, E.J. 2010. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*, **121**: 505—511.

Mitchell, G.F., Hwang, S.J., Vasan, R.S., Larson, M.G., Pencina, M.J., Hamburg, N.M., Vita, J.A., Levy, D. and Benjamin, E.J. 2010. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*, **121**: 505—511.

Mitchell, G.F., Hwang, S.J., Vasan, R.S., Larson, M.G., Pencina, M.J., Hamburg, N.M., Vita, J.A., Levy, D. and Benjamin, E.J. 2010. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*, **121**: 505—511.

Mungati, M**.**, Manangazira, P., Takundwa, L., Gombe, N.T., Rusakaniko, S. and Tshimanga M. 2014. 2012. Factors affecting diagnosis and management of hypertension in Mazowe District and Mashonaland Central Province in Zimbabwe, *BMC cardiovascular disorders*, **14**: 102.

Nadruz, W., Shah, A.M. and Solomon, S.D. 2017. Diastolic Dysfunction and Hypertension. *Medical Clinics of North America*, **101**: 7—17.

Norman, R., Gaziano, T., Laubscher, R., Steyn, K. and Bradshaw, D. 2007. Estimating the burden of disease attributable to high blood pressure in South Africa in 2000. *South African Medical Journal*, **97**: 692—698.

Norton, G.R., Maseko, M., Libhaber, E., Libhaber, C.D., Majane, O.H.I., Dessein, P., Sareli, P. and Woodiwiss, A.J. 2008. Is prehypertension an independent predictor of target organ changes in young-to-middle-aged persons of African descent?. *Journal of Hypertension*, **26**: 2279—2287.

Nunez, E., Arnett, D.K., Benjamin, E.J., Liebson, P.R., Skelton, T.N., Taylor, H. and Andrew, M. 2005. Optimal threshold value for left ventricular hypertrophy in blacks: the Atherosclerosis Risk in Communities study. *Hypertension*, **45**: 58—63.

O'Rourke, M.F. and Hashimoto, J. 2007. Mechanical factors in arterial aging: a clinical perspective. *Journal of the American College of Cardiology*, **50**: 1—13.

Oe, Y., Shimbo, D., Ishikawa, J., Okajima, O., Hasegawa, T., Diz, K.M., Muntner, P., Homma, S. and Schwartz, J.E. 2013. Alterations in diastolic function in masked hypertension: findings from the masked hypertension study. *American Journal of Hypertension*, **26**: 808—815.

Okin, P.M., Hille, D.A., Kjeldsen, S.E. and Devereux, R.B. 2017. Combining ECG Criteria for Left Ventricular Hypertrophy Improves Risk Prediction in Patients With Hypertension. *Journal of American Heart Association*, DOI: 10.1161.

Opie, L.H. 2004. The metabolic vicious cycle in heart failure. *Lancet*, 364: 1733—1734.

Payne, R.A., Wilkinson, I.B. and Webb, D.J. 2010. Arterial stiffness and hypertension: emerging concepts. *Hypertension*, **55**: 9—14.

Rahmouni, K. 2010. Leptin—Induced Sympathetic Nerve Activation: Signaling Mechanisms and Cardiovascular Consequences in Obesity. *Current Hypertension Reports*, 6: 104—209.

Rampal, L., Rampal, S., Azhar, M.Z. and Rahman, A.R. 2008. Prevalence, awareness, treatment and control of hypertension in Malaysia: a national study of 16,440 subjects. *Public Health*, **11**: 8—11**.**

Rayner, B., Jones, E., Veriava, Y. and Seedat, Y.K. 2019. South African Hypertension Society commentary on the American College of Cardiology/American Heart Association hypertension guidelines. *Cardiovascular Journal of Africa*, **30**: 184—187.

Redfield, M.M., Jacobsen, S.J., Burnett, J.C. Jr., Mahoney, D.W., Bailey, K.R. and Rodeheffer, R.J. 2003. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Journal of the American Medical Associatio*, **289**: 194—202.

Rossi, G.P., Belfiore, A., Bernini, G., Fabris, B., Caridi, G., Ferri, C., Giacchetti, G., Letizia, C., Maccario, M., Mannelli, M., Palumbo, G., Patalano, A., Rizzoni, D., Rossi, E., Pessina, A.C. and Mantero, F. 2008. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. *Journal of Clinical Endocrinology and Metabolism*, **93**:2566—2571.

Russell, L.B., Valiyeva, E. and Carson, J.L. 2004. Effects of prehypertension on admissions and deaths: a simulation. *Archives of Internal Medicine*, **164**: 2119–2124.

Safar, M.E., Thomas, F., Blacher, J., Nzietchueng, R., Bureau, J.M., Pannier, B. and Benetos, A. Metabolic syndrome and age-related progression of aortic stiffness. *Journal of American College of Cardiology*, **47**: 72—75.

Safar, M.E., Toto—Moukouo, J.J., Bouthier, J.A., Asmar, R.E., Levenson, J.A., Simon, A.C. and London, G.M. 1987. Arterial dynamics, cardiac hypertrophy, and antihypertensive treatment. *Circulation*, **75**: 156—161.

Sahn, D.J., Allen, H.D., Anderson, R. and Goldberg, S.J. 1978. Echocardiographic Diagnosis of Atrial Septal Aneurysm in an Infant with Hypoplastic Right Heart Syndrome. *Chest*, **73**: 227—230.

Santos, A.B., Gupta, D.K., Bello, N.A., Gori, M., Claggett, B., Fuchs, F.D., Shah, A.M., Coresh, J., Sharrett, A.R., Cheng, S. and Solomon, S.D. 2016. Prehypertension is associated with abnormalities of cardiac structure and function in the atherosclerosis risk in communities study. *American Journal of Hypertension*, **29**: 568—574.

Schillaci, G., Verdecchia, P., Porcellati, C., Cuccurullo, O., Cosco, C. and Perticone, F. 2000. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension*, **35**: 580—586.

Schling, P., Mallow, H., Trindl, A. and Loffler, G. 1999. Evidence for a local renin angiotensin system in primary cultured human preadipocytes. *International Journal* of *Obesity and Related Metabolic Disorders*, **23**: 336—334.

Seedat, Y.K., Rayner, B.L. and Veriava, Y., 2014. South African Hypertension Practice Guideline 2014. *Cardiovascular Journal of Africa,* **25**: 288—294.

Shah, S.J., Kitzman, D.W., Borlaug, B.A., van Heerebeek, L., Zile, M.R., Kass, D.A. and Paulus, M.R. 2003. Phenotype-specific treatment of heart failure with preserved ejection fraction: A multiorgan roadmap. *Circulation*, **134**: 73—90.

Shatat, I.F., Freeman, K.D., Vuguin, P.M., Dimartino-Nardi, J.R. and Flynn, J.T. 2009. Relationship between adiponectin and ambulatory blood pressure in obese adolescents. *Pediatric Research*, **65**: 691—695.

Shatat, I.F., Freeman, K.D., Vuguin, P.M., Dimartino—Nardim, J.R. and Flynn, J.T. 2009. Relationship between adiponectin and ambulatory blood pressure in obese adolescents. *Pediatric Research*, **65**: 691—695.

Shenoy, U. and Cassis, L. 1997. Characterization of renin activity in brown adipose tissue. *American Journal of Physiology*, **272**: C989—C999.

Shiburi, C.P., Staessen, J.A., Maseko, M., Wojciechowska, W., Thijs, L., Van Bortel, L.M., Woodiwiss, A.J. and Norton, G.R. 2006. Reference values for

SphygmoCor measurements in South Africans of African ancestry*. American Journal of Hypertension*, **19**: 40—46.

Shikai, Y.U. and Carmel, M.M. 2020. Central Versus Peripheral Artery Stiffening and Cardiovascular Risk. *Arteriosclerosis Thrombosis and Vascular Biology*, **40**: 1028—1033.

Sliwa, K., Skudicky, D., Candy, G., Bergemann, A., Hopley, M. and Sareli, P. 2002. The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. *European Journal of Heart Failure*, **4**: 305—309.

Sutton-Tyrrell, K., Najjar, S.S., Boudreau, R.M., Venkitachalam, L., Kupelian, V., Simonsick, E.M., Havlik, R., Lakatta, E.G., Spurgeon, H., Kritchevsky, S., Pahor, M., Bauer, D. and Newman, A. 2005. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults: Health ABC Study. *Circulation*, **111**: 3384—3390.

The 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. 2018. Clinical Practice Guideline. *Hypertension*, **71**: e113—e115.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure — The JNC 7 Report. *The Journal of American Association*, **289**: 2560—2572.

Thomopoulos, C., Parati, G. and Zanchetti, A. 2014. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and metaregression analyses of randomized trials. *Journal of Hypertension*, **32**: 2285—2295.

Tomaschitz, A., Pilz, S. and Ritz. 2010.Aldosterone and arterial hypertension. Nat Rev Endocrinol, **6**: 83—93.

Townsend, R.R., Wilkinson, I.B., Schiffrin, E.L., Avolio, A.P., Chirinos, J.A., Cockcroft, J.R., Heffernan, K.S., Lakatta, E.G., McEniery, C.M., Mitchell, G.F. and Najjar, S.S. 2015. Recommendations for improving and standardizing vascular research on arterial stiffness: A scientific statement from the American Heart Association. *Hypertension*, **66**: 698—722.

van Bortel, L.M., Laurent, S. and Boutouyrie, P. 2012. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *Journal of Hypertension*, **30**: 445—448.

Verma, A. and Solomon, S.D. 2009. Diastolic dysfunction as a link between hypertension and heart failure. *Medical Clinics of North America*, **93**: 647—664.

Vlachopoulos, C., Aznaouridis, K., O'Rourke, M.F., Safar, M.E., Baou, K. and Stefanadis, C. 2010. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *European Heart Journal*, **31**: 1865—1871.

Wan, S.H., Vogel, M.W. and Chen, H.H. 2014. Pre-clinical diastolic dysfunction. *Journal of American College of Cardiology*, **63**: 407—416.

Wang, Y. and Wang, Q.J. 2004.The prevalence of prehypertension and hypertension among US adults according to the new Joint National Committee guidelines: new challenges of the old problem. *Archives of Internal Medicine*, **164**: 2126—2134.

Whelton, P.K., Carey, R.M., Aronow, W.S., Casey Jr, D.E., Karen J. Collins, K.J., Himmelfarb, C.D., Sondra M. DePalma, S.M., Gidding, S., Jamerson, K.A., M D Jones, D.W., MacLaughlin, E.J., Muntner, P., Ovbiagele, B., Smith Jr, S.C., Spencer, C.C., Stafford, R.S., Taler, S.J., Thomas, R.J., Williams Sr, K.A., Williamson, J.D. and Wright Jr, J.T. 2018. The 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*, **71**: e13–e115.

Williams, B., Mancia, G., Spiering, W., Rosei, E.A., Azizi, M., Burnier, M., Clement, D.L., Coca, A., Redon, G.J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S.E., Kreutz, R., Laurent, S., Lip, G.Y.H., McManus, R., Narkiewics, K., Ruschitzka, F., Schmieder, R.E., Shlyakhto, E., Tsioufis, C., Aboyans, V. and Desormais, I. 2018. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Journal of Hypertension*, 36: 1953–2041.

Willum-Hansen, T., Staessen, J.A.,Torp-Pedersen, C., Susanne Rasmussen, S., Lutgarde Thijs, L., Hans Ibsen, H., and Jeppesen, J. 2006. Prognostic Value of Aortic Pulse Wave Velocity as Index of Arterial Stiffness in the General Population. *Circulation*, 113: 664—670.

World Health Organisation. 2013. A global brief on Hypertension: Silent killer, global public health crisis. *World Health Day 2013.*

World Health Organization. 2010. Global status report on noncommunicable diseases. Geneva: World Health Organization, 2011.

World Health Organization. 2014. Global status report on noncommunicable diseases. Geneva: World Health Organization, 2014.

World Health Organization., 2000. Obesity : preventing and managing the global epidemic report of a WHO consultation (No. 894). World Health Organization. Geneva, Switzerland.

Woroniecki, R.P., Kahnauth, A., Laurie E Panesar, L.E. and Supe-Markovina, K. 2017. Left Ventricular Hypertrophy in Pediatric Hypertension: A Mini Review. *Frontiers in Pediatrics*, **5**: doi: 10.3389/fped.2017.00101.

Ye, Z.W., Wu, X.M. and Jiang, J.G. 2009. Expression changes of angiotensin II pathways and bioactive mediators during human preadipocytes—visceral differentiation. *Metabolism*, **58**: 1288—1296.

Yu, S. and McEniery, C.M. 2020. Central Versus Peripheral Artery Stiffening and Cardiovascular Risk. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **40**: 1028—1033.

Zhang, Y., Kollias, G., Argyris, A.A., Papaioannou, T.G., Tountas, C., Konstantonis, G.D., Achimastos, A., Blacher, J., Safar, M.E., Sfikakis, P.P. and Protogerou, A.D. 2015. Association of left ventricular diastolic dysfunction with 24-h aortic ambulatory blood pressure: the SAFAR study. *Journal Human Hypertension*, **29**: 442—448.

Appendix 1: Ethical clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Miss Caroline Motheo Mokwena

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190646

NAME: (Principal Investigator)	Miss Caroline Motheo Mokwena
DEPARTMENT:	Physiology
PROJECT TITLE:	Prehypertension and target organ changes in salt sensitive African population
DATE CONSIDERED:	28/06/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof M. Maseko, Dr B. Lembede and Ms G. Tade
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/08/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized
to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Change of title

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

08 March 2021
Person No: 1895614
TAA

Ms CM Mokwena
P.O Box 1741
Dennilton
1030
South Africa

Dear Ms Caroline Mokwena

Master of Science in Medicine: Change of title of research

I am pleased to inform you that the following change in the title of your Dissertation for the degree of **Master of Science in Medicine** has been approved:

From:	**Prehypertension and target organ changes in salt sensitive African population**
To:	**Prehypertension and target organ changes in an African population**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3: Consent form

Human 

Nutrition

Research Laboratory

South African Hypertension and Diet Study (SAHDS)

Written consent form

The aim and procedures of this study have been explained to me by the investigators. I have read and understood the information sheet provided. I have also had the opportunity to ask questions and have considered the answers given to me. I understand that participation in this study is voluntary, that I may withdraw my consent at any time; and that if I choose to do so my decision will not have any negative impact on me in any way.

I hereby freely give my informed consent to participate in this study.

Name of participant : _____

Participant code : _____

Signature : _____

Date : _____

To be filled by the investigators

I confirm that I have fully explained the nature of the study and the procedures to be performed to the above-named participant.

Name :_____

Signature :_____

Date :_____

Appendix 4: Questionnaire

	Personal information											
1.	Participant No.		Gender		Male		Date of Birth		Ethnicity			
1.					Female		Age					
2.	**Medical History**											
2.1	**History of non-communicable diseases?**		YES		NO		**Examples, Hypertension, Chronic Kidney disease, Diabetes**					
	If YES, specify											
2.2	**Are you using hypertension treatment or Medicinal plants?**						YES		NO			
2.2.1	**If YES, how long (in years)?**											
2.2.2	**Describe the regimen**											
2.3	**Please, specify whether some of your relatives currently suffer (or have suffered) from high blood pressure (hypertension)**											
2.3.1	**Your Father**						Yes		No		Unknown	
	Your grandfather (Father's side)						Yes		No		Unknown	
	Your grandmother (Father's side)						Yes		No		Unknown	
	Your mother						Yes		No		Unknown	
	Your grandfather (mother's side)						Yes		No		Unknown	
	Your grandmother (Mother's side)						Yes		No		Unknown	
	1 or more of your own children						Yes		No		Unknown	

	1 or more of your own grandchildren	Yes		No		Unknown	
	1 or more brothers or sisters of your father	Yes		No		Unknown	
	1 or more brothers or sisters of your mother	Yes		No		Unknown	
	1 or more of your own brothers or sisters	Yes		No		Unknown	

2.4	**Marital status**	Single		Married		Widowed						
2.5	**Are you still attending school?**	Yes		No								
2.6	**Which is the highest level of education which you successfully completed?**											
2.7	**Do you currently exert any professional or occupational activity?**	**Yes**		**No**								
	If yes: What is your present occupation? Please, provide a detailed description of your current job below.											
2.8	**If you currently do not exert any professional activity, which was the last job you had?**											
2.8.1		**Years**										
2.8.2	**Please, provide a detailed description of your activities at your previous work.**											
3.	**Please, specify whether you suffer from diseases affecting your:**											
3.1.1	**Heart**	Yes		No		Unknown						
3.1.2	**Kidneys**	Yes		No		Unknown						
4.	**Were you ever told by a doctor or health professional that you have an elevated blood pressure?**	Yes		No		Unknown						
5.	**Are you currently in good health?**	Yes		No		Unknown						

6	**Did you ever take or are you taking now drugs which eliminate salt and make you pass urine more** **frequently or in larger amounts? If yes, explain below**	Yes		No		Unknown	
7.	**Did you ever take pain-killers on a regular basis, for instance against headaches, tooth pain, painful periods, etc... ?** **If yes, explain below**	Yes		No			

8.	**Did you take medicines during the past 2 weeks? if yes, explain below**	Yes		No	
9.1	**Do you currently smoke? If yes, explain the frequency, type and amount per day**	Yes		No	
9.2	**Did you smoke in the past? If yes, explain below**				
10.1	**Do you currently consume alcoholic beverages? If yes, explain the frequency, type and amount per day below**	Yes		No	
10.2	**Did you consume alcohol beverages in the past? If yes, explain**	Yes		No	
11	**Do you drink coffee or caffeine-containing beverages (cola) on a regular base? If yes, give details below**	Yes		No	
12.	**Do you practice any sports activities on a regular basis? If yes, explain the frequency, type and intensity below**	Yes		No	
Please note that this section is for females only					

13.1	**Did you already have your periods?**	Yes		No	
13.2	**Have you ever taken “The Pill”? If yes, explain the regimen below**	Yes		No	

13.3	**Have you ever used other contraceptive methods? If Yes, explain the regimen below**					Yes		No	
14.1	**Are you pregnant at present?**	Yes		No		Unknown		
14.2	**Have you been pregnant before?**					Yes		No	
15.	**This section is for women 30 years and older**								
15.1	**Do you still have your periods? If No, explain below**					Yes		No	
15.2	**At present are your periods suppressed by taking "the pill"?**					Yes		No	
15.3	**At present are your periods suppressed by any other contraceptive method? If Yes, explain the regimen below**					Yes		No	
END								

DECLARATION

Please, provide your signature to give your approval or disapproval to use this information in our study.

Signature:_____ Date: _____