THE PREVALENCE OF MASKED HYPERTENSION SUBTYPES: IT'S ASSOCIATION WITH CARDIOVASCULAR ORGAN CHANGES AND RENAL DYSFUNCTION IN A POPULATION OF AFRICAN DESCENT

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, School of Physiology, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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DECLARATION

I, Franswell Thamsanqa Nyundu declare that this thesis is my own unaided work, except where stated. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. The work contained in this thesis has not been submitted for any degree or examination at this University, or any other University.

Franswell Thamsanqa Nyundu……..…….……... on this……09.....Day of ……APRIL…….2020

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 M17-04-16

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DEDICATION

This thesis is dedicated to my baby girl, Thandolwethu Keatlegile Nyundu

RESEARCH OUTPUTS

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ABSTRACT

Cardiovascular diseases are a leading cause of preventable mortality and morbidity worldwide and hypertension is the most prominent established risk factor for these diseases. In Africa, the burden of hypertension is increasing at a faster rate as compared to other parts of the world. Predictions based on the current data indicate that the burden of hypertension is still on the rise. In addition, the prevalence of hypertension in Africa is underreported and underestimated due to the use of conventional blood pressure monitoring. The introduction of home blood pressure monitoring and ambulatory blood pressure has made it easy to identify other forms of hypertension such as white coat hypertension and masked hypertension. White coat hypertension has less detrimental cardiovascular consequences whereas masked hypertension has adverse consequences that may be similar to sustained hypertension. Most of the studies conducted on masked hypertension have not taken into account the various subtypes of masked hypertension therefore very little is known about masked hypertension subtypes especially in African populations. Moreover, a number of studies have investigated the impact of hypertension on cardiovascular target organ damage but very little is known about the association between masked hypertension subtypes and cardiovascular target organ damage. Therefore, in this thesis I determined the prevalence of masked hypertension subtypes and the association between masked hypertension subtypes and cardiovascular target organ damage in a population of African ancestry. I also investigated if masked hypertension is associated with renal dysfunction independent of dietary salt intake in this population. Finally I investigated the relationship between masked hypertension subtypes and nocturnal blood pressure dipping.

In a population sample of 1310 participants, I measured conventional and 24-hour ambulatory blood pressure, collected 24-hour and spot urine samples, and collected blood samples, determined left ventricular mass and arterial stiffness using echocardiography and applanation

tonometry respectively. Masked hypertension was subdivided into three subtypes. These subtypes are 24-hour masked hypertension, night-time masked hypertension and daytime masked hypertension. Twenty-four-hour masked hypertension is whereby 24-hour ambulatory blood pressure is ≥130/80 mm Hg. Night-time masked hypertension is where night-time ambulatory blood pressure is ≥120/70 mm Hg. Daytime masked hypertension refers to an ambulatory blood pressure of ≥135/85 mm Hg. These ambulatory blood pressures are elevated in spite of a normal conventional blood pressure of < 140/90 mm Hg.

The results show that the prevalence of the subtypes of masked hypertension in population of African descent was 7% for 24-hour masked hypertension, 15% for night-time masked hypertension and 9% for daytime masked hypertension. All subtypes of masked hypertension were significantly associated with smoking and alcohol consumption (24-hour masked hypertension $p<0.0001$; night-time masked hypertension $p<0.0001$; daytime MH $p<0.0001$). Pulse wave velocity, was significantly higher in all the mask hypertension subtypes compared to the normotensives; 24-hour masked hypertension ($p= 0.0029$), night-time masked hypertension ($p=0.0061$) daytime masked hypertension ($p=0.0069$). Left ventricular mass was also significantly increased in all masked hypertensive subtypes compared to normotensives; 24-hour MH ($p= 0.0003$), night-time MH ($p<0.0001$) daytime MH ($p=0.0010$). Dietary salt intake was not associated with any masked hypertension subtype. However, microalbuminuria was significantly higher in the night-time masked hypertensives (3.6±2.1 mg/mmol) compared to the 24-hour (1.4± 0.4 mg/mmol) and daytime (0.9±0.3 mg/mmol) masked hypertensives groups. In my assessment of the relationship between nocturnal blood pressure dipping and masked hypertension subtypes, the results show that nocturnal blood pressure non-dipping is associated with all masked hypertension subtypes; 24-hour masked hypertension ($p=0.0021$), daytime masked hypertension ($p= 0.0002$) and night-time masked hypertension ($p< 0.0001$).

These results show that in a population of African descent, night-time masked hypertension is the most prevalent form of hypertension and all masked hypertension subtypes are associated with cigarette smoking and alcohol intake. Furthermore, all masked hypertension subtypes are related to arterial stiffness and left ventricular hypertrophy. When assessing kidney function and masked hypertension, the results indicate that only night-time masked hypertension is associated with renal dysfunction and this relationship is independent of dietary salt intake. The importance of these findings is that in African populations, smoking, alcohol intake and nocturnal blood pressure non-dipping predict masked hypertension above dietary salt intake. Therefore, strategies to reduce masked hypertension related cardiovascular target organ damage should focus on these parameters.

LIST OF ABBREVIATIONS

24-h	24-hour period
ABP	Ambulatory Blood Pressure
ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
AHA	American Heart Association
ANG	Angiotensin
ANS	Autonomic Nervous System
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
CBP	Conventional Blood Pressure
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CO	Cardiac Output
CVDs	Cardiovascular Diseases
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
DBP24	24 Hour Diastolic Blood Pressure

DBPD	Daytime Diastolic Blood Pressure
DBPN	Nighttime Diastolic Blood Pressure
DM	Diabetes Mellitus
ESH	European Society of Hypertension
ET	Epidemiological Transition
ET-1	Endothelin 1
GFR	Glomerular Filtration Rate
HbA1c	Glycated Haemoglobin
HBPM	Home Blood Pressure Monitoring
HF	Heart Failure
HT	Hypertension
JHS	Jackson Heart Study
LVH	Left Ventricular Hypertrophy
LVM	Left Ventricular Mass
LVMI	Left Ventricular Mass Index
MAP	Mean Arterial Pressure
MH	Masked Hypertension
MUCH	Masked Uncontrolled Hypertension
NO	Nitric Oxide

PP	Pulse Pressure
PWV	Pulse Wave Velocity
RAAS	Renin Angiotensin Aldosterone System
SA	South Africa
SAHDS	South African Hypertension and Diet Study
SBP	Systolic Blood Pressure
SBP24	24 Hour Systolic Blood Pressure
SBPD	Daytime Systolic Blood Pressure
SBPN	Night-time Systolic Blood Pressure
SD	Standard Deviation
SOWETO	Southern Western Township
SSA	Sub-Sahara Africa
SV	Stroke Volume
TOD	Target Organ Damage
TRP	Total Peripheral Resistance
WC	Waist Circumference
WCHT	White Coat Hypertension
WHO	World Health Organisation
WHR	Waist-to-Hip-Ratio

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CHAPTER ONE: Definitions of Masked Hypertension and its Relevance in Cardiovascular Diseases

1.1 Introduction

Cardiovascular diseases (CVDs) which include diseases of the heart, cerebrovascular diseases, and peripheral vascular diseases have become endemic globally (Gaziano et al., 2006). According to the World Health Organisation (WHO), CVDs are indisputably a leading cause of preventable mortality and morbidity worldwide (Santulli, 2013). They are accountable for over 17.3 million deaths per year (Zhang et al., 2016). Their occurrence is no longer limited to developed countries only, but the prevalence of these diseases is escalating even in low income and developing areas such as those in Sub-Sahara-Africa (SSA). Majority (82%) of premature deaths due to CVDs are occurring in low income countries (Puska et al., 2011). The increase in the prevalence of CVDs in low-income areas is parallel with the forecast of the WHO, which predicted that in a 10-year period from 2006 to 2016, deaths due to non-communicable diseases would increase by more than 24% in Africa (Bradshaw et al., 2003). In South Africa, non-communicable disease, counting CVDs are responsible for an estimated 43% of total adult deaths and CVDs account for almost a fifth of these deaths (Bradshaw et al., 2003, Sliwa et al., 2008). Typically, infectious diseases have been the main cause of death in low-income areas. However, the epidemiological transition (ET) has fuelled CVD risk factors such as dyslipidaemia, diabetes, obesity, hypertension (HT), metabolic and endothelial dysfunctions and consequently hastening mortality rates in low-income areas. These risk factors promote the progression of CVDs because they share some form of interrelation and interaction through one pathophysiological mechanism or another (Mozaffarian et al., 2008, Murray et al., 2003). While all of these risk factors contribute to the progression of CVDs, HT is an acknowledged and most prominent established risk factor for CVD (Okpechi et al., 2007). There is evidence to support that HT contributes to a significant percentage of CVD mortality and morbidity globally.

Out of ~17 million deaths due to CVDs worldwide, 7.5 million deaths and 57 million disability adjusted life years are attributed to poorly controlled HT (Delacroix et al., 2014). In Africa, this burden is rising at a faster rate as compared to other parts of the world (Adeloye and Basquill, 2014). The fraction of the worldwide burden of disease attributable to HT has increased considerably from about 4.5% in the year 2000 to 7% in 2010, and is still rising (van de Vijver et al., 2013). Apparently HT was virtually absent in Africa in the first half of the twentieth century, however, estimates now show that over 40% of adults in most parts of Africa have HT (Addo et al., 2007). Epidemiological data demonstrates that the prevalence of HT has amplified significantly over the years and that in the year 2000; ~80 million adults had HT in SSA. Predictions suggests that the number will increase to ~150 million by the year 2025 (Opie and Seedat, 2005). Further, to support the suggestion that HT has become the single most important cause of mortality and morbidity in areas of Africa, evidence shows that complications of HT, particularly stroke and heart failure have also become progressively more common in areas where HT is on the rise (Mensah, 2008, Walker et al., 2000). In line with this information, a recent systematic review has shown that in the last 10 years, systolic BP has risen highest in most of Africa more than in any other region of the world (Ogah and Rayner, 2013).

As highlighted earlier, the prevalence of CVDs and their risk factors such as HT have increased as a manifestation of the ET in the SSA region as observed in other parts of the world (Dalal et al., 2011). The ET is a result of changes in economic development, which alters the population structure and thereby causing a change in health and disease pattern in societies. As the societies develop, non-communicable diseases including CVDs become more prevalent due to changes in environmental and behavioural determinants (Omran, 2005).

Unsurprisingly, HT has since become a major problem in African countries experiencing the ET (Ibrahim and Damasceno, 2012). Even though a higher incidence of HT is reported for SSA compared to other regions of the world (Ogah and Rayner, 2013), experts are of the view that the real burden of HT is still far from being comprehended in this region. The reason for this opinion is based on the knowledge from earlier studies conducted in the 1980s and early 1990s, which were established on the old classification of HT (≥160/95 mm Hg). (Mancia et al., 2013). The current guidelines of the European Society of Hypertension (ESH) base HT on the classification of ≥140/90 mm Hg (Williams et al., 2018). Therefore this means that the old classification may have possibly underestimated the prevalence of HT in Africa in comparison to newer surveys (Chopra and Ram, 2019).

This information therefore suggests that HT is a condition that has largely been under-detected in Africa. Further, it should be put into account that prevalence reports in Africa are based on the use of conventional blood pressure (CBP) measurements. Although CBP measurement has traditionally been the standard BP monitoring tool in practice for many years, it is now widely recognised that this method has many potential limitations (Conen et al., 2014). New evidence has since emerged that CBP does not offer accurate diagnosis of HT because it does not take into account the fact that BP has a natural circadian rhythm and it fluctuates throughout the day (Williams et al., 2013). Additionally, other individuals do not exhibit a raised BP reading during a doctor's visit. Fortunately, in recent decades, techniques have been developed that allow BP measurements to be taken outside the physician's office by using either ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM). These techniques in combination with CBP measurements have allowed for the cross-classification of patients according to office and out of the office BP measurement (Alwan et al., 2014, Zhang et al., 2015). This cross-classification outlines four (4) groups as shown in Table 1.1:

Table 1.1: Cross classification of hypertension patients according to office and out-of-office BP measurements

1. Normotensives	Patients with normal office and out-of-office BP
2. White-Coat Hypertensives	Patients with office hypertension but normal out of-office BP
3. Sustained Hypertensives	Patients with hypertension on office and out-of-the-office measurement
4. Masked Hypertensives	Patients with normal office BP, but out-of-office hypertension

Although CBP monitoring does provide a comprehensive spectrum of HT, this cross-classification however shows that it still offers a useful insight in reporting and managing HT even in modern days. CBP monitoring has customarily depended on the use of sphygmomanometer being connected to a mercury column and readings taken by a clinical observer (doctor or nurse). Nonetheless, in recent decades, mercury sphygmomanometers have been gradually replaced by automated oscillometric devices due to environmental hazards associated with mercury handling (Wijkman et al., 2009). A clear advantage of automated measurement in the office setting involves its simplicity. In addition, it may prove cost effective by avoiding repetitive training of health care professionals in auscultation which is associated with observer error and low reproducibility (Patil, 2013).

As highlighted previously, BP measurements taken from an out-of-office (clinical) setting by the patient or someone else through the use of automated techniques such as HBPM and by ABMP has become prominent in the reporting and management of HT (Pickering, 1996). The rapid growth of HBPM has gained preference because it has few advantages over CBP monitoring. These advantages include technical progress, growing awareness of the importance of regular HBPM, acknowledgment of the usefulness of HBPM by international hypertension management guidelines, and a broader availability of HBPM devices (Parati et al., 2008). The latter does not apply to low income areas such as SSA due to lack of affordability. In addition, HBPM measurements are more reproducible than clinic BP. Also, studies have shown that the relationship between HBPM and cardiovascular risk is sharper than for CBP (Parati et al., 2008).

The major aspect of HBPM is that it is able categorise patients with office HT but normal out of-office BP; an effect known as white-coat hypertension (WCHT). The white-coat effect is eliminated because these measurements are taken in the usual environment of each patient which is away from the clinical setting (Parati et al., 2010). Although HBPM has several advantages, it proves less favourable when compared with ABPM because it does not allow for the assessment of BP during sleep and during the time when patients are going about their daily activities (Kikuya et al., 2008, Parati and Bilo, 2008).

Furthermore, ABPM offers a more precise way of quantifying short term BP variability and circadian rhythms by showing detailed changes on BP levels throughout the day and night (Dolan et al., 2004). Over and above the aforementioned advantages of the ABMP when compared to both CBP and HBPM, the ABPM affords a superior predictive value for cardiovascular events and it is a more consistent and reliable instrument in forecasting target organ damage (TOD) (Hara et al., 2012, Lehmannn et al., 2013). Furthermore, neither

conventional office BP monitoring nor HBPM has sufficient sensitivity or specificity to replace ABPM as the reference standard (Hodgkinson et al., 2011).

Through its ability to measure BP during the day and night, the use of the 24-hour ABPM has aided in uncovering a particular group of HT patients who exhibit different characteristics from those who have sustained HT and WCHT (Verberk et al., 2008). These patients have normal office BP, but have an elevated out-of-office BP (Ogedegbe et al., 2010). This group of patients are known as masked hypertensives (MH). Sometimes MH is interchangeably tagged "isolated home HT", "reverse WCHT", "white-coat normotension", "isolated ambulatory HT", and "reverse white-coat effect". The ESH in its practice guidelines for clinic, ambulatory and HBPM has referred this phenomenon to patients in whom CBP measurement is normal (< 140/90 mm Hg) but ABPM are increased (> 135/85 mm Hg) (Parati et al., 2014). Briefly, the HT is hidden (masked) pending ABPM (Bobrie et al., 2008, Pickering et al., 2002), and this definition should be strictly restricted to untreated HT patients. Thus, in the present thesis, the definition of MH refers to untreated MH patients.

Up to date, a few studies as summarised in Table 2.3 have assessed the consequences of MH and observations suggest that MH poses similar risks for cardiovascular organ damage as sustained HT (Bobrie et al., 2008). In comparison to sustained HT and MH, WCHT has a comparatively non-threatening outcome. However, the danger is that if it is not recognized, it results in needless lifelong use of antihypertensive medications, which may cause unnecessary side effects (Dolan et al., 2004). Since WCHT has substantially low risk of cardiovascular events and the risks of sustained HT are well documented, it is therefore crucial to get a broader knowledge about MH in a South African population of African descent where the relevance MH has not be assessed. In the context of the present thesis, "African descent" refers to blacks of African origin.

Therefore, in chapters to come, I have investigated the prevalence of MH and its subtypes in particular, its association with smoking and alcohol consumption in a South African population of African descent. I have also investigated the association between MH and TOD. I have also investigated the relationship between MH and urinary electrolytes, micro-albumin in urine and its clinical relevance in an exclusive population of African descent.

1.1.1 Problem Statement

The prevalence of HT is high in people of African descent when compared to other ethnic populations of the world (Abdalla et al., 2016). Literature also indicates that in African populations, HT is underreported and is poorly controlled (Opie and Seedat, 2005, Ogah and Rayner, 2013). Dejectedly, evidence indicate that HT is more complex and carries far greater consequences in people of African descent (Opie and Seedat, 2005). Also, it is highly documented that HT is the dominant risk factor for CVDs in African populations (Seedat, 2007, Gaziano, 200, Celermajer et al., 2012). Over and above, the introduction of ABPM and the discovery of MH has indicated that true prevalence and consequence of HT in Africa is still not fully expounded. Indeed, MH is a condition discovered in recent times, it has not been extensively studied in people of African Descent especially in a South African framework. There is limited literature regarding MH in SA and Africa in general. Literature suggests that MH is associated with risks for CVD however most of these reports have been published in Americans, Europeans, and Japanese. Data pertaining to the prevalence rates of MH reported using ABPM in African populations whose CVD risk profile is high is still lacking. In a South African context, to my knowledge, there are two studies in South Africa, which have investigated MH and its potential effects on cardiovascular outcomes (Ware et al., 2016, Thompson et al., 2016). However, one of the available studies (Ware et al., 2016) on MH used a small sample size (*n=81*), and the other available study (Thompson et al., 2016) was

conducted with mixed ethnic groups (54 % whites). In addition, in both studies, the prevalence rates of MH were reported using only 24-hr ABP. Therefore, in this thesis, the prevalence rates of MH was reported on a larger sample size of exclusively blacks of African Descent. Furthermore, in this thesis MH was categorised into its subtypes i.e. 24-hr MH, Daytime MH, and Night-time MH. The association with TOD was compared in all the different subtypes to determine which subtype of MH carries more cardiovascular consequences. The approach to categorise the subtypes of MH helps to identify which physiological and environmental factors may play a role in the pathogenesis of the different subtypes of MH. The previously reported rates of MH using only 24-hr ABP fails to stratify the probable causes of MH. To effectively address this issue, the use of ABPM was utilised to screen participants with MH who on the basis of CBP measurements cannot be diagnosed as hypertensive. MH was then categorised in its three different subtypes.

1.1.2 Objectives

The primary objectives of the current study were therefore:

a) to determine the prevalence of the sub-types of MH in a South African population of African descent.

b) to investigate if cigarette smoking and alcohol consumption are associated with any subtype of masked hypertension in a South African population of African descent.

c) to determine if masked hypertension is associated with TOD in a South African population of African descent.

d) to investigate the relevance of a non-dipping blood pressure profile in masked hypertension in a South African population of African descent.

e) to determine if masked hypertension is associated with salt intake assessed through 24-hour urine collection.

Before discussing the contexts relating to MH and HT, it is however important to expound on the properties of BP regulation.

CHAPTER TWO

Understanding Blood Pressure Dynamics and Current Knowledge of Ambulatory Blood Pressure Monitoring in Masked Hypertension

2.1 Properties of Blood Pressure

Blood pressure is a product of primarily two forces i.e. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (AHA, 2017, Gunasekaran, 2013), and it is influenced by cardiac output (CO), total peripheral resistance (TRP) and arterial stiffness (Rehman and Nelson, 2018, Imai et al., 1996). A change in BP such as an increase in SBP has long been known to be a major risk factor for cardiovascular morbidity and mortality (Forouzanfar et al., 2017, Lough, 2015). Furthermore, studies have shown that a lower SBP is associated with reduced cardiovascular disease mortality and frequency (Bundy et al., 2017, Graudal et al., 2017, Tedla et al., 2017). An elevated DBP on the other hand has been shown to be associated with frequency of coronary heart disease (AHA, 2017, Rahimi et al., 2017). Never the less, SBP is a more important prognostic indicator for cardiovascular risk when compared to DBP (Webb and Treacher, 2015). In addition, SBP is a therapeutic target when lowering BP as it carries more cardiovascular consequences (Gosmanova et al., 2016, Van Bortel et al., 2001). Therefore, in this thesis, unless otherwise stated, a change in BP refers to a change in SBP. The variables involved in BP are well regulated in order to maintain perfusion pressure necessary for oxygen and nutrient supply to the tissues. However, there are some variations in BP throughout the day in response to intrinsic as well as extrinsic factors (Safar, 2001).

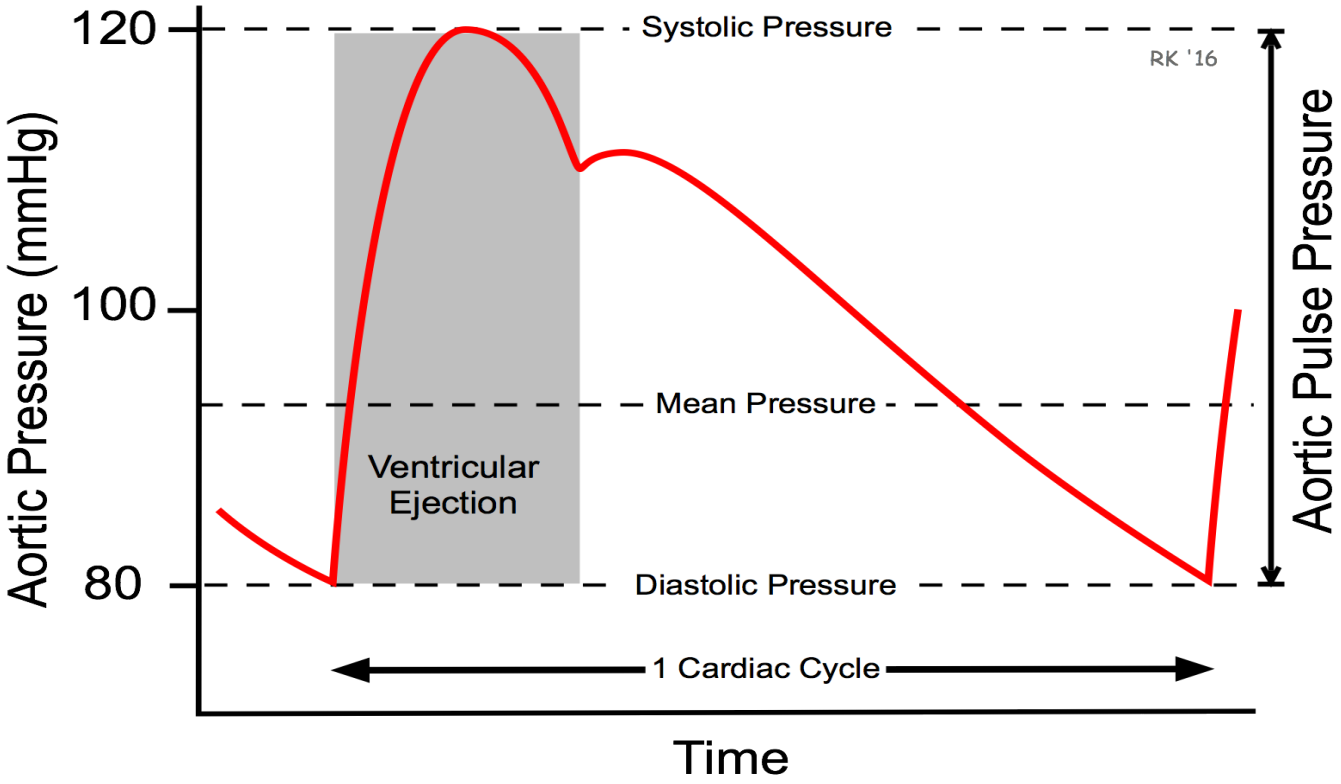

Figure 2.1: Arterial blood pressure during a single cardiac cycle (Sherwood, 2015).

The SBP is the peak pressure exerted in the arteries when blood is pumped into them during ventricular systole. The diastolic blood pressure DBP is the lowest pressure exerted in the arteries when blood is drained off into the vessel downstream during ventricular diastole. The PP is the difference between the SBP and DBP. The mean arterial pressure MAP is the average pressure throughout the cardiac cycle (Sherwood, 2015).

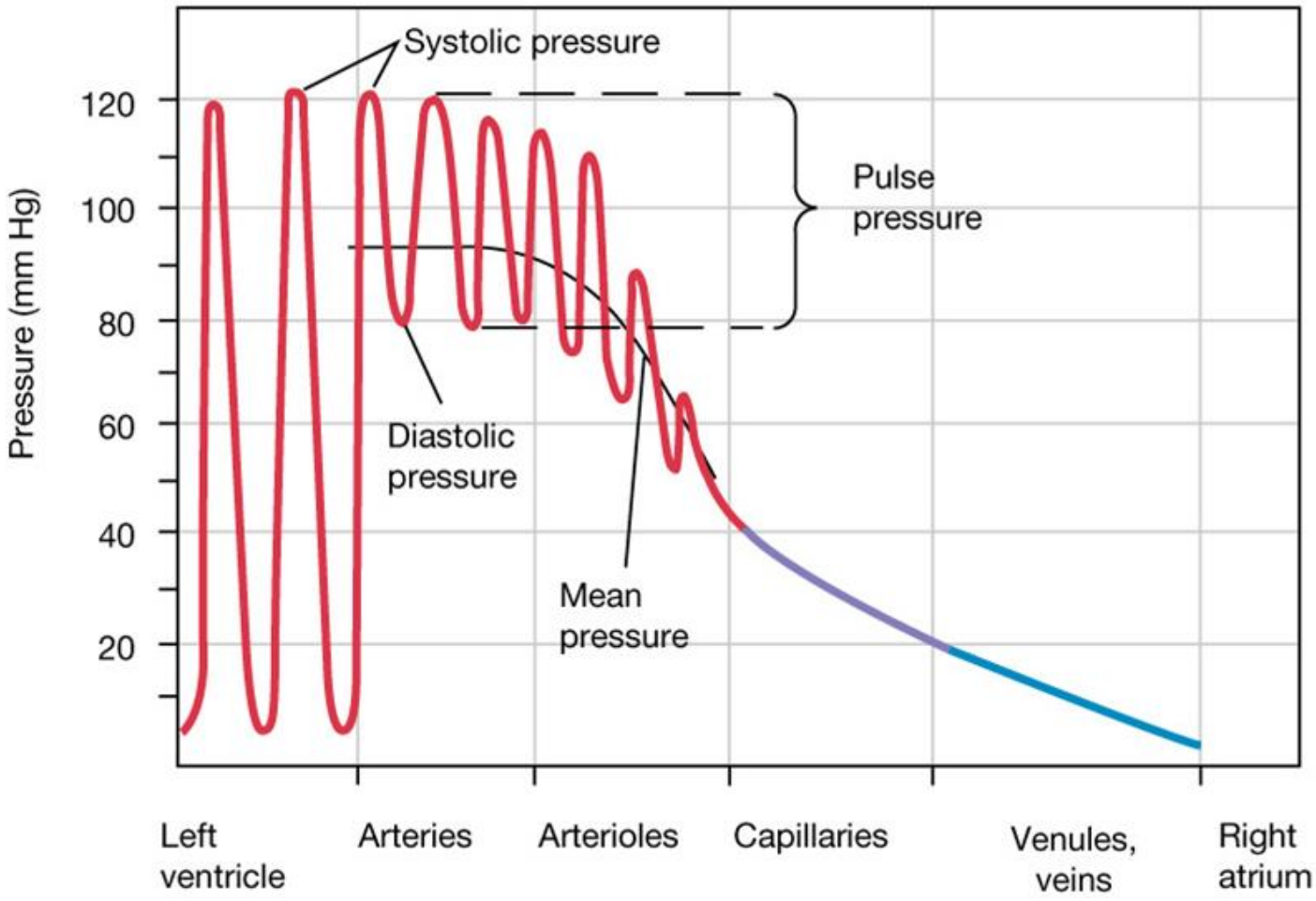

Figure 2.2: Blood pressure throughout the systemic circulation (Sherwood, 2015)

Left ventricular pressure swings between a low pressure of 0 mm Hg during diastole to high pressure of 120 mm Hg during systole. Arterial BP fluctuates between a peak SBP of 120 mm Hg and a low DBP of 80 mm Hg in each cardiac cycle. The arterioles have a high resistance. Therefore, BP drops swiftly and the systolic to diastolic swings in pressure are converted to a non-pulsatile pressure when blood flows through flows through the arterioles. The pressure continue to decline at a slower rate as blood flows through the capillaries and venous system (Sherwood, 2015).

2.1.1 Blood pressure variability

BP variability is a multifarious occurrence that comprises both short-term and long-term components, and it can be studied by the standard deviation (SD) of BP values over a defined period of the day or by the night-to-day BP ratio (Sterling, 2004). In a quest to understand why and how BP changes, it is important to have information about the factors to which BP responds to on a daily basis.

All quantifiable changes in BP relate to beat-to beat variations in the heart which are controlled by the activities of the brain. Factors such as respiration influence the pulse wave of blood for very short intervals as it is ejected from the heart (Parati et al., 2015). Effective upkeep of tissue perfusion and adequate tissue oxygen (O_2) exchange and the release of carbon dioxide (CO_2) in the cells under metabolically interactive processes requires a continuous interplay between respiratory, cardiac, and vascular system. The respiratory activities stimulate a number of sensory system integrated in the brainstem that lead to modulation of sympathetic nervous outflow and subsequently physiologic variability in BP (Parati et al., 2003). Therefore, these noticeable short-term rise and fall in BP occur within a 24-h period and in addition to beat-to-beat variations, they also comprise minute-to-minute, hour-to-hour, and day-to-night fluctuations (Gillian et al., 2003).

Except for the acute metabolically collaborative processes aimed at maintaining homeostasis, all other BP variations are regulated by an interplay of humoral and hormonal contributions that are controlled by the brain in response to external and internal stimuli. These BP variations occur to adapt people to their circumstance and environment (Duranton et al., 2018). Blood pressure fluctuates continuously to make individuals adjust to their ever-changing environments and daily conditions. Internal and external environmental factors modify BP level and follows cyclic patterns of several phases corresponding to days (circadian rhythms), weeks (circaseptan), seasonal, as well as yearly (circannual) fluctuations in BP (Aubinière-

Robb et al., 2013, Duranton et al., 2018). Circadian rhythms of BP relate to physiological and behavioural changes occurring between waking up and sleeping. These circadian BP variations reflect adaptive responses to routine activity and postural variations related with everyday life processes as well as processes occurring during sleep (James, 2013). In addition, it is known that circadian the rhythm of BP is harmonized with the sleep-wake cycle and it also displays a corresponding variability with that of the heart rate (HR) rhythm (Hjortskov et al., 2004). Concerning seasonal BP variations, the physiological responses are due to beat-to-beat regulations in relation to external stimuli accompanied with various sociocultural changes allied with seasonal traditions (Woodhouse et al., 1993).

The seasonal change in BP is associated with a number of climatic factors including external temperature, humidity, rainfall, and daylight duration. For this reason, it has been suggested that BP level and seasonality varies across locations with different climates (Modesti, 2013). In addition, BP seasonality has been reported to follow a geographic trend wherein higher BP levels were observed in populations closer to the poles (Brennan et al., 1982, James, 2013).

The literature therefore indicates that BP changes mirrors the adaptive responses to customary activities associated with everyday life practices. The BP variations are related to changes in the stressfulness of varying environments. It is also suggested that in addition to the already mentioned factors, other influences such as mood affect BP variation (Anderson et al., 2017). Consequently, due to this continued change in BP, the individual does not possess a single “stable state” in BP but rather has a number of varied homeostatic BP states which are linked to their ever changing interior and exterior environments (Gillian et al., 2003, James, 2013).

BP variability plays an important role in forecasting cardiovascular consequences attributed to HT. Even though adverse cardiovascular outcomes of HT are largely attributed

on mean BP values, supplementary evidence shows that these consequences might also be influenced by BP variability (Parati et al., 2013). Studies have shown that mutually, short-term and long-term escalations in BP variability are associated with development, progression, and severity of TOD and with an increased occurrence of cardiovascular mortality independent of a rise in mean BP (Parati et al., 2012, Parati et al., 2015). These homeostatic states embrace other physiological processes that parallel BP states.

2.1.2 The circadian blood pressure profile

A number of physiological processes have circadian variations; for example, the sleep-wake cycle, the body-temperature cycle as well as endocrine cycles. Studies have previously demonstrated that these rhythms are compactly interconnected and that the internal clock deeply interacts with environmental factors to maintain the internal balance (Pannain and Van Cauter, 2007). Comprehension of these physiological processes has prompted an interest regarding the chronological deviations of BP in healthy humans (Gnocchi and Bruscalupi, 2017). Some studies have suggested that in addition to the heart rate rhythm, circadian BP is also harmonised with the sleep-wake cycle as well as endocrine rhythms (Pannain and Van Cauter, 2007, Smolensky et al., 2007, Morris et al., 2012).

These circadian patterns of BP together with the seasonal patterns are clinically important because they may interfere with the diagnosis of hypertension and may inform on a patient's cardiovascular status (Duranton et al., 2018). The circadian rhythm of BP is characterised by diurnal and nocturnal variation within a 24-hour period. Essentially, BP declines during sleep and rises at the time of waking up.

The decrease in BP at night is characterised by 10% to 20% drop in BP from daytime to night-time although inter-individual differences do exist (Okamoto et al., 2009). Blood pressure dipping is considered on the basis of SBP variation instead of DBP as SBP carries

more clinical consequences (Bundy et al., 2017, Okamoto et al., 2009). This dynamic nature of reduction in BP at night is known as “dipping’, and individuals who do not exhibit this BP reduction are called “non-dippers” (Mahabala et al., 2013). In addition, there is a group of individuals who display a contrary upsurge in BP during the night and are labelled “reverse dippers”. This condition is characterized by an even augmented night-time BP when compared to daytime BP values (Cuspidi et al., 2017).

Primarily, the dipping pattern is caused by physiological sympathetic activity fall and parasympathetic activity rise at night. This BP fall is linked to the central autonomic drive regulated by baroreflex mechanisms, which appears to be a vital determinant of diurnal BP variability (Sherwood, 2011). Contrary, the non-dipping display is associated with ailments and disturbances of the chronological circadian rhythms (Dubielski et al., 2016). In addition, because baroreflex sensitivity increases during sleep while BP decreases, there is a possibility that differences may exist in baroreflex sensitivity between non-dippers and dippers.

Daytime BP measurements do not necessarily offer a truthful accuracy as compared to night-time BP regarding the prognosis of HT. This is mainly because night-time BP represents the basal BP and is symbolic of the true BP status of an individual (Hansen et al., 2011). Therefore, the non-dipping BP pattern is a useful indicator because it has been recognised to encourage the severity of HT. However, it is not clear as to whether a non-dipping BP profile has similar ramifications in MH. A non-dipping BP has also been shown in several studies to have a strong association with TOD at the cardiac, cerebrovascular and vascular level (Brantsma et al., 2006). Fargart et al (1995) demonstrated that a non-dipping BP profile is responsible for a substantial degree of an increase in left ventricular mass (LVM), carotid intima media thickness (CIMT), and microalbuminuria.

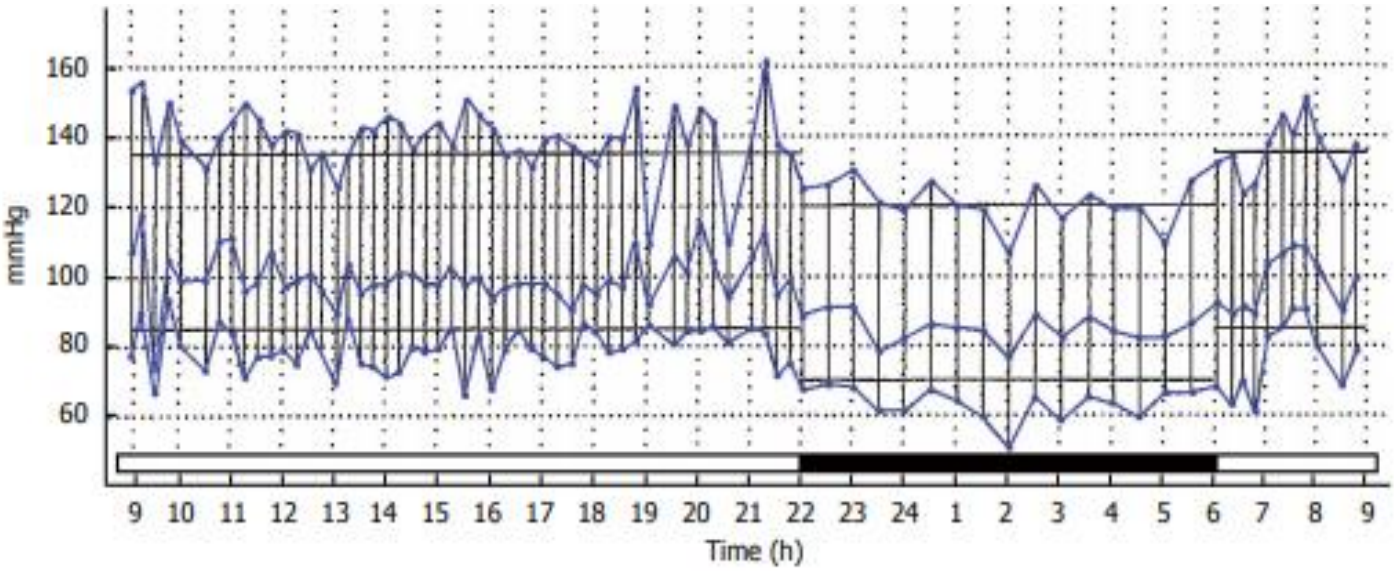

Figure 2.3: ABPM showing average BP values throughout a 24-hour period and the dipping BP profile. ABPM, Ambulatory blood pressure monitoring. BP, blood pressure (Larochelle, 2002).

2.2 Non-dipping blood pressure and masked hypertension

There is an indication that impaired nocturnal dipping (non-dipping and reverse dipping) and nocturnal HT may play an important role in the development of MH (Franklin et al., 2016). This is often suspected in obese individuals, those with sleep apnoea, have high salt intake, chronic kidney disease, and those with autonomic dysfunction (Israel et al., 2011). However, the mechanisms involved are not clearly understood. In addition, studies have also demonstrated that, when paralleled with other racial groups, Africans show less "dipping" in BP at night. This "non-dipping" BP status may predispose an individual to MH (Franklin et al., 2016), nonetheless, it is not clear as to whether a non-dipping BP status directly impacts on MH or whether there are other contributory factors that work through the non-dipping BP profile to cause HT or MH. In addition to the non-dipping BP profile, several other factors such as increased physical activity, smoking, alcohol use, cardio metabolic parameters, and psychological factors such anxiety and stress have been implicated in the pathogenesis of MH (Makris et al., 2009, Verberk et al., 2008, Pickering et al., 2007). However, the mechanisms linking these factors to MH have not been clarified.

The applicability of a non-dipping BP profile as well as some of the other implicated factors in the occurrence of MH in a population of African descent are examined in later sections. Before I explore the relevance of these physiological and behavioural factors in MH, I will first highlight the physiological processes involved in BP regulation

2.3 Physiological control of blood pressure

Homeostasis is a relatively steady state of the internal body environment maintained by living organisms, despite changes in internal and external environments. This dynamic state of equilibrium is conducive for functioning of the organism and it includes many variables, such as body temperature, BP and fluid balance being kept within certain pre-set limits (Cannon, 1929).

All physiological systems in the body function as a collective to achieve this desirable state. However, the cardiovascular system's contribution to maintain nutrient and O_2 supply to fulfil cellular requirements is of critical. Therefore, in order to ensure an effective blood flow and supply to the tissues, it is of utmost importance to regulate BP at a stable and optimal level. Regulation of BP or the MAP is reliant on cardiac output (CO) as well as total peripheral resistance (TPR) and involves two basic mechanisms of control i.e. short-term mechanisms and long-term mechanisms (Pappano and Wier, 2018, Boron and Boulpaep, 2012).

The short-term mechanisms of BP regulation mainly controls blood vessel diameter, HR as well as heart contractility (Hall, 2015). These adjustments are subject to the influence of the autonomic nervous system (ANS) (Guyenet, 2006). The long-term mechanisms of BP control are primarily intended for regulating blood volume. Hormones that control blood volume by controlling salt and water achieve this through long-term control of BP (Cowley Jr, 1992). This BP control mechanisms is coupled with capillary-fluid shift mechanism. Furthermore, individual organs and tissues can also regulate their own local blood flow in order to meet their own perfusion requirements as long as the MAP is preserved at an optimal level (Thrasher, 2004).

The BP regulatory systems of the body work in a closed negative feedback control loop. This loop functions in such a way that it tends to reduce the fluctuations between the system output and a desired output, which is the optimal functional range (Hall, 2015).

2.3.1 Short-term blood pressure regulation

Short-term BP regulation becomes in effect in a matter of seconds, shortly after an acute change in BP. The most prominent aspect of the short-term BP control is the speed of response. The ANS is the major role player in short-term BP control as it employs both the sympathetic and parasympathetic branches to collaborate in regulating BP levels thus altering the HR, vessel diameter, and heart contractility (Guyenet, 2006). Both branches of the ANS innervate the heart, therefore can effectively modify the speed of contraction of the heart as well the strength of contraction of the heart. By altering the HR and heart contractility, the ANS regulates CO, which in turn influences BP. For instance, when the sympathetic NS is dominant, it increases HR and contractility; as a result, this increases CO and BP.

On the other hand, stimulation of the parasympathetic NS causes a decrease in HR, and in this manner, it causes a decreases CO (Dibona, 2002). The sympathetic NS has varying effects on the blood vessels of the circulatory tree. In the arterioles, the sympathetic NS causes vasoconstriction, which in turn increase resistance to blood flow, thus increasing BP. Vasoconstriction of some larger arteries and veins under the influence of the sympathetic NS ensures an increase in venous return and consequently CO (Esler, 2000). Some of the BP regulatory mechanism mediated by the ANS are incorporated in the summary of homeostatic systems involved in BP regulation in (Table 2.1). However, the baroreflex mechanism is the most vital feature of the ANS's BP regulatory contribution. It safeguards marginal BP variability as an individual is going about their daily activities. This mechanisms monitors BP

deviation from the normal range and through a cascade of events modifies the HR and TPR (Furlan et al., 2001).

2.3.1.1 The Baroreflex mechanism

This mechanism constitutes arterial baroreceptors, which are mechanical stretch receptors located mainly in the aortic arch as well as the carotid sinuses. With respect to their anatomical location, the aortic baroreceptors relay information via the vagus nerve to the central nervous system (CNS) pertaining to BP applied on the aorta which is applicable to the systemic circulation. Conversely, the baroreceptors located in the carotid sinuses relay information to the CNS via the glossopharyngeal nerve (Furlan et al., 2001). The information from the carotid sinuses tells about BP applicable to the brain. Information relayed by both sets of baroreceptors is conveyed through the release of neurotransmitters in the solitary tract nucleus of the brainstem (Benarroch, 2008).

The baroreceptor's response is triggered by a change in BP caused by blood flowing through the aorta and the carotid arteries. These stretch baroreceptors of the aorta and carotid arteries depolarise when blood vessels stretch due BP. Their depolarisation results in action potentials being directed through the afferent NS to the CNS. When BP increases, it accordingly increases the stretch applied on the blood vessels and as a result, the rate of firing of the baroreceptors increases. Thus, through the efferent portion of the ANS, CO and TPR are adjusted accordingly to control BP. These aspects of the circulatory system are attuned through the processes involving the sympathetic NS and the parasympathetic NS already mentioned (Eckberg and Sleight, 1992, Mancia and Mark, 1983, Ogoh et al., 2005).

Apart from the short-term BP control mechanisms, other regulatory mechanisms occur in a matter of minutes to hours. These mechanisms help in controlling BP when the nervous system becomes less effective and the long-term regulatory systems are yet to be triggered. For example, the Renin-Angiotensin vasoconstrictor mechanism plays a crucial role particularly in low BP. The kidneys secrete an enzyme renin when arterial BP falls below normal. Renin then stimulates the production of angiotensin (ANG) I through the conversion of angiotensinogen (Laragh, 1973). Angiotensin I is then converted to ANG II by the angiotensin-converting-enzyme (ACE). Angiotensin II is a potent vasoconstrictor whose role is to bind to the ANG receptor type 1 (AT_1) on arteriolar smooth muscles to cause arteriolar vasoconstriction and thus elevating BP by increasing the TPR. The conversion of ANG I to ANG II requires several collaborative steps, which causes the process to take several minutes before being operational. Essentially, stimulation of the AT_1 receptor by ANG II triggers a cascade of intracellular events initiated by the activation of G-protein (Patel et al., 2018, Brinks, & Eckhart, 2010). In turn, G-protein activates several intracellular pathways including the production of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) through the catalytic effect of phospholipase-C (PLC) (Demoliou-Mason, 1998, Owens, 1995). Phospholipase-C binds to IP3 receptor on the endoplasmic reticulum to mobilise the release of Ca^{2+} from intracellular stores. Activation of DAG by protein kinase-C results in Ca^{2+} entry across the plasma membrane (Billups et al., 2006). The Ca^{2+} entry across the plasma membrane and release from intracellular stores subsequently leads to myosin light chain phosphorylation and ultimately vasoconstriction (Patel et al., 2018).

Another BP control mechanism that provisionally becomes active before long-term control becomes activated is the capillary fluid shift mechanism (Montani and Van Vliet, 2009). This control mechanism works by adjusting blood volume in the blood vessels particularly the capillaries. The hydrostatic pressures and oncotic pressures that exist across the

capillary wall determine the equilibrium of fluid exchange across the capillary wall (Himeno et al., 2016). The capillary blood pressure, the interstitial fluid pressure and the colloid osmotic pressure of the plasma control this fluid exchange (Guyton, 1991). A net loss of fluid from the capillary at the arteriolar end is compensated by a net gain at the venous end, resulting in maintenance of a fluid balance. Therefore, net fluid movements and volume regulation depends on of fluid filtration, reabsorption and lymphatic drainage (Waghmare and Srivastava, 2016). When BP is low in the capillaries, fluid is shifted from the interstitial spaces into the blood vessel. Vice versa, when BP is high in the blood vessels, the fluid is absorbed into the interstitial space from the capillaries and thus reduces blood volume and pressure (Guyton, 1991, Guyton et al., 1972).

Additional BP control mechanism that occur in the interim before long-term mechanisms can kick in include the stress-relaxation mechanisms (Kaplan, 2010). When BP increases, the blood vessel relaxes and stretches due to the rise in pressure. This relaxation and stretch accommodates the rise in pressure and thus reduces the TPR (Hall, 2015).

2.3.2 Long-term blood pressure regulation

Nonetheless, having noted the above BP control mechanisms, the major mechanism responsible for BP control is the renin-angiotensin-aldosterone-system (RAAS). The kidney being the chief organ responsible for long-term BP control mediates this system. The RAAS is a powerful mechanism that plays an essential role in homeostatic regulation of tissue perfusion, extracellular volume and arterial BP (Guyton, 1991). As previously highlighted, it involves the already mentioned enzyme renin whose role is to convert angiotensinogen into ANG I. The active renin secretion is governed by several factors that respond to a drop in arterial BP. These factors include a renal baroreceptor mechanism, which is located in the afferent arteriole of the

glomerulus in the kidney that detects a change in renal perfusion pressure (Atlas, 2007). The other aspect promoting renin secretion is an altered sodium chloride delivery to the kidney. This alteration is detected by the macula densa cells of the distal tubule, which lie in proximity to the juxtaglomerular cells (Weir and Dzau, 1999). Both the juxtaglomerular cells and the macula densa cells form the juxtaglomerular apparatus, which regulate the filtration rate and help regulate BP (Tobian, 1962).

Stimulation of the beta-1 adrenergic receptors by sympathetic nerves causes the release of renin. After production of ANG I by renin, the inactive ANG I is then hydrolysed by ACE into ANG II. ACE is a membrane-bound exopeptidase found in various locations including vascular endothelial cells and renal proximal tubule cells. Angiotensin converting enzyme also metabolises other peptides such as bradykinin and kallidin whose actions result in vasodilation (Ferrario and Strawn, 2006, Vickers et al., 2002, Witherow et al., 2001) as summarised in Table 2.1. Essentially, the enzymatic function of ACE ultimately favours vasoconstriction and opposes vasodilation (Jafar et al., 2003). Angiotensin II formed by the enzymatic activity of ACE is a biologically active and potent vasoconstrictor and it is the principal basis for the number of RAAS induced physiological actions. Angiotensin II induces its physiological actions by binding to one of four receptors (AT_1 to AT_4) (Goodfriend et al., 1996). However, the AT_1 receptor appears to be the crucial mediator of the functions of ANG II. These actions are effected on the cardiovascular system, the kidney itself, as well as the sympathetic NS. Angiotensin II causes a discriminatory vasoconstriction of renal arterioles, and by so doing, it reduces blood flow through the kidneys leading to less fluid being filtered (Schupp et al., 2004, Burnier, 2001). Angiotensin II also mediates vasoconstriction on the peritubular capillaries causing salt and water reabsorption by the renal tubules. It also has a direct effect on the tubular cells themselves to increase salt and water reabsorption (Schrier, 2006, Laragh, 1962). Furthermore, ANG II has an indirect effect on fluid preservation by stimulating the adrenal

glands to release aldosterone, which is dedicated to causing supplementary water and salt retention. This system works contrariwise to the pressure diuresis mechanism (summarised in Table 2.1), where the kidneys excrete large volumes of urine when BP rises. It also counteracts the pressure natriuresis mechanisms where salt excretion is increased.

Even though the RAAS system plays a pivotal role in long-term control of BP, constant activation or inappropriate stimulation may cause the development of HT and related CVDs (Guyton et al., 1972, Montani and Van Vliet, 2009). Since BP is regulated by several interacting mechanisms at various levels. Failure of one or more of these mechanisms may lead to poor control of BP, and consequently contributing to the development of HT. In addition, BP may be chronically elevated above normal levels in pathophysiological conditions, causing HT and thereby leading to the development of CVDs and increased mortality (Männistö et al., 2013, Gray et al., 2011). Nonetheless, as to whether MH develops from the same BP regulatory failures as seen in sustained HT or whether MH can be observed in similar pathophysiological conditions as evident in sustained HT is an unsettled enquiry.

Table 2.1: Summary of Homeostatic Blood Pressure Regulatory Mechanisms

Homeostatic Blood Pressure Regulatory Mechanisms	**Effects on BP**
Central nervous system's ischemic response	Reduced blood flow or less nutrient and O_2 in the vasomotor centre of the brain triggers it to send a signal to the body via the sympathetic branch of the ANS, in an attempt to quickly elevate BP back up to normal levels after in response to hypovolemia.
Carotid and aortic chemoreceptor reflexes	Chemoreceptors detect the lack of O_2 and an increase in CO_2 as well as accumulation of hydrogen, thus exciting the vasomotor centre to increase HR and cause vasoconstriction.
Bainbridge reflex	An increase in central venous pressure caused by an increased blood volume is detected by stretch receptors (Cardiac Receptors) located in both atria at the veno-atrial junctions leading to an increase in HR.
The RAAS system	A hormonal homeostatic system that regulates BP and fluid balance by controlling salt and water balance in the kidneys.
Arterial baroreceptor reflexes	Increased BP stretches the wall of the aorta and carotid arteries causing baroreceptors to fire action potentials at a higher than normal rate, exciting the vagal centre and causing vasodilation and decreasing HR.
Stress-relaxation mechanisms	Increase BP causes the blood vessel walls to relax, thus resulting in a stretch of the blood vessel to accommodate the increased blood.
Natriuretic peptides	Induced urinary excretion of salt by kidneys in response to increased BP. It inhibits renal and vascular effects of angiotensin II. It causes cardiac and vascular dilation.
Capillary fluid shift mechanism	Responsible for maintaining blood pressure by the slow shift of fluid between the intravascular compartment and the interstitial fluid compartment, which acts as an 'overflow' reservoir for excess fluid
Renal kallikrein kinin system	Responds to increased sodium and thus causes in increase in sodium and water secretion, resulting in a decrease in BP.
Endothelium derived vasoactive substances	Substances produced by the endothelial cells which regulate vascular smooth muscle either as vasodilators or vasoconstrictors.
Renin-Angiotensin vasoconstrictor mechanism	Short term effects of angiotensin II; stimulate arteriolar vasoconstriction and causing an increase in peripheral resistance and an increase in BP

2.4 Sustained and masked hypertension: causes and similarities.

Hypertension in general involves several risk factors and causes, and in the majority of patients with primary HT there is no tangible cause. This is because the risk factors for HT are of a multifarious origin. Some of the causes are modifiable and some cannot be modified (Ott et al., 2013, Calhoun, 2013). Global approaches to minimise the strain of CVDs due to HT have always encouraged life style changes. This is because lifestyle habits which contribute to the development of HT can be modified (Dzudie et al., 2016). These global strategies have placed a focus on behavioural factors such as physical inactivity, tobacco smoking, alcohol intake, and unhealthy diets.

It is well documented that these aforementioned behavioural and environmental factors contribute to chronic diseases of lifestyle such as obesity, diabetes mellitus, and dyslipidaemia which through numerous pathophysiologic mechanisms promote the development of HT (Hopkins et al., 1996). Apart from the habitual contributory factors to HT, there is another category comprising of non-modifiable causes of HT and these count those traits such as age, gender, genetics, and ethnicity, which are inescapable and cannot be changed.

2.4.1 Age

Age progression is an acknowledged independent risk factor for the development of sustained HT. It is a natural change that goes together with a diminished and modified physiological function of organ systems that control BP (Brandes et al., 2005). There are structural and functional impairment of endothelial cells with concurrent changes in the expression and release of vasoactive mediators such as nitric oxide (NO) and endothelin-1 (ET-1) which accompanies ageing (Camici et al., 2009). Additionally, other important properties of the endothelium are depleted with aging, whereas inflammatory activity and oxidative stress increases (Brandes et al., 2005). The aging blood vessels slowly become stiff and constricted, revealing a diminished ability to expand when blood is pumped; a characteristic of hardened arteries, thus increasing TRP and BP. This sustained increase in BP eventually progresses to HT. Another feature that escalates BP in the elderly is the decrease in physical activity (Kaplan, 2010, Brandes et al., 2005).

However, it is not clear if aging is associated with MH (Verberk et al., 2008). Contrary to MH, the phenomenon of WCHT has been shown to associate with aging (Pickering et al., 2002). Since MH is equivalent to a negative WCHT effect, it is therefore proposed that MH is less prevalent with an increase in age (Pickering et al., 2002). To support this notion, a Danish study showed that 86% of men aged 42 had daytime ABP higher than CBP, while this was true for only 51% of men aged 72 (Pickering et al., 2002). In line with the findings of the Danish study, an Italian study conducted by Sega et al. (2005) also showed that ABPM displays a much less increase with age than CBP. However, it is not know as to whether MH bears any relationship with age in a South African population of African ancestry.

2.4.2 Gender

Sexual dimorphism in arterial BP has been observed and reported as early as adolescence and continues all through adulthood (Dubey et al., 2002). Men are have a relatively higher BP as compared to women through much of life regardless of race or ethnical origin (Santulli, 2013). A large body of data on CBP measurements including studies by Boynton and Todd (1947) revealed that SBP and DBP are significantly higher in men than in premenopausal woman of the same age. Even in animal models of HT, studies have shown that females have lower BP than males (Xue et al., 2007). The differences in BP levels between age-matched men and women is said to be accounted for by sex hormones, primarily oestrogen and testosterone where the absence of oestrogen in males or after menopause in females is independently associated with an increase in BP and CVD (Barton et al., 2012). Pertaining to BP measured through ABPM, MH is reported to be associated with male sex and young age (Ben-Dov et al., 2005). In agreement with this, literature describing both treated and untreated patients with MH shows that the percentage of men as compared to women is higher (Matsui et al., 2007, Selenta et al., 2000).

2.4.3 Ethnicity and Genetics

There is clear discrepancy in ethnic or racial groups regarding sustained HT. For decades, data has consistently showed that HT is more common, more severe, and progresses much faster in people of African origin as compared to whites in America (Agyemang and Bophal, 2002, Booth et al., 2016). In Europe, people of African descent have higher mortality rates due to HT when compared to those of other ethnic origins (Jones and Hall, 2006). When comparing people of African descent to descendants of other ethnic origin, Africans tend to have a higher nocturnal BP and a smaller difference between daytime pressures. Despite past and recent

research debates, it remains an epidemiological puzzle to explain the increased risk of HT experienced by people of African ancestry when compared to other ethnic groups. Several researchers have long proposed that BP in African lineage is heightened by the incidence of high "salt sensitivity" as compared to their ethnic counterparts, though the mechanism responsible for the increased incidence of salt sensitivity in blacks is poorly understood (Rayner and Spence, 2017, He and MacGregor, 2010, Meneton et al., 2005).

In addition to this trait of "salt sensitivity" there is extensive evidence that supports the presence of a genetic component in BP regulation. Approximately 20% to 60% of BP variability in a population is genetically determined (Wei et al., 2017, Von Wowern et al., 2003). A vast number of candidate genes have been tested for relationship with BP regulation for many years without resounding results due to the imprecise manner of inheritance. However, studies including the one conducted by Kouremenos et al. (2014) in a Greek population indicate a successful detection and correlation of genes that are associated with BP regulation and HT. This study outlined the candidate genes with intra-familial predisposition to HT. Many population studies have also established greater similarity concerning BP genetics in intra-family sceneries than between families (Doris, 2011, Barlassina et al., 2002).

Also, adoption studies have revealed that the familial presence of HT is not simply due to shared environment. The familial heredity of HT is positively correlated with the number of first degree hypertensive relatives. This implies that individuals who have two or more first degree relatives with HT develop HT four times as often by the age of 40, three times as often by the age of 50 and twice as often by the age of 60 compared to individuals with no family history of HT (Wei et al., 2017, Barlassina et al., 2002). This evidence stresses the importance of genetic heritage especially at an early age of onset of the HT disease (Von Wowern et al., 2003). Nonetheless, it is not known if genetic heritage plays a role in MH as evident in sustained HT. Literature indicates that prevalence rates of MH in population-based studies

counting the Jackson Heart Study (JHS) show that people of African origin have higher prevalence incidence among population based studies, although not markedly high (Morris and Bisognano, 2017, Odili et al., 2016). Even with these findings, it is unfortunate that only few studies have directly paralleled MH prevalence rates across ethnic groups (Diaz et al., 2014). More studies are required to investigate the relevance of ethnic or racial and genetic link in MH.

2.5 The prevalence of masked hypertension

Theoretically, the incidence of MH indicates the lack of ability to diagnose HT through CBPM in a clinical setting. Failure to detect an elevated out of office BP has resulted in the under estimation of HT prevalence (Wang et al., 2017). This failure has contributed to the fuelling of CVDs. Nonetheless, a number of studies have reported on the prevalence of MH. These average frequency rates of MH have been reported to range between 10%-to-25% (Sega et al., 2005, Parati et al., 2010), and even as high as 60% in other studies (Larsen et al., 2014, Ishikawa et al., 2006). The exact status of MH at a population level is still unclear as the reported prevalence rates of MH varies considerably from population to population. These notable differences in the prevalence of MH are due to a number of factors counting disparities in measurement techniques, and patient characteristics (Diaz et al., 2014).

Nonetheless, ABPM remains the golden standard for diagnosing MH, but HBPM is also recommended when ABPM is not available (Lehmann et al., 2013). Ambulatory blood pressure monitoring has many technical advantages over HBPM because it offers assessment of BP during sleep and provides an added advantage of telling about short term BP variability and circadian rhythms by showing thorough details on BP changes throughout the day and night (Peacock et al., 2014). Indeed, a number of studies have reported the frequency rates of MH using HBPM because of its cost effectiveness as compared to ABPM (Stergiou et al., 2014,

Viera et al., 2016). However, studies have indicated that performing ABPM will detect many individuals with MH who have an increased risk of CVDs as opposed to HBPM (Hodgkinson et al., 2011, Parati et al., 2014). To support this argument, Stergiou et al. (2014) reported a 20% to 30% disagreement in the diagnosis of MH using HBPM and ABPM. In another report, Viera et al. (2016) stated that the sensitivity for detecting MH were 23% for HBPM and 67% for ABPM. These reports indicate that there is an underestimation of the prevalence of MH when HBPM is used as compared to ABPM.

There are additional aspects to be taken into account when HBPM is used in the diagnosis of MH. It should be considered that HBP measurements are taken under standardised environmental conditions and that body position is adjusted to accommodate for the measurement. On the contrary, ABPM measurements take place while the subject is moving freely and is engaging in their daily activities and engaging in many other behavioural patterns that may indiscriminately have a substantial effect on BP (Rothwell, 2010, Niiranen et al., 2010). These daily activities not accounted for by HBPM obtained under resting environmental conditions of measurements can result in a considerable increase in BP, which when measured through ABPM reveals high estimates (Viera et al., 2016).

The use of either HBPM or ABPM in reporting prevalence rates of MH makes the comparison of data between studies to be difficult. Apart from the already mentioned patient characteristics and differences in measurement techniques, cut-off points for BP levels account for much of the wide range in prevalence estimates (Hodgkinson et al., 2011).

Prevalence rates of MH have always been reported solely on 24-hr MH and not the subtypes of MH i.e. 24-hr, daytime and night-time MH. The threshold for hypertension diagnosis using ABPM classifies MH into three subtypes as indicated in Table 2.2.

Table 2.2: Ambulatory blood pressure and home blood pressure values

	Interval	Normal (mm Hg)	Elevated (mm Hg)
HBPM	Daytime	<135/85	≥135/85
ABPM	24-hr	<130/80	≥130/80
ABPM	Daytime	<135/85	≥135/85
ABPM	Nigh-time	<120/70	≥125/75

HBPM: Home blood pressure measurements; ABPM: Ambulatory blood pressure measurements; 24-hr: 24-hour; mm Hg: millimetre mercury. Modified from (Franklin et al., 2017).

Table 2.3: Prevalence rates of masked hypertension in various populations of the world.

Study	Ethnic population group	Number of study participants	% Masked Hypertension
(Rhee et al., 2016)	Koreans	462	16.2
(Booth et al., 2016)	African Americans	1148	52.2
(Sega et al., 2001)	Italians	1631	9
(Larsen et al., 2014)	African Americans	73	45
(Ben-Dov et al., 2005)	Jews/Arabic	487	11
(Enström et al., 1991)	Swedish	48	25
(Hansen et al., 2006)	Danish	1700	9
(Ishikawa et al., 2006)	Japanese	405	61
(Leitão et al., 2007)	Brazilians	135	30
(Lurbe et al., 2005)	Spaniards	592	10
(Márquez et al., 2006)	Spaniards	1153	9
(Matsuoka and Awazu, 2004)	Japanese	103	11
(Ohkubo et al., 2005)	Japanese	1332	17
(Sakaguchi et al., 2005)	Japanese	148	33
(Selenta et al., 2000)	White Americans and Asian Americans	319	23

Data presented on table 2.3 indicate a higher prevalence of MH in African Americans and in Japanese. However, it should be noted that the higher incidence of MH in the study conducted by Booth et al. (2016) is attributed the fact that the study included MH patients who are taking hypertensive medications and are said to be "treated MH". The other study by Larsen et al. (2014) also displayed a higher incidence of MH in a population of African Americans. Nonetheless, the study sample only had 73 participants with valid data, indicating a small sample size that might have overestimated the incidence of MH. In addition, the high prevalence of MH in the Japanesse population (Ishikawa et al., 2006) was reported for "Masked Morning Hypertension" detected by HBPM in medicated hypertensive patients and not those considered to be normotensive and without HT treatment.

Data on MH in African populations is still lacking and information with accurate statistics is required to establish a truthful estimate of the exact prevalence of MH in these populations. People in African populations possess the highest burden of CVDs and the mortality rates due to HT may actually be powered by MH. The detriment of MH is that patients are not aware of their BP status and therefore do not receive hypertensive treatment thereby contributing to the poor control of HT. Moreover, it is not clear as to whether MH occurs in all populations and whether individuals in all populations with MH have a sufficiently high overall cardiovascular risk to warrant concern. Studies conducted to-date suggest that as compared to normotensive individuals, individuals with MH may indeed be at risk for cardiovascular events (Drawz et al., 2016, Franklin et al., 2016).

These reports show that the relationship between MH and CVDs is as strong as that observed for sustained HT (Scuteri et al., 2016), indicating that MH patients have a higher risk of TOD such as increased arterial stiffness similar to sustained HT patients (Peacock et al., 2014). Assessment of arterial stiffness using pulse wave velocity (PWV) has been shown to provide prognostic information beyond that provided by traditional cardiovascular risk factors,

including age, gender, BP, cholesterol, diabetes mellitus, and smoking (Matsui et al., 2007). Although studies have indicated that arterial stiffness is present in MH patients (Takeno et al., 2012), thus far, no study has been conducted in this population group of African descent to assess the association between arterial stiffness with MH. Additionally, it is not established if arterial stiffness occurs in all subtypes of MH particularly in this population group of African descent.

Table 2.4: Prevalence reports of masked hypertension from pooled studies in African population.

Study	Number of participants	% Masked Hypertension
(Abir-Khalil et al., 2009)	2462	33
(Etyang et al., 2016)	371	4
(Bochud et al., 2009)	415	4
(Henine et al., 2016)	2367	9
(Ivy et al., 2015)	79	28
(Maseko et al., 2013)	750	18
(Omboni et al., 2016)	368	5
(Thompson et al., 2016)	396	18
(Takah et al., 2014)	500	25
(Ware et al., 2016)	81	31

2.6 Masked hypertension and cardiovascular organ changes

Conventional blood pressure monitoring which measures brachial BP has been the traditional method for diagnosis HT and has been understood to represent systemic BP. However, MAP, which represents the average BP, does not remain constant along the arterial tree (Avolio et al., 2009) as illustrated in figure 2.2. Therefore, the unearthing of central BP measurement has shown that brachial BP does not represent the true force loaded on the heart, the kidney, and the brain. Central BP has been shown to relate more strongly with CVDs outcome than CBP. Accordingly, when central BP is elevated, TOD ensues. On the contrary, when central BP falls drastically, organ failure results due to low perfusion.

The carotid-femoral PWV is recognised as the gold standard method of evaluating arterial stiffness (Hansen et al., 2006), and its importance in cardiovascular risk stratification has been demonstrated in numerous studies including (Hametner et al., 2013, Chen et al., 2015). During ventricular ejection, a pressure wave is produced in the conductive arteries. The speed at which these waves travel along the arterial tree is known as the PWV (Townsend et al., 2016). At large conduit arteries, where there is high resistance as well as in bifurcations, the wave is reflected back to the heart through a waveform. The waveform that is produced constitutes a forward wave as well as a backward wave or reflected wave (Sibiya et al., 2015). In compliant arteries, the reflected wave returns to the ascending aorta during diastole thereby augmenting DBP. In non-compliant arteries or stiffened arteries, the reflected wave arises in late systole instead of arriving during diastole and therefore it impairs coronary circulation and tissue oxygenation (Gao et al., 2016). Not only does the arterial stiffness affect the magnitude and timing of the reflected wave, it also increases the PWV (Covic and Siriopol, 2015).

Stiffening of the arterial walls occurs when there is a structural as well functional alteration in the arteries, and is mainly caused by the aging. Aging results in a diminished expression and release of vasoactive mediators (Camici et al., 2009). However, the structural and functional remodelling in the arterial walls is also accelerated by CVDs, and in turn arterial stiffening hasten CVDs. Stiff arteries are characterised by an increased lumen size, thickening of the medial layer of the arteries, and a decrease in elasticity of the elastic fibre (Sun, 2015, Jablonski et al., 2015). Arterial stiffness due to degeneration of the elastic fibre affects pressure and flow pulsitility and hence it promotes TOD by interfering with the regulation of BP.

As indicated, remodelling of the arterial structure and function is understood to play a crucial role in the pathogenesis of CVDs. The increase in PWV, which is an index of arterial stiffness as well as the amplitude of the forward and reflected waves serve as the main causes of increased SBP as well as PP, associated with stiffened arteries predominantly in aging (Covic and Siriopol, 2015, Cunha et al., 2015). Consequently, the increased SBP and PP leads to HT. A number of studies have indicated that arterial stiffness as assessed by PWV is associated with HT (Chen et al. 2015; Hansen et al. 2006). In addition, HT is more prevalent in older individuals. Indeed, the structural and functional changes that lead to arterial stiffness are chiefly associated with aging. However, it is not clear as to whether arterial stiffness is present in a younger age group. We recollect that Mancia et al. (1995) and Rasmussen et al. (1998) indicated that ABP shows much less increase with age when compared with CBP.

Nonetheless, Hänninen et al. (2013) indicated that MH is associated with an increased PWV. This may suggest that arterial stiffness may be present even in the younger age group who are reported to be more liable to MH when compared to the elderly. Categorically, recent studies have indicated that PWV is increased in MH similarly to sustained HT (Kenny et al., 2017, Zhang et al., 2018). Other studies have shown that PWV is slightly higher in patients who have elevated night-time ABP as compared to Daytime BP (Drawz et al., 2016). However,

it is uncertain if all subtypes of MH in this population group of African descent have increased PWV comparable to sustained HT. Further, literature indicates that PWV in MH individuals is slightly lower than in sustained HT but significantly higher than normotensive individuals (Faria et al., 2015, Tientcheu et al., 2015). Either way, evidence suggests that MH may not be a benign condition and may be as detrimental as sustained HT (Gijón-Conde et al., 2017). Literature also shows that apart from arterial stiffness, the risk for cardiovascular mortality and morbidity due to MH may relate to other cardiovascular organ changes such as increased LVM. Data indicates published by kawano et al. (2008) and Kotsis et al. (2008) indicates that individuals with MH have increased LVM. However, there are contradictory reports regarding the extent of LVM when MH individuals are compared to both normotensives and those with sustained HT. Some reports suggests that the values of LVM index (LVMI) are similar in individuals with MH and those with sustained HT (Palla et al., 2018). Nonetheless, other reports indicate that LVMI are significantly higher in MH individuals when compared to true normotensives but are slightly lower when compared to those with sustained HT (Tadic et al., 2017, Cuspidi et al., 2014). Certainly HT is associated with increased LVM. The mechanism of increased LVM or left ventricular hypertrophy (LVH) in HT appears to be multifactorial, however, the conventional theory is that of hypertrophy for adaptation (Peer et al., 2013). The increase in myocardial muscle mass in LVH is a compensatory mechanism that occurs because of an increased peripheral pressure or volume overload (Cacciapuoti, 2011). Nonetheless, this cascade of compensatory responses alters myocardial cellular structure, the myocardium and ventricular mass and leading to fibrosis (Minamino-Muta et al., 2017). This pathological remodelling of the cardiac structure is known to be associated with an increased risk of cardiovascular events (Cacciapuoti, 2011). Nevertheless, data on the association between MH and LVMI in a population of African Descent are scanty such that it is not clear if LVMI is

similar in MH and sustained HT. Additionally, it is not clear if LVM is increased in all subtypes of MH when compared to true normotensives.

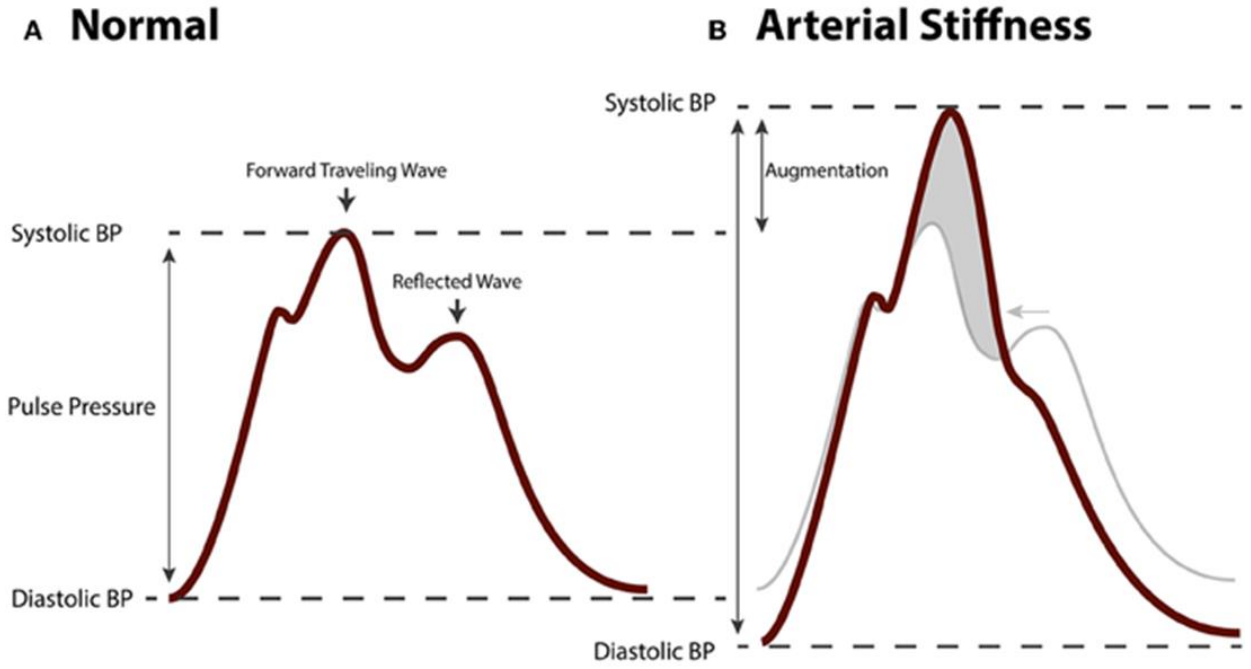

Figure 2.4: Aortic pressure wave as determined by the combined effect of the aortic forward and reflected pressure waves. Panel A representing a normal pressure waveform. Panel B represents a pressure waveform observed in arterial stiffness (Van Varik et al., 2012).

2.7 Masked hypertension and its association with kidneys dysfunction

As previously indicated, reports show that elevated ABPM levels relate to higher cardiovascular risk similar to sustained HT (Tientcheu et al., 2015, Hoshide et al., 2016). In addition to increasing cardiovascular risks, sustained HT is widely known to accelerate deterioration in kidney function (Mennuni et al., 2014). However, it is not clear as to whether renal injury is included in the varieties of potential end-organ damage related to MH (Cerasola et al., 2008). In addition, there is lack of literature pertaining to MH and renal TOD. Nevertheless, literature has indicated that in sustained HT, kidney injury represents a persistent occurrence that include multiple mechanisms resulting in glomerular, tubular or interstitial damage (Webster et al., 2017, Humphrey et al., 2016).

The extent of nephropathy depends on numerous factors, including individual vulnerability and the degree of hypertension (Mennuni et al., 2014). The early indicator of imminent hypertensive nephropathy is microalbuminuria, defined as urinary excretion of albumin at a rate of 20-200 mg/min (Mennuni et al., 2014, Nabbaale et al., 2015). Microalbuminuria has been demonstrated to forecast cardiovascular complications, and all-cause mortality independent of traditional risk factors (Abdelhafiz et al., 2011). Additionally, even minor degrees of renal dysfunction as shown by the initial sign of microalbuminuria entail an enhanced cardiovascular risk (Feng et al., 2017).

Patients with microalbuminuria may progress to chronic kidney disease (CKD) characterised by an elevated serum creatinine concentration and decreased glomerular filtration rate (GFR). Redon et al. (1994) reported that patients with elevated microalbuminuria (>30 mg/24h) had significantly higher mean ABP values (SBP and DBP) as compared to patients

with normal microalbuminuria (<30 mg/24h) in a 24 hour period. However, this study by Redon et al. (1994) was conducted in patients with essential HT and not MH. In addition, Lurbe et al. (2002) also indicated that in patients with higher microalbumin, daytime DBP was slightly higher as compared to patients with normal microalbuminuria. Furthermore, DBP and SBP during the night-time period were significantly higher in patients with higher microalbuminuria values as compared to normal microalbuminuria. However, this study by Lurbe et al. (2002) was conducted in patients with Type 1 diabetes mellitus. Therefore, in the present study, I investigated if any subtype of MH are associated with renal TOD assessed by microalbuminuria in a South African population of African descent. Furthermore, it is not known if persons with MH do or do not have a physiologic renal defect in their ability to handle electrolytes such as sodium (Na^+).

2.8 Dietary sodium intake in its relationship with masked hypertension.

Literature has for a long time indicated that excessive Na^+ intake predisposes individuals to HT (Laatikainen et al., 2016, Ha, 2014). What is more concerning for people of African descent is that data has reliably shown that Na^+ dependant HT is more common and more serious in this population group (Tully et al., 2015, Thomas et al., 2018). Further, this population group presents with higher mortality rates due to HT that relates to excessive Na^+ intake (Rayner and Spence, 2017). Even though numerous studies support that the relationship between excess Na^+ intake and HT is concrete, the mechanisms involved in this relationship are not conclusive. There is controversy relating to the involvement of Na^+ intake in HT. This is because when comparing between races, the consumption of Na^+ appears to be similar, however the disease outcome is different (He and MacGregor, 2010, Meneton et al., 2005). In certain groups, particularly blacks of African origin, there is a considerable rise in BP in

response to Na^+ intake particularly when potassium intake is inadequate, a phenomenon known as salt sensitivity. Numerous papers have demonstrated the actuality of salt sensitivity in blacks of African descent. More grippingly, it appears that salt sensitivity is also present in the elderly of African descent, however, it is not a common occurrence in younger individuals (Weinberger, 1996, Morris et al., 1999, Kurtz and Morris, 2017).

It is reported that the occurrence of salt sensitivity may be hereditary (Rassler, 2010). Literature also suggests that a number of occurrences such as primary microvascular disease, acquired renal injury as well as alteration in renal vasoconstrictor-vasodilator balance may be responsible for salt sensitivity (Rodriguez-Iturbe and Johnson, 2010, Johnson et al., 2002, Nakagawa et al., 2003). In addition to the role of Na^+ intake in HT, it is also proposed that a decrease in K^+ intake is also involved in the development of HT (Alderman, 2002). Indeed, in salt-sensitive individuals, low K^+ diets are implicated, such that acute K^+ depletion induces salt sensitivity. Also, chronic hypokalaemia, which is associated with tubulointerstial injury, may induce salt sensitivity. Previous studies have indicated that high K^+ intake reduces BP considerably (Houston, 2011). However, it has since emerged that what is more important in the regulation of BP is the ratio of Na^+/K^+ instead of either electrolytes alone (Zhang et al., 2013).

Therefore, the imbalance in the Na^+/K^+ ratio where Na^+ intake is high and K^+ intake is low appears to be essential in the development of HT. Nonetheless, it is not known as to whether the increase in BP in response to increase in Na^+ intake or a decrease K^+ intake is appropriate in individuals with MH who in many cases appear to be younger and may not be suspected for HT. Therefore, in the present thesis, I assessed if 24-h urinary Na^+ excretion as an index of intake is associated with any subtype of MH in a population of African descent.

CHAPTER THREE

The Prevalence of Masked Hypertension Sub-Types in People of African Descent: The Impact of Smoking and Alcohol Intake

Abstract

The prevalence of MH varies in different studies due to the different methods of assessment as well as the cut-off points used in the in the different studies. The exact causes of this phenomenon are not clear. However, some studies have suggested that MH is associated with cigarette smoking and alcohol consumption. In the current study the frequency of MH subtypes was assessed using ABPM in adults in of African descent. The association between cigarette smoking, alcohol consumption and MH was assessed. One thousand two hundred and nineteen (1219) South Africans of African descent were randomly recruited for the study and CBP, ABPM, body mass, height and waist circumference were measured. However, only 796 had successful ABPM. Of the 796 participants, 598 were normotensive based on CBP measurements (<140/90 mm Hg) and were not taking antihypertensive medication. Only 198 were hypertensive based on CBP measurements (≥140/90 mm Hg). Out of the 598 participants who were perceived to be normotensives, 7% (*n*42) had 24-hour MH, 15% (*n*91) had night-time MH and 9% (*n*56) had daytime MH. There were more smokers in the daytime MH (25%) while 24-hour and night-time MH were similar at 18%. Alcohol consumption was similar for Daytime MH and nigh-time MH at 25%, and 18% for 24-hr MH. All subtypes of MH were significantly associated with smoking and alcohol consumption i.e. 24-hr MH $p<0.0001$; night-time MH $p<0.0001$; Daytime MH $p<0.0001$. Findings of the current study indicate that factors such as smoking and alcohol consumption should be used as indicators for a possible presence of MH.

3.1 Introduction

Guidelines for the measurement of BP indicate that CBP measurements are the primary method of BP assessment in the diagnosis and management of hypertension (Conen et al., 2014, Ishikawa et al., 2011). However, evidence presented in longitudinal and cross-sectional studies has reliably indicated that ABPM has a better prognostic ability over CBP monitoring in that it is more accurate in detecting and forecasting HT (Mortensen et al., 2017, Etyang et al., 2016). The clear advantage of ABPM is that BP status can be monitored even when the patient is engaging in their regular day-to-day activities (Shimbo et al., 2016). In addition, ABPM eliminates the white coat effect and reveals MH (Pierdomenico and Cuccurullo, 2011, Verdecchia et al., 2007). This group of patients do not display an increased BP in clinical settings but have an elevated out of office BP. Since its initial unearthing by Pickering et al. (2002), the prevalence of MH has been reported to vary greatly in different population groups ranging between 9% to 25% (Franklin et al., 2016). However most of these reports have described the incidence of MH based on a single categorisation of 24-h and not further subdivided into daytime and night-time MH. Furthermore, in different population groups it is not exclusively established as to which factors may systematically elevate out of office BP or lead to MH. However, the constant recording of BP readings in an ABP monitor can assist investigators in extrapolating data relating to the effects of environmental and behavioural factors such as smoking and alcohol consumption and their possible relationship with MH (Mallion et al., 2006, Virdis et al., 2010, Yano and Bakris, 2013). Additionally, it is not clear if smoking is associated with all subtypes of MH. On the other hand, alcohol consumption has been shown to be associated with MH, even though the association appears to be weak (Yano and Bakris, 2013). Nonetheless, there is no clear cut evidence on the association between

alcohol consumption and any subtype of MH. In this thesis, I therefore assessed the prevalence of MH and its subtypes in adults in an urban developing community of Africa descent. I also assessed if smoking and alcohol consumption characterises patients with MH and whether smoking and alcohol are associated with any subtype of MH.

3.2 Methodology

3.2.1 Ethical approval

The current study forms part of the ongoing South African Hypertension and Diet Study (SAHDS) and the study design has been described in brief in publications (Maseko et al., 2018, Maseko et al., 2013). It was conducted according to the principles outlined in the Declaration of Helsinki (WMA, 2001). The University of the Witwatersrand Human Research Ethics Committee (Medical) granted ethics approval for the current study (approval number: M17-04-16).

3.2.2 Study group

South Africans of black African ancestry from the Nguni, Sotho and Venda tribes with common ancestral backgrounds were randomly recruited from the Southern Western Township (SOWETO) of Johannesburg metropolitan area. Adult participants from the age of 18 were included in the study. There was no upper age limit for the participants; a lower age limit was included as BP rapidly increases with age below this value. One thousand two hundred and nineteen (1219) South Africans of black African ancestry were randomly recruited for the measurement of conventional, ambulatory, and central BP and anthropometric measurements which included body mass, height and waist circumference. An ABP recording was considered successful if more than 20 hours of recordings and more than 10 and 5 readings for the computation of daytime and night-time means respectively were obtained. Of the 1219 participants enrolled in the study, 423 were excluded from the analysis because they failed to meet the pre-specified quality criteria for ABP recordings.

Figure 3.1: Geographical map of Soweto where participants were recruited for the study.

3.2.3 Clinical and demographic information

Participants completed a standard questionnaire. In order to avoid translational errors, the questionnaire was not translated into an African language, but study assistants familiar with all languages spoken in the participating townships and who either previously lived in SOWETO or currently reside in SOWETO assisted with the completion of each questionnaire. Only same sex assistants were used to assist each participant with the completion of the questionnaire. Assistance was only provided when requested. The majority of participants were reasonably proficient in English. Ambiguities in answers to the questionnaire were double-checked. The questionnaire requested specific answers 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). If participants were unable to provide the name of medication taken, a home visit was arranged to obtain this information. In addition, prior and current occupation, level of education, smoking status (including the number of cigarettes smoked in the past and at the present time), and current daily alcohol consumption (beer, traditional beer or other forms of alcohol and the daily quantity) were recorded. With respect to smoking effects, the number of cigarettes currently smoked or previously smoked (if a previous smoker) per day, the age of starting and ending (if a previous smoker), and whether when partaking of the habit, smoke is inhaled, were recorded. The smoking of greater than 20 cigarettes a day was considered heavy smoking (Verdecchia et al., 1995), 10-20 cigarettes a day was considered moderate smoking (Minami et al 2009) and <10 cigarettes a day was therefore considered as mild smoking. Pertaining to alcohol consumption, the questionnaire comprised questions on alcohol behaviour i.e. yes or no questions for alcohol use (yes, current or former use; no, never used), the quantity, frequency of intake and the type of alcoholic beverage. Furthermore, the questionnaire requested information on 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. Data pertaining to females' menstrual history, number of pregnancies and oral contraceptive use was recorded. Most of the questions simply required a "Yes"-"No" answer, but understanding was assessed by requesting some short answers.

3.2.4 Anthropometric measurements

Height and weight were measured using standard approaches with the participants standing and wearing indoor clothes with no shoes as described (Shiburi et al., 2006). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured at the end of a gentle expiration, at the point midway

between the lowest rib and the iliac crest with the subject standing. Hip circumference was measured using a standard approach and waist-to-hip ratio (WHR) calculated. Triceps and subscapular skin-fold thickness were determined using a Harpenden skin-fold callipers and the mean of these values obtained for statistical analyses. Participants were identified as being overweight if their BMI was ≥25 kg.m^2 and obese if their BMI was ≥30 kg.m^2. Standard laboratory blood tests of renal function, liver function, haematological parameters, blood glucose, lipid profiles and glycated haemoglobin (HbA1c) were performed. Diabetes mellitus or inappropriate blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or a percentage HbA1c (Roche Diagnostics (Mannheim,Germany) >6.1% (Peters et al., 1996).

3.2.5 Conventional blood Pressure measurements

Blood pressure measurements were taken using a standard mercury sphygmomanometer during a clinic visit. All readings had to be within 4 mm Hg of the reference standard. A standard cuff with a 12-24 cm inflatable bladder was used, but if upper arm circumference exceeded 31 cm, larger cuffs with a 15-35 cm inflatable bladder were used. After 10 minutes of rest in the seating position, five consecutive BP readings were taken 60 seconds apart with the subject in a sitting position, followed by a pulse rate count. The cuff was deflated at approximately 2 mm Hg per second and phase I (systolic) and phase V (diastolic) BP recorded to the nearest 2 mm Hg according to the recommendations of the European Society of Hypertension (EHS, 2018). The average of the five readings was taken as the office BP. In the present study quality control of CBP assessments was assessed as previously described (Kuznetsova et al. 2002). A diagnosis of hypertension was made if participants were receiving antihypertensive therapy and/or if the average values for the clinic readings was ≥140/90 mm Hg.

3.2.6 Ambulatory Blood Pressure

Twenty-Four hour ABPM was performed using oscillometric monitors (SpaceLabs, model 90207). Ambulatory monitors were calibrated monthly against a mercury manometer. The non-dominant arm was selected for BP monitoring. The size of the cuff was the same as that which was used for CBP measurements. The monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 and then 30-minute intervals from 22:00 to 06:00. Participants kept a diary card for the duration of the recordings to note the time of going to bed in the evening and getting up in the morning. The times when going to bed and getting out of bed in the morning were used to determine the awake and sleep periods of the day. Participants were also asked to record the time when taking medication in those receiving medication and any times when they either smoked or took caffeine-containing or alcoholic beverages. Participants were asked to pursue their normal daily activities and to keep the cuff arm steady during measurements. From the subject's diary card data I determined the awake and asleep periods. On average, the participants went to bed at 19:00 h and woke up at 05:00 h. Considering these patterns of daily activities, the daytime and night-time intervals were defined as time intervals ranging from 09:00 h to 19:00 h and from 23:00 h to 05:00 h respectively. These fixed clock-time intervals (Thijs et al., 1992) were defined in order to eliminate the transition periods (evening and morning) during which BP changes rapidly in most participants. On completion of the recording, the data were transferred to a computer for analysis. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive recordings (Thijs et al., 1992). Data from participants enrolled in the study whose ambulatory BP 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 excluded from the analysis. Ambulatory BP data were expressed as 24-hour average systolic and diastolic BP, 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.

Figure 3.2: Spacelabs model 90207 ambulatory BP monitor

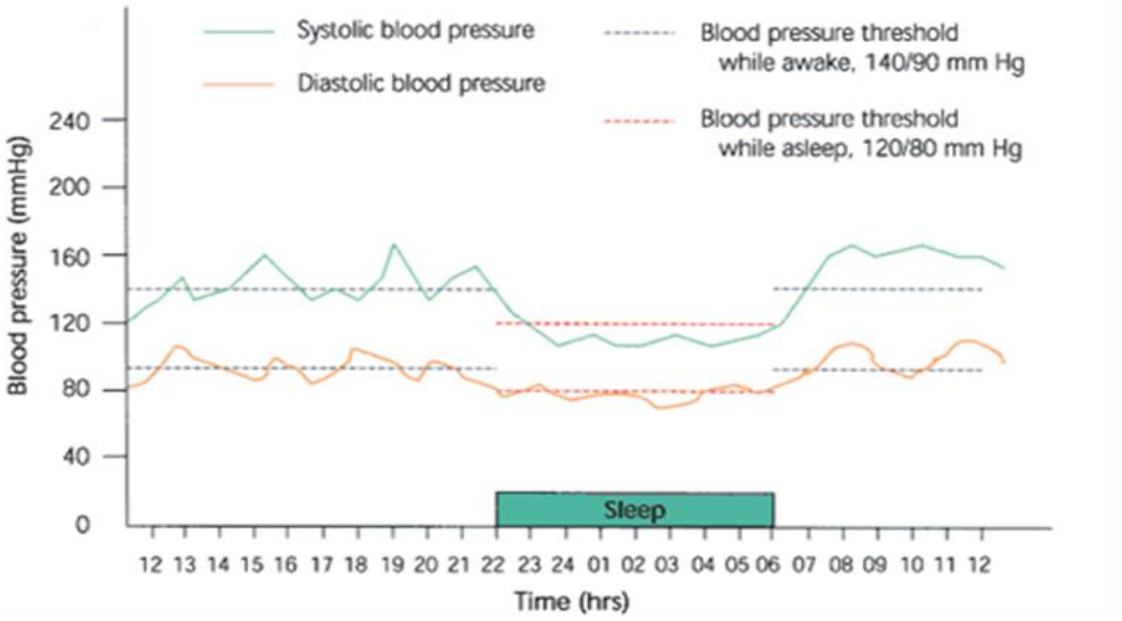

Figure 3.3: Representative data obtained from an ABPM for analysis purposes.

3.1.1 Definitions of analysis

Definitions for sustained hypertension from auscultatory measurements (≥140 mm Hg systolic BP or 90 mm Hg diastolic BP) and ambulatory BP (≥135 mm Hg systolic BP or 85 mm Hg diastolic BP) values were based on published guidelines (World Health Organization; Guidelines Committee of the European Society of Hypertension, 2018; Williams et al., 2003). The presence of hypertension was identified if participants were either receiving antihypertensive medication, or had an elevated auscultatory BP value obtained in a clinic environment. The classification of MH was already described in Table 2.2 on Chapter 2, page 35. Overweight and obesity were defined using body mass index thresholds of between 25 - ≤30 kg/m^2 for overweight and ≥30 kg/m^2 for obesity. The presence of Diabetes mellitus (DM) or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA1c value greater than 6.1%. Database management and statistical analyses were performed with SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA). Data from individual participants were averaged and expressed as mean standard deviation (SD). Departure from normality was evaluated using Shapiro-Wilk's statistic and skewness by the computation of the coefficient of skewness, i.e., the third moment about the mean divided by the cube of the standard deviation. The normal distribution was used to determine the significance of the coefficient of skewness. Comparisons between CBP and daytime ABP values and CBP and 24 hour BP values were made using repeated measures ANOVA. Limits of agreement between CBP measurements made on different occasions and between CBP and daytime ABP measurements were determined using a Bland Altman plot. Differences in agreement between CBP and ABP values (e.g. home CBP-daytime ABP versus clinic CBP-daytime ABP) was determined from differences in the standard deviations of the mean differences between the measurements using a Wilcoxon signed rank test. Regression analysis was performed to determine relationships between CBP and ABP measurements and

the correlation coefficients of the CBP-ABP relationships obtained from different CBP measurements compared using a procedure that accounts for non-independent correlation coefficients. Receiver operating characteristics curve (ROC) analysis comprised calculation of the area under the curve (AUC). The ROC curve represented a graphic relationship between both sensitivity and specificity as well as positive and negative predictive values and accuracy. The AUC values provided a measure of the diagnostic accuracy (i.e. sensitivity and specificity) of the test with values from 0.5 to 0.7 representing low accuracy; values from 0.7 to 0.9 representing tests that are good; and values greater than 0.9 representing tests with high or excellent diagnostic accuracy. When making comparisons between data, a P value of less than 0.05 was used as an indicator of statistical significance

3.3 Results

Table 3.1 gives the general characteristics of the study population. Table 3.2 provides the general hemodynamics of the study population. The ABPM SBP and DBP levels fall within the normal ranges in the general population. Of the 796 participants, only 198 were hypertensive based on CBP measurements (≥140/90 mm Hg) and ABPM, 598 were normotensive based on CBP measurements (<140/90 mm Hg) and were not taking hypertensive medication. Out of the 598 participants who were perceived to be normotensives (CBP <140/90 mm Hg), 7% (*n*42) had 24-hour MH, 15% (*n*91) had night-time MH and 9% (*n*56) had daytime MH. Based on both CBP and ABP measurements, only 409 participants were true normotensives. There were more smokers in the daytime MH (25%) (P <0.0001) while 24-hour and night-time MH were similar at 18% (P <0.0001).

Table 3.1: General characteristics of the study population

	All participants (N= 796)
Age (years)	44.2 ±18.1
Body Weight (kg)	74.8 ±18.6
BMI (kg/m^2)	28.9 ±7.6
Overweight/Obese (%)	64
Smoking (%)	15
Alcohol (%)	21
Hypertensives (%)	38
Diabetes (%)	8
Female (%)	64

BMI, body mass index; ± values are expressed as mean SD.

Table 3.2: Haemodynamic characteristics of the study population in mmHg

Index	Mean	SD	P5	P50	P95
SBP24	118.3	±14.9	97.7	115.4	147.4
DBP24	72.6	±10.2	58.3	71.3	91.7
SBPD	122.5	±14.7	102.6	119.7	151.3
DBPD	77.6	±10.4	63.3	76.1	97.3
SBPN	111.3	±17.2	89.9	107.6	145.4
DBPN	64.9	±11.7	48.6	63.4	86.0
SBPC	128.3	±20.9	100.0	124.4	170.0
DBPC	83.7	±11.8	66.4	82.4	104.4

mmHg, millimetre mercury; SBP24, 24-hour systolic blood pressure; DBP24, 24-hour diastolic blood pressure; SBPD, daytime systolic blood pressure; DBPD, daytime diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, nigh-time diastolic blood pressure; SBPC, conventional systolic blood pressure; DBPC, conventional diastolic blood pressure. ± data are expressed in SD.

Table 3.3: Clinical characteristics of the different sub-types of masked hypertension, normotensives and sustained hypertensives.

	Total population	24-hr masked	Daytime masked	Night-time masked	Normotensives	Sustained hypertensives
Number	796	42	56	91	409	198
Age (years)	44.1±18.1	42.3 ±19.7	45.3 ±19.1	48.1 ±18.1	39.3 ±16.6	58.9 ±14.2
BMI (kg/m^2)	28.9 ±7.6	32.1 ±8.9	30.3 ±9.1	31.3 ±9.5	27.9 ±7.4	31.8 ±7.3
Overweight/Obese %	64	72	64	68	58	82
Smoking %	15	18	25	18	15	12
Alcohol %	21	18	25	25	20	19
Diabetic %	8	24	20	25	12	16

BMI, body mass index.

Table 3.4 Roc association for masked hypertension versus smoking.

	AUC	CI	P value
24-hour MH	0.70±0.04	62-79	<0.0001 ***
Night-time MH	0.71±0.03	65-77	<0.0001 ***
Day-time MH	0.67±0.04	0.60-0.75	<0.0001 ***

AUC, area under the curve; CI, confidence interval. 24h-MH, 24-hour masked hypertension; N-MH, night-time masked hypertension; D-MH, daytime masked hypertension. ***p<0.0001. ***Adjusted for age, BMI, the presence of diabetes mellitus or an HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake and CBP.

Table 3.5: Roc association for masked hypertension versus alcohol consumption

	AUC	CI	P value
24-hour MH	0.66±0.04	0.59-0.79	<0.0001 ***
Night-time MH	0.71±0.03	0.65-0.77	<0.0001 ***
Day-time MH	0.70±0.04	0.61-0.78	<0.0001 ***

AUC, area under the curve; CI, confidence interval. 24h-MH, 24-hour masked hypertension; N-MH, night-time masked hypertension; D-MH, daytime masked hypertension. ***p<0.0001. ***Adjusted for age, BMI, the presence of diabetes mellitus or an HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake and CBP.

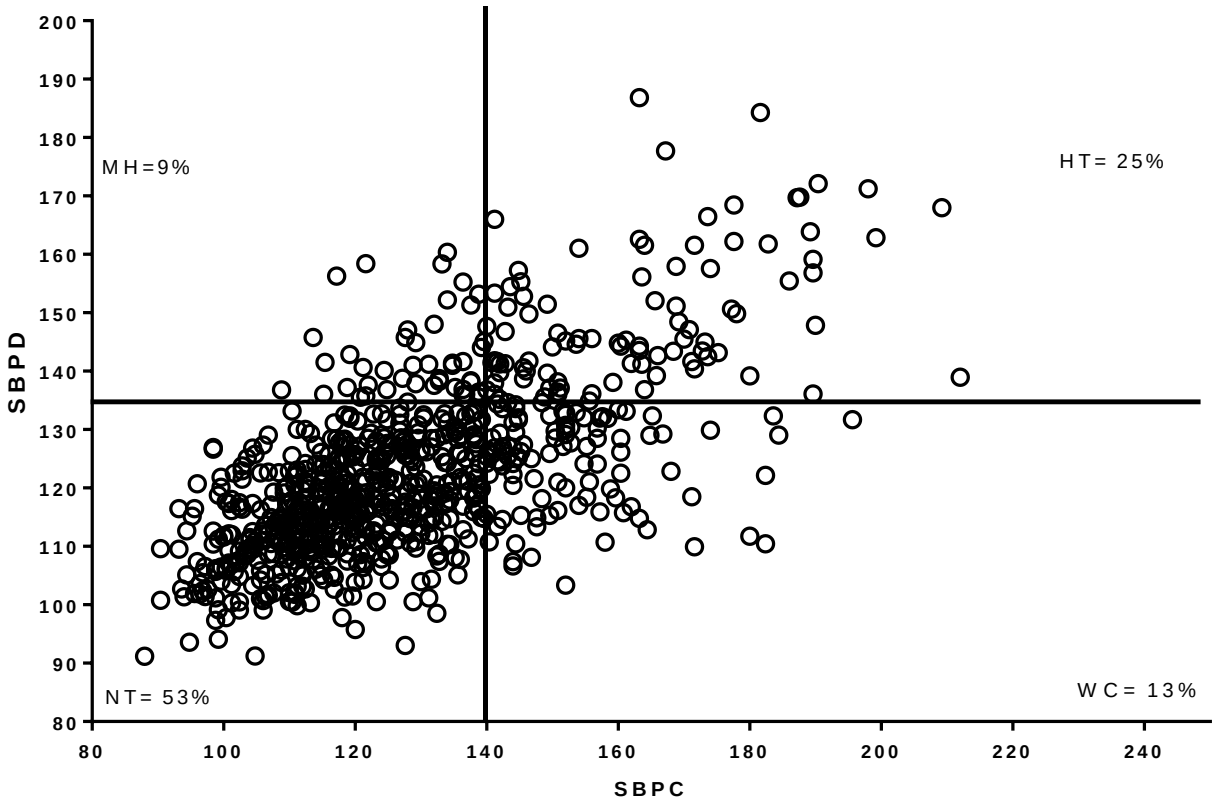

Figure 3.4: Scatter plot illustrating the cross-classification of normotensives, white coat hypertensives, sustained hypertensive and masked hypertensive groups in our study population. Relationship between conventional systolic BP (SBPC) and daytime systolic ABP (SBPD) showing the proportion of participants with either normal or increased SBPC or SBPD values. The solid lines represent current CBP and ABP thresholds. The daytime BP thresholds are derived from defined outcome-driven thresholds (Abdalla et al., 2016). In this thesis, 38% (796) had HT based only on CBP measurement. However, after employing ABPM, only 25% (*n*198) had sustained HT, indicating that 13% (*n*104) of the population had WCHT. Using the classical threshold of average daytime ABP values (135/85 mm Hg), 9% of the population had MH, and 53% were normotensive based on both CBP and ABPM.

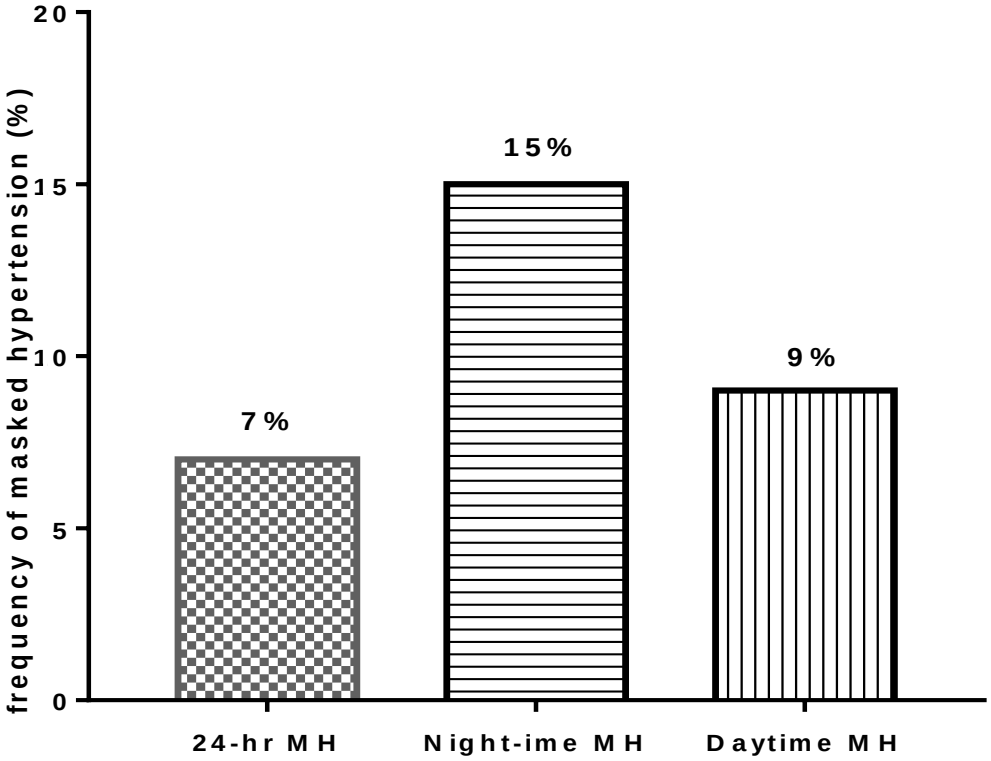

Figure 3.5: The prevalence of masked hypertension sub-types in the population group based on ABPM. Prevalence is reported in percentage (%).

3.4 Discussion

The present study shows that in a developing community of African Ancestry 9% have Daytime MH, 15% have night-time MH, and 7% have 24-h MH. This is the first study to investigate the different subtypes of MH in this population group. Few studies have reported on the prevalence of the subtypes of MH, however, other studies such as those conducted by Zhang et al. (2018) and Kawano et al. (2008) only categorised the subtypes into morning (daytime) MH and night-time MH as they had reported the prevalence using HBPM. Nonetheless, studies that have categorised MH subtypes in 24-hr MH, night-time MH and daytime MH include the JHS conducted by Booth et al. (2016) in an exclusively African American population with prevalence of MH subtypes of 31.7% 24-hr MH, 48.2% night-time MH, and 28.2% daytime MH. Another study that has categorised MH into the three subtypes include that of Asayama et al. (2014) where 24-hr MH was 13.8%, night-time and daytime MH were 17.0% and 19.1% respectively. However, findings of the study by Asayama et al. (2014) was reported based on randomly recruited population cohorts that formed part of the IDACO database which comprised multi-ethnic populations.

Already indicated, the prevalence rates reported in different studies vary due to methodological techniques, disease status of participants and many other factors including ethnicity and gender. It should be noted that the difference in prevalence rates of the present study and that conducted by Booth et al. (2016) is accredited the fact that in their study, they included MH patients who are taking medication and are labelled “treated MH”. The prevalence of the subtypes MH in the present study is therefore lower as compared to that of Booth et al. (2016) because I only included untreated patients in the definition of MH. In addition, differences in the prevalence rates of MH and its subtypes relates to race and ethnicity. This could potentially explain the differences with regard to the report by Asayama et al. (2014).

The diversities in the prevalence rates between the current study and those by Kawano et al. (2008), Asayama et al. (2014), Booth et al. (2016) and Zhang et al. (2018) may relate to the diagnostic cut-off point and the definitions of MH used (Diaz et al., 2014). Several studies have reported the prevalence rates of MH using only the 24-hr period and other studies have reported the prevalence rates using HBPM. However, in the present study, I used the ABPM to report the prevalence rates of MH in a population of African descent and further categorised the MH into subtypes as previously described. This is because; the ABPM has provided numerous plausible reasons for its preferred use in uncovering MH and its regard as the golden standard tool for BP monitoring. Also, in the present study I have followed the guidelines of the ESH and the European Society of Cardiology for the management of arterial HT (Williams et al., 2018). These guidelines recommend the use of separate cut-off points for daytime, night-time, and 24-hr BP. Indeed, the classification of MH based on the threshold values aided in identifying the MH subtype with the highest percentage in this population. By categorising MH into the different subtypes, the possible causes responsible for each subtype are better investigated. In this population group, night-time MH was the most common form of MH followed by daytime MH, and lastly 24-hour MH. These results are keeping with those reported by Booth et al. (2016) in an exclusively African American population. The high prevalence of night-time MH as compared to the other forms of MH in a population of African of descent could be due to a number of conditions that relate to a non-dipping BP such as salt sensitivity, obesity and disturbances in the ANS. Studies have previously reported that people of African Descent are salt sensitive and tend to show less dipping (Rayner and Spence, 2017, Pilic et al., 2016).

Essentially, findings of the current study indicates that smoking was significantly associated with all subtypes of MH. Furthermore, there were more smokers in the daytime MH

(25%) while 24-hr and night-time MH were similar at 18%. These findings are keeping with previous reports which showed that smokers tend to have a high daytime ABP in comparison to their clinic BP (Mann et al., 1991, Groppelli et al., 1992, Narkiewicz et al., 1995, Ohta et al., 2016). This is indicative of the opinion that ABP of smokers is increased during daytime when they are likely to be smoking as compared to their clinic BP when they are not likely to be smoking. Wing et al. (2002) also indicated that smoking predicted MH in the Second Australian National Blood Pressure Study. Again, Bobrie et al. (2004) also reported that in an elderly population of the SHEAF study whose BP was determined using self-monitoring HBP measurements, MH was high in those who reported to be smokers and past smokers. In another report by Makris et al. (2009), it was indicated that MH was associated with passive smoking in a dose related manner. Further, Leone (2011) reported that acute exposure to passive smoking affects vasodilation due to a reduced release of NO or arterial stiffness and subsequently an increase in BP. In addition, previous studies have indicated that both active cigarette smoking and passive cigarette exposure results in a decline in vasodilatory function of the endothelium resulting in an elevated BP (McVeigh et al., 1996, Celermajer et al., 1993). Indeed, active and passive exposure to cigarette smoke has been shown to be associated with structural as well as functional changes in the endothelium (Barbera et al., 2001). Endothelial cells are responsible for continuously expressing the enzyme nitric oxide synthase, which synthesizes NO from L-arginine (Förstermann et al., 2017). Cigarette smoke has been shown to supress the activity of nitric oxide synthase in endothelial cells, which results in the dysregulation of the endothelium derived NO, thus reducing the vasodilatory effect of NO (Van Keulen et al., 2017). The structural alteration in the endothelium occurs in chronic cigarette smoking, whereas the functional changes leading to depletion of NO is mainly due to the acute effect of cigarette smoking (Serban et al., 2016, Daiber et al., 2017).

In addition to the structural and functional changes to the endothelium, cigarette smoking exerts an acute hypertensive effect, through the stimulation of the SNS (Talukder et al., 2010). Smoking is accompanied with a threefold increase in the levels of epinephrine, which in turn stimulates beta 1 and 2, as well as alpha adrenergic receptors leading to vasoconstriction which elevates BP (Virdis et al., 2010). The acute effect of cigarette smoke may potentially explain the occurrence of MH due to smoking. Although not all participants in the daytime MH subgroup reported smoking as a behavioural pattern, it is likely that a considerable number of those who have daytime MH may be exposed to secondary or passive smoking during the day, either at work or at home. In this study, the overall percentage of smokers inclusive of normotensives, MH, as well as sustained HT was 15.2%. However, this number does not put into considerations those individuals who may potentially be exposed to secondary smoking.

Although further investigation is required, these findings are indicative of the possibility that even those who are not active smokers may be affected by cigarette smoking, and in this manner may experience an increase ABP during the time that they are potentially exposed. In support of the argument that smoking elevates daytime ABP, Ohta et al. (2016) indicated that cigarette smoking increases daytime ABP as well as the HR and these increases are associated with attenuation of the parasympathetic NS, thus amplifying the SNS.

Categorically, previous reports have indicated that smoking raises BP by causing vasoconstriction and accelerated HR as an acute SNS effect (Okubo et al., 2002). I speculate that these effects may be pronounced in daytime MH. In addition, functional variables such as arterial stiffness and BP have been reported to increase immediately after smoking (Camplain et al., 2015). The latter may be due to alterations of the dynamic vessel wall properties that follows exposure to smoking (Rhee et al., 2007).

Findings of this thesis also indicate that alcohol consumption was significantly associated with all subtypes of MH. However, when considering the percentage distribution, there were fewer drinkers (18%) in the 24-hr MH group, while Daytime and night-time MH were parallel at 25 %. Several studies have reported that regular alcohol intake is a determinant for MH (Yano and Bakris, 2013). However, there is scarcity in literature indicative of the subtype of MH with an obvious association with regular alcohol intake. Ishikawa et al. (2006) stated that regular consumption of alcohol was an independent determining factor for morning MH. However, in their study, Ishikawa et al. (2006) determined MH using self-observing HBPM. In another study by Kawano et al. (2008), it was suggested that evening alcohol consumption was responsible for morning MH. However, in both studies, it is not clear as to which time intervals were used to determine morning MH. In this thesis, the categorisation of the subtypes of MH into daytime and night-time interludes were established as time intervals stretching between 09:00 h to 19:00 h and from 23:00 h to 05:00 h in that order. These fixed clock-time intervals were defined in order to disregard the changeover phases (evening and morning) during which BP deviates rapidly in most individuals (Thijs et al., 1992). It is however possible that the morning MH recorded in Ishikawa et al. (2006) and Kawano et al. (2008) fell within the time category of the daytime MH. On condition that these were the circumstances, it would explain the heighted incidence of alcohol consumption in the daytime MH group of our study population.

As far as the high incidence of nigh-time MH is concerned, it is suspected that the increase in BP at night in those who consumed alcohol was due to the pressor effect of evening alcohol consumption. Studies counting that of Kodavali and Townsend (2006) as well as Lucas et al. (2005) demonstrated the pressor effect of alcohol where BP increase was observed within 1h after consuming alcohol. Although abstract, findings of this study suggest that the increase in night-time ABP in those with night MH who consume alcohol in the evening may be

subjected to the pressor effect of alcohol soon after consuming alcohol. Similarly, those who experience an increased ABP during the day and reported to be regular drinkers of alcohol may be subjected to the pressor effect of alcohol when consumed during daytime hours.

What is more remarkable with the BP response to alcohol is that this increase is not sustained (Kodavali and Townsend, 2006). This suggests that daytime and night-time MH may occur soon after the alcohol consumption and then ABP may revert back to a clinically non-elevated state. In addition, the rise in BP due to alcohol appears not to be connected with the activation of the SNS. Rather, this rise in BP is due to the direct effect of alcohol on vasoconstriction.

This vasoconstriction appears to be due to calcium ions since chronic alcohol consumption alters vascular smooth muscle membrane transport that increases intracellular free calcium concentration (Howes and Reid, 1986). This is supported by the finding that the administration of calcium channel blockers soon after consumption inhibits this vasoconstriction (Oshita et al., 1993).

In addition, alcohol enhances vasoconstriction initiated by vasopressin and catecholamines. The synergistic effects of these substances tend to inhibit endothelium-dependant vasodilation (Brizzolara et al., 1994). However, these effects of alcohol on blood vessels depend on the concentrations of alcohol. In addition, BP elevation due to alcohol varies according to duration as well as the time of the last drink (Ryan and Howes, 2002, FAZIO et al., 2001, Howes and Reid, 1986). Similar to a study conducted by Kawano (2010) findings of the current study suggest that the pressor mechanism may be involved in alcohol-induced BP elevation and that the alcohol itself manipulates the difference in the morning to evening BP.

Furthermore Kawano (2010) indicated that alcohol seems to exert a significant effect on circadian BP variation. However, it has minor influence on the average 24-h ABP. It appears that it is the effect of chronic consumption of large amounts of alcohol which results in

noticeable changes in BP resulting in MH. Nonetheless, findings of this study may have underreported the exact incidence of alcohol consumption since the occurrence was dependent on a self-reporting.

The most important clinical finding of the present study is that the prevalence of MH is heightened in a population of African descent and it is present in different subtypes. Findings of this study suggests that behavioural factors such as smoking and alcohol consumption are associated with MH. Although it may be practically difficult to diagnose MH in clinical settings due to the scarcity of ABPM, behavioural aspects such as smoking and alcohol consumption, which are shown to be associated with MH, should be used as risk factors for the possible presence of MH.

CHAPTER FOUR

The Impact of Masked Hypertension Sub-types on Arterial Stiffness and Left Ventricular Mass in an Urban Developing Community of South Africa

Abstract

Ambulatory blood pressure profiles provide a better index of cardiovascular TOD. However, ABPM has added some complexities to the clinical scenario in that it has revealed participants with MH whose cardiovascular risk is not clearly understood. It appears that participants with MH may have hypertensive TOD such as increased arterial stiffness and LVM hence may indeed be at risk of cardiovascular events. However, it is not certain if participants with MH in all populations have a sufficiently high overall cardiovascular risk to warrant a global health concern. Furthermore, it is not clear whether participants with MH share more similarities with true normotensives as compared to sustained hypertensives. Therefore, the aim of chapter 4 was to assess if any subtype of MH is associated with increased arterial stiffness and increased LVM and to investigate whether the phenomenon of "high-normal" BP is present in any of the subtype of MH in a population of African descent. Six hundred and ninety-nine (699) participants from SOWETO successfully completed both ABP, echocardiography as well as PWV measurements using applanation tonometry. Normotensive where categorized based on CBP measurements (<140/90 mm Hg) and were not taking hypertensive medication. Only 198 participants were hypertensive based on CBP measurements (≥140/90 mm Hg). Out of the participants who were perceived to be normotensives 7% had 24-hour MH, 15% had night-time MH and 9% had daytime MH. The 24-h MH and daytime MH groups were classified as having high-normal BP based on CBP measurements. The night-time MH were pre-hypertensive based on CBP measurements. After correcting for covariates (age, gender, BMI, drinking and smoking), PWV was significantly higher in all the MH subtypes compared to the normotensives; 24-hour MH ($p= 0.0029$), night-time MH ($p=0.0061$) daytime MH ($p=0.0069$). LVM was significantly higher in in all MH subtypes compared to normotensives ; 24-hour MH ($p= 0.0003$), night-time MH ($p<0.0001$) daytime MH ($p=0.0010$).

4.1 Introduction

Ambulatory blood pressure profiling provides a better index of cardiovascular TOD such as increased arterial stiffness and LVM (Algamal, 2016, Trudel et al., 2013). In addition, it offers a unique opportunity to understand MH (Cuspidi et al., 2015, Trudel et al., 2013). Nevertheless, the importance of MH at a population level remains unclear since few studies have evaluated its relevance in the continuum of CVDs. Studies conducted to-date indicate that as compared to normotensive participants, participants with MH may have hypertensive TOD and hence may indeed be at risk of cardiovascular events (Drawz et al., 2016). However, it is not certain as to whether participants with MH in all populations have a sufficiently high overall cardiovascular risk to warrant a global health concern. Furthermore, it is not clear as to whether participants with MH share clinical similarities as those with sustained HT or those who are true normotensives (Androulakis et al., 2017, Cuspidi et al., 2015). According to the WHO and the international society of hypertension, an overlap does exist between true normotensives and sustained hypertensives when CBPM is employed, and this category of patients are referred to as having "high normal" BP (WHO-ISH, 1999). Normotensive participants with SBP of 130 – 139 mm Hg or DBP of 85-90 mm Hg are categorised within the group of patients with high normal BP. It is suggested that individuals with high normal BP are likely to have an increased risk of CVDs (Vasan et al., 2001, Miyai et al., 2000). However, since there is scarcity of information, it is not clear as to whether MH shares a similar CDV risk profile with those who have high normal BP. Certainly, numerous studies have indicated that the risk of CVD increases progressively as BP increases from relatively low levels, moreover this risk is associated with age (Taddei, 2009, Lakatta and Levy, 2003). However, other studies indicate that younger individuals are more likely to have daytime ABP values that are higher than CBP values; therefore, one of the assumptions is that participants with MH may be younger (Dolan and James, 2017). Yet, some studies do not support this notion (Diaz et al., 2014, Thompson

et al., 2016). For instance, Odili et al. (2016) indicated that the odds of MH were significantly associated with an older age. In addition, aging has been shown to be associated with arterial stiffness (Sun, 2015, Mitchell et al., 2004) and that arterial stiffness has been shown to relate to MH (Schultz et al., 2011, Kotsis et al., 2011). Nonetheless, it has not been elucidated if arterial stiffness is associated with all subtypes of MH. In addition to arterial stiffness, evidence from cross-sectional studies and meta analysis has indicated that individuals with MH have increased LVM as compared to normotensive participants. Cuspidi et al. (2019) demonstrated that individuals with MH exhibited a greater LVM as compared to normotensive participants and had an increased long term risk of developing LVH. Adding to this, Pierdomenico et al. (2018) reported that LVM in participants with MH was slightly lower than that observed in participants with sustained HT. These findings may suggest that MH is a transition state between normotension and sustained HT. Furthermore, Cuspidi et al. (2019) and Bello et al. (2010) reported that normotensive individuals with a high-normal blood pressure had slightly higher LVM as compared to those without a high-normal BP. Nonetheless, it is not certain as to whether an overlap does exist between high-normal BP and ABP in any of the MH subgroups of this population of African Descent. Therefore, in chapter 4, I assessed whether arterial stiffness characterises individuals with MH and whether increased arterial stiffness is associated with any subtype of MH in this population group. Similarly, I assessed if an increased LVM characterises any subtype of MH. Further, I investigated as to whether the phenomenon of high-normal BP corresponds to any subtype of MH.

4.2 Methodology

4.2.1 *Ethical approval*

Ethical approval for this study was obtained as described in section 3.2 of this thesis.

4.2.2 *Study group*

Details of the recruitment of the participants that made up the study group have been described in section 3.2 of the present thesis. The present study was conducted in 796 participants with 24-hour ambulatory BP values that met with pre-specified quality control criteria (longer than 20 hours and more than 10 and 5 readings for the computation of day and night means, respectively). Of the 796 participants only 699 had PWV measurements taken using applanation tonometry. A further 489 participants completed echocardadiographic meausrements as explained in section 4.2.6 below. The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (approval number: M17-04-16). This study forms part of the ongoing South African Hypertension and Diet Study (SAHDS) and the study design has been described in brief in publications (Maseko et al., 2018, Maseko et al., 2013) .

4.2.3 *Clinical, demographic and anthropometric measurements*

A standardized questionnaire was administered to obtain demographic and clinical data as described earlier. See section 3.2 of the present thesis for details.

4.2.4 *Conventional blood pressure*

Conventional blood pressure was measured as described in Section 3.2 of this thesis.

4.2.5 *Ambulatory blood pressure monitoring*

Twenty-four-hour ABP monitoring was performed using oscillometric monitors (Spacelabs, model 90207) on the same day as the clinic CBP recordings. Details have been explained in Section 3.2 of the present thesis.

4.2.6 *Pulse wave velocity*

Central BP, PP, aortic PWV and AIc were estimated using techniques previously described by Sibiya et al. (2015). Participants had rested for 15 minutes in the supine position. arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 6.21 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). These measurements were done to determine central pressures and the pressure components. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. The pulse wave was calibrated by manual measurement (auscultation) of BP taken immediately before the recordings. From a validated inbuilt transfer function an aortic waveform was generated from which central systolic, diastolic and mean arterial BP were derived. The magnitude of the forward pressure component (P1) was determined as the difference between the inflection point at the end of the first systolic shoulder and central diastolic BP (i.e. the height of the first systolic shoulder). The magnitude of the augmented pressure (AP) wave was determined as the difference between central systolic BP and the inflection point at the end of the first systolic shoulder. Central PP (PPc) was calculated as the difference between central SBP and central DBP and MAP was calculated as [central diastolic BP + 1/3(central PP)]. Although applanation tonometry at the carotid artery is the most accurate non-invasive assessment of the forward and augmented

pressures, carotid tonometry cannot be reliably applied in obesity (Sibiya et al., 2015). Considering the likelihood of obesity in the study participants, I therefore assessed the pressure components of PPc using radial tonometry. Central AIc was determined as the augmented pressure wave/PP, expressed as a percentage. The reflected wave transit time (RWTT) was determined from the beginning of the incident wave to the end of the first systolic shoulder (i.e., duration of the first systolic shoulder) (Mitchell, 2004) Aortic PWV was measured from sequential waveform measurements at carotid and femoral sites as previously described (Shiburi et al., 2006). The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch. Pulse wave transit time i.e. the time it takes the pulse wave to travel from the carotid to the femoral site, was determined as the difference between the times taken to generate the femoral and carotid pulse waveforms. To assess the differences in time of the generation of the femoral and carotid pulse waveforms, a single lead electrocardiogram was performed concurrently with pulse waveform sampling. Aortic PWV was calculated as distance (meters) divided by transit time (seconds).

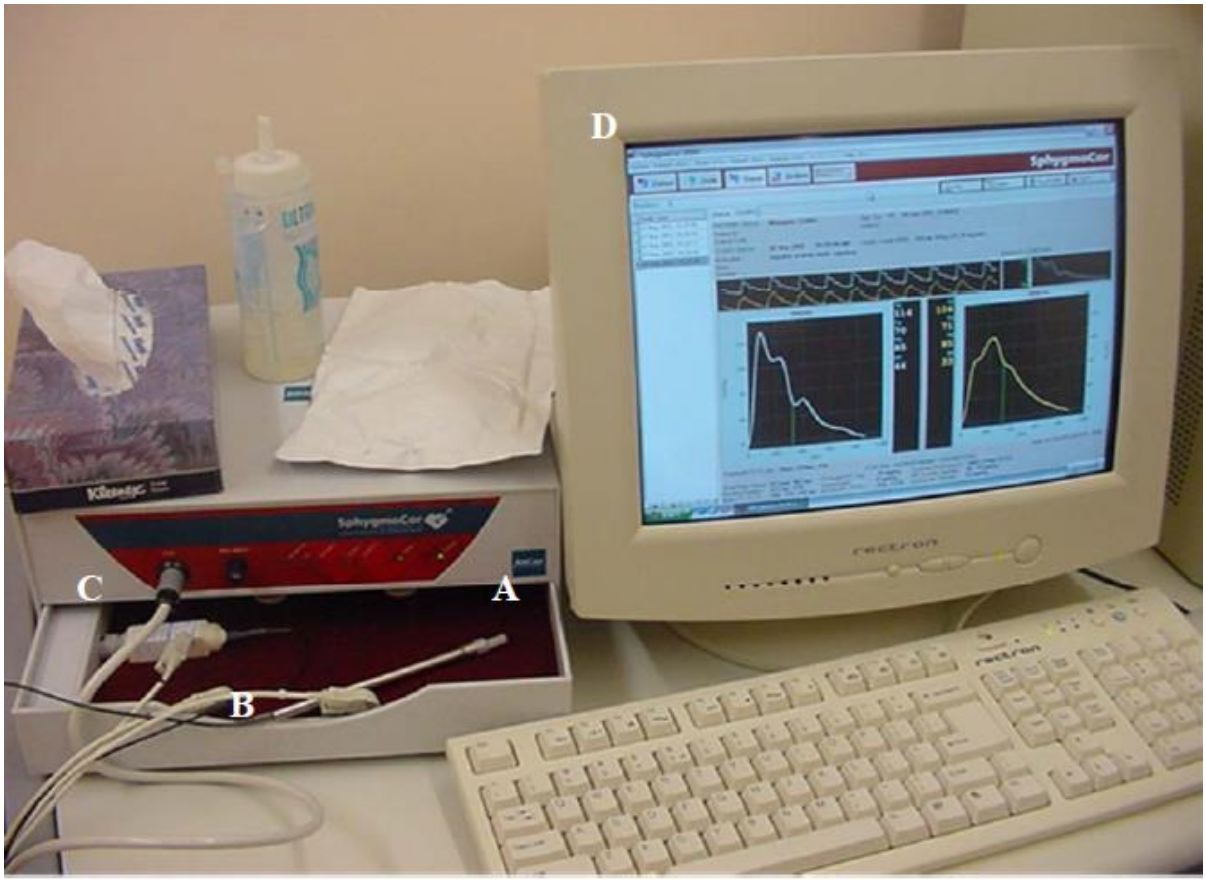

Figure 4.1: SphygmoCor device coupled to an applanation tonometer used to determine central (aortic) haemodynamics and aortic PWV

A: Applanation tonometer.

B: Electrocardiograph electrodes.

C: SphygmoCor device.

D: Image of radial artery and aortic pressure waves recorded from a participant

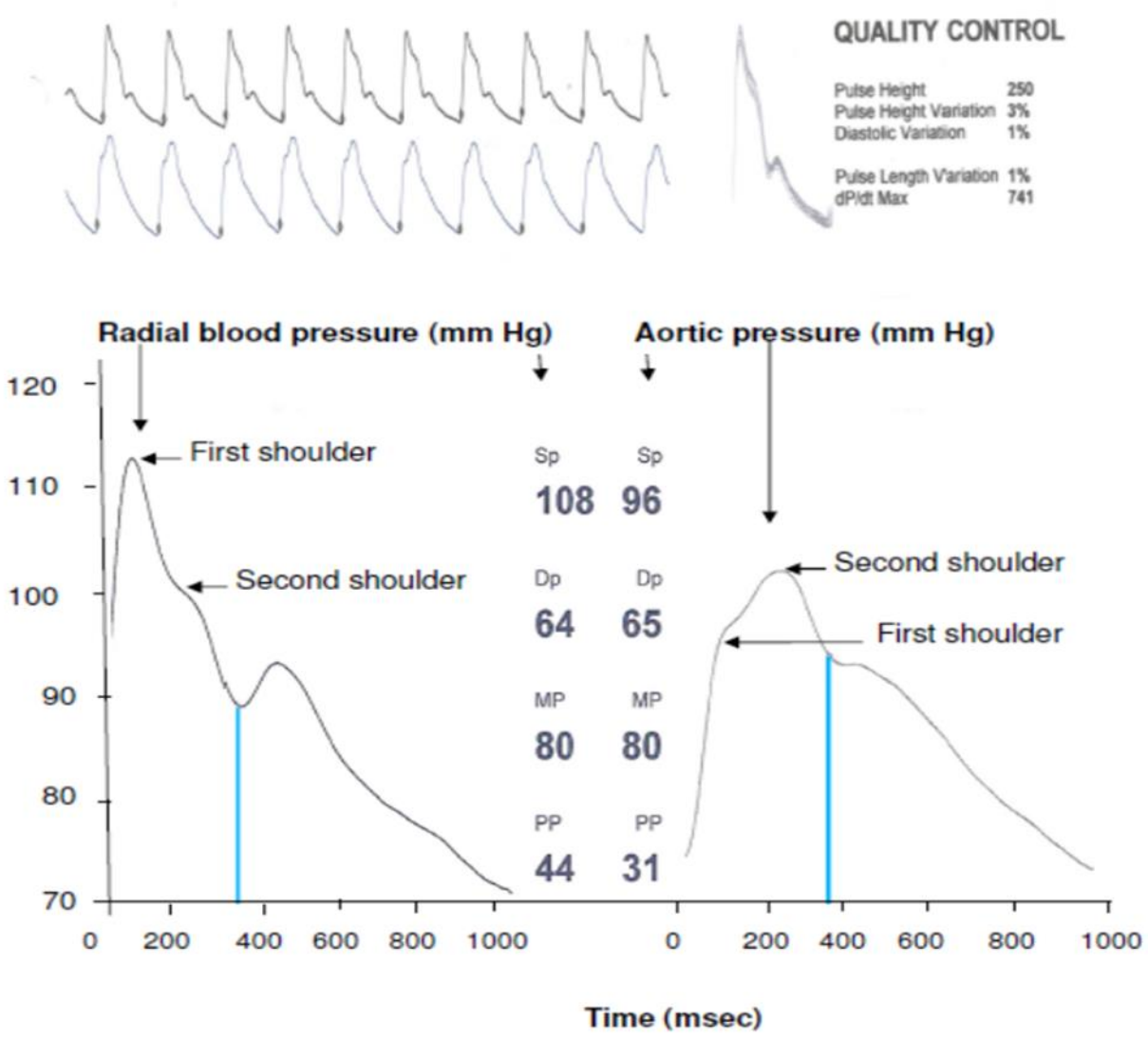

Figure 4.2: Example of a pulse wave recording obtained to determine central haemodynamics. The figure shows the radial artery pulse wave obtained from applanation tonometry (lower left panel) and the aortic pulse wave derived from a population-based transfer function built into the software (lower right panel). The first and second systolic shoulders are identified. See text for a further description. Quality control assessments are shown in the top panel. Sp, systolic blood pressure (BP); Dp, diastolic BP; MP, mean arterial pressure; PP, pulse pressure.

4.2.7 *Echocardiographic measurements*

Left ventricular end diastolic internal diameter and septal (anterior) wall and posterior wall thickness were determined from transthoracic two-dimensional targeted M-mode echocardiographic images obtained in the parasternal long-axis as previously described by Norton et al. (2012). Variables were analysed according to the American Society of Echocardiography convention (Sahn et al., 1978). All measurements were recorded and analysed off-line by experienced study assistants who were unaware of the clinical data of the participants and who had a low degree of inter- and intra-observer variability. Only M-mode images of acceptable quality were analysed (see Figure 4.3). In this regard, acceptable quality was considered to exist when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surface of the septal and posterior wall were clearly visible when imaging at the optimal angle of incidence (perpendicular to the posterior wall) and close to the mitral leaflets. Left ventricular mass (LVM) was determined using a standard formula (Devereux et al., 2004) and indexed (LVMI) to height$^{2.7}$ (LVMI-ht$^{2.7}$) and to body surface area (LVMI-BSA). Left ventricular relative wall thickness (RWT) was defined as (LV anterior + posterior wall thickness at end diastole)/LV end diastolic diameter. LVH was identified as an LVMI-BSA>95 g/m^2 for women and >115 g/m^2 for men. Concentric LV remodelling was identified as a RWT ≥0.42, and eccentric LVH as a RWT<0.42 with an increased LVMI-BSA.

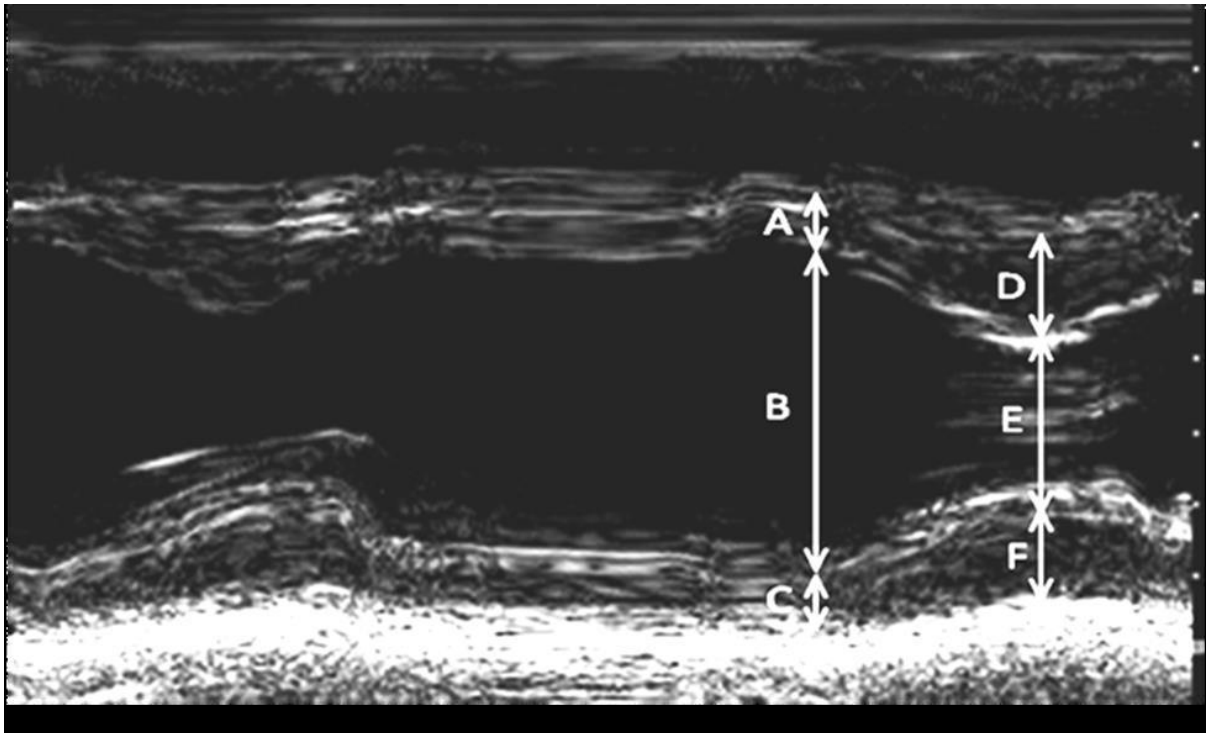

Figure 4.3: Example of an M-mode echocardiographic image obtained in the parasternal long-axis of the heart. M-mode images were used to determine left ventricular end diastolic internal diameter and septal and posterior wall thickness dimensions.

A: Left Ventricular Septal Wall Thickness at End Diastole

B: Left Ventricular End Diastolic Diameter

C: Left Ventricular Posterior Wall Thickness at End Diastole

D: Left Ventricular Septal Wall Thickness at End Systole

E: Left Ventricular End Systolic Diameter

F: Left Ventricular Posterior Wall Thickness at End Systole

4.2.8 *Data analysis*

Database management and statistical analyses were performed with SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA). All statistical calculations [Student-test, ANCOVA, ANOVA, Shapiro-Wilk's statistic, Wilcoxon signed rank test , ROC curve analysis for sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios for positive and negative tests were determined as previously described in Section 3.2. Ambulatory BP data were expressed as average daytime (awake), average night-time (sleep) or average 24 hour systolic and diastolic BP and the the threshold for hypertension diagnosis and classification into MH using ABPM was previously described in section 3.2. Data from individual participants were averaged and expressed as mean±SD.

4.3 Results

Regarding the MH subtypes, 7% had 24-hour MH, 15% had night-time MH and 9% had daytime MH. After correcting for covariates (age, gender, BMI, drinking and smoking), PWV was significantly higher in all the MH subtypes compared to the normotensives; 24-hour MH (p= 0.0029), night-time MH (p=0.0061) daytime MH (p=0.0069). LVM was significantly higher in in all MH subtypes compared to normotensives ; 24-hour MH (p= 0.0003), night-time MH (p<0.0001) daytime MH (p=0.0010).

Table 4.1: Characteristics of the study population

	Total population	Males	Females
Number	796	295	501
Age (years)	43.7±14.9	44.3±19.1	44.1±17.6
BMI (kg/m^2)	29.4±7.7	25.4±4.9	31.8±7.9
Smokers (%)	16	37	5
Alcohol intake (%)	21	38	11
Diabetes (%)	12	13	13
Hypertension (%)	37	25	39
24-H MH (%)	7	7	7
Daytime MH (%)	9	12	8
Night-time MH (%)	15	17	14

%, Percentage; MH, masked hypertension.

Table 4.2: Haemodynamic characteristics of the study participants (mmHg)

	Total Population	24hr masked	Daytime masked	Night time Masked	Normotensives	Hypertensives
Sbp24	118.3 ±14.9	141.0 ± 11.0	136.9 ±11.6	131.7 ±11.5	113.6 ±11.1	132.6 ±16.2
Dbp24	72.6 ±10.2	83.1 ±9.3	80.6 ±9.7	80.2 ±9.1	69.9 ±8.0	80.8 ±11.6
Sbpn	111.3 ±17.2	136.1 ±18.8	126.6 ±20.9	129.7 ±13.8	106.3 ±12.9	126.6 ±19.5
Dbpn	64.9 ±11.7	75.3 ±11.9	70.3 ±12.5	75.3 ±8.5	62.0 ±9.4	73.6 ±13.6
Sbpd	122.5 ±14.7	142.8 ±9.2	142.7 ±7.1	132.8 ±11.8	118.0 ±16.0	135.9 ±15.9
Dbpd	77.6 ±10.4	86.9 ±9.4	86.9 ±9.4	83.3 ±9.2	75.1 ±8.4	85.4 ±11.9
Sbpc	128.3 ±20.9	130.4±7.7††	130.1 ±8.2††	128.0 ±8.6	118.7 ±11.7	157.3 ±15.4
Dbpc	83.7 ±11.8	85.3 ±8.8††	84..8 ±9.8	85.6 ±9.8††	78.9 ±9.3	95.3 ±10.9

†† Denotes high normal blood pressure; mmHg, millimetre mecury; SBP24, 24-hour systolic blood pressure; DBP24, 24-hour diastolic blood pressure; SBPD, daytime systolic blood pressure; DBPD, daytime diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, nigh-time diastolic blood pressure; SBPC, conventional systolic blood pressure; DBPC, conventional diastolic blood pressure. ± Values are expressed in SD.

Table 4.3: Roc association of masked hypertension subtypes versus pulse wave velocity.

	AUC	CI	P value
24-hour MH	0.73±0.05	63-0.83	=0.0029 *
Night-time MH	0.72±0.04	65-77	=0.0061 *
Day-time MH	0.69±0.05	0.60-0.78	=0.0069 *

AUC, area under the curve; CI, confidence interval. 24h-MH, 24-hour masked hypertension; N-MH, night-time masked hypertension; D-MH, daytime masked hypertension. *p<0.05.

Table 4.4: Roc association of masked hypertension versus left ventricular mass.

	AUC	CI	P value
24-hour MH	0.66±0.04	0.59-0.79	=0.0003 *
Night-time MH	0.71±0.03	0.65-0.77	<0.0001 **
Day-time MH	0.70±0.04	0.61-0.78	=0.0010 *

AUC, area under the curve; CI, confidence interval. 24h-MH, 24-hour masked hypertension; N-MH, night-time masked hypertension; D-MH, daytime masked hypertension. **p<0.0001; *p<0.05.

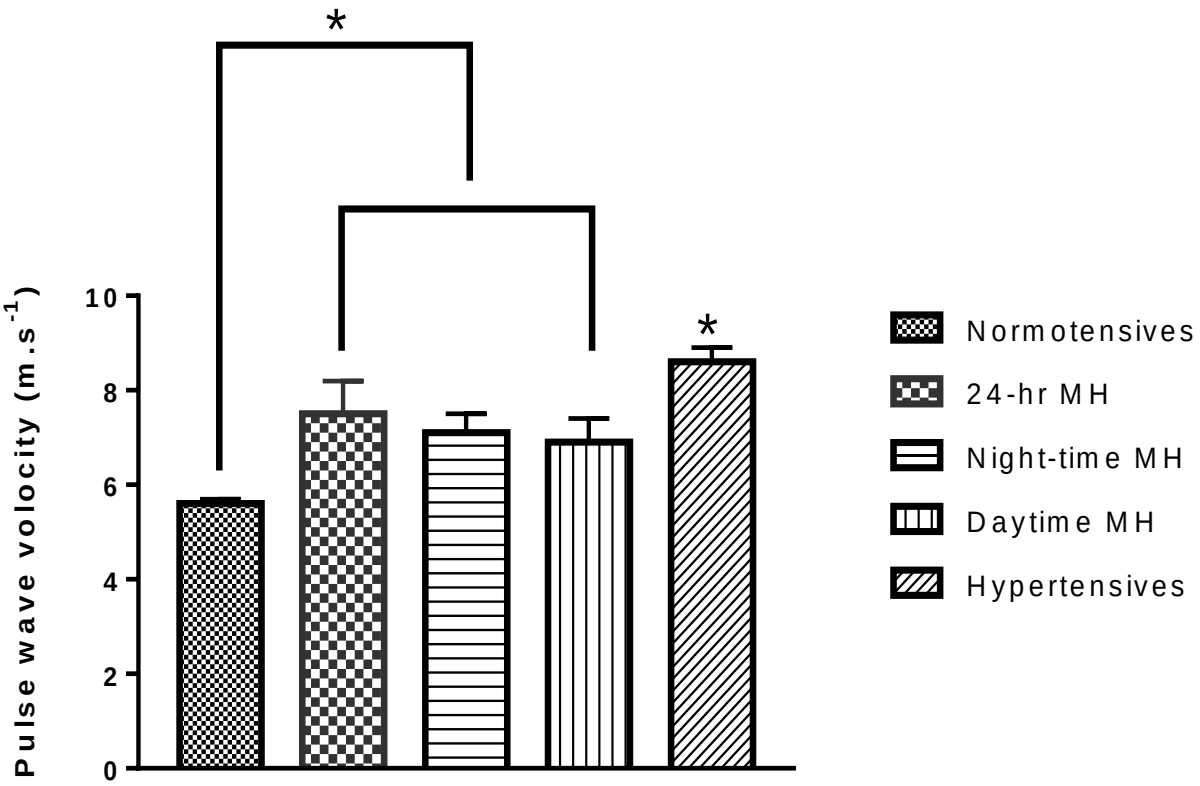

Figure 4.4: Pulse Wave Velocity versus masked hypertension.

*p<0.05. *Adjusted for age, BMI, the presence of diabetes mellitus or an HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake and CBP. In the general population, PWV was significantly higher in all the MH subtypes compared to the normotensives; 24-hour MH (p= 0.0029), night-time MH (p=0.0061) daytime MH (p=0.0069).

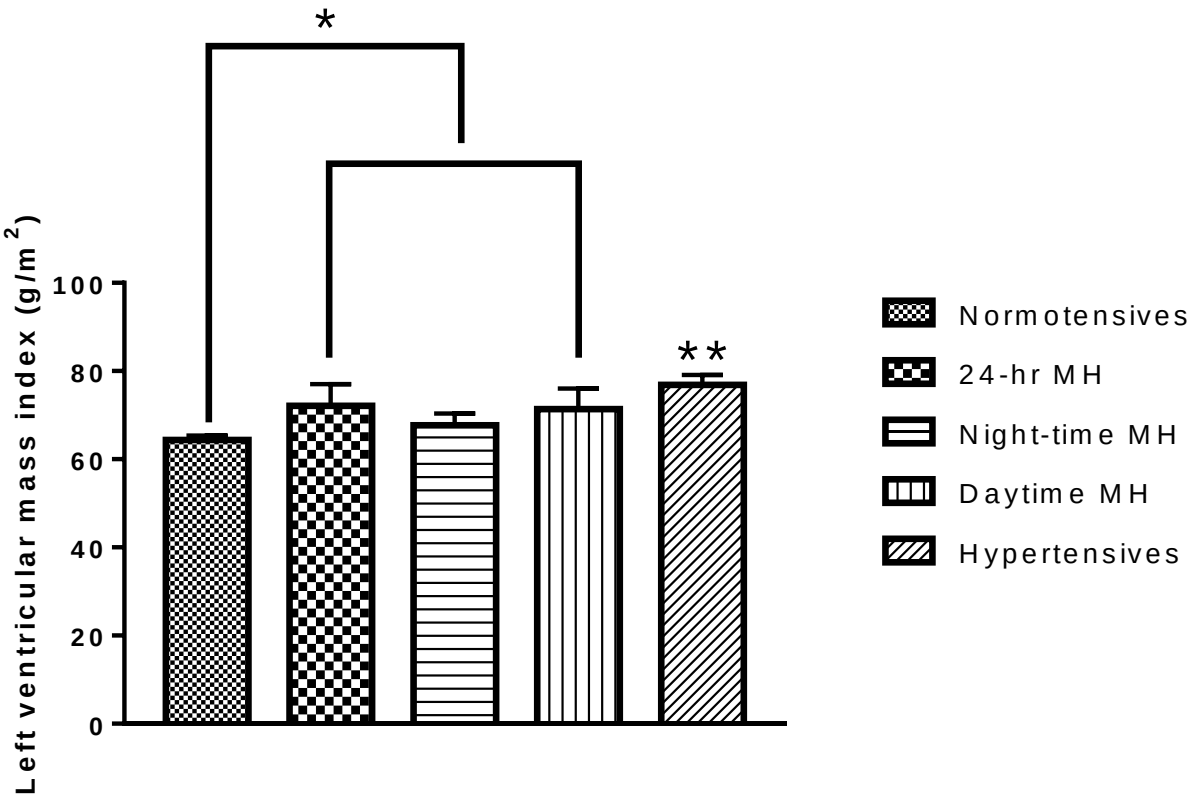

Figure 4.5: Left ventricular mass versus masked hypertension

**p<0.0001; *p<0.05. Adjusted for age, BMI, the presence of diabetes mellitus or an HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake and CBP. After correcting for covarieties LVM was significantly higher in in all MH subtypes compared to normotensives ; 24-hour MH (p= 0.0003), night-time MH (p<0.0001) daytime MH (p=0.0010).

4.4 Discussion

Masked hypertension is seen as a transition phase from normotension to sustained HT arising from high-normal BP (Franklin et al., 2016). The WHO and ISH have rendered the classification of normotensive individuals with a SBP of 130 to 139 mm Hg and a DBP of 85 to 89 mm Hg as having high-normal BP based on CBPM (Organization and Group, 2003, WHO-ISH, 1999). Although information relating to the exact and comparative degree of CVD risk in individuals with high-normal BP levels is scarce, literature suggests that even the slightest increase in BP formerly thought to be normal may increase the risk of untimely CVD mortality and morbidity (Vasan et al., 2001). In addition, literature indicates that there is a twofold more probability that individuals with high-normal BP progress to HT at a faster and greater rate than those with sternly normotensive BP status, which in turn inclines their rank to a higher CVD risk category (Kokubo et al., 2008).

This idea should be concerning given that in this study, participants in both 24-hr and daytime MH subtypes fell within the category of high-normal clinic SBP levels as compared to true normotensive. The sustained hypertensive group had elevated SBP based on CBP measurements. The night-time MH group were slightly below the category of high-normal BP, however, the cardiovascular risk in these patients still persist as they fall within another category labelled “prehypertension” (PHT). The Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) describes the category of PHT as patients with CBP measurements of 120 to 139 mm Hg SBP or 80 to 90 mm Hg DBP. Liszka et al. (2005) and Qureshi et al. (2005) indicated that PHT is associated with increased risk of major cardiovascular events independently of other cardiovascular risk factors. In addition to the CBP measurements, the average SBP (ABPM) levels in the subtypes of MH were 141.0 mm Hg ± 11.0 for 24-h MH, 136.9 mm Hg ±11.6 for daytime MH, and 131.7 mm Hg ±11.5 for Night-time MH as compared to an average SBP of 113.6 mm Hg ±11.1 for the

normotensive group. This observation is in line with previous reports (Franklin et al., 2016, O'brien et al., 2013a). The importance of these findings should be acknowledged with the urgency of the accompanying consequences. Indeed, it is reported that a 10 mm Hg increase in ABPM, is significantly associated with increased risk for strokes and cardiovascular events with hazard ratios ranging from 1.11 to 1.42 (Siu, 2015, Ohkubo et al., 2005). Although these increases in ABP may appear to be modest, if coupled with additive effects of other risk factors for CVDs, the cardiovascular outcome may be more damaging (de la Sierra et al., 2012, Mancia et al., 2006).

The phenomenon of high-normal BP appears to be characterised by SNS activation. This disturbance in the neurogenic balance where there is a sympathetic dominance appears to be elicited by metabolic changes, coupled with reflex alterations, and other factors. In time, these interaction progresses the condition to HT (Seravalle et al., 2015, Grassi and Ram, 2016). Although there is no clear-cut evidence, studies have suggested that SNS may play a role in the pathogenesis of MH as it appears that MH occurs in patients with a stressful lifestyle (Kawano et al., 2008). Landsbergis et al. (2013) indicated that BP may not be elevated during clinical measurements, however, if the individual is subjected to stress at home or at work, the BP may be elevated during the stressful circumstances, and thus can only be manifested by ABPM. Indeed, the population group of the current study has previously been reported to have stressful lifestyle (Reimann et al., 2013, Mashele et al., 2010), and stress has certainly been shown to have a positive association with an increase in BP (Birditt et al., 2015, Carroll et al., 2011). In the same population group of blacks of African descent, (Malan et al., 2014) indicated the occurrence of sympathetic disturbance suggestive of sympathetic activity modulation, augmented vascular α-adrenergic response, and a diminished ß-adrenergic responsiveness demonstrated by ABPM. Although I did not measure sympathetic activity, findings of the

current study are suggestive of sympathetic disturbances in all three subgroups of MH as proposed in the development of MH in other studies.

Furthermore, previous studies have shown that MH is associated with subclinical TOD even without progressing to sustained HT (Stergiou et al., 2014, Drawz et al., 2016), which indicates that a high-normal CBP correspondent to MH may be associated with TOD. In addition, it has been suggested that patients with MH possess similar CVD risk such as LVMI, arterial stiffness, and renal dysfunction as observed in those who have sustained HT (Ware et al., 2016, Thompson et al., 2016).

In my study population, PWV, a surrogate marker used to assess the stiffness of arteries was significantly higher in all MH subtypes as compared to normotensives, but slightly lower in MH as compared to sustained HT; 24-hour MH ($p= 0.0029$), night-time MH ($p=0.0061$) daytime MH ($p=0.0069$). These data further support the view that MH is a precursor for sustained HT and that MH progresses to sustained HT overtime and that during this transition phase, MH parallels to a high-normal CBP. The increase in PWV in MH as compared to normotensives may suggest baroreceptor dysfunction which is associated with BP variability in the early pathogenesis of MH, this may be particularly true since arterial stiffness is characteristic of baroreceptor dysfunction and an increased volume sensitivity (Mitchell, 2014, Gupta et al., 2016).

In addition, baroreceptor reflex dysfunction has a modifying influence on sympathetic activity and cardiovascular homeostasis, thus affecting the arteriolar tone (Kawano et al., 2008). Also, on large arteries, vessel stiffness may be accompanied with reduced cardiovagal baroreceptor reflex sensitivity, with a resultant increase in BP variability characteristic of HT (Lee and Oh, 2010). Studies have long proposed that arterial stiffness is a result of sustained HT (Safar and London, 2000). However, recent literature suggests that the contrary is also true whereby arterial stiffness mainly due to ageing contributes to the pathogenesis and progression

of HT (Franklin, 2005). With ageing, there is structural remodelling of the arteries that result in thickening of the elastic arteries and a decrease in elastic properties leading to arterial stiffening thus increases PWV (Pierce et al., 2016). Since it is reported that sustained HT poses a similar cardiovascular risk as MH, it is possible that the mechanism of arterial stiffening leading to sustained HT could be similar in the development of MH. Although not elucidated, there could be an intricate interaction between arterial stiffness and MH as marked in sustained HT. However, differing from sustained HT, findings of this study showed that all subtypes of MH have no relationship with advancement in age in a South African population of African ancestry, a finding consistent with previous reports in other population groups (Barton et al., 2012, Lee and Oh, 2010). Studies have previously indicated that arterial stiffening is accompanied with aging, but findings of this study shows that arterial stiffness as assessed by PWV is present individuals who have MH irrespective of the subtype of MH. This indicates that other mechanisms excluding the natural biological aging attenuates structural compliance of arteries in younger individuals with MH.

This is the first study to investigate the occurrence of MH and its subtypes in this population. Although I did not compare the incidence of MH between males and females of the present study, however, previous studies have indicated that MH is predominant in the male gender and young age as compared to females (Hänninen et al., 2013). Therefore, an inference can be drawn from previous studies regarding the heightened occurrence of MH in males as compared to females (Hänninen et al., 2013, Ben-Dov et al., 2005). Literature has long indicated that BP is generally higher in men than in premenopausal woman of the same age (Barton et al., 2012). These differences in BP levels between age-matched men and woman is accounted for by sex hormones, primarily oestrogen and testosterone where the absence of oestrogen in males or after menopause in females is independently associated with an increase in BP (Barton et al., 2012). In addition, the increase in ABP in males indicate a hyperactive

sympathetic activity due to daily stresses as compared to their female counterparts, and stress has been implicated in vascular stiffening (Lee and Oh, 2010). I posit that other factors, which have been previously identified such as smoking and alcohol consumption (Ben-Dov et al., 2005), may be involved in arterial stiffening in the subgroups of MH. Previous data in this population group showed that young males tended to smoke and had increased alcohol consumption (Woodiwiss et al., 2011). These findings could potentially explain the increased incidence of MH in the younger males since smoking is known to cause arterial stiffness (Verberk et al., 2008) and thus potentially affect the arteriolar compliance overtime (Husain et al., 2014, Verberk et al., 2008). Certainly, the loss of arterial compliance and elasticity leads to an increased force of contraction of the heart muscles which in turn causes LVH. Indeed, arterial stiffening causes an increased load on the left ventricle by elevating pressure pulsitility, thereby increasing the early systolic load. In addition, the stiffening results in an early return of the reflected wave thus increasing late systolic load (Mitchell, 2014). The resultant adjustment in left ventricular loading and loading sequence contributes to systolic and diastolic dysfunction and consequently cause left ventricular structural remodelling. This mechanism has long been proposed for sustained HT; however, it is unclear if MH employs a similar mechanism in LVM remodelling.

Findings of the current study show that all subtypes of MH had a significantly higher LVMI as compared to normotensives. However, all the subtypes of MH had a slightly lower LVMI when compared to sustained HT. The findings of this study indicate that the LVMI of MH subtypes is intermediate between the normotensives and the sustained HT, and it progressively increases from normotensive to MH and to sustained HT. These findings further support the view that MH is a transition state between normotension and sustained HT. Indeed Tadic et al. (2016) indicated that the impairment of cardiac function as seen in LVH in MH is lower than that observed in sustained HT. The reason for the greatly increased LVM in

sustained HT is because of the heightened afterload observed in untreated HT patients. Nonetheless, the increased LVM in MH as compared to normotensives is supported by the view that ABP elevation is induced by sympathetic activity due to stresses during the day, and exaggerated increase in BP due to activity or exercise (Cuspidi et al., 2015, Tadic et al., 2017).

In addition, findings of this study showed a significant and direct association between SBP and LVMI in both night-time and sustained HT. The modulated cardiac mass in the nightime MH group suggests that there is sympathetic NS activation in this group that increases BP during the night. Also, because baroreflex sensitivity has been implicated in ANS imbalance, an impaired baroreflex mechanism may increase volume sensitivity thus increasing pressure overload in individuals with night-time MH thus affecting left ventricular function leading to an increase in LVM (Indumathy et al., 2015, Grassi et al., 2014)

Lastly these data show that MH and sustained HT are associated with TOD and both carry CVD risk as previous studies have reported (Takeno et al., 2012, Kotsis et al., 2008). Nonetheless, as to whether the cardiovascular risks in MH and sustained HT are similar remains controversial since other studies have reported a higher LVMI in MH than in sustained HT (Algamal, 2016). In addition, the discrepancies in the relationship between the subtypes of MH and LVMI suggest that a more complex relationship between MH and LVMI exist and that further investigation is required.

The notable findings of this study are that MH falls within the category of normotension based on CBP monitoring, and that MH carries a significantly increased risk for cardiovascular TOD. The data indicates that patients with MH tend to have a high-normal BP on CBP monitoring which should serve as a red flag for suspicion of the presence of MH even when ABPM is not used. Current guidelines for the management and treatment of high BP do not consider MH as a clinical entity in which pharmacological intervention is required. Therefore, in instances where patients may present with high-normal BP, the health care practitioners

should consider using ABPM. Since MH appears to be a transition state between normotension and sustained HT, ABPM appears to be a valuable tool for identifying these patients to protect them against potential progression to sustained HT, and protect them against progression of TOD.

CHAPTER FIVE

The Association Between Night-time Masked Hypertension and Renal Dysfunction

Abstract

Hypertension has previously been shown to relate to urinary Na^+ excretion and TOD including renal dysfunction and this association has been shown to be strong in people of African Descent. Microalbuminuria is regarded as the initial sign of renal dysfunction. It is not known if all sub-types of MH are associated with renal dysfunction as assessed through microalbuminuria. It is also not clear if any subtype of MH is associated with urinary Na^+ excretion as an index of Na^+ intake. Therefore, in the present study, the aim was to assess if microalbuminuria is associated with any sub-type of MH and to investigate if any subtype of MH has any relationship with Na^+ intake in a semi-urban population of African descent. Four hundred and ninety-nine (499) South Africans of African descent were randomly recruited for the measurement of CBP, ABPM, urine electrolytes and hormonal assessment. Target organ effects of MH were determined from urinary microalbumin-to-creatinine ratios (ACR). Microalbuminuria was significantly high in night-time MH group (3.6±2.1 mg/mmol), when compared to the other subtypes of MH i.e. 24-hr MH (1.4± 0.4 mg/mmol), 24-hr MH (0.9±0.3 mg/mmol). For the true normotensive and sustained hypertensive groups, microalbuminuria was (1.1±0.3 mg/mmol), and (1.6 ±0.3 mg/mmol) respectively. Night-time MH is more closely associated with renal dysfunction as assessed through microalbuminuria than any other sub-type of MH, normotension and sustained HT. There was no association between Na^+ intake and any subtype of MH. The relationship between Na^+ intake and ABP in the 24hr masked hypertension sub-type was SBP (p= 0.8018), SBP (p= 0.2754) for daytime MH, and the relationship was SBP (p= 0.6915) for the night-time MH.

5.1 Introduction

Hypertension has previously been shown to closely relate to TOD including renal dysfunction (Bidani and Griffin, 2004), and this association has been shown to be strong in people of African Descent (Klag et al., 1997, Pogue et al., 2009). Hypertension is a predisposing cause for renal dysfunction (Tozawa et al., 2003), and almost 80% of individuals with chronic kidney disease (CKD) have HT (Klag et al., 997). Essentially, in conditions such as CKD and in HT, there are structural changes in the kidneys that result in physiological alterations of renal function (Webster et al., 2017, Heron et al., 2016). The initial sign of renal dysfunction that may be due to HT is the presence of the protein albumin in urine. Albumin is the most abundant serum protein and it makes up approximately 60% of serum proteins. Normally, functional kidneys reabsorb almost all the filtered albumin in the proximal convoluted tubule of the kidneys. However, very small amounts of albumin can be present in the urine (Sugahara et al., 2017).

Detection of levels of albumin excretion at a rate of 20-30mg/min in the urine indicates looming renal dysfunction (Mennuni et al., 2014), a condition termed microalbuminuria. The levels of microalbuminuria can be expressed in two different ways, i.e. as a concentration or as a ratio of albumin-to-creatinine. The detection of microalbuminuria serves as an important tool since it can predict cardiovascular complications and renal dysfunction associated with HT (Abdelhafiz et al., 2011). In recent decades, there has been divisions in the classification of HT, and the unearthing of MH has exhumed numerous concerns about its role in CVDs and renal dysfunction. It has also been suggested that MH relates with many adverse effects in view of TOD (Tientcheu et al., 2015). A few studies counting Hata et al. (2017), Agarwal (2016), and Leitão et al. (2007) have suggested that MH is associated with microalbuminuria. However, it is not known whether all sub-types of MH are associated with renal dysfunction as assessed through microalbuminuria, an early sign of renal dysfunction.

Increased Na^+ intake has previously been shown to be associated with an elevated blood pressure (BP) (Rhee et al., 2014). Numerous reports have indicated that salt-dependant HT is more common and carries more clinical consequences in people of African lineage as compared to other races (Agyemang and Bhopal, 2002). This is alarming given that other reports indicate that Africans have a tendency to develop HT at an early age when compared to Caucasian counterparts (Jones and Hall, 2006). Even though there is extensive data that persuasively reveals that Na^+ intake is associated with HT or an elevated BP, there is still some criticism to this association. The relationship between HT and Na^+ intake remains controversial in that it is poorly understood and studies have yielded different findings on this association (Drenjančević-Perić et al., 2011).

The unearthing of masked hypertension (MH) has undoubtedly added some complexities in the general understanding of HT and its causes. There is a lack of literature regarding the relationship between Na^+ intake and MH. Essentially, a question of debate is that; does excessive Na^+ intake play a role in the pathogenesis of MH? To my knowledge, there is only a single study by Stolarz-Skrzypek et al. (2018) in Poland, which has attempted to answer this question in healthy individuals. In their study, Stolarz-Skrzypek et al. (2018) indicated that increased Na^+ intake was associated with MH; however, their definition of MH was restricted to 24-hr MH and their study participants were exclusively Caucasian. Another study by Uzu et al. (2012) also investigated the association between high Na^+ intake and the incidence of MH. However, the drawback of the study by Uzu et al. (2012) is that they investigated the association between Na^+ and MH in a Japanese population with type 2 diabetes and treated hypertension. Despite the knowledge that people of African ancestry are more susceptible to Na^+ dependant HT, there is no report in any African population that has investigated the relationship between Na^+ intake and MH. Nevertheless, studies that advocate for a reduction in Na^+ consumption have indicated that reducing Na^+ intake will reduce BP in hypertensives

and thus reducing the overall incidence of CVDs (O'Shaughnessy, 2006). However, it is uncertain if this approach is applicable to individuals with MH.

Even though there are gripping global results regarding the relationship between Na^+ intake and HT, previous studies conducted in this population of African descent have revealed inconsistent findings on this relationship with one study revealing a modest relationship (Michel et al., 2014), while others displayed no relationship (Millen et al., 2013, Scott et al., 2011). The contradictory findings of these studies are symbolic of the multifarious and complex nature of the relationship between HT and Na^+ intake. These previous findings reported in this population of African descent were conducted using CBP measurements. Therefore, it is also not clear if any subtype of MH is associated with urinary Na^+ excretion as an index of Na^+ intake. In the present study, the aim was to assess if microalbuminuria is associated with any sub-type of MH and to investigate if any subtype of MH has any relationship with Na^+ intake in a population of African descent.

5.2 Methodology

5.2.1 Study group

Details of the recruitment of the participants that made up the study group have been described in section 3.2 of the present thesis. The present study was conducted in 499 participants.

5.2.2 Clinical, demographic and anthropometric measurements

A standardized questionnaire was administered to obtain demographic and clinical data as described earlier. See section 3.2 of the present thesis for details.

5.2.3 Conventional blood pressure

The participants'sitting CBP was measured as described in section 3.2 of the present thesis.

5.2.4 Ambulatory blood pressure monitoring

Twenty-four hour ambulatory BP monitoring was performed on the same day as CBP measurements using ABPM (SpaceLabs, model 90207) as described in section 3.2 of the present thesis. The identification of day and night periods were similarly described in section 3.2 of the present thesis.

5.2.5 Determination of urinary electrolyte excretion rates

Timed urine samples were obtained over at least a 24-hour period after discarding urine obtained immediately prior to the collection period. Urine Na^+, K^+, mg^{2+} and creatinine concentrations were measured by the South African National Health Laboratory Services (NHLS) accredited for these measurements. Twenty-four hour urine Na^+ excretion rates were calculated from the product of urine volume and urine electrolyte concentration. Creatinine clearance was determined from the product of urine volume and urine creatinine concentrations/plasma creatinine concentration. The quality of urine samples was determined by constructing regression relations between 24-hour urine creatinine and body weight and 24-hour urine volume and age in gender-specific groups. Based upon the 95% confidence intervals for each group, a 24-hour urine sample was considered acceptable if 24-hour urine creatinine (mmol) was >3.5 and <35 for males and >3.5 and <30 for females. Samples with urine volumes <300 mls/day were also assumed to be incomplete urine collections. These approaches are standard approaches and have been published on numerous occasions by other groups (Kuznetsova et al., 2004).

5.2.6 Determination of microalbuminuria

Urinary microalbumin and creatinine concentrations were determined from spot urine samples and expressed as the ratio between urinary micro-albumin and creatinine concentrations (ACR). Microalbumin concentrations in the urine were determined using an immuno-turbidimetric assay (Roche Tina-quant albumin assay; Roche Diagnostics GmbH, Mannheim, Germany) (measurement range of 3–400 mg/l or 0.046–6.08 μmol/l). The quality of urine samples was determined as previously described in section 5.2.1. Microalbuminuria was defined according to a new definition (a low level of albuminuria which does not include the threshold level of the conventional definition): when ACR in males was from 1.2 to 2.5 mg/mmol or 1.7 to 3.5 mg/mmol in females as opposed to the conventional definition: when the ACR was > 2.5 mg/mmol and ≤ 25 mg/mmol in males or > 3.5 mg/mmol and ≤ 25 mg/mmol in females (Alharf et al., 2016).

5.2.7 Blood collection and determination of

Blood samples were obtained in the supine position after 10 minutes of rest in the morning between 10:00 and 12:00 hours on the day of the clinic visit. After centrifugation, plasma samples were stored at -70°C until the time of analysis. Samples were analysed by the South African NHLS for full blood count and differential count, to measure urea, creatinine and serum electrolyte concentrations, as well as hormones renin and aldosterone concentrations. Blood glucose measurement were determined as the percentage of glycated hemoglobin (HbA1c) . The presence of Diabetes mellitus (DM) or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA1c value greater than 6.1%.

5.2.8 Data analysis

All statistical calculations were performed using SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA) as described in section 3.2. Ambulatory BP data were expressed as average daytime (awake), average night-time (sleep) or average 24 hour systolic and diastolic BP and the the threshold for hypertension diagnosis and classification into MH using ABPM was previously described in section 3.2. Data from individual participants were averaged and expressed as mean±SD.

5.3 Results

Table 5.1 gives a description of the general and anthropometric characteristics of the study population. The characteristics include age, BMI, alcohol consumption, smoking, and diabetes status. Table 5.2 gives the haemodynamic characteristics of the study population. Table 5.3 depicts the hormonal and electrolytes levels in the different sub-types of masked hypertension as well as the normotensives and sustained hypertension as well as serum and urinary electrolyte values. Table 5.4 indicates the odds ratio of developing microalbuminuria in the different subtypes of MH. The results indicate that night-time MH group had the likelihood of having microalbuminuria. On a stepwise regression analysis, data revealed that there was no association between ABP and Na^+ excretion as an index of Na^+ intake. All different sub-types of MH yielded no significant association between Na^+ intake and ABP. The relationship between Na^+ intake and ABP in the 24hr MH sub-type SBP (p= 0.8018), In the daytime MH sup-type, SBP (p= 0.2754), In the night-time MH the relationship was SBP (p= 0.6915). Nigh-time MH was the most common sub-type of MH. Microalbuminuria was significantly high in night-time MH group (3.6±2.1 mg/mmol), as compared to the subtypes of MH i.e. 24-hr MH (1.4± 0.4 mg/mmol), 24-hr MH (0.9±0.3 mg/mmol). For the true normotensive and sustained Hypertensive groups, microalbuminuria was (1.1±0.3 mg/mmol), and (1.6 ±0.3 mg/mmol)

respectively. Night-time MH is more closely associated with renal dysfunction as assessed through microalbuminuria than any other sub-type of MH, normotension and sustained HT.

Table 5.1: General characteristics of the study population

	Total population	Male	Female
Number	499	182	317
Age (years)	45.8±18.5	46.6±19.6	45.4±17.8
BMI (kg/m^2)	29.4±7.7	25.1±4.9	31.8±7.9
Smoking (%)	15	34	4
Alcohol (%)	21	42	12
Diabetes (%)	9	10	8
Hypertension (%)	31	25	34

BMI, body mass index. %, percentage.

Table 5.2: Haemodynamic characteristics of the study population in mmHg.

	Total Population	24hr masked	Daytime masked	Night time Masked	Normotensives	Hypertensives
Sbp24	1187.5 ±13.8	141.9 ± 10.9	137.2 ±10.9	132.1 ±10.7	113.2 ±9.7	131.8 ±16.6
Dbp24	73.4 ±9.8	82.4 ±9.5	81.2 ±9.9	81.1 ±6.1	69.7 ±9.1	83.1 ±12.4
Sbpn	113.4 ±17.4	138.4 ±17.6	126.9 ±21.2	129.9 ±12.7	105.8 ±10.8	128.4 ±18.8
Dbpn	65.1 ±10.9	77.5 ±11.3	71.1 ±10.5	75.9 ±7.9	62.4 ±8.9	75.3 ±11.3
Sbpd	123.5 ±13.9	143.0 ±9.4	143.4 ±7.6	133.1 ±12.4	118.5 ±15.9	135.6 ±13.8
Dbpd	75.9 ±10.2	87.3 ±8.9	87.1 ±9.1	84.1 ±9.3	75.8 ±7.9	85.1 ±10.4
Sbpc	127.7 ±21.4	131.2±7.5	131.3 ±7.4	127.9 ±6.6	119.1 ±10.2	155.8 ±13.9
Dbpc	82.9 ±12.1	84.9 ±8.2	85..2 ±7.8	84.1 ±8.8	79.6 ±8.1	95.1 ±11.3

mmHg, millimetre mercury; SBP24, 24-hour systolic blood pressure; DBP24, 24-hour diastolic blood pressure; SBPD, daytime systolic blood pressure; DBPD, daytime diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, nigh-time diastolic blood pressure; SBPC, conventional systolic blood pressure; DBPC, conventional diastolic blood pressure. Values are expressed in means ± SD.

Table: 5.3 hormone and electrolyte levels of the different sub-types of masked hypertension as well as the normotensives and sustained hypertension

	Total population	24hr masked	Daytime masked	Night time Masked	Normotensives	Hypertensives
Renin (pg/ml)	36.6 ±73.7	34.3 ±52.2	38.1±55.1	33.6 ±48.6	39.5±80.8	27.2±47.0
Aldost (ng/dl)	200.7±167.4	187.8±13.9	203.9±144.5	194.9±154.6	195.9±166.0	214.5±171.3
ARR (ng/dl/ng/l)	27.4 ±53.1	41.2±42.3	31.3±35.1	28.6±41.6	21.5±32.9	44.5±86.4
Agt (µg/ml)	29.2 ±11.8	27.8±8.3	28.3±7.2	27.2±8.9	28.9±12.2	30.1±10.8
SNA (mmol/l)	137.4±2.6	138.9±2.9	138.4±2.6	137.8±2.7	137.4±2.6	137.6±2.7
Smg (mmol/l)	0.84±0.09	0.85±0.08	0.86±0.09	0.85±0.10	0.84±0.10	0.83±0.09
K^+ (mmol/l)	28.46±24.0	26.04±23.5	27.2±27.0	26.5±19.8	29.7±23.5	25.0±15.6
Mg (mmol/l)	2.27±1.93	2.56±3.16	2.4±3.7	2.26±2.19	2.39±2.09	1.92±1.33
Na^+ (mmol/l)	105.6±78.4	102.2±85.1	85.0±85.3	113.5±105.8	108.8±83.8	96.5±60.1
Nak	4.38±3.19	4.49±2.58	3.6±1.7	4.7±3.2	4.4±3.5	4.4±2.1

Aldost, aldosterone; ARR, aldosterone-to-renin ratio; Agt, angiotensin. SNA, serum sodium; smg, serum magnesium; K^+, potassium; mg, urinary magnesium; Na^+, urine sodium; Nak, urinary sodium-to-potassium ratio.

Table 5.4: Odds ratio of developing microalbuminuria daytime, night-time and 24-hour masked hypertensives.

	Odds ratio	CI	P value
24-hr MH	1.006	0.937 – 1.079	0.8787
Night-time MH	1.264	1.062 – 1.505	0.0084*
Daytime MH	0.990	0.880 – 1.112	0.8451

MH, masked hypertension; CI, confidence intervals. *p<0.05.

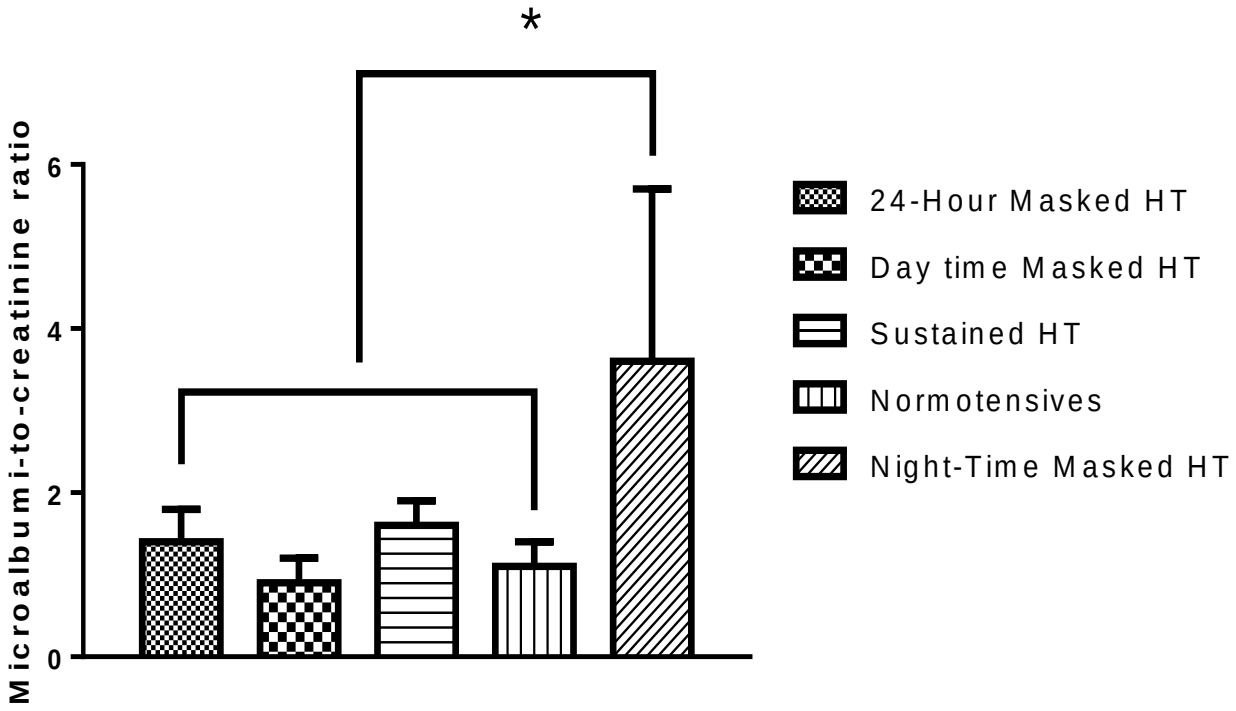

Figure 5.1: Values of microalbumin to creatinine ratio in the different of masked hypertension, normotensives and sustained hypertensives. Bars represent mean standard deviations. *p<0.05. HT, hypertension.

5.4 Discussion

The primary finding of the present study is that night-time MH is the most prevalent form of MH. These findings are not unique to this population in that Booth et al. (2016) also reported that night-time MH was the commonest form of MH in a population of African Americans of the JHS. The findings of the present study indicate that night-time MH is more closely associated with renal dysfunction as assessed through microalbuminuria than any other sub-type of MH, normotension and sustained HT.

Previous studies have proposed that MH is associated microalbuminuria (Hata et al., 2017, Agarwal, 2016). However, to my knowledge, studies that have investigated the relationship between MH and microalbuminuria did not categorise MH into its sub-types and this is the first study to investigate the association between the sub-types of MH and microalbuminuria in a black population of African Descent. Indeed, Hata et al. (2017) indicated that MH was associated with microalbuminuria. However, differing from the present study, their study (Hata et al., 2017) was conducted in general population of exclusively Japanese participants and only daytime MH was considered.

Tillin et al. (2005) indicated that the prevalence of microalbuminuria varies according to ethnicity; therefore, the findings of the previous study may not be relatable to the present study. In a different report, Agarwal (2016) also indicated that MH was associated with microalbuminuria; however, this study was conducted in a mixed population of individuals with CKD and masked uncontrolled HT (MUCH). The definition of MUCH states that these patients have a pharmacological control of clinic BP (<140/90 mmHg on average of three clinic visits by CBP measurement) but elevated ABPM. As indicated earlier, in the present study, the definition of MH was restricted to untreated patients with normal CBP but elevated out-of-office ABP.

Lurbe et al. (2002) indicated that ABPM was superior to CBP in forecasting development of microalbuminuria over time although their study was conducted in patients with DM. The findings of the current study also indicate that ABPM is superior in forecasting microalbuminuria even in healthy individuals. In addition, current guidelines for the detection, prevention, and treatment of HT and CKD, have factored in microalbuminuria as a determinant of CVD and renal risk (Williams et al., 2018). In a previous report, Oliveras et al. (2011) indicated that an elevated night-time BP is associated with microalbuminuria. However, this association was reported on patients with resistant HT. There has been a consideration on the impact of elevated night-time BP in relation to normal day CBP levels with regard to cardiovascular and renal risks (Velasquez et al., 2016, Drawz et al., 2016). It appears that categorising MH patients according to their dipping BP status offers more information on their renal and cardiovascular risk (Gijón-Conde et al., 2017). Certainly, night-time hypertension is said to occur in a number of conditions that elicit a non-dipping BP status including renal dysfunction (Kario, 2018). It was previously indicated by Kimura (2008) that the kidneys play a vital role in the maintenance of the BP circadian rhythm, and that kidney dysfunction as seen in microalbuminuria associates with the loss of the physiologic decline in nocturnal BP (Brantsma et al., 2006, Cirillo et al., 2000). It has been previously suggested that non-dipping causes an increase in night-time BP (Kario, 2018, Irvin et al., 2018), and that non-dipping is associated with microalbumin (Duggal et al., 2017, Heggie et al., 2008). However, the association between non-dipping and microalbuminuria in the studies Duggal et al. (2017) and Heggie et al. (2008) was reported in patients with DM and sustained HT. Nonetheless, the findings of the current study also indicate that microalbuminuria is associated with night-time MH even in individuals who are without DM and who are considered healthy.

It has long been indicated by Bianchi et al. (1994) that urine albumin excretion and microalbuminuria in non-dippers is significantly greater as compared to non-dippers. In the

same report by Bianchi et al. (1994), there was a significant correlation between night-time SBP and DBP with microalbuminuria. Although this study was conducted in patients with essential HT, it appears that an elevated night-time ABP mediated by a non-dipping BP is responsible for kidney dysfunction. The findings of the current study also indicate the presence of microalbumin in urine in individuals who have an elevated SBP and DBP during the night. In addition, Lurbe et al. (2002) stated that the risk for microalbuminuria was 70% greater in non-dippers as compare to dippers. Indeed, other studies have confirmed the relationship between microalbuminuria an elevated night-time BP even in patients who display the dipping pattern (Syrseloudis et al., 2011). The increased levels of microalbuminuria in patients with an elevated night-time BP suggest a greater renal damage in these patients (De Gaudio et al., 2000). It has been previously indicated that renal damage and impaired glomerular permeability contributes to the pathophysiology of microalbuminuria (Singh and Satchell, 2011, Dalla Vestra et al., 2003).

It appears that the elevated night-time BP induces structural changes on the glomerular filtration barrier leading to hyper-filtration of albumin into urine. It has been postulated that an elevated night-time BP is as a result of impaired function of the RAAS where there is a diminished renal capacity to excrete Na^+ during the day (Akita et al., 2003). The reduced renal capacity to excrete Na^+ elevates night-time BP by enhancing the pressure natriuresis in compensation for Na^+ retention during the day (Akita et al., 2003). This mechanism occurs in individuals who are said to be salt sensitive (Sachdeva and Weder, 2006).

Indeed, this population of African descent has been previously reported to be salt sensitive and tends to show less dipping during the night (Maseko et al., 2006). The microalbuminuria in the night-time MH group could potentially be due the effects of non-dipping that increases BP at night. In a similar population of salt sensitive individuals, Fukuda et al. (2004) demonstrated that the nocturnal natriuresis was increased with night-time BP and

that this elevated BP at night or during sleep may continue until the excess Na^+ is adequately excreted in to urine. However, this elevated night-time BP influences the deterioration in renal function as evident in the association between night-time BP and microalbuminuria. Previous studies have shown that targeting the reduction in night-time BP tends to decrease albumin excretion in urine (Oliveras et al., 2011). Drawz et al. (2016) indicated that using diuretics and ACE inhibitors as well as ANG receptor blockers was associated with a lower night-time BP.

The use of diuretics and ACE inhibitors as well as ANG receptor blockers influences the decrease in nocturnal pressure natriuresis by decreasing in Na^+ retention and consequently the pressure natriuresis. Nevertheless, in the present study we did not investigate drug therapy because treatment approaches for patients with MH are still inconclusive and debatable. Findings of the present study indicate that compared to participants without night-time MH (those who are true normotensives, 24-h MH, daytime MH, and those with sustained HT), are less likely to present with microalbuminuria. In light of this findings, we propose that supplementary research regarding the impact of night-time BP on TOD be further investigated. Furthermore, data of the present thesis indicate that Na^+ excretion was not associated with either CBP or ABP any subtype of MH. These results are keeping with previous reports particularly those conducted in the same population group (Scott et al., 2011, Millen et al., 2013) as well as those conducted in other populations groups (Shin et al., 2014, Staessen et al., 1993). However, differing from the present study, the latter studies by Shin et al. (2014) and Staessen et al. (1993), a positive correlation was observed between Na^+ excretion and night-time BP. Indeed, Na^+ excretion rates are not constant throughout the dary; it appears that Na^+ excretion rates are increased at night and are positively correlated with night-time BP when aldosterone levels fall (Davies et al., 1999, Smith et al., 1988). The elevated aldosterone levels during the day favors Na^+ retention. However, at night when the aldosterone levels fall, Na^+ excretion is favored (Spence and Rayner, 2018). Moreover, the tendency to retain Na^+ is more

pronounced in obese individuals particularly black individuals of African descent (Akintunde et al., 2017). Findings of the current study indicate that aldosterone levels were increased in both the daytime MH group and sustained HT as compared to the other subtypes of MH and normotension. Consequently, the Na^+ excretion is decreased in both the daytime MH group and sustained HT when compared to the other groups. Rayner and Spence (2017) indicated that over activity of the aldosterone-sensitive epithelial Na^+ channel on the renal tubules is responsible for the increase in BP as it is the final regulator of Na^+ balance in the kidneys. They also suggested that this over activity might be due to over expression of aldosterone owing to genetic mutations in aldosterone synthetase (cytochrome P450, family 11, subfamily b, member 2). In addition, chimerism of aldosterone synthetase may result in greater synthesis of aldosterone and subsequently increased Na^+ retention (Laffer et al., 2014). In addition, Tu et al. (2014) indicated that some people of African descent have variant genes that predisposes them to primary aldosteronism. In addition, another potential mechanism for increased aldosterone levels in a number of individuals of African descent relates to ET-1 has long been established (Saito et al., 1990). It is possible that individuals of African descent in the current study may have variant genes that predisposes them to primary aldosteronism thus increasing Na^+ retention. Tan et al. (2017) indicated that ET-1 has similar contractile, proliferative, and aldosterone stimulation properties similar to ANG II. Furthermore, the levels of ET-1 have been reported to be 3 to 4 times higher in many people of African Descent. Although in the current study, I did not study genetic composition of the different MH subtypes, the daytime MH and sustained HT group may have an increase in ET-1 levels thus stimulating the production of aldosterone, increased volume expansion and ultimately increase in BP.

Blood pressure is expected to be low at night as compared to daytime pressures. Nonetheless, if Na^+ is retained during the day, as is the case with blacks of African descent, this Na^+ is likely be excreted more at night and necessitates the pressure-natriuresis mechanism

to elevate night-time BP in order to drive the excretion of Na^+ at night. Consequently, the increase in night-time BP results in a non-dipping BP status. Indeed, black individuals of African descent have a predisposition to retain Na^+ (Akintunde et al., 2017), and have a propensity to salt (Na^+) sensitivity (Rayner and Spence, 2017) and accordingly are liable to be non-dippers (Jingi et al., 2017, Flack et al., 2015). Additionally, Na^+ retention by the kidneys during the day also favors fluid retention, which is related to a low renal perfusion pressure. Therefore, when an individual adopts a horizontal position during the night, the pooled blood is remobilized, leading to an increased venous return, SV, CO and accordingly BP is elevated thus contributing to a nocturnal increase in BP (Liu et al., 2003).

In conclusion, the current study indicates that night-time MH is a significant predictor of renal dysfunction as assessed by the presence of microalbumin in urine. Findings of the current study indicate that the presence of night-time MH causes renal dysfunction independent of sustained HT. Therefore, the routine use of ABPM may aid in diagnosing renal dysfunction that may be caused by nigh-time MH.

CHAPTER SIX

The Impact of Obesity and a non-Dipping Blood Pressure Status on Masked Hypertension in a Population of African Descent

Abstract

A non-dipping BP status has been suggested as a possible cause for MH and it appears that non-dipping occurs in individuals who are obese. In the present study, the aim was to investigate if non-dipping BP and indices of obesity are associated with any sub-type of MH in a population of African descent. Five hundred and forty-seven participants were enrolled in this study and had their 24-hour urine and blood samples collected. The participants had successfully completed ABPM and CBP measurements. The SBP dipping percentage for the total population was 9%; 24-h MH was at 5% SBP dipping; 12% SBP dipping for daytime MH group; 2% SBP dipping for Nigh-time MH group; 10% for the normotensive group; whereas the sustained HT group had a 7% SBP dipping. Findings of the present study indicate that all the subgroups of MH were obese according to BMI (kg/m^2); 24-hr MH (32.1 ±8.9 kg/m^2); daytime MH (30.3 ±9.1 kg/m^2); night-time MH (31.3 ±9.5 kg/m^2) similar to the sustained HT group (31.8 ±7.3 kg/m^2). The only group that was not classified as obese was the normotensive group; however, this group was overweight according to BMI (27.9 ±7.4 kg/m^2). On a stepwise regression analysis, findings of the current study indicated that BMI as an index of obesity was not associated with any subtype of MH; 24-hr MH SBP ($p= 0.3750$), daytime MH SBP ($p= 0.4544$), and night-time MH SBP ($p= 0.8827$). After correcting for covariates, multi-regression analysis showed that non-dipping was positively associated with all forms of MH SBP24 ($p= 0.0021$), SBPD ($p= 0.0002$) and SBPN ($p< 0.0001$). However, sustained HT did not correlate with a non-dipping BP profile ($p= 0.2467$).

6.1 Introduction

It is well recognised that a non-dipping BP profile has a budding potential to be an important clinical entity as it proves to be useful in predicting increased CVD risk, including in normotensive individuals (Yano and Kario, 2012, Fagard et al., 2009). A non-dipping BP profile has been shown to correlate with sustained HT and TOD (Wolf et al., 2010, Hoshide et al., 2016, Routledge et al., 2007). Non-dipping BP has been shown to associate with HT. However, it appears that a non-dipping BP pattern interacts with other risk factors such as obesity in its excursion to cause HT (Ukkola et al., 2009). In addition, a non-dipping BP status has been suggested as a possible cause of MH though there is no conclusive evidence for this association and details are superficial (Franklin et al., 2017). Also, the relevance of obesity related non-dipping BP profile in MH is unclear. Furthermore, obesity is considered based on BMI or WHR assessment (Nishida et al., 2010). Even so, there is scarcity of data relating BMI or measurement of WC and WHR to MH. A large body of evidence has proposed that obesity-related HT involves an increased sympathetic nerve activity, which may contribute to this association (Kushiro et al., 1991). Similarly, an impaired sympathetic NS is frequently associated with a non-dipping BP profile (Sherwood et al., 2011). However, it is uncertain whether this proposed mechanism is the solitary link between either obesity and MH or non-dipping and MH. Furthermore, it is possible that each subtype of MH will relate differently to obesity and non-dipping BP. In addition, each subtype of MH may have a specific cause pertinent to it and that not all subtypes of MH emanate from a single liable mechanism. Therefore, in the present study, the aim was to investigate if a non-dipping BP profile and BMI as an index of obesity are related to any subtype of MH in a population of African descent.

6.2 Methodology

6.2.1 Study group

Details of the recruitment of the participants that made up the study group have been described in section 3.2 of the present thesis. The present study was conducted in 547 participants who successfully completed a 24-h urine collection.

6.2.2 Clinical, demographic and anthropometric measurements

A standardized questionnaire was administered to obtain demographic and clinical data as described earlier. See section 3.2 of the present thesis for details.

6.2.3 Conventional blood pressure

The participants'sitting CBP was measured as described in section 3.2 of the present thesis.

6.2.4 Ambulatory blood pressure monitoring

Twenty-four hour ambulatory BP monitoring was performed on the same day as CBP measurements using ABPM (SpaceLabs, model 90207) as described in section 3.2 of the present thesis. The identification of day and night periods were similarly described in section 3.2 of the present thesis.

6.2.5 Data analysis

For details of analysis, see section 3.2 of this thesis. All statistical calculations [Student-test, ANCOVA, ANOVA, Shapiro-Wilk's statistic, Wilcoxon signed rank test , ROC curve analysis for sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios for positive and negative tests were determined as previously described in Section 3.2.]

and were performed with SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA)

6.3 Results

In this population sample, nocturnal BP dipping varied among the different categories of HT status as well as in the different MH sub-types. The SBP dipping percentage for the total population was 9%; 24-h MH was at 5% SBP dipping; 12% SBP dipping for daytime MH group; 2% SBP dipping for nigh-time MH group; 10% for the normotensive group; whereas the sustained HT group had a 7% SBP dipping. Data in the present study indicates that all the subgroups of MH were obese according to BMI (kg/m^2); 24-hr MH (32.1 ±8.9 kg/m^2); daytime MH (30.3 ±9.1 kg/m^2); night-time MH (31.3 ±9.5 kg/m^2) similar to the sustained HT group (31.8 ±7.3 kg/m^2). The only group that was not classified as obese was the normotensive group; however, this group was overweight according to BMI (27.9 ±7.4 kg/m^2). On a stepwise regression analysis, data of the present thesis showed that BMI as an index of obesity was not associated with any subtype of MH; 24-hr MH SBP ($p= 0.3750$), daytime MH SBP ($p= 0.4544$), and night-time MH SBP ($p= 0.8827$). After correcting for covariates, multi-regression analysis showed that non-dipping was positively associated with all forms of MH SBP24 ($p= 0.0021$), SBPD ($p= 0.0002$) and SBPN ($p< 0.0001$). However, sustained HT did not correlate with a non-dipping BP profile ($p= 0.2467$).

Table 6.1: General characteristics of the study population.

	Total population	24hr masked	Daytime masked	Night time Masked	Normotensives	Hypertensives
Number	547	23	17	90	404	143
Age (years)	45.2±18.5	47.3±21.3	49.5±20.8	45.8±19.3	40.3±17.4	59.1±14.1
BMI (kg/m^2)	29.1±7.8	33.2±9.3	33.9±8.6	30.1±8.2	28.1±7.6	31.8±7.5
Female (%)	63	57	56	54	65	59
Smoking (%)	15	13	19	16	16	14
Alcohol (%)	23	22	22	30	23	24
Diabetes (%)	9	22	22	22	7	33

BMI, body mass index; %, percentage.

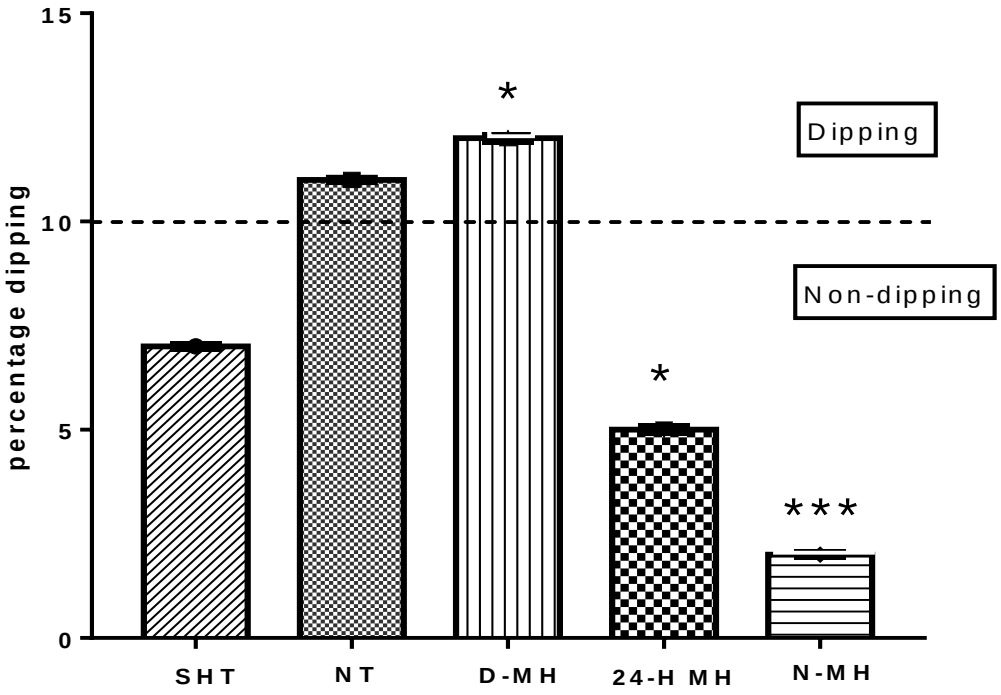

Figure 6.1: Percentage of dipping blood pressure profile among the different sub-types of masked hypertension, normotension and sustained hypertension.

*p<0.05. ***p<0.0001. *Adjusted for age, BMI, the presence of diabetes mellitus or an HbA1c>6.1%, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake and CBP. After correcting for covarieties, 24-hr MH was significantly associated with non-dipping (p= 0.0021) (r^2 = 0.56); Daytime MH (p=0.0002) (r^2= 0.55); night-time MH (p<0.0001) (r^2= 0.51). The SBP dipping percentage for the total population was 9%; 24-h MH was at 5% SBP dipping; SBP dipping for Daytime MH group 12%; SBP dipping for Nigh-time MH group 2%; Normotensive group 10%; SBP dipping for sustained HT group 7%. 24h-MH, 24-hour masked hypertension; D-MH, daytime masked hypertension; N-MH, night-time masked hypertension; NT, normotension; SHT, sustained hypertension.

6.4 Discussion

Findings of the present study indicate that in a population of Blacks of African descent, nocturnal BP dipping is attenuated in individuals who have all forms of MH independent of sustained HT. The results also show that individuals with night-time MH displayed the least BP dipping status indicating that BP did not change much between daytime BP values as compared to night-time values. Additionally, in this population group, Night-time MH was the predominant form of MH. It has been previously indicated that night-time MH occurs in a number of conditions that contribute to a non-dipping BP status such obesity. The population of the current study is characterised by an increased incidence of obesity (Maunganidze et al., 2013'Maseko et al., 2018). Results of the current study indicate that all the subgroups of MH were obese according to BMI similar to the sustained HT group. The only group that was not classified as obese was the normotensive group; however, this group was overweight according to BMI. Nonetheless, a non-dipping BP profile has previously been shown to be associated with obesity (Kawano et al., 2008) and that non-dipping is associated with MH (Franklin et al., 2017). Previous studies have indicated that obese individuals exhibit extracellular fluid volume expansion due to their capacity to retain Na^+. Obese individuals also have increased blood flow in many tissues and have increased venous return and CO (Hall, 2003). Cardiac output increases in corresponding to weight gain because blood flow should supply the increased adipose tissue and other tissues to meet metabolic demands (Hall, 2003). The non-dipping BP pattern occurs through the mechanism already explained in section 5.4 of the present thesis when an individual adopts a horizontal position (Liu et al., 2003). In addition to a non-dipping BP profile, multiple observational studies have indicated that excess weight gain is associated with increased sympathetic activity, especially in the kidney and that increased sympathetic activity raises BP mainly through the renal sympathetic nerves (Karaagac et al., 2014). An increased SNS activity is mediated by an increase in renin secretion, a reduced renal blood flow

as well as an increase in renal tubular reabsorption. In turn, this enhanced SNS activity has an anti-natriuretic effect (Karaagac et al., 2014). The release of norepinephrine stimulates β2-adrenergic receptors which leads to activation of the Na-Cl cotransporter through suppression of the serine-threonine protein kinase WNK4 in the distal tubule (Kotsis et al., 2005). The impaired SNS also accounts for non-dipping in obese individuals and may play a central role in non-dipping dependant MH (Kotsis et al., 2005). Literature suggests that obesity may contribute to MH through non-dipping BP, which is influenced by fluid volume expansion and activated SNS (Özkan et al., 2018)

The normotensive group and the daytime MH subtype of the present study are the only groups that displayed a normal dipping BP profile, which lies within the category of 10% to 20%. However, this increase in ABP of the daytime MH during the day may be caused by other factors which are responsible for increasing the sympathetic activity during the day such as those already explained in chapter 3. The normal dipping BP status displayed by the daytime MH group is keeping with previous reports. Indeed, Birkenhäger and Van den Meiracker (2007) suggested that daytime inactivity contributes to a decrease in the normally occurring nocturnal decline in BP such that individuals who are inactive during the day are more likely to be diagnosed as non-dippers and are prone to have increased CV events. This further supports that the daytime MH group may be subjected to daytime stresses related to increased physical activity thus display a better dipping BP status at night when the daytime stresses disappear (O'Shea and Murphy, 2000).

In conclusion, the presence of obesity related indices should be used to predict the presence of MH. Since pharmacological intervention is not considered for patients with MH, early-stage, intervention, such as lifestyle modification might be useful for these individuals. Findings of the current study also indicates that nigh-time MH occurs in conditions that favour a non-dipping BP profile.

CHAPTER SEVEN
Summary and Conclusion

7.1 Summary and conclusion

Notwithstanding the fact that there is availability of tools for monitoring BP, however, MH remains a multifaceted and intricate clinical phenomenon that has not been fully elucidated. From a pathophysiological, clinical, diagnostic, and treatment viewpoint, this condition has not been fully elucidated (Presta et al., 2018). Indeed, the clinical phenomenon of MH exists in noteworthy numbers in this population group of Africa descent as well as in other studies. The data presented in the present thesis warrant a heightened level of concern given that these results stem from an exclusively black African population whose risk profile for CVDs is great when paralleled to other population groups. It is also clear that MH should be taken seriously because findings of the current study as well as other studies conducted to-date indicate that individuals with MH may certainly be at risk of cardiovascular events.

Findings from the current study indicates that as compared to normotensives, individuals with MH share almost similar characteristics with those who have sustained HT and both present with TOD (Banegas et al., 2014). In addition, given the high prevalence of MH in my study population, the findings of this study supports the routine use of ABPM. These results suggests that CBP measured in clinical settings may not be adequate in identifying individuals with elevated BP in this population of African Descent. It is for this reason, that the results of the current study endorse the importance of employing ABPM for CVD risk stratification in this population of African descent in individuals who do not have an elevated CBP. However, it remains impractical to perform ABPM on every patient due to the lack of access and the cost implications accompanying this method of measurement. Therefore, further investigation into cost effective methods and strategies that can accurately detect MH is of paramount importance.

As noted earlier in Chapter 2, some studies have reported MH prevalence rates based on HBPM. Indeed, some reports advocate for the use of HBPM in reporting MT, while some

reports support for the use of HBPM in special circumstances and in combination with ABPM to help authenticate outcomes (Parati et al., 2008). Nonetheless, in the current study, the disadvantages of entirely relying on HPBM have been scrutinised in Chapter 2, and they include the lack of ability to assess BP during sleep and telling about short term BP variability as well as circadian rhythms. The HBPM does not cater for the details on BP changes throughout the day and night. In addition, HBPM is less sensitive as compared to ABPM therefore has an increased potential for BP underestimation.

However, based on the constraint that it is impractical to use ABPM on every patient who may visit a clinical setting, it is therefore important to device means that can aid in identifying individuals who may have an increased level of being suspected for MH.

Angeli et al. (2010), proposed an algorithm for the identification and management of individuals with MH. Figure 7.1 depicts the several suggested steps that are recommended to aid in the identification and management of individuals with MH. In the current study, this model has been adopted because it can assist in answering the question of "which individuals should be monitored using ABPM?" given that due to the scarcity of ABPM, not all individuals can be monitored using ABPM. Findings of the current study have identified indicative risk factors that are associated with MH and should channel the health care providers to investigate for the presence of MH. It is therefore, presently recommended that even though patients may appear to be normotensive by CBP, the following factors should direct for further scrutiny for MH through ABPM.

1. If an individual has a family history of HT.
2. If an individual has other cardiovascular risk factors such as obesity or diabetes.
3. individuals with kidney disease.
4. individuals with behavioural CVDs risk factors (e.g. smoking, alcohol intake, poor diet etc.)

5. Young male individuals, particularly those with job related stress.
6. Individuals who exhibit a higher average SBP in based on CBP monitoring.

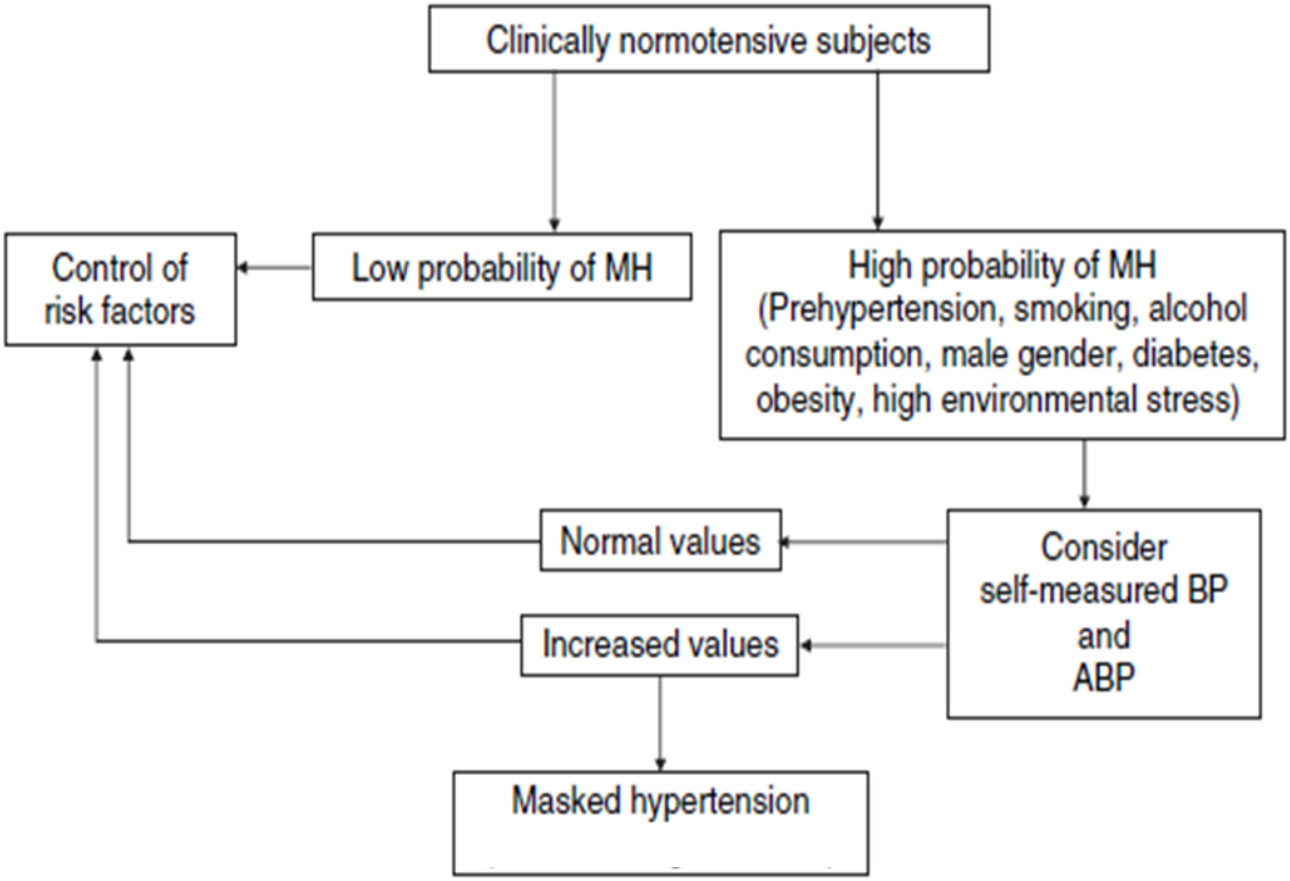

Figure 7.1: Suggested procedure to be considered for the identification and management of individuals with MH based on the presence of risk factors that can selectively raise ambulatory blood pressure independent of conventional blood pressure measurements. Adopted from Ageli et al., (2010)

Its is not certain if a connection does exist between MH and any genetic or biologic predisposition that may explain the elevated incidence of MH in this population group of African descent. Certainly, this link has not been studied in this population group or any other African population group. However, there is a level of suspicion that genetic susceptibility may play a role in the development of MH (Muntner et al., 2015). This notion is encouraged by the understanding that MH is a transition phase from a normotensive state towards a sustained HT state. Thus, from a genetics point of view, it has been shown that indeed, individuals who stem from first or second degree lineages with HT, tend to develop HT from the age of 50 yrs (Agarwal et al., 2005). Since the findings of the current study and findings from other reports suggests that individuals with MH are much younger, it can be argued that, MH may be transition between normotension and sustained HT in those who have a genetic predisposition before the age of 50 yrs.

However, if it there is no proof that MH stems from genetic predisposition. It is therefore substantial to draw an inference based on findings from previous reports that other risk factors such as young age, male sex and psychosocial stress play a prominent role in MH. It is easy to miss the opportunity to diagnose MH in younger individuals who present with "normal" CBP values in clinical settings. This may also be attributed to the narrative that younger individuals are not likely to have HT. On the other hand, the opportunity to report the true incidence of MH in this population group may be missed due to this condition being more prevalent in the male sex. Inopportunely, our recruitment was randomised and more women than men participated in the study. Therefore, the disparity in the ratio of males to females in the current study could account for a potential underreporting.

A detailed questionnaire should be used as a tool to help disclose activities that may relate to daily stresses. Virtually, individuals with MH may exhibit a lower level anxiety when monitored in a clinical setting because situations that trigger stress are omitted in such settings.

In addition, stress levels may proceed from a number of factors counting high job strain, work related and effort-reward imbalance (Ware et al., 2016). Adding to this, Landsbergis et al. (2013) proposed a component of elevated daytime ABP that only occurs at work to be considered "masked workplace hypertension". In light of this finding that ABP is generally higher during working hours than during times when individuals are at home (Schnall et al., 1992), it is plausible to suggest that work stressors are responsible for the casual increase in work ABP (Schwartz et al., 1994).

Therefore, in the quest to identify MH, it is important to consider work related stresses as significant risk factors for MH. Principally, majority of the participants in the current study come from disadvantaged economic backgrounds and many of which have a low level of education, which translates to low income. Consequently, they work in labour intense industries, where there is high job strain. These factors may play a crucial role in the increased levels of stress and depression thus contributing to MH (Ware et al., 2016, Peacock et al., 2014). In addition to stress related factors that may contribute to MH, lifestyle factors appear to play an important role in the progression of MH.

Similar to sustained HT, MH has been reported to occur in chronic diseases of lifestyle including obesity and DM. Certainly, in the current study, it was observed that all subtypes of MH belonged in the category of obese individuals. Additionally, an increase in BMI was similar for MH and sustained HT, whereas a lower BMI was true for normotensives. Also, Özkan et al. (2018) demonstrated that the prevalence of MH was higher in patients with obesity. In addition, it appears that BMI is not the only index of obesity that is associated with MH. Asayama et al. (2009) found that WC was significantly higher in both sustained HT and MH participants.

Further, in the same study by Asayama et al. (2009), it was demonstrated that increases in anthropometric indices of obesity counting WC, BMI and WHR were associated with MH.

It also appears that there are discrepancies regarding sex-specific associations of BMI and WC in MH, wherein mean BMI and WC are significantly higher in males with MH as compared to females with MH of similar mean BMI and WC (Sato et al., 2008, Ugajin et al., 2005). Although there was no significant association of BMI with any subtype of MH in the current study, the previous studies aforementioned indicate that individuals who are obese but have normal CBP values should be suspected for MH and therefore should be candidate for ABPM to authenticate the presence or absence of MH. Based on the findings of the current study, obesity did not have any implications on MH. Nonetheless, since obesity has been previously shown to be associated with sustained HT, it is therefore logical to employ ABPM on individuals who are obese.

In addition, Kenny et al. (2017) also indicated that in obese patients, MH was associated with the presence of DM. It is therefore important to further pay attention to patients who have DM, as they are prone to have MH. Although in the present thesis, there were no correlations between DM and MH due to the low prevalence of DM reported in this study based on abnormal blood glucose control defined as the use of insulin or oral hypoglycaemic agents or an HbA1c value greater than 6.1%. However, Franklin et al. (2013) demonstrated that patients with untreated MH in a diabetic population characterised at least 29% of those who were deemed to be normotensive on CBP measurements, and further presented with a greater risk for cardiovascular events than those with true normotension. In addition to the above mentioned study, other studies (Leitão et al., 2007, Liu et al., 1999, Ogedegbe et al., 2010) also emphasised that individuals with DM not only present with a high incidence of MH, but have a heightened CVD risk profile that matches those with sustained HT coupled with high rates of TOD.

Furthermore, IDACO indicated that the CVD risk profile in DM patients is the accumulation of the combined effects of DM itself accompanied with additive effects of the

risk of HT (Sehestedt et al., 2011). Indeed, Parati et al. (2011) suggested that strict antihypertensive drug control of CBP (SBP <130 mm Hg and DBP <80 mm Hg) seem to be an appropriate strategy in decreasing stroke events, particularly in young individuals who have DM and those who appear to have DM for short durations. Contrary to this viewpoint, Reboldi et al. (2011) and (2012) suggested that the customary antihypertensive drug technique to control CBP (SBP <140 mm Hg and DBP <90 mm Hg) appears to be more appropriate for decreasing CVD events related to ischemic heart disease in DM patients who are older and have longer duration of DM. Nonetheless, the aforementioned strategies for CBP reduction were proposed for DM patients with sustained HT.

Over and above that, there is no credible literature on studies in patients with DM and MH to warrant the profit that may be offered by antihypertensive drug therapy. In addition, there are no cut-off points to indicate how low to go in reducing daytime and night-time ABP values to warrant an optimal decline in cardiovascular risk (Franklin et al., 2013). Therefore, it is vital to consider lifestyle modifications that may aid in reducing ABP values to an optimal range in diabetics who have MH. Even so, the initial step would be to identify individuals with DM, consider ABPM, and if the values classify for MH, then control risk factors (Angeli et al., 2010).

Findings of the current study indicated that daytime and 24-hr MH subtypes were parallel with a high-normal CBP and that night-time MH was parallel with PHT. These results are backed by several other studies counting Kenny et al. (2017) and Lovibond et al. (2011) who have indicated that MH was associated with high-normal BP when compared to true normotensive individuals. Other studies including Viera et al. (2010) and Bobrie et al. (2008) suggested that MH may indicate a missed diagnosis of HT due to BP variability. In addition, failure to realise that high-normal BP is a red flag for MH could definitely result in a delayed diagnosis in such patients, which in turn hastens the subclinical TOD associated with MH.

Literature also indicates that the prospect of MH at a clinical level may not be limited in identifying high-normal BP, but also considering the occurrence of PHT. Pierdomenico and Cuccurullo (2011) reported that in a population sample of people who had PHT measured by CBP, participants with MH among that cohort had a higher cardiovascular risk as compared to those who only had PHT. In a different perspective, Shimbo et al. (2016) reported that MH and PHT independently are both associated with CVD risk comparative to sustained HT. Other reports indicate that prevalence of PHT may be asymmetrically higher in MH. The opportunity to identify both high-normal and PHT in the general population allows for the chance to engagement ABPM in exploring for the presence of MH. Therefore, findings of the current study indicate that in a clinical setting, high-normal BP and PHT are present. Therefore, the presence of high-normal and PHT should be used as a premonition to question the likelihood of the presence MH.

Data in the present thesis indicated that all subtypes of MH in this population group are associated with arterial stiffness, increased LVM, and kidney dysfunction. Numerous studies have demonstrated that cardiovascular risks associated with MH appear to be similar to those observed in individuals with sustained HT (Hänninen et al., 2013, Hoshide et al., 2016, Konstantopoulou et al., 2010). As highlighted, some evidence of research campaign for antihypertensive drug therapy in MH, however it is not clear if early drug therapy based on ABPM or even HBPM may provide a better cardiovascular protection than conventional methods of HT management (White and Morganroth, 1989). Some researchers are of the view that treatment recommendations may be premature, particularly in patients with early TOD; therefore, in such circumstances individuals with MH should undergo lifestyle changes to halt the progression of TOD or even the advancement of MH to sustained HT (Angeli et al., 2010). Evidence has been presented in the present thesis to shown how behavioural lifestyle factors such as smoking and alcohol consumption relates to MH. It is therefore recommended that

individuals who smoke and those who consume alcohol should be screened for MH using ABPM.

Another modifiable risk factor that should be taken into account in this population group of African descent is that of dietary salt/Na^+ consumption. It has already been established that this population group is salt sensitive, thus an increased dietary intake of Na^+ may predisposed individuals to MH as is the case with sustained HT. Although there was no significant relationship between dietary Na^+ and any form of MH in the current study, it should be recalled that even with the high incidence of HT in this population group, previous studies could not find any association between Na^+ intake and BP. However, in light of these findings, these results are not conclusive because a study conducted in the same population by Maseko et al. (2018) put it into perspective that the heightened incidence of obesity in this population masks the relationship between Na^+ intake BP.

Importantly, It has also been highlighted in Chapter 3 of the current study is that MH occurs in different subtypes in this population and that night-time MH is the most common form of MH. This further indicates that MH occurs in a multitude of varied circumstances that elevate BP often during the night than during the day. It has been argued that a non-dipping BP profile is an important contributor to night-time MH. Therefore, factors that have been described previously to encourage a non-dipping BP status should be considered in the investigation of MH.

Briefly, the findings of the current study propose that, (i) MH may exist as an intermediate phenotype transiting from normotension to sustained HT. (ii) MH is associated with TOD even without developing to sustained HT. (iii) MH has varied unrelated risk factors. (iv) MH is encouraged in conditions that result in non-dipping. (v) Although underreported, people of African descent have a high prevalence of MH.

7.2 Study limitations and future perspective

The current study had some limitations, which included the cross-sectional design. Participants were randomly recruited and consequently the ratio of male to female was unbalanced.

The outcomes of this study should be interpreted within the perspective of its confines. Although MH status was determined by a single ABP measurement, it should be considered that ABP is more reliable and more reproducible, therefore repeated measurements were not required to determine the true prevalence in this population. Findings of the current study have important implications for future research, as well as for the diagnosis and treatment of hypertension in black South Africans of African Descent. Indeed, results of the current study indicate that more mechanisms that are complex exist in the development and sequelae of MH and that further investigation is required. Also, it is unknown if genetic predisposition plays a role in the development of any subtype of MH, therefore future studies are needed to investigate if a genetic component is involved in the development of MH. Data in this thesis and other previous studies indicates that WC rather than BMI better predicts CVDs and is associated with MH. It is encouraged for future studied to consider obesity based on WC rather than BMI alone.

To identify the possible causes of MH from a clinical perspective, routine medical check-up is encouraged in individuals who may be prone to develop MH. This is because early diagnosing of MH may aid to culminate modifiable risk factors that have been implicated in MH thus assist in delivering long-lived solid resolution on reducing CVDs burden related to MH. Lastly, the current study was conducted in a population of exclusively blacks of African descent therefore the results of the current study should not be theorised to other ethnic groups; however, the results can be used as a foundation for assessment between studies.

CHAPTER EIGHT
References

8.1 References

Abdalla, M., Booth, J. N., Seals, S. R., Spruill, T. M., Viera, A. J., Diaz, K. M., Sims, M., Muntner, P. & Shimbo, D. 2016. Masked hypertension and incident clinic hypertension among blacks in the Jackson Heart Study. *Hypertension***,** HYPERTENSIONAHA. 115.06904.

Abdelhafiz, A. H., Ahmed, S. & El Nahas, M. 2011. Microalbuminuria: marker or maker of cardiovascular disease. *Nephron Experimental Nephrology,* 119**,** e6-e10.

Abir-Khalil, S., Zaîmi, S., Tazi, M., Bendahmane, S., Bensaoud, O. & Benomar, M. 2009. Prevalence and predictors of white-coat hypertension in a large database of ambulatory blood pressure monitoring. *Eastern Mediterranean health journal,* 15.

Addo, J., Smeeth, L. & Leon, D. A. 2007. Hypertension in Sub-Saharan Africa. *Hypertension,* 50**,** 1012-1018.

Adeloye, D. & Basquill, C. 2014. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. *PLoS One,* 9**,** e104300.

Adrogué, H. J. & Madias, N. E. 2014. Sodium surfeit and potassium deficit: keys to the pathogenesis of hypertension. *Journal of the American Society of Hypertension,* 8**,** 203-213.

Agarwal, A., Williams, G. H. & Fisher, N. D. 2005. Genetics of human hypertension. *Trends in Endocrinology & Metabolism,* 16**,** 127-133.

Agarwal, R. 2016. Albuminuria and masked uncontrolled hypertension in chronic kidney disease. *Nephrology Dialysis Transplantation,* 32**,** 2058-2065.

Agyemang, C. & Bhopal, R. 2002. Is the blood pressure of South Asian adults in the UK higher or lower than that in European white adults? A review of cross-sectional data. *Journal of human hypertension,* 16**,** 739.

AHA 2017. What is high blood pressure? *South Carolina State Documents Depository*.

AHA, A. H. A. 2012. All about heart rate (pulse). *Retrieved from*.

Akintunde, A., Nondi, J., Gogo, K., Jones, E. S., Rayner, B. L., Hackam, D. G. & Spence, J. D. 2017. Physiological phenotyping for personalized therapy of uncontrolled hypertension in Africa. *American Journal of Hypertension,* 30**,** 923-930.

Akita, S., Sacks, F. M., Svetkey, L. P., Conlin, P. R. & Kimura, G. 2003. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on the pressure-natriuresis relationship. *Hypertension,* 42**,** 8-13.

Alderman, M. H. 2002. Salt, blood pressure and health: a cautionary tale. *International Journal of Epidemiology,* 31**,** 311-316.

Algamal, A. M. 2016. Frequency of masked hypertension and its relation to target organ damage in the heart. *The Egyptian Heart Journal,* 68**,** 53-57.

Alharf, A., Cleland, S., Webster, J., Mcinnes, G. & Padmanabhan, S. 2016. Microalbuminuria in participants with hypertension attending specialist blood pressure clinics. *Journal of Human Hypertension,* 30**,** 527.

Alwan, H., Pruijm, M., Ponte, B., Ackermann, D., Guessous, I., Ehret, G., Staessen, J. A., Asayama, K., Vuistiner, P. & Younes, S. E. 2014. Epidemiology of masked and white-coat hypertension: the family-based SKIPOGH study. *PloS one,* 9**,** e92522.

Anderson, D. T., Ierulli, J., Oddo, T., Blackwell, C., Kuhns, C. & Omelchenko, N. 2017. Blood Pressure Variations During the Day. *Proceedings of the West Virginia Academy of Science,* 89.

Androulakis, E., Papageorgiou, N., Lioudaki, E., Chatzistamatiou, E., Zacharia, E., Kallikazaros, I. & Tousoulis, D. 2017. Subclinical Organ Damage in White-Coat Hypertension: The Possible Role of Cystatin C. *The Journal of Clinical Hypertension,* 19**,** 190-197.

Angeli, F., Reboldi, G. & Verdecchia, P. 2010. Masked hypertension: evaluation, prognosis, and treatment. *American Journal of Hypertension,* 23**,** 941-948.

Asayama, K., Sato, A., Ohkubo, T., Mimura, A., Hayashi, K., Kikuya, M., Yasui, D., Kanno, A., Hara, A. & Hirose, T. 2009. The association between masked hypertension and waist circumference as an obesity-related anthropometric index for metabolic syndrome: the Ohasama study. *Hypertension Research,* 32**,** 438.

Asayama, K., Thijs, L., Li, Y., Gu, Y.-M., Hara, A., Liu, Y.-P., Zhang, Z., Wei, F.-F., Lujambio, I. & Mena, L. J. 2014. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. *Hypertension,* 64**,** 935-942.

Atlas, S. A. 2007. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *Journal of Managed Care Pharmacy,* 13**,** 9-20.

Aubinière-Robb, L., Jeemon, P., Hastie, C. E., Patel, R. K., Mccallum, L., Morrison, D., Walters, M., Dawson, J., Sloan, W. & Muir, S. 2013. Blood pressure response to patterns of weather fluctuations and effect on mortality. *Hypertension***,** HYPERTENSIONAHA. 111.00686.

Avolio, A. P., Butlin, M. & Walsh, A. 2009. Arterial blood pressure measurement and pulse wave analysis—their role in enhancing cardiovascular assessment. *Physiological measurement,* 31**,** R1.

Banegas, J. R., Ruilope, L. M., De La Sierra, A., De La Cruz, J. J., Gorostidi, M., Segura, J., Martell, N., García-Puig, J., Deanfield, J. & Williams, B. 2014. High prevalence of masked uncontrolled hypertension in people with treated hypertension. *European heart journal,* 35**,** 3304-3312.

Barbera, J. A., Peinado, V. I., Santos, S., Ramirez, J., Roca, J. & Rodriguez-Roisin, R. 2001. Reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers. American journal of respiratory and critical care medicine, 164, 709-713.

Barlassina, C., Lanzani, C., Manunta, P. & Bianchi, G. 2002. Genetics of essential hypertension: from families to genes. *Journal of the American Society of Nephrology,* 13**,** S155-S164.

Barton, M., Prossnitz, E. R. & Meyer, M. R. 2012. Testosterone and Secondary Hypertension. *Hypertension,* 59**,** 1101-1103.

Bello, V. D., Talini, E., Dell'omo, G., Giannini, C., Delle Donne, M. G., Canale, M. L., Nardi, C., Palagi, C., Dini, F. L. & Penno, G. 2010. Early left ventricular mechanics abnormalities in prehypertension: a two-dimensional strain echocardiography study. *American Journal of Hypertension,* 23**,** 405-412.

Ben-Dov, I. Z., Ben-Arie, L., Mekler, J. & Bursztyn, M. 2005. In clinical practice, masked hypertension is as common as isolated clinic hypertension: predominance of younger men. *American Journal of Hypertension,* 18**,** 589-593.

Benarroch, E. E. 2008. The arterial baroreflex: functional organization and involvement in neurologic disease. *Neurology,* 71**,** 1733-1738.

Bianchi, S., Bigazzi, R., Baldari, G., Sgherri, G. & Campese, V. M. 1994. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *American Journal of Hypertension,* 7**,** 23-29.

Bidani, A. K. & Griffin, K. A. 2004. Pathophysiology of hypertensive renal damage: implications for therapy. *Hypertension,* 44**,** 595-601.

Birditt, K. S., Newton, N. J., Cranford, J. A. & Ryan, L. H. 2015. Stress and negative relationship quality among older couples: Implications for blood pressure. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences,* 71**,** 775-785.

Birkenhäger, A. & Van Den Meiracker, A. 2007. Causes and consequences of a non-dipping blood pressure profile. *Neth J Med,* 65**,** 127-131.

Bobrie, G., Chatellier, G., Genes, N., Clerson, P., Vaur, L., Vaisse, B., Menard, J. & Mallion, J.-M. 2004. Cardiovascular prognosis of masked hypertension detected by blood pressure self-measurement in elderly treated hypertensive patients. *Jama,* 291**,** 1342-1349.

Bobrie, G., Clerson, P., Menard, J., Postel-Vinay, N., Chatellier, G. & Plouin, P.-F. 2008. Masked hypertension: a systematic review. *Journal of Hypertension,* 26**,** 1715-1725.

Bochud, M., Bovet, P., Vollenweider, P., Maillard, M., Paccaud, F., Wandeler, G., Gabriel, A. & Burnier, M. 2009. Association between white-coat effect and blunted dipping of nocturnal blood pressure. *American Journal of Hypertension,* 22**,** 1054-1061.

Booth, J. N., Diaz, K. M., Seals, S. R., Sims, M., Ravenell, J., Muntner, P. & Shimbo, D. 2016. Masked hypertension and cardiovascular disease events in a prospective cohort of blacks: the Jackson Heart Study. *Hypertension***,** HYPERTENSIONAHA. 116.07553.

Boron, W. F. & Boulpaep, E. L. 2012. *Medical Physiology, 2e Updated Edition E-Book: with STUDENT CONSULT Online Access,* Elsevier Health Sciences.

Boynton, R. E. & Todd, R. L. 1947. Blood pressure readings of 75,258 university students. *Archives of Internal Medicine,* 80**,** 454-462.

Bradshaw, D., Groenewald, P., Laubscher, R., Nannan, N., Nojilana, B., Norman, R., Pieterse, D., Schneider, M., Bourne, D. E. & Timæus, I. M. 2003. Initial burden of disease estimates for South Africa, 2000. *South African Medical Journal,* 93**,** 682-688.

Brandes, R. P., Fleming, I. & Busse, R. 2005. Endothelial aging. *Cardiovascular research,* 66**,** 286-294.

Brantsma, A. H., Bakker, S. J., De Zeeuw, D., De Jong, P. E. & Gansevoort, R. T. 2006. Urinary albumin excretion as a predictor of the development of hypertension in the general population. *Journal of the American Society of Nephrology,* 17**,** 331-335.

Brennan, P., Greenberg, G., Miall, W. & Thompson, S. 1982. Seasonal variation in arterial blood pressure. *Br Med J (Clin Res Ed),* 285**,** 919-923.

Brizzolara, A. L., Morris, D. G. & Burnstock, G. 1994. Ethanol affects sympathetic cotransmission and endothelium-dependent relaxation in the rat. *European journal of pharmacology,* 254**,** 175-181.

Bundy, J. D., Li, C., Stuchlik, P., Bu, X., Kelly, T. N., Mills, K. T., He, H., Chen, J., Whelton, P. K. & He, J. 2017. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA cardiology,* 2**,** 775-781.

Burnier, M. 2001. Angiotensin II type 1 receptor blockers. *Circulation,* 103**,** 904-912.

Cacciapuoti, F. 2011. Molecular mechanisms of left ventricular hypertrophy (LVH) in systemic hypertension (SH)—possible therapeutic perspectives. *Journal of the American Society of Hypertension,* 5**,** 449-455.

Calhoun, D. A. 2013. Apparent and true resistant hypertension: Why not the same? *Journal of the American Society of Hypertension,* 7**,** 509-511.

Camici, G. G., Sudano, I., Noll, G., Tanner, F. C. & Lüscher, T. F. 2009. Molecular pathways of aging and hypertension. *Current opinion in nephrology and hypertension,* 18**,** 134-137.

Camplain, R., Meyer, M. L., Tanaka, H., Palta, P., Agarwal, S. K., Aguilar, D., Butler, K. R. & Heiss, G. 2015. Smoking behaviors and arterial stiffness measured by pulse wave velocity in older adults: The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Hypertension,* 29**,** 1268-1275.

Cannon, W. B. 1929. Organization for physiological homeostasis. *Physiological reviews,* 9**,** 399-431.

Carroll, D., Phillips, A. C., Der, G., Hunt, K. & Benzeval, M. 2011. Blood pressure reactions to acute mental stress and future blood pressure status: data from the 12-year follow-up of the West of Scotland Study. *Psychosomatic medicine,* 73**,** 737-742.

Cerasola, G., Mulè, G., Cottone, S., Nardi, E. & Cusimano, P. 2008. Hypertension, microalbuminuria and renal dysfunction: the Renal Dysfunction in Hypertension (REDHY) study. *endothelium,* 12**,** 13.

Celermajer, D. S., Chow, C. K., Marijon, E., Anstey, N. M. & Woo, K. S. 2012. Cardiovascular disease in the developing world: prevalences, patterns, and the potential of early disease detection. *Journal of the American College of Cardiology,* 60**,** 1207-1216.

Celermajer DS, Sorensen KE, Georgakopoulos D. 1993. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88:2149–55.

Chamontin, B., Amar, J., Garelli-Flores, I. & Salvador, M. 1996. Dippers and non-dippers among overweight hypertensive men. *Blood pressure monitoring,* 1**,** 329-332.

Chopra, H. & Ram, C. V. S. 2019. Recent guidelines for hypertension: a clarion call for blood pressure control in India. *Circulation research,* 124**,** 984-986.

Cirillo, M., Stellato, D., Laurenzi, M., Panarelli, W., Zanchetti, A. & De Santo, N. G. 2000. Pulse pressure and isolated systolic hypertension: association with microalbuminuria. *Kidney international,* 58**,** 1211-1218.

Conen, D., Aeschbacher, S., Thijs, L., Li, Y., Boggia, J., Asayama, K., Hansen, T. W., Kikuya, M., Björklund-Bodegård, K. & Ohkubo, T. 2014. Age-Specific Differences Between Conventional and Ambulatory Daytime Blood Pressure ValuesNovelty and Significance. *Hypertension,* 64**,** 1073-1079.

Covic, A. & Siriopol, D. 2015. Pulse wave velocity ratio: the new "gold standard" for measuring arterial stiffness. Am Heart Assoc.

Cowley Jr, A. W. 1992. Long-term control of arterial blood pressure. *Physiological reviews,* 72**,** 231-300.

Cunha, P. G., Cotter, J., Oliveira, P., Vila, I., Boutouyrie, P., Laurent, S., Nilsson, P. M., Scuteri, A. & Sousa, N. 2015. Pulse wave velocity distribution in a cohort study: from arterial stiffness to early vascular aging. *Journal of Hypertension,* 33**,** 1438-1445.

Cuspidi, C., Facchetti, R., Bombelli, M., Tadic, M., Sala, C., Grassi, G. & Mancia, G. 2019a. High Normal Blood Pressure and Left Ventricular Hypertrophy Echocardiographic Findings From the PAMELA Population. *Hypertension,* 73**,** 612-619.

Cuspidi, C., Facchetti, R., Quarti-Trevano, F., Sala, C., Tadic, M., Grassi, G. & Mancia, G. 2019b. Incident Left Ventricular Hypertrophy in Masked Hypertension. *Hypertension,* 74**,** 56-62.

Cuspidi, C., Sala, C., Tadic, M., Gherbesi, E., De Giorgi, A., Grassi, G. & Mancia, G. 2017. Clinical and prognostic significance of a reverse dipping pattern on ambulatory monitoring: an updated review. *The Journal of Clinical Hypertension,* 19**,** 713-721.

Cuspidi, C., Sala, C., Tadic, M., Rescaldani, M., Grassi, G. & Mancia, G. 2014. Untreated masked hypertension and subclinical cardiac damage: a systematic review and meta-analysis. *American Journal of Hypertension,* 28**,** 806-813.

Cuspidi, C., Sala, C., Tadic, M., Rescaldani, M., Grassi, G. & Mancia, G. 2015. Untreated Masked Hypertension and Subclinical Cardiac Damage: A Systematic Review and Meta-analysis. *Am J Hypertens,* 28**,** 806-13.

Dalal, S., Beunza, J. J., Volmink, J., Adebamowo, C., Bajunirwe, F., Njelekela, M., Mozaffarian, D., Fawzi, W., Willett, W. & Adami, H.-O. 2011. Non-communicable

diseases in sub-Saharan Africa: what we know now. *International journal of epidemiology,* 40**,** 885-901.

Dalla Vestra, M., Masiero, A., Roiter, A. M., Saller, A., Crepaldi, G. & Fioretto, P. 2003. Is podocyte injury relevant in diabetic nephropathy?: Studies in patients with type 2 diabetes. *Diabetes,* 52**,** 1031-1035.

Davies, E., Holloway, C. D., Ingram, M. C., Inglis, G. C., Friel, E. C., Morrison, C., Anderson, N. H., Fraser, R. & Connell, J. M. 1999. Aldosterone excretion rate and blood pressure in essential hypertension are related to polymorphic differences in the aldosterone synthase gene CYP11B2. *Hypertension,* 33**,** 703-707.

De Gaudio, A., Adembri, C., Grechi, S. & Novelli, G. 2000. Microalbuminuria as an early index of impairment of glomerular permeability in postoperative septic patients. *Intensive care medicine,* 26**,** 1364-1368.

Delacroix, S., Chokka, R. G. & Worthley, S. G. 2014. Hypertension: pathophysiology and treatment. *J Neurol Neurophysiol,* 5**,** 2.

De La Sierra, A., Banegas, J. R., Segura, J., Gorostidi, M., Ruilope, L. M. & Investigators, C. E. 2012. Ambulatory blood pressure monitoring and development of cardiovascular events in high-risk patients included in the Spanish ABPM registry: the CARDIORISC Event study. *Journal of Hypertension,* 30**,** 713-719.

Devereux, R. B., Wachtell, K., Gerdts, E., Boman, K., Nieminen, M. S., Papademetriou, V., Rokkedal, J., Harris, K., Aurup, P. & Dahlöf, B. 2004. Prognostic significance of left ventricular mass change during treatment of hypertension. *Jama,* 292**,** 2350-2356.

Diaz, K. M., Veerabhadrappa, P., Brown, M. D., Whited, M. C., Dubbert, P. M. & Hickson, D. A. 2014. Prevalence, determinants, and clinical significance of masked hypertension in a population-based sample of African Americans: the Jackson Heart Study. *American Journal of Hypertension,* 28**,** 900-908.

Dibona, G. F. 2002. Sympathetic nervous system and the kidney in hypertension. *Current opinion in nephrology and hypertension,* 11**,** 197-200.

Dobre, D., Kjekshus, J., Rossignol, P., Girerd, N., Benetos, A., Dickstein, K. & Zannad, F. 2018. Heart rate, pulse pressure and mortality in patients with myocardial infarction complicated by heart failure. *International journal of cardiology,* 271**,** 181-185.

Dolan, E., Stanton, A., Atkins, N., Den Hond, E., Thijs, L., Mccormack, P., Staessen, J. & O'brien, E. 2004. Determinants of white-coat hypertension. *Blood pressure monitoring,* 9**,** 307-309.

Doris, P. A. 2011. The genetics of blood pressure and hypertension: the role of rare variation. *Cardiovascular therapeutics,* 29**,** 37-45.

Drawz, P. E., Alper, A. B., Anderson, A. H., Brecklin, C. S., Charleston, J., Chen, J., Deo, R., Fischer, M. J., He, J. & Hsu, C.-Y. 2016. Masked hypertension and elevated night-time blood pressure in CKD: prevalence and association with target organ damage. *Clinical Journal of the American Society of Nephrology,* 11**,** 642-652.

Drenjančević-Perić, I., Jelaković, B., Lombard, J. H., Kunert, M. P., Kibel, A. & Gros, M. 2011. High-salt diet and hypertension: focus on the renin-angiotensin system. *Kidney and blood pressure Research,* 34**,** 1-11.

Dubey, R. K., Oparil, S., Imthurn, B. & Jackson, E. K. 2002. Sex hormones and hypertension. *Cardiovascular research,* 53**,** 688-708.

Dubielski, Z., Zamojski, M., Wiechecki, B., Możeńska, O., Petelczyc, M. & Kosior, D. A. 2016. The current state of knowledge about the dipping and non-dipping hypertension. *Arterial Hypertension,* 20**,** 33-43.

Duggal, A., Bal, B. & Singh, N. 2017. Study of dipping and non-dipping patterns in patients of type 2 diabetes mellitus with hypertension and its association with microalbuminuria. *Ann Int Med Den Res,* 3**,** 20-24.

Duranton, F., Kramer, A., Szwarc, I., Bieber, B., Gayrard, N., Jover, B., Vetromile, F., Massy, Z. A., Combe, C. & Tentori, F. 2018. Geographical variations in blood pressure level and seasonality in hemodialysis patients. *Hypertension,* 71**,** 289-296.

Dzudie, A., Kane, A., Kramoh, E., Anzouan-Kacou, J.-B., Damourou, J. M., Allawaye, L., Nzisabira, J., Mousse, L., Balde, D. & Nouhom, O. 2016. Development of the roadmap for reducing cardiovascular morbidity and mortality through the detection, treatment and control of hypertension in Africa: report of a working group of the PAS CAR Hypertension Task Force: meeting report. *Cardiovascular Journal of Africa,* 27**,** 200-202.

Eckberg, D. L. & SLEIGHT, P. 1992. *Human baroreflexes in health and disease,* Oxford University Press.

Enström, I., Thulin, T. & Lindholm, L. 1991. How good are standardized blood pressure recordings for diagnosing hypertension? A comparison between office and ambulatory blood pressure. *Journal of Hypertension,* 9**,** 561-566.

Esler, M. 2000. The sympathetic system and hypertension. *American Journal of Hypertension,* 13**,** 99S-105S.

Etyang, A. O., Warne, B., Kapesa, S., Munge, K., Bauni, E., Cruickshank, J. K., Smeeth, L. & Scott, J. A. G. 2016. Clinical and Epidemiological Implications of 24-Hour Ambulatory Blood Pressure Monitoring for the Diagnosis of Hypertension in Kenyan Adults: A Population-Based Study. *Journal of the American Heart Association,* 5**,** e004797.

Fagard, R., Thijs, L., Staessen, J. A., Clement, D., De Buyzere, M. & De Bacquer, D. 2009. Night–day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. *Journal of human hypertension,* 23**,** 645.

FARIA, R. A., PAIVA, A. G., POZZAN, R., MAGALHAES, M. E. C., CAMPANA, E. M. G., FONSECA, F. L., GOMES, M. A. M. & BRANDAO, A. A. 2015. 24h central blood

pressure and pulse wave velocity in normotensive, hypertensive, white coat hypertension and masked hpertension young adults. *Journal of the American Society of Hypertension,* 9**,** e30.

Fazio, M., Bardelli, M., Macaluso, L., Fiammengo, F., Mattei, P. L., Bossi, M., Fabris, B., Fischetti, F., Pascazio, L. & Candido, R. 2001. Mechanics of the carotid artery wall and baroreflex sensitivity after acute ethanol administration in young healthy volunteers. *Clinical Science,* 101**,** 253-260.

Feng, L., Khan, A. H., Jehan, I., Allen, J. & Jafar, T. H. 2017. Albuminuria and kidney function as prognostic marker of left ventricular mass among South Asians with hypertension. *Journal of the American Society of Hypertension,* 11**,** 811-822. e2.

Ferrario, C. M. & Strawn, W. B. 2006. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *The American journal of cardiology,* 98**,** 121-128.

Flack, J. M., Bhatt, D. L., Kandzari, D. E., Brown, D., Brar, S., Choi, J. W., D'agostino, R., East, C., Katzen, B. T. & Lee, L. 2015. An analysis of the blood pressure and safety outcomes to renal denervation in African Americans and Non-African Americans in the SYMPLICITY HTN-3 trial. *Journal of the American Society of Hypertension,* 9**,** 769-779.

Forouzanfar, M. H., Liu, P., Roth, G. A., Ng, M., Biryukov, S., Marczak, L., Alexander, L., Estep, K., Abate, K. H. & Akinyemiju, T. F. 2017. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *Jama,* 317**,** 165-182.

Franklin, S. S. 2005. Arterial stiffness and hypertension: a two-way street? *Hypertension,* 45**,** 349-351.

Franklin, S. S., O'brien, E. & Staessen, J. A. 2017. Masked hypertension: understanding its complexity. *European heart journal,* 38**,** 1112-1118.

Franklin, S. S., Rader, F. & Victor, R. G. 2016. What Is the Significance of Masked Hypertension Versus Incident Hypertension in Blacks? *Hypertension,* 68**,** 30-31.

Franklin, S. S., Thijs, L., Li, Y., Hansen, T. W., Boggia, J., Liu, Y., Asayama, K., Björklund-Bodegård, K., Ohkubo, T. & Jeppesen, J. 2013. Masked hypertension in diabetes mellitus: treatment implications for clinical practice. *Hypertension,* 61**,** 964-971.

Förstermann, U., Xia, N. & Li, H. 2017. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circulation research, 120, 713-735.

Fukuda, M., Munemura, M., Usami, T., Nakao, N., Takeuchi, O., Kamiya, Y., Yoshida, A. & Kimura, G. 2004. Nocturnal blood pressure is elevated with natriuresis and proteinuria as renal function deteriorates in nephropathy. *Kidney international,* 65**,** 621-625.

Furlan, R., Jacob, G., Palazzolo, L., Rimoldi, A., Diedrich, A., Harris, P. A., Porta, A., Malliani, A., Mosqueda-Garcia, R. & Robertson, D. 2001. Sequential modulation of cardiac autonomic control induced by cardiopulmonary and arterial baroreflex mechanisms. *Circulation,* 104**,** 2932-2937.

Gao, M., Rose, W. C., Fetics, B., Kass, D. A., Chen, C.-H. & Mukkamala, R. 2016. A simple adaptive transfer function for deriving the central blood pressure waveform from a radial blood pressure waveform. *Scientific reports,* 6**,** 33230.

Gaziano, T., Reddy, K. S., Paccaud, F., Horton, S. & Chaturvedi, V. 2006. Cardiovascular disease. *Disease Control Priorities in Developing Countries. 2nd edition.* The International Bank for Reconstruction and Development/The World Bank.

Gaziano, T. A. 2008. Economic burden and the cost-effectiveness of treatment of cardiovascular diseases in Africa. *Heart,* 94**,** 140-144.

Gijón-Conde, T., Graciani, A., López-García, E., Guallar-Castillón, P., García-Esquinas, E., Rodríguez-Artalejo, F. & Banegas, J. R. 2017. Short-term variability and nocturnal decline in ambulatory blood pressure in normotension, white-coat hypertension,

masked hypertension and sustained hypertension: a population-based study of older individuals in Spain. *Hypertension Research,* 40**,** 613.

Gillian, H. I., D James, G. & E Crews, D. 2003. Blood pressure variation in the institutionalized elderly. *Collegium antropologicum,* 27**,** 47-55.

Gnocchi, D. & Bruscalupi, G. 2017. Circadian rhythms and hormonal homeostasis: pathophysiological implications. *Biology,* 6**,** 10.

Goodfriend, T. L., Elliott, M. E. & Catt, K. J. 1996. Angiotensin receptors and their antagonists. *New England Journal of Medicine,* 334**,** 1649-1655.

Gosmanova, E. O., Mikkelsen, M. K., Molnar, M. Z., Lu, J. L., Yessayan, L. T., Kalantar-Zadeh, K. & Kovesdy, C. P. 2016. Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. *Journal of the American College of Cardiology,* 68**,** 1375-1386.

Grassi, G. & Ram, V. S. 2016. Evidence for a critical role of the sympathetic nervous system in hypertension. *Journal of the American Society of Hypertension,* 10**,** 457-466.

Grassi, G., Seravalle, G., Brambilla, G., Pini, C., Alimento, M., Facchetti, R., Spaziani, D., Cuspidi, C. & Mancia, G. 2014. Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension. *International journal of cardiology,* 177**,** 1020-1025.

Graudal, N. A., Hubeck-Graudal, T. & Jurgens, G. 2017. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database of Systematic Reviews*.

Gray, L., Lee, I.-M., Sesso, H. D. & Batty, G. D. 2011. Blood pressure in early adulthood, hypertension in middle age, and future cardiovascular disease mortality: HAHS (Harvard Alumni Health Study). *Journal of the American College of Cardiology,* 58**,** 2396-2403.

Groppelli, A., Giorgi, D., Omboni, S., Parati, G. & Mancia, G. 1992. Persistent blood pressure increase induced by heavy smoking. *J hypertens,* 10**,** 495-499.

Gunasekaran, V. 2013. *Continuous non-invasive arterial blood pressure measurement using photoplethysmography*. UC San Diego.

Gupta, A., Jain, G., Kaur, M., Jaryal, A. K., Deepak, K. K., Bhowmik, D. & Agarwal, S. K. 2016. Association of impaired baroreflex sensitivity and increased arterial stiffness in peritoneal dialysis patients. *Clinical and experimental nephrology,* 20**,** 302-308.

Guyenet, P. G. 2006. The sympathetic control of blood pressure. *Nature Reviews Neuroscience,* 7**,** 335.

Guyton, A. C. 1991. Blood pressure control--special role of the kidneys and body fluids. *Science,* 252**,** 1813-1816.

Guyton, A. C., Coleman, T. G. & Granger, H. J. 1972. Circulation: overall regulation. *Annual review of physiology,* 34**,** 13-44.

Ha, S. K. 2014. Dietary Salt Intake And Hypertension. *Electrolytes & Blood Pressure,* 12**,** 7-18.

Hall, J. E. 2015. *Guyton and Hall textbook of medical physiology e-Book*, Elsevier Health Sciences.

Hänninen, M.-R. A., Niiranen, T. J., Puukka, P. J., Kesäniemi, Y. A., Kähönen, M. & Jula, A. M. 2013. Target organ damage and masked hypertension in the general population: the Finn-Home study. *Journal of Hypertension,* 31**,** 1136-1143.

Hansen, T. W., Jeppesen, J., Rasmussen, S., Ibsen, H. & Torp-Pedersen, C. 2006. Ambulatory blood pressure monitoring and risk of cardiovascular disease: a population based study. *American Journal of Hypertension,* 19**,** 243-250.

Hansen, T. W., Li, Y., Boggia, J., Thijs, L., Richart, T. & Staessen, J. A. 2011. Predictive role of the night-time blood pressure. *Hypertension,* 57**,** 3-10.

Hara, A., Tanaka, K., Ohkubo, T., Kondo, T., Kikuya, M., Metoki, H., Hashimoto, T., Satoh, M., Inoue, R. & Asayama, K. 2012. Ambulatory Versus Home Versus Clinic Blood Pressure. *Hypertension,* 59**,** 22-28.

Hata, J., Fukuhara, M., Sakata, S., Arima, H., Hirakawa, Y., Yonemoto, K., Mukai, N., Kitazono, T., Kiyohara, Y. & Ninomiya, T. 2017. White-coat and masked hypertension are associated with albuminuria in a general population: the Hisayama Study. *Hypertension Research,* 40**,** 937.

He, F. J. & Macgregor, G. A. 2010. Reducing population salt intake worldwide: from evidence to implementation. *Progress in cardiovascular diseases,* 52**,** 363-382.

Heggie, A. J., Adamson, K. A., Marioni, R. E., Padfield, P. L. & Strachan, M. W. 2008. Is non-dipping of nocturnal blood pressure in type 2 diabetes associated with increased incidence of microalbuminuria? *The British Journal of Diabetes & Vascular Disease,* 8**,** 136-139.

Henine, N., Kichou, B., Kichou, L., Benbouabdellah, M., Boubchir, M., Madiou, A., Hammouche, A. & Saheb, B. Prevalence of true resistant hypertension among uncontrolled hypertensive patients referred to a tertiary health care center. Annales de cardiologie et d'angeiologie, 2016. 191-196.

Heron, M., Anderson, R. N. & Brief, N. D. 2016. Changes in the leading cause of death: recent patterns in heart disease and cancer mortality. *Cancer,* 400**,** 600000.

Hjortskov, N., Rissén, D., Blangsted, A. K., Fallentin, N., Lundberg, U. & Søgaard, K. 2004. The effect of mental stress on heart rate variability and blood pressure during computer work. *European journal of applied physiology,* 92**,** 84-89.

Hodgkinson, J., Mant, J., Martin, U., Guo, B., Hobbs, F., Deeks, J., Heneghan, C., Roberts, N. & Mcmanus, R. 2011. Relative effectiveness of clinic and home blood pressure

monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. *Bmj,* 342**,** d3621.

Hopkins, P. N., Hunt, S. C., Wu, L. L., Williams, G. H. & Williams, R. R. 1996. Hypertension, dyslipidemia, and insulin resistance: links in a chain or spokes on a wheel? *Current opinion in lipidology,* 7**,** 241-253.

Hoshide, S., Kabutoya, T., Eguchi, K. & Kario, K. 2016. Mps 04-02 Association Between Blood Pressure Reduction And Preclinical Target Organ Damage In Masked Hypertension. *Journal of Hypertension,* 34**,** e87.

Houston, M. C. 2011. The importance of potassium in managing hypertension. *Current hypertension reports,* 13**,** 309-317.

Howes, L. & Reid, J. 1986. The effects of alcohol on local, neural and humoral cardiovascular regulation. *Clinical Science,* 71**,** 9-15.

Humphrey, J. D., Harrison, D. G., Figueroa, C. A., Lacolley, P. & Laurent, S. 2016. Central artery stiffness in hypertension and aging: a problem with cause and consequence. *Circulation research,* 118**,** 379-381.

Husain, K., Ansari, R. A. & Ferder, L. 2014. Alcohol-induced hypertension: Mechanism and prevention. *World journal of cardiology,* 6**,** 245.

Ibrahim, M. M. & Damasceno, A. 2012. Hypertension in developing countries. *The Lancet,* 380**,** 611-619.

Imai, Y., Tsuji, I., Nagai, K., Sakuma, M., Ohkubo, T., Watanabe, N., Ito, O., Satoh, H., Hisamichi, S. & Abe, K. 1996. Ambulatory blood pressure monitoring in evaluating the prevalence of hypertension in adults in Ohasama, a rural Japanese community. *Hypertension Research,* 19**,** 207-212.

Indumathy, J., Pal, G. K., Pal, P., Ananthanarayanan, P. H., Parija, S. C., Balachander, J. & Dutta, T. K. 2015. Decreased baroreflex sensitivity is linked to sympathovagal

imbalance, body fat mass and altered cardiometabolic profile in pre-obesity and obesity. *Metabolism,* 64**,** 1704-1714.

Irvin, M. R., Booth Iii, J. N., Sims, M., Bress, A. P., Abdalla, M., Shimbo, D., Calhoun, D. A. & Muntner, P. 2018. The association of nocturnal hypertension and nondipping blood pressure with treatment-resistant hypertension: The Jackson Heart Study. *The Journal of Clinical Hypertension,* 20**,** 438-446.

Ishikawa, J., Ishikawa, Y., Edmondson, D., Pickering, T. G. & Schwartz, J. E. 2011. Age and the difference between awake ambulatory blood pressure and office blood pressure: a meta-analysis. *Blood pressure monitoring,* 16.

Ishikawa, J., Kario, K., Eguchi, K., Morinari, M., Hoshide, S., Ishikawa, S. & Shimada, K. 2006. Regular alcohol drinking is a determinant of masked morning hypertension detected by home blood pressure monitoring in medicated hypertensive patients with well-controlled clinic blood pressure: the Jichi Morning Hypertension Research (J-MORE) study. *Hypertension research,* 29**,** 679-686.

Israel, S., Israel, A., Ben-Dov, I. Z. & Bursztyn, M. 2011. The morning blood pressure surge and all-cause mortality in patients referred for ambulatory blood pressure monitoring. *American Journal of Hypertension,* 24**,** 796-801.

Ivy, A., Tam, J., Dewhurst, M. J., Gray, W. K., Chaote, P., Rogathi, J., Dewhurst, F. & Walker, R. W. 2015. Ambulatory blood pressure monitoring to assess the white-coat effect in an elderly east African population. *The Journal of Clinical Hypertension,* 17**,** 389-394.

Jablonski, K. L., Donato, A. J., Fleenor, B. S., Nowlan, M. J., Walker, A. E., Kaplon, R. E., Ballak, D. B. & Seals, D. R. 2015. Reduced large elastic artery stiffness with regular aerobic exercise in middle-aged and older adults: potential role of suppressed nuclear factor κ B signalling. *Journal of Hypertension,* 33**,** 2477.

Jafar, T. H., Stark, P. C., Schmid, C. H., Landa, M., Maschio, G., De Jong, P. E., De Zeeuw, D., Shahinfar, S., Toto, R. & Levey, A. S. 2003. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Annals of internal medicine,* 139**,** 244-252.

James, G. D. 2013. Ambulatory blood pressure variation: allostasis and adaptation. *Autonomic Neuroscience,* 177**,** 87-94.

Jingi, A. M., Kuate-Mfeukeu, L., Amougou, S. N., Hamadou, B., Nganou, C. N., Ateba, N. A., Wawo, E. G. & Kingue, S. 2017. Office versus ambulatory blood pressure measurements in diagnosing diurnal hypertension in sub-Saharan Africans: a comparative cross-sectional study in Cameroon. *Journal of Xiangya Medicine,* 2.

Johnson, R. J., Herrera-Acosta, J., Schreiner, G. F. & Rodríguez-Iturbe, B. 2002. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. *New England Journal of Medicine,* 346**,** 913-923.

Jones, D. W. & Hall, J. E. 2006. Racial and ethnic differences in blood pressure. Am Heart Assoc.

Kaplan, N. M. 2010. *Kaplan's clinical hypertension*, Lippincott Williams & Wilkins.

Karaagac, K., Vatansever, F., Tenekecioglu, E., Ozluk, O. A., Kuzeytemiz, M., Topal, D. & Yilmaz, M. 2014. The relationship between non-dipper blood pressure and thoracic aortic diameter in metabolic syndrome. *The Eurasian journal of medicine,* 46**,** 120.

Kario, K. 2018. Nocturnal hypertension: new technology and evidence. *Hypertension,* 71**,** 997-1009.

Kawano, Y. 2010. Physio-pathological effects of alcohol on the cardiovascular system: its role in hypertension and cardiovascular disease. *Hypertension Research,* 33**,** 181.

Kawano, Y., Horio, T., Matayoshi, T. & Kamide, K. 2008. Masked hypertension: subtypes and target organ damage. *Clinical and experimental hypertension,* 30**,** 289-296.

Kenny, I. E., Saeed, S., Gerdts, E., Midtbo, H., Halland, H. & Lonnebakken, M. T. 2017. Masked hypertension in obesity: potential predictors and arterial damage. *Blood Press Monit,* 22**,** 12-17.

Kikuya, M., Ohkubo, T., Metoki, H., Asayama, K., Hara, A., Obara, T., Inoue, R., Hoshi, H., Hashimoto, J. & Totsune, K. 2008. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis. *Hypertension,* 52**,** 1045-1050.

Kimura, G. 2008. Kidney and circadian blood pressure rhythm. *Hypertension,* 51**,** 827.

Klag, M. J., Whelton, P. K., Randall, B. L., Neaton, J. D., Brancati, F. L. & Stamler, J. 1997. End-stage renal disease in African-American and white men: 16-year MRFIT findings. *Jama,* 277**,** 1293-1298.

Kodavali, L. & Townsend, R. R. 2006. Alcohol and its relationship to blood pressure. *Current hypertension reports,* 8**,** 338-344.

Kokubo, Y., Kamide, K., Okamura, T., Watanabe, M., Higashiyama, A., Kawanishi, K., Okayama, A. & Kawano, Y. 2008. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension,* 52**,** 652-659.

Konstantopoulou, A., Konstantopoulou, P., Papargyriou, I., Liatis, S., Stergiou, G. & Papadogiannis, D. 2010. Masked, white coat and sustained hypertension: comparison of target organ damage and psychometric parameters. *Journal of human hypertension,* 24**,** 151.

Kotsis, V., Stabouli, S., Bouldin, M., Low, A., Toumanidis, S. & Zakopoulos, N. 2005. Impact of obesity on 24-hour ambulatory blood pressure and hypertension. *Hypertension,* 45**,** 602-607.

Kotsis, V., Stabouli, S., Karafillis, I., Papakatsika, S., Rizos, Z., Miyakis, S., Goulopoulou, S., Parati, G. & Nilsson, P. 2011. Arterial stiffness and 24 h ambulatory blood pressure

monitoring in young healthy volunteers: The early vascular ageing Aristotle University Thessaloniki Study (EVA–ARIS Study). *Atherosclerosis,* 219**,** 194-199.

Kotsis, V., Stabouli, S., Toumanidis, S., Papamichael, C., Lekakis, J., Germanidis, G., Hatzitolios, A., Rizos, Z., Sion, M. & Zakopoulos, N. 2008. Target organ damage in "white coat hypertension" and "masked hypertension". *American Journal of Hypertension,* 21**,** 393-399.

Kouremenos, N., Zacharopoulou, I. V., Triantafyllidi, H., Zacharopoulos, G. V., Mornos, C., Filippatos, G., Lekakis, J., Kremastinos, D., Manolis, A. I. & Gavras, H. 2014. Genes and genetic variations involved in the development of hypertension: focusing on a Greek patient cohort. *Hellenic J Cardiol,* 55**,** 9-16.

Kurtz, T. W. & Morris, R. C. 2017. What abnormalities initiate salt-induced increases in blood pressure according to the autoregulation and vasodysfunction theories for salt sensitivity? *Kidney international,* 92**,** 1015-1016.

Kushiro, T., Kobayashi, F., Osada, H., Tomiyama, H., Satoh, K., Otsuka, Y., Kurumatani, H. & Kajiwara, N. 1991. Role of sympathetic activity in blood pressure reduction with low calorie regimen. *Hypertension,* 17**,** 965-968.

Laatikainen, T., Nissinen, A., Kastarinen, M., Jula, A. & Tuomilehto, J. 2016. Blood pressure, sodium intake, and hypertension control: lessons from the North Karelia Project. *Global heart,* 11**,** 191-199.

Laffer, C. L., Elijovich, F., Eckert, G. J., Tu, W., Pratt, J. H. & Brown, N. J. 2014. Genetic variation in CYP4A11 and blood pressure response to mineralocorticoid receptor antagonism or ENaC inhibition: an exploratory pilot study in African Americans. *Journal of the American Society of Hypertension,* 8, 475-480.

Lakatta, E. G. & 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.

Landsbergis, P. A., Dobson, M., Koutsouras, G. & Schnall, P. 2013. Job strain and ambulatory blood pressure: a meta-analysis and systematic review. *American journal of public health,* 103**,** e61-e71.

Laragh, J. H. 1962. Hormones and the pathogenesis of congestive heart failure: vasopressin, aldosterone, and angiotensin II: further evidence for renal-adrenal interaction from studies in hypertension and in cirrhosis. *Circulation,* 25**,** 1015-1023.

Laragh, J. H. 1973. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *The American journal of medicine,* 55**,** 261-274.

Larochelle, P. 2002. Circadian variation in blood pressure: dipper or nondipper. *The Journal of Clinical Hypertension,* 4**,** 3-8.

Larsen, T. R., Gelaye, A., Waanbah, B., Assad, H., Daloul, Y., Williams, F., Williams, M. & Steigerwalt, S. 2014. Prevalence of masked hypertension in African Americans. *The Journal of Clinical Hypertension,* 16**,** 801-804.

Law, M., Frost, C. & Wald, N. 1991. By how much does dietary salt reduction lower blood pressure? III--Analysis of data from trials of salt reduction. *Bmj,* 302**,** 819-824.

Lee, H.-Y. & Oh, B.-H. 2010. Aging and arterial stiffness. *Circulation Journal,* 74**,** 2257-2262.

Lehmannn, M., Zeymer, U., Dechend, R., Kaiser, E., Hagedorn, I. & Deeg, E. 2013. Ambulatory blood pressure monitoring: is it mandatory for blood pressure control in treated hypertensive patients. *Int J Cardiol,* 168**,** 2255-63.

Leitão, C. B., Canani, L. H., Kramer, C. K., Boza, J. C., Pinotti, A. F. & Gross, J. L. 2007. Masked hypertension, urinary albumin excretion rate and echocardiographic parameters in putatively normotensive type 2 diabetes mellitus patients. *Diabetes Care*.

Leone, A. 2011. Does smoking act as a friend or enemy of blood pressure? Let release Pandora's box. *Cardiology research and practice,* 2011.

Liszka, H. A., Mainous, A. G., King, D. E., Everett, C. J. & Egan, B. M. 2005. Prehypertension and cardiovascular morbidity. *The Annals of Family Medicine,* 3**,** 294-299.

Liu, J. E., Roman, M. J., Pini, R., Schwartz, J. E., Pickering, T. G. & Devereux, R. B. 1999. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Annals of internal medicine,* 131**,** 564-572.

Liu, M., Takahashi, H., Morita, Y., Maruyama, S., Mizuno, M., Yuzawa, Y., Watanabe, M., Toriyama, T., Kawahara, H. & Matsuo, S. 2003. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. *Nephrology Dialysis Transplantation,* 18**,** 563-569.

Lough, M. E. 2015. *Hemodynamic Monitoring-E-Book: Evolving Technologies and Clinical Practice*, Elsevier Health Sciences.

Lovibond, K., Jowett, S., Barton, P., Caulfield, M., Heneghan, C., Hobbs, F. R., Hodgkinson, J., Mant, J., Martin, U. & Williams, B. 2011. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *The lancet,* 378**,** 1219-1230.

Lucas, D. L., Brown, R. A., Wassef, M. & Giles, T. D. 2005. Alcohol and the cardiovascular system: research challenges and opportunities. *Journal of the American College of Cardiology,* 45**,** 1916-1924.

Lurbe, E., Redon, J., Kesani, A., Pascual, J. M., Tacons, J., Alvarez, V. & Batlle, D. 2002. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *New England Journal of Medicine,* 347**,** 797-805.

Lurbe, E., Torro, I., Alvarez, V., Nawrot, T., Paya, R., Redon, J. & Staessen, J. A. 2005. Prevalence, persistence, and clinical significance of masked hypertension in youth. *Hypertension,* 45**,** 493-498.

Mahabala, C., Kamath, P., Bhaskaran, U., Pai, N. D. & Pai, A. U. 2013. Antihypertensive therapy: nocturnal dippers and nondippers. Do we treat them differently? *Vascular health and risk management,* 9**,** 125.

Makris, T. K., Thomopoulos, C., Papadopoulos, D. P., Bratsas, A., Papazachou, O., Massias, S., Michalopoulou, E., Tsioufis, C. & Stefanadis, C. 2009. Association of passive smoking with masked hypertension in clinically normotensive nonsmokers. *American Journal of Hypertension,* 22**,** 853-859.

Malan, L., Hamer, M., Frasure-Smith, N., Steyn, H. S. & Malan, N. T. 2014. Cohort profile: sympathetic activity and ambulatory blood pressure in Africans (SABPA) prospective cohort study. *International journal of epidemiology,* 44**,** 1814-1822.

Mallion, J.-M., Clerson, P., Bobrie, G., Genes, N., Vaisse, B. & Chatellier, G. 2006. Predictive factors for masked hypertension within a population of controlled hypertensives. *Journal of Hypertension,* 24**,** 2365-2370.

Mancia, G., Facchetti, R., Bombelli, M., Grassi, G. & Sega, R. 2006. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension,* 47**,** 846-53.

Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Böhm, M., Christiaens, T., Cifkova, R., De Backer, G. & Dominiczak, A. 2013. 2013 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). *Blood pressure,* 22**,** 193-278.

Mancia, G. & Mark, A. L. 1983. Arterial baroreflexes in humans. *Handbook of physiology, section,* 2**,** 755-793.

Mann, S. J., James, G. D., Wang, R. S. & Pickering, T. G. 1991. Elevation of ambulatory systolic blood pressure in hypertensive smokers: a case-control study. *Jama,* 265**,** 2226-2228.

Männistö, T., Mendola, P., Vääräsmäki, M., Järvelin, M.-R., Hartikainen, A.-L., Pouta, A. & Suvanto, E. 2013. Elevated Blood Pressure in Pregnancy and Subsequent Chronic Disease RiskClinical Perspective. *Circulation,* 127**,** 681-690.

Márquez, E. C., Casado, J. M., Pardo, J. A., Vazquez, I., Guevara, B. & Rodriguez, J. 2006. Prevalence of white-coat hypertension and masked hypertension in the general population, through home blood pressure measurement. *Atencion primaria,* 38**,** 392-398.

Maseko, M., Mercy, M., Abdulraheem, B.-A., Edgar, P., Bongubuhle, M. & Thamsanqa, N. 2018. Obesity masks the relationship between dietary salt intake and blood pressure in people of African ancestry: the impact of obesity on the relationship between sodium and blood pressure. *Cardiovascular journal of Africa,* 29**,** 172.

Maseko, M. J., Majane, H. O., Milne, J., Norton, G. R. & 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., Woodiwiss, A. J., Libhaber, C. D., Brooksbank, R., Majane, O. H. & Norton, G. R. 2013. Relations between White coat effects and left ventricular mass index or arterial stiffness: role of nocturnal blood pressure dipping. *American Journal of Hypertension,* 26**,** 1287-1294.

Mashele, N., Van Rooyen, J. M., Malan, L. & Potgieter, J. C. 2010. Cardiovascular function and psychological distress in urbanised black South Africans: the SA BPA study. *Cardiovascular journal of Africa,* 21**,** 206.

Matsui, Y., Eguchi, K., Ishikawa, J., Hoshide, S., Shimada, K. & Kario, K. 2007. Subclinical arterial damage in untreated masked hypertensive participants detected by home blood pressure measurement. *American Journal of Hypertension,* 20**,** 385-391.

Matsuoka, S. & Awazu, M. 2004. Masked hypertension in children and young adults. *Pediatric nephrology,* 19**,** 651-654.

Maunganidze, F., Woodiwiss, A. J., Libhaber, C. D., Maseko, M. J., Majane, O. H. & Norton, G. R. 2013. Obesity markedly attenuates the validity and performance of all electrocardiographic criteria for left ventricular hypertrophy detection in a group of black African ancestry. *Journal of Hypertension,* 31**,** 377-383.

McVeigh GE, Lemay L, Morgan D, Cohn JN. 1996. Effects of long-term cigarette smoking on endothelium-dependent responses in humans. Am J Cardiol; 78:668–72.

Meneton, P., Jeunemaitre, X., De Wardener, H. E. & Macgregor, G. A. 2005. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiological reviews,* 85**,** 679-715.

Mennuni, S., Rubattu, S., Pierelli, G., Tocci, G., Fofi, C. & Volpe, M. 2014. Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage. *Journal of human hypertension,* 28**,** 74.

Mensah, G. A. 2008. Epidemiology of stroke and high blood pressure in Africa. *Heart,* 94**,** 697-705.

Michel, F. S., Norton, G. R., Maseko, M. J., Majane, O. H., Sareli, P. & Woodiwiss, A. J. 2014. Urinary angiotensinogen excretion is associated with blood pressure independent of the

circulating renin–angiotensin system in a group of African ancestry. *Hypertension,* 64**,** 149-156.

Millen, A. M., Norton, G. R., Majane, O. H., Maseko, M. J., Brooksbank, R., Michel, F. S., Snyman, T., Sareli, P. & Woodiwiss, A. J. 2013. Insulin resistance and the relationship between urinary Na+/K+ and ambulatory blood pressure in a community of African ancestry. *American Journal of Hypertension,* 26**,** 708-716.

Minamino-Muta, E., Kato, T., Morimoto, T., Taniguchi, T., Inoko, M., Haruna, T., Izumi, T., Miyamoto, S., Nakane, E. & Sasaki, K. 2017. Impact of the left ventricular mass index on the outcomes of severe aortic stenosis. *Heart,* 103**,** 1992-1999.

Mitchell, G. F. 2004. Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications. *Current hypertension reports,* 6**,** 436-441.

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

Mitchell, G. F., Parise, H., Benjamin, E. J., Larson, M. G., Keyes, M. J., Vita, J. A., Vasan, R. S. & Levy, D. 2004. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension,* 43**,** 1239-1245.

Miyai, N., Arita, M., Morioka, I., Miyashita, K., Nishio, I. & Takeda, S. 2000. Exercise BP response in participants with high-normal BP: exaggerated blood pressure response to exercise and risk of future hypertension in participants with high-normal blood pressure. *Journal of the American College of Cardiology,* 36**,** 1626-1631.

Modesti, P. A. 2013. Season, temperature and blood pressure: a complex interaction. *European journal of internal medicine,* 24**,** 604-607.

Montani, J. P. & Van Vliet, B. N. 2009. Understanding the contribution of Guyton's large circulatory model to long-term control of arterial pressure. *Experimental physiology,* 94**,** 382-388.

Morris, J. H. & Bisognano, J. D. 2017. Masked hypertension: finding trouble under the disguise. Am Heart Assoc.

Morris, C. J., Aeschbach, D. & Scheer, F. A. 2012. Circadian system, sleep and endocrinology. *Molecular and cellular endocrinology,* 349**,** 91-104.

Morris Jr, R. C., Sebastian, A., Forman, A., Tanaka, M. & Schmidlin, O. 1999. Normotensive salt sensitivity: effects of race and dietary potassium. *Hypertension,* 33**,** 18-23.

Mortensen, R. N., Gerds, T. A., Jeppesen, J. L. & Torp-Pedersen, C. 2017. Office blood pressure or ambulatory blood pressure for the prediction of cardiovascular events. *European heart journal,* 38**,** 3296-3304.

Mozaffarian, D., Wilson, P. W. & Kannel, W. B. 2008. Beyond established and novel risk factors. *Circulation,* 117**,** 3031-3038.

Muntner, P., Lewis, C. E., Diaz, K. M., Carson, A. P., Kim, Y., Calhoun, D., Yano, Y., Viera, A. J. & Shimbo, D. 2015. Racial differences in abnormal ambulatory blood pressure monitoring measures: Results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Hypertens,* 28**,** 640-8.

Murray, C. J., Lauer, J. A., Hutubessy, R. C., Niessen, L., Tomijima, N., Rodgers, A., Lawes, C. M. & Evans, D. B. 2003. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *The Lancet,* 361**,** 717-725.

Nabbaale, J., Kibirige, D., Ssekasanvu, E., Sebatta, E. S., Kayima, J., Lwabi, P. & Kalyesubula, R. 2015. Microalbuminuria and left ventricular hypertrophy among newly diagnosed black African hypertensive patients: a cross sectional study from a tertiary hospital in Uganda. *BMC research notes,* 8**,** 198.

Nakagawa, T., Kang, D.-H., Ohashi, R., Suga, S.-I., Herrera-Acosta, J., Rodriguez-Iturbe, B. & Johnson, R. J. 2003. Tubulointerstitial disease: role of ischemia and microvascular disease. *Current opinion in nephrology and hypertension,* 12**,** 233-241.

Narkiewicz, K., Maraglino, G., Biasion, T., Rossi, G., Sanzuol, F. & Palatini, P. 1995. Interactive effect of cigarettes and coffee on daytime systolic blood pressure in patients with mild essential hypertension. HARVEST Study Group (Italy). Hypertension Ambulatory Recording VEnetia STudy. *Journal of Hypertension,* 13**,** 965-970.

Niiranen, T. J., Hanninen, M.-R., Johansson, J., Reunanen, A. & Jula, A. M. 2010. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: the Finn-Home study. *Hypertension,* 55**,** 1346-1351.

Nishida, C., Ko, G. & Kumanyika, S. 2010. Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on Waist Circumference and Waist–Hip Ratio. *European journal of clinical nutrition,* 64**,** 2.

Norton, G. R., Majane, O. H., Maseko, M. J., Libhaber, C., Redelinghuys, M., Kruger, D., Veller, M., Sareli, P. & Woodiwiss, A. J. 2012. Brachial Blood Pressure–Independent Relations Between Radial Late Systolic Shoulder-Derived Aortic Pressures and Target Organ Changes. *Hypertension,* 59**,** 885-892.

O'shea, J. C. & Murphy, M. B. 2000. Nocturnal blood pressure dipping: a consequence of diurnal physical activity blipping? *American Journal of Hypertension,* 13**,** 601-606.

O'brien, E., Parati, G. & Stergiou, G. 2013a. Ambulatory blood pressure measurement: what is the international consensus? *Hypertension,* 62**,** 988-994.

O'brien, E., Parati, G., Stergiou, G., Asmar, R., Beilin, L., Bilo, G., Clement, D., De La Sierra, A., De Leeuw, P. & Dolan, E. 2013b. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *Journal of Hypertension,* 31**,** 1731-1768.

O'shaughnessy, K. M. 2006. Role of diet in hypertension management. *Current hypertension reports,* 8**,** 292-297.

Odili, A. N., Thijs, L., Hara, A., Wei, F.-F., Ogedengbe, J. O., Nwegbu, M. M., Aparicio, L. S., Asayama, K., Niiranen, T. J. & Boggia, J. 2016. Prevalence and Determinants of Masked Hypertension Among Black Nigerians Compared With a Reference PopulationNovelty and Significance. *Hypertension,* 67**,** 1249-1255.

Ogah, O. S. & Rayner, B. L. 2013. Recent advances in hypertension in sub-Saharan Africa. *Heart***,** heartjnl-2012-303227.

Ogedegbe, G., Agyemang, C. & Ravenell, J. E. 2010. Masked hypertension: evidence of the need to treat. *Current hypertension reports,* 12**,** 349-355.

Ogoh, S., Fisher, J. P., Dawson, E. A., White, M. J., Secher, N. H. & Raven, P. B. 2005. Autonomic nervous system influence on arterial baroreflex control of heart rate during exercise in humans. *The Journal of physiology,* 566**,** 599-611.

Ohkubo, T., Kikuya, M., Metoki, H., Asayama, K., Obara, T., Hashimoto, J., Totsune, K., Hoshi, H., Satoh, H. & Imai, Y. 2005. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring: 10-year follow-up from the Ohasama study. *Journal of the American College of Cardiology,* 46**,** 508-515.

Ohta, Y., Kawano, Y., Hayashi, S., Iwashima, Y., Yoshihara, F. & Nakamura, S. 2016. Effects of cigarette smoking on ambulatory blood pressure, heart rate, and heart rate variability in treated hypertensive patients. *Clinical and Experimental Hypertension,* 38**,** 510-513.

Okamoto, L. E., Gamboa, A., Shibao, C., Black, B. K., Diedrich, A., Raj, S. R., Robertson, D. & Biaggioni, I. 2009. Nocturnal blood pressure dipping in the hypertension of autonomic failure. *Hypertension,* 53**,** 363-369.

Okpechi, I., Oluleye, T., Bekibele, C., Adedapo, K., Adebiyi, A., Ogah, O. & Salako, B. 2007. Unexpectedly high prevalence of target-organ damage in newly diagnosed Nigerians with hypertension: cardiovascular topic. *Cardiovascular Journal of South Africa,* 18**,** 77-83.

Okubo, Y., Miyamoto, T., Suwazono, Y., Kobayashi, E. & Nogawa, K. 2002. An association between smoking habits and blood pressure in normotensive Japanese men. *Journal of human hypertension,* 16**,** 91.

Oliveras, A., Armario, P., Martell-Clarós, N., Ruilope, L. M. & De La Sierra, A. 2011. Urinary albumin excretion is associated with nocturnal systolic blood pressure in resistant hypertensives. *Hypertension,* 57**,** 556-560.

Omboni, S., Aristizabal, D., De La Sierra, A., Dolan, E., Head, G., Kahan, T., Kantola, I., Kario, K., Kawecka-Jaszcz, K. & Malan, L. 2016. Hypertension types defined by clinic and ambulatory blood pressure in 14 143 patients referred to hypertension clinics worldwide. Data from the ARTEMIS study. *Journal of Hypertension,* 34**,** 2187-2198.

Omran, A. R. 2005. The epidemiologic transition: a theory of the epidemiology of population change. *The Milbank Quarterly,* 83**,** 731-757.

Opie, L. H. & Seedat, Y. K. 2005. Hypertension in sub-Saharan African populations. *Circulation,* 112**,** 3562-3568.

Organization, W. H. & Group, I. S. O. H. W. 2003. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *Journal of Hypertension,* 21**,** 1983-1992.

Oshita, M., Takei, Y., Kawano, S., Yoshihara, H., Hijioka, T., Fukui, H., Goto, M., Masuda, E., Nishimura, Y. & Fusamoto, H. 1993. Roles of endothelin-1 and nitric oxide in the mechanism for ethanol-induced vasoconstriction in rat liver. *The Journal of clinical investigation,* 91**,** 1337-1342.

Ott, C., Schneider, M. P. & Schmieder, R. E. 2013. Ruling out secondary causes of hypertension. *EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology,* 9**,** R21-8.

Özkan, S., Ata, N. & Yavuz, B. 2018. Increased masked hypertension prevalence in patients with obesity. *Clinical and Experimental Hypertension,* 40**,** 780-783.

Palla, M., Saber, H., Konda, S. & Briasoulis, A. 2018. Masked hypertension and cardiovascular outcomes: an updated systematic review and meta-analysis. *Integrated blood pressure control,* 11**,** 11.

Pannain, S. & Van Cauter, E. 2007. Modulation of endocrine function by sleep-wake homeostasis and circadian rhythmicity. *Sleep Medicine Clinics,* 2**,** 147-159.

Pappano, A. J. & Wier, W. G. 2018. *Cardiovascular physiology: mosby physiology monograph series*, Elsevier Health Sciences.

Parati, G. & Bilo, G. 2008. Clinical relevance of day-by-day blood pressure and heart rate variability. *Hypertension,* 52**,** 1006-1008.

Parati, G., Bilo, G. & Ochoa, J. E. 2011. Benefits of tight blood pressure control in diabetic patients with hypertension: importance of early and sustained implementation of effective treatment strategies. *Diabetes Care,* 34**,** S297-S303.

Parati, G., Izzo Jr, J. L. & Gavish, B. 2003. Respiration and blood pressure. *Hypertension Primer. 3rd ed. Baltimore: Lippincott Williams and Wilkins***,** 117-20.

Parati, G., Ochoa, J. E. & Bilo, G. 2012. Blood pressure variability, cardiovascular risk, and risk for renal disease progression. *Current hypertension reports,* 14**,** 421-431.

Parati, G., Ochoa, J. E., Lombardi, C. & Bilo, G. 2013. Assessment and management of blood-pressure variability. *Nature Reviews Cardiology,* 10**,** 143.

Parati, G., Ochoa, J. E., Lombardi, C. & Bilo, G. 2015. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. *Current hypertension reports,* 17**,** 23.

Parati, G., Stergiou, G., O'brien, E., Asmar, R., Beilin, L., Bilo, G., Clement, D., De La Sierra, A., De Leeuw, P. & Dolan, E. 2014. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *Journal of Hypertension,* 32**,** 1359-1366.

Parati, G., Stergiou, G. S., Asmar, R., Bilo, G., De Leeuw, P., Imai, Y., Kario, K., Lurbe, E., Manolis, A. & Mengden, T. 2008. European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *Journal of Hypertension,* 26**,** 1505-1526.

Parati, G., Stergiou, G. S., Asmar, R., Bilo, G., De Leeuw, P., Imai, Y., Kario, K., Lurbe, E., Manolis, A. & Mengden, T. 2010. European Society of Hypertension practice guidelines for home blood pressure monitoring. *Journal of human hypertension,* 24**,** 779-785.

Patil, B. 2013. Auscultatory and Oscillometric methods of Blood pressure measurement: a Survey. *measurement,* 3.

Peacock, J., Diaz, K. M., Viera, A. J., Schwartz, J. E. & Shimbo, D. 2014. Unmasking masked hypertension: prevalence, clinical implications, diagnosis, correlates and future directions. *Journal of human hypertension,* 28**,** 521-528.

Peer, M., Boaz, M., Zipora, M. & Shargorodsky, M. 2013. Determinants of left ventricular hypertrophy in hypertensive patients: identification of high-risk patients by metabolic, vascular, and inflammatory risk factors. *International Journal of Angiology,* 22**,** 223-228.

Peters, A. L., Davidson, M. B., Schriger, D. L. & Hasselblad, V. 1996. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. *Jama,* 276**,** 1246-1252.

Pickering, T. 1996. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. *American Journal of Hypertension,* 9**,** 1-11.

Pickering, T. G., Davidson, K., Gerin, W. & Schwartz, J. E. 2002. Masked hypertension. *Hypertension,* 40**,** 795-796.

Pickering, T. G., Eguchi, K. & Kario, K. 2007. Masked hypertension: a review. *Hypertension Research,* 30**,** 479.

Pierce, G. L., Harris, S. A., Seals, D. R., Casey, D. P., Barlow, P. B. & Stauss, H. M. 2016. Estimated aortic stiffness is independently associated with cardiac baroreflex sensitivity in humans: role of ageing and habitual endurance exercise. *Journal of human hypertension,* 30**,** 513.

Pierdomenico, S. D. & Cuccurullo, F. 2011. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated participants: an updated meta analysis. *American Journal of Hypertension,* 24**,** 52-58.

Pierdomenico, S. D., Lapenna, D., Bucci, A., Tommaso, R. D., Mascio, R. D., Manente, B. M., Caldarella, M. P., Neri, M., Cuccurullo, F. & Mezzetti, A. 2005. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. *American Journal of Hypertension,* 18**,** 1422-1428.

Pierdomenico, S. D., Pierdomenico, A. M., Coccina, F., Clement, D. L., De Buyzere, M. L., De Bacquer, D. A., Ben-Dov, I. Z., Vongpatanasin, W., Banegas, J. R. & Ruilope, L. M. 2018. Prognostic value of masked uncontrolled hypertension: systematic review and meta-analysis. *Hypertension,* 72**,** 862-869.

Pilic, L., Pedlar, C. R. & Mavrommatis, Y. 2016. Salt-sensitive hypertension: mechanisms and effects of dietary and other lifestyle factors. *Nutrition reviews,* 74**,** 645-658.

Pogue, V., Rahman, M., Lipkowitz, M., Toto, R., Miller, E., Faulkner, M., Rostand, S., Hiremath, L., Sika, M. & Kendrick, C. 2009. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension,* 53**,** 20-27.

Presta, V., Figliuzzi, I., D'agostino, M., Citoni, B., Miceli, F., Simonelli, F., Coluccia, R., Musumeci, M. B., Ferrucci, A. & Volpe, M. 2018. Nocturnal blood pressure patterns and cardiovascular outcomes in patients with masked hypertension. *The Journal of Clinical Hypertension,* 20**,** 1238-1246.

Puska, P., Mendis, S., Norrving, B. & Organization, W. H. 2011. *Global atlas on cardiovascular disease prevention and control,* Geneva: World Health Organization.

Qureshi, A. I., Suri, M. F. K., Kirmani, J. F., Divani, A. A. & Mohammad, Y. 2005. Is prehypertension a risk factor for cardiovascular diseases? *Stroke,* 36**,** 1859-1863.

Ragot, S., Herpin, D., Siché, J. P., Ingrand, P. & Mallion, J. M. 1999. Autonomic nervous system activity in dipper and non-dipper essential hypertensive patients. What about sex differences? *Journal of Hypertension,* 17**,** 1805-1811.

Rahimi, K., Mohseni, H., Otto, C. M., Conrad, N., Tran, J., Nazarzadeh, M., Woodward, M., Dwyer, T. & Macmahon, S. 2017. Elevated blood pressure and risk of mitral regurgitation: A longitudinal cohort study of 5.5 million United Kingdom adults. *PLoS medicine,* 14**,** e1002404.

Rassler B. 2010. The renin-angiotensin system in development of salt-sensitive hypertension in animal models and humans. *Pharmaceuticals* 3: 940-960

Rayner, B. L. & Spence, J. D. 2017. Hypertension in blacks: insights from Africa. LWW.

Reboldi, G., Gentile, G., Angeli, F., Ambrosio, G., Mancia, G. & Verdecchia, P. 2011. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73 913 patients. *Journal of Hypertension,* 29**,** 1253-1269.

Reboldi, G., Gentile, G., Manfreda, V. M., Angeli, F. & Verdecchia, P. 2012. Tight blood pressure control in diabetes: evidence-based review of treatment targets in patients with diabetes. *Current cardiology reports,* 14**,** 89-96.

Redelinghuys, M., Norton, G. R., Scott, L., Maseko, M. J., Brooksbank, R., Majane, O. H., Sareli, P. & Woodiwiss, A. J. 2010. Relationship between urinary salt excretion and pulse pressure and central aortic hemodynamics independent of steady state pressure in the general population. *Hypertension,* 56**,** 584-590.

Redon, J., Liao, Y., Lozano, J. V., Miralles, A., Pascual, J. M. & Cooper, R. S. 1994. Ambulatory blood pressure and microalbuminuria in essential hypertension: role of circadian variability. *Journal of Hypertension,* 12**,** 947-953.

Rehman, S. & Nelson, V. L. 2018. Blood Pressure Measurement. In *StatPearls [Internet]*. StatPearls Publishing.

Reimann, M., Hamer, M., Malan, N. T., Schlaich, M. P., Lambert, G. W., Ziemssen, T., Boeger, R. H. & Malan, L. 2013. Effects of acute and chronic stress on the L-arginine nitric oxide pathway in black and white South Africans: the sympathetic activity and ambulatory blood pressure in Africans study. *Psychosomatic medicine,* 75**,** 751-758.

Rhee, M.-Y., Kim, J.-H., Shin, S.-J., Gu, N., Nah, D.-Y., Hong, K.-S., Cho, E.-J. & Sung, K.-C. 2014. Estimation of 24-hour urinary sodium excretion using spot urine samples. *Nutrients,* 6**,** 2360-2375.

Rhee, M.-Y., Kim, S.-W., Choi, E.-H., Kim, J.-H., Nah, D.-Y., Shin, S.-J. & Gu, N. 2016. Prevalence of masked hypertension: a population-based survey in a large city by using

24-hour ambulatory blood pressure monitoring. *Korean circulation journal,* 46**,** 681-687.

Rhee, M.-Y., Na, S.-H., Kim, Y.-K., Lee, M.-M. & Kim, H.-Y. 2007. Acute effects of cigarette smoking on arterial stiffness and blood pressure in male smokers with hypertension. *American Journal of Hypertension,* 20**,** 637-641.

Rodriguez-Iturbe, B. & Johnson, R. J. 2010. The role of renal microvascular disease and interstitial inflammation in salt-sensitive hypertension. *Hypertension Research,* 33**,** 975.

Rothwell, P. M. 2010. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *The Lancet,* 375**,** 938-948.

Routledge, F. S., Mcfetridge-Durdle, J. A. & Dean, C. 2007. Night-time blood pressure patterns and target organ damage: a review. *Canadian Journal of Cardiology,* 23**,** 132-138.

Ryan, J. & Howes, L. 2002. Relations between alcohol consumption, heart rate, and heart rate variability in men. *Heart,* 88**,** 641-642.

Sachdeva, A. & Weder, A. B. 2006. Nocturnal sodium excretion, blood pressure dipping, and sodium sensitivity. *Hypertension,* 48**,** 527-533.

Safar, M. E. 2001. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. *Current opinion in nephrology and hypertension,* 10**,** 257-261.

Safar, M. E. & London, G. M. 2000. Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hypertension. *Journal of Hypertension,* 18**,** 1527-1535.

Sahn, D. J., Demaria, A., Kisslo, J. & Weyman, A. F. 1978. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation,* 58**,** 1072-1083.

Sakaguchi, K., Horimatsu, T., Kishi, M., Takeda, A., Ohnishi, Y., Koike, T., Fujisawa, T. & Maeda, M. 2005. Isolated home hypertension in the morning is associated with target organ damage in patients with type 2 diabetes. *Journal of atherosclerosis and thrombosis,* 12**,** 225-231.

Santulli, G. 2013. Epidemiology of cardiovascular disease in the 21st century: updated numbers and updated facts. *J Cardiovasc Dis,* 1**,** 1-2.

Sato, A., Asayama, K., Ohkubo, T., Kikuya, M., Obara, T., Metoki, H., Inoue, R., Hara, A., Hoshi, H. & Hashimoto, J. 2008. Optimal cutoff point of waist circumference and use of home blood pressure as a definition of metabolic syndrome: the Ohasama study. *American Journal of Hypertension,* 21**,** 514-520.

Saito, Y., Nakao, K., Mukoyama, M. & Imura, H. 1990. Increased plasma endothelin level in patients with essential hypertension. *The New England journal of medicine,* 322.

Schiffrin, E. 2016. Sp 02-5 Do We Need A New Definition Of Hypertension? *Journal of Hypertension,* 34**,** e194.

Schnall, P. L., Schwartz, J. E., LANDSBERGIS, P. A., WARREN, K. & PICKERING, T. G. 1992. Relation between job strain, alcohol, and ambulatory blood pressure. *Hypertension,* 19**,** 488-494.

Schrier, R. W. 2006. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *The American journal of medicine,* 119**,** S47-S53.

Schultz, M. G., Hare, J. L., Marwick, T. H., Stowasser, M. & Sharman, J. E. 2011. Masked hypertension is "unmasked" by low-intensity exercise blood pressure. *Blood pressure,* 20**,** 284-289.

Schupp, M., Janke, J. R., Clasen, R., Unger, T. & Kintscher, U. 2004. Angiotensin type 1 receptor blockers induce peroxisome proliferator–activated receptor-γ activity. *Circulation,* 109**,** 2054-2057.

Schwartz, J. E., Warren, K. & Pickering, T. G. 1994. Mood, location and physical position as predictors of ambulatory blood pressure and heart rate: Application of a multi-level random effects model. *Annals of Behavioral Medicine,* 16**,** 210-220.

Scott, L., Woodiwiss, A. J., Maseko, M. J., Veliotes, D. G., Majane, O. H., Paiker, J., Sareli, P. & Norton, G. R. 2011. Aldosterone-to-renin ratio and the relationship between urinary salt excretion and blood pressure in a community of African ancestry. *American Journal of Hypertension,* 24**,** 951-957.

Scuteri, A., Morrell, C. H., Alghatrif, M., Saba, P. S., Terracciano, A., Ferreli, L. A. P., Loi, F., Marongiu, M., Pilia, M. G. & Delitala, A. 2016. Gender specific profiles of white coat and masked hypertension impacts on arterial structure and function in the SardiNIA study. *International journal of cardiology,* 217**,** 92-98.

Seedat, Y. 2007. Impact of poverty on hypertension and cardiovascular disease in sub-Saharan Africa. *Cardiovascular journal of Africa,* 18**,** 316.

Sega, R., Facchetti, R., Bombelli, M., Cesana, G., Corrao, G., Grassi, G. & Mancia, G. 2005. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation,* 111**,** 1777-83.

Sega, R., Trocino, G., Lanzarotti, A., Carugo, S., Cesana, G., Schiavina, R., Valagussa, F., Bombelli, M., Giannattasio, C. & Zanchetti, A. 2001. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension. *Circulation,* 104**,** 1385-1392.

Sehestedt, T., Hansen, T. W., Li, Y., Richart, T., Boggia, J., Kikuya, M., Thijs, L., Stolarz-Skrzypek, K., Casiglia, E. & Tikhonoff, V. 2011. Are blood pressure and diabetes additive or synergistic risk factors? Outcome in 8494 participants randomly recruited from 10 populations. *Hypertension Research,* 34**,** 714.

Selenta, C., Hogan, B. E. & Linden, W. 2000. How often do office blood pressure measurements fail to identify true hypertension?: an exploration of white-coat normotension. *Archives of Family Medicine,* 9**,** 533.

Seravalle, G., Lonati, L., Buzzi, S., Cairo, M., Trevano, F. Q., Dell'oro, R., Facchetti, R., Mancia, G. & Grassi, G. 2015. Sympathetic nerve traffic and baroreflex function in optimal, normal, and high-normal blood pressure states. *Journal of Hypertension,* 33**,** 1411-1417.

Sherwood, A., Routledge, F. S., Wohlgemuth, W. K., Hinderliter, A. L., Kuhn, C. M. & Blumenthal, J. A. 2011. Blood pressure dipping: ethnicity, sleep quality, and sympathetic nervous system activity. *American Journal of Hypertension,* 24**,** 982-988.

Sherwood, L. 2015. *Human physiology: from cells to systems*, Cengage learning.

Shiburi, C. P., Staessen, J. A., Maseko, M., Wojciechowska, W., Thijs, L., Van Bortel, L. M., Woodiwiss, A. J. & Norton, G. R. 2006. Reference values for SphygmoCor measurements in South Africans of African ancestry. *American Journal of Hypertension,* 19**,** 40-46.

Shimbo, D., Abdalla, M., Falzon, L., Townsend, R. R. & Muntner, P. 2016. Studies comparing ambulatory blood pressure and home blood pressure on cardiovascular disease and mortality outcomes: a systematic review. *Journal of the American Society of Hypertension,* 10**,** 224-234. e17.

Shin, J., Xu, E., Lim, Y. H., Choi, B. Y., Kim, B. K., Lee, Y. G., Kim, M. K., Mori, M. & Yamori, Y. 2014. Relationship between nocturnal blood pressure and 24-h urinary sodium excretion in a rural population in Korea. *Clinical hypertension,* 20**,** 9.

Sibiya, M. J., Woodiwiss, A. J., Booysen, H. L., Raymond, A., Millen, A. M., Maseko, M. J., Majane, O. H., Sareli, P., Libhaber, E. & Norton, G. R. 2015. Reflected rather than forward wave pressures account for brachial pressure-independent relations between

aortic pressure and end-organ changes in an African community. *Journal of Hypertension,* 33**,** 2083-2090.

Singh, A. & Satchell, S. C. 2011. Microalbuminuria: causes and implications. *Pediatric Nephrology,* 26**,** 1957-1965.

Siu, A. L. 2015. Screening for high blood pressure in adults: US Preventive Services Task Force recommendation statement. *Annals of internal medicine,* 163**,** 778-786.

Sliwa, K., Wilkinson, D., Hansen, C., Ntyintyane, L., Tibazarwa, K., Becker, A. & Stewart, S. 2008. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *The Lancet,* 371**,** 915-922.

Smith, W., Crombie, I., Tavendale, R., Gulland, S. & Tunstall-Pedoe, H. 1988. Urinary electrolyte excretion, alcohol consumption, and blood pressure in the Scottish heart health study. *BMJ,* 297**,** 329-330.

Smolensky, M. H., Hermida, R. C., Castriotta, R. J. & Portaluppi, F. 2007. Role of sleep-wake cycle on blood pressure circadian rhythms and hypertension. *Sleep medicine,* 8**,** 668-680.

Spence, J. D. & Rayner, B. L. 2018. Hypertension in blacks: individualized therapy based on renin/aldosterone phenotyping. Hypertension, 72, 263-269.

Staessen, J. A., Birkenhäger, W., Bulpitt, C. J., Fagard, R., Fletcher, A. E., Lijnen, P., Thijs, L. & Amery, A. 1993. The relationship between blood pressure and sodium and potassium excretion during the day and at night. *Journal of Hypertension,* 11**,** 443-447.

Stergiou, G. S., Asayama, K., Thijs, L., Kollias, A., Niiranen, T. J., Hozawa, A., Boggia, J., Johansson, J. K., Ohkubo, T. & Tsuji, I. 2014. Prognosis of White-Coat and Masked HypertensionNovelty and Significance. *Hypertension,* 63**,** 675-682.

Sterling, P. 2004. Principles of allostasis: optimal design, predictive regulation, pathophysiology, and rational. *Allostasis, homeostasis, and the costs of physiological adaptation,* 17.

Stolarz-Skrzypek, K., Bednarski, A., Barton, H., Olszanecka, A., Wojciechowska, W., Kawecka-Jaszcz, K. & Czarnecka, D. 2018. High Sodium Intake Is Associated With Masked Hypertension In The General Population. *Journal of Hypertension,* 36**,** e171.

Sugahara, S., Kume, S., Takeda, N., Chin-Kanasaki, M., Araki, H., Yanagita, M., Araki, S.-I. & Maegawa, H. 2017. Mp017 Protein O− Glcnacylation Regulates Mitochondrial Function And Albumin Reabsorption In Proximal Tubular Cells O-Glcnacylation Regulates Mitochondrial Function And Albumin Reabsorption In Proximal Tubular Cells. *Nephrology Dialysis Transplantation,* 32**,** iii435-iii435.

Sun, Z. 2015. Aging, arterial stiffness, and hypertension. *Hypertension,* 65**,** 252-256.

Syrseloudis, D., Tsioufis, C., Andrikou, I., Mazaraki, A., Thomopoulos, C., Mihas, C., Papaioannou, T., Tatsis, I., Tsiamis, E. & Stefanadis, C. 2011. Association of night-time hypertension with central arterial stiffness and urinary albumin excretion in dipper hypertensive participants. *Hypertension Research,* 34**,** 120.

Taddei, S. 2009. Blood pressure through aging and menopause. *Climacteric,* 12**,** 36-40.

Tadic, M., Cuspidi, C., Pencic, B., Andric, A., Pavlovic, S. U., Iracek, O. & Celic, V. 2016. The interaction between blood pressure variability, obesity, and left ventricular mechanics: findings from the hypertensive population. *Journal of Hypertension,* 34**,** 772-780.

Tadic, M., Cuspidi, C., Radojkovic, J., Rihor, B., Kocijanic, V. & Celic, V. 2017. Masked Hypertension and Left Atrial Dysfunction: A Hidden Association. *J Clin Hypertens (Greenwich),* 19**,** 305-311.

Takah, N., Dzudie, A., Ndjebet, J., Wawo, G., Kamdem, F., Monkam, Y., Luma, H., Ngu, K. B. & Kengne, A. P. 2014. Ambulatory blood pressure measurement in the main cities of Cameroon: prevalence of masked and white coat hypertension, and influence of body mass index. *The Pan African medical journal,* 19.

Takeno, K., Mita, T., Nakayama, S., Goto, H., Komiya, K., Abe, H., Ikeda, F., Shimizu, T., Kanazawa, A. & Hirose, T. 2012. Masked hypertension, endothelial dysfunction, and arterial stiffness in type 2 diabetes mellitus: a pilot study. *American Journal of Hypertension,* 25**,** 165-170.

Talukder, M. H., Johnson, W. M., Varadharaj, S., Lian, J., Kearns, P. N., El-Mahdy, M. A., Liu, X. & Zweier, J. L. 2010. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. *American Journal of Physiology-Heart and Circulatory Physiology*, 300, H388-H396.

Tan, J. W., Gupta, T., Manosroi, W., Yao, T. M., Hopkins, P. N., Williams, J. S., Adler, G. K., Romero, J. R. & Williams, G. H. 2017. Dysregulated aldosterone secretion in persons of African descent with endothelin-1 gene variants. *JCI insight,* 2.

Tedla, Y. G., Yano, Y., Carnethon, M. & Greenland, P. 2017. Association between long-term blood pressure variability and 10-year progression in arterial stiffness: the multiethnic study of atherosclerosis. *Hypertension,* 69**,** 118-127.

Thijs, L., Staessen, J. A. & Fagard, R. 1992. Analysis of the diurnal blood pressure curve. *High Blood Pressure and Cardiovascular Prevention,* 1**,** 17-28.

Thomas, S. J., Booth Iii, J. N., Dai, C., Li, X., Allen, N., Calhoun, D., Carson, A. P., Gidding, S., Lewis, C. E. & Shikany, J. M. 2018. Cumulative incidence of hypertension by 55 years of age in blacks and whites: the CARDIA Study. *Journal of the American Heart Association,* 7**,** e007988.

Thompson, J. E., Smith, W., Ware, L. J., Mels, C. M., Van Rooyen, J. M., Huisman, H. W., Malan, L., Malan, N. T., Lammertyn, L. & Schutte, A. E. 2016. Masked hypertension and its associated cardiovascular risk in young individuals: the African-PREDICT study. *Hypertension Research,* 39**,** 158-165.

Thrasher, T. N. 2004. Baroreceptors and the long-term control of blood pressure. *Experimental physiology,* 89**,** 331-335.

Tientcheu, D., Ayers, C., Das, S. R., Mcguire, D. K., De Lemos, J. A., Khera, A., Kaplan, N., Victor, R. & Vongpatanasin, W. 2015. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: analysis from the Dallas Heart Study. *Journal of the American College of Cardiology,* 66**,** 2159-2169.

Tillin, T., Forouhi, N., Mckeigue, P. & Chaturvedi, N. 2005. Microalbuminuria and coronary heart disease risk in an ethnically diverse UK population: a prospective cohort study. *Journal of the American Society of Nephrology,* 16**,** 3702-3710.

Tobian, L. 1962. Relationship of juxtaglomerular apparatus to renin and angiotensin. *Circulation,* 25**,** 189-192.

Townsend, R. R., Rosendorff, C., Nichols, W. W., Edwards, D. G., Chirinos, J. A., Fernhall, B. & Cushman, W. C. 2016. American Society of Hypertension position paper: central blood pressure waveforms in health and disease. Elsevier.

Tozawa, M., Iseki, K., Iseki, C., Kinjo, K., Ikemiya, Y. & Takishita, S. 2003. Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension,* 41**,** 1341-1345.

Trudel, X., Milot, A. & Brisson, C. 2013. Persistence and progression of masked hypertension: a 5-year prospective study. *International Journal of Hypertension*, 2013.

Tu, W., Eckert, G. J., Hannon, T. S., Liu, H., Pratt, L. M., Wagner, M. A., Dimeglio, L. A., Jung, J. & Pratt, J. H. 2014. Racial differences in sensitivity of blood pressure to aldosterone. *Hypertension,* 63**,** 1212-1218.

Tully, M., Kos, A., Eastwood, D., Kusch, J. & Kotchen, T. 2015. Implementation of an adjunct strategy to reduce blood pressure in blacks with uncontrolled hypertension: a pilot project. *Ethnicity & disease,* 25**,** 168.

Turner, J. R., Viera, A. J. & Shimbo, D. 2015. Ambulatory blood pressure monitoring in clinical practice: a review. *The American journal of medicine,* 128**,** 14-20.

Ugajin, T., Hozawa, A., Ohkubo, T., Asayama, K., Kikuya, M., Obara, T., Metoki, H., Hoshi, H., Hashimoto, J. & Totsune, K. 2005. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. *Archives of Internal Medicine,* 165**,** 1541-1546.

Ukkola, O., Vasunta, R.-L. & Kesäniemi, Y. A. 2009. Non-dipping pattern in ambulatory blood pressure monitoring is associated with metabolic abnormalities in a random sample of middle-aged participants. *Hypertension Research,* 32**,** 1022.

Uzu, T., Nakao, K., Kume, S., Araki, H., Isshiki, K., Araki, S.-I., Kawai, H., Ugi, S., Kashiwagi, A. & Maegawa, H. 2012. High sodium intake is associated with masked hypertension in Japanese patients with type 2 diabetes and treated hypertension. *American Journal of Hypertension,* 25**,** 1170-1174.

Van Bortel, L. M., Struijker-Boudier, H. A. & Safar, M. E. 2001. Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension,* 38**,** 914-921.

Van De Vijver, S., Akinyi, H., Oti, S., Olajide, A., Agyemang, C., Aboderin, I. & Kyobutungi, C. 2013. Status report on hypertension in Africa--consultative review for the 6th Session of the African Union Conference of Ministers of Health on NCD's. *Pan Afr Med J,* 16**,** 38.

Van Keulen, H., Gomes, A., Toffolo, M., Oliveira, E., Silva, L., Alves, C., Almeida, C., Dutra, S., Aguiar, A. & Ferreira, A. 2017. Serum levels of nitric oxide and cytokines in smokers at the beginning and after 4 months of treatment for smoking cessation. International journal of cardiology, 230, 327-331.

Van Varik, Bernard & Rennenberg, Roger & Reutelingsperger, Chris & Kroon, Abraham & de Leeuw, Peter & Schurgers, Leon. 2012. Mechanisms of arterial remodeling: Lessons from genetic diseases. Frontiers in genetics. 3. 290. 10.3389/fgene.2012.00290.

Vasan, R. S., Larson, M. G., Leip, E. P., Evans, J. C., O'donnell, C. J., Kannel, W. B. & Levy, D. 2001. Impact of high-normal blood pressure on the risk of cardiovascular disease. *New England journal of medicine,* 345**,** 1291-1297.

Velasquez, M. T., Beddhu, S., Nobakht, E., Rahman, M. & Raj, D. S. 2016. Ambulatory blood pressure in chronic kidney disease: ready for prime time? *Kidney international reports,* 1**,** 94-104.

Verberk, W. J., Kessels, A. G. & De Leeuw, P. W. 2008. Prevalence, causes, and consequences of masked hypertension: a meta-analysis. *American Journal of Hypertension,* 21**,** 969.

Verdecchia, P., Angeli, F., Gattobigio, R., Borgioni, C., Castellani, C., Sardone, M. & Reboldi, G. 2007. The clinical significance of white-coat and masked hypertension. *Blood pressure monitoring,* 12**,** 387-389.

Verdecchia, P., Schillaci, G., Borgioni, C., Ciucci, A., Zampi, I., Battistelli, M., Gattobigio, R., Sacchi, N. & Porcellati, C. 1995. Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in essential hypertension. *Journal of Hypertension,* 13**,** 1209-1215.

Vickers, C., Hales, P., Kaushik, V., Dick, L., Gavin, J., Tang, J., Godbout, K., Parsons, T., Baronas, E. & Hsieh, F. 2002. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase (ACE2). *Journal of Biological Chemistry*.

Virdis, A., Giannarelli, C., Fritsch Neves, M., Taddei, S. & Ghiadoni, L. 2010. Cigarette smoking and hypertension. Current pharmaceutical design, 16, 2518-2525.

Viera, A. J., Hinderliter, A. L., Kshirsagar, A. V., Fine, J. & Dominik, R. 2010. Reproducibility of masked hypertension in adults with untreated borderline office blood pressure: comparison of ambulatory and home monitoring. *American Journal of Hypertension,* 23**,** 1190-1197.

Viera, A. J., Lin, F. C., Tuttle, L. A., Olsson, E., Girdler, S. S. & Hinderliter, A. L. 2016. Examination of Several Physiological and Psychosocial Factors Potentially Associated With Masked Hypertension Among Low-Risk Adults. *J Clin Hypertens (Greenwich),* 18**,** 784-9.

Virdis, A., Giannarelli, C., Fritsch Neves, M., Taddei, S. & Ghiadoni, L. 2010. Cigarette smoking and hypertension. *Current pharmaceutical design,* 16**,** 2518-2525.

Von Wowern, F., Bengtsson, K., Lindgren, C. M., Orho-Melander, M., Fyhrquist, F., Lindblad, U., Råstam, L., Forsblom, C., Kanninen, T. & Almgren, P. 2003. A genome wide scan for early onset primary hypertension in Scandinavians. *Human molecular genetics,* 12**,** 2077-2081.

Walker, R. W., Mclarty, D. G., Kitange, H. M., Whiting, D., Masuki, G., Mtasiwa, D. M., Machibya, H., Unwin, N. & Alberti, K. M. 2000. Stroke mortality in urban and rural Tanzania. *The Lancet,* 355**,** 1684-1687.

Wang, Y. C., Shimbo, D., Muntner, P., Moran, A. E., Krakoff, L. R. & Schwartz, J. E. 2017. Prevalence of masked hypertension among US adults with nonelevated clinic blood pressure. *American journal of epidemiology,* 185**,** 194-202.

Ware, L. J., Rennie, K. L., Gafane, L. F., Nell, T. M., Thompson, J. E., Van Rooyen, J. M., Schutte, R. & Schutte, A. E. 2016. Masked Hypertension in Low-Income South African Adults. *The Journal of Clinical Hypertension,* 18**,** 396-404.

Webb, I. & Treacher, D. 2015. Cardiovascular Physiology. *Clinical Intensive Care Medicine.* World Scientific.

Webster, A. C., Nagler, E. V., MORTON, R. L. & MASSON, P. 2017. Chronic kidney disease. *The Lancet,* 389**,** 1238-1252.

Wei, L. K., Au, A., Teh, L. K. & Lye, H. S. 2017. Recent Advances in the Genetics of Hypertension. *Hypertension: from basic research to clinical practice***,** 561-581.

Weinberger, M. H. 1996. Salt sensitivity of blood pressure in humans. *Hypertension,* 27**,** 481-490.

Weir, M. R. & Dzau, V. J. 1999. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *American Journal of Hypertension,* 12**,** 205S-213S.

White, W. B. & Morganroth, J. 1989. Usefulness of ambulatory monitoring of blood pressure in assessing antihypertensive therapy. *American Journal of Cardiology,* 63**,** 94-98.

WHO-ISH 1999. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *J hypertens,* 17**,** 151-184.

Wijkman, M., Länne, T., Engvall, J., Lindström, T., Östgren, C. J. & Nystrom, F. H. 2009. Masked nocturnal hypertension—a novel marker of risk in type 2 diabetes. *Diabetologia,* 52**,** 1258.

Williams, B., Lacy, P. S., Baschiera, F., Brunel, P. & Düsing, R. 2013. Novel Description of the 24-Hour Circadian Rhythms of Brachial Versus Central Aortic Blood Pressure and the Impact of Blood Pressure Treatment in a Randomized Controlled Clinical TrialNovelty and Significance. *Hypertension,* 61**,** 1168-1176.

Williams, B., Mancia, G., Spiering, W., Rosei, E. A., Azizi, M., Burnier, M., Clement, D. L., Coca, A., De Simone, G. & Dominiczak, A. 2018. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of

HypertensionThe Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Journal of Hypertension,* 36**,** 1953-2041.

Wing, L. M., Brown, M. A., Beilin, L. J., Ryan, P., Reid, C. M. & Committee, A. M. 2002. Reverse white-coat hypertension'in older hypertensives. *Journal of Hypertension,* 20**,** 639-644.

Witherow, F. N., Helmy, A., Webb, D. J., Fox, K. A. & Newby, D. E. 2001. Bradykinin contributes to the vasodilator effects of chronic angiotensin-converting enzyme inhibition in patients with heart failure. *Circulation,* 104**,** 2177-2181.

WMA 2001. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human participants. *Bulletin of the World Health Organization,* 79**,** 373.

Wolf, J., Hering, D. & Narkiewicz, K. 2010. Non-dipping pattern of hypertension and obstructive sleep apnea syndrome. *Hypertension Research,* 33**,** 867.

Woodhouse, P. R., Khaw, K.-T. & Plummer, M. 1993. Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. *Journal of Hypertension,* 11**,** 1267-1274.

Woodiwiss, A. J., Scott, L., Maseko, M. J., Majane, O. H., Vengethasamy, L., Redelinghuys, M., Sareli, P. & Norton, G. R. 2011. Relationship of predominantly mild current smoking to out-of-office blood pressure in a community sample in Africa. Journal of Hypertension, 29, 854-862.

Xue, B., Johnson, A. & Hay, M. 2007. Sex differences in angiotensin II-induced hypertension. *Brazilian journal of medical and biological research,* 40**,** 727-734.

Yano, Y. & Bakris, G. L. 2013. Recognition and management of masked hypertension: a review and novel approach. *Journal of the American Society of Hypertension,* 7**,** 244-252.

Yano, Y. & Kario, K. 2012. Nocturnal blood pressure and cardiovascular disease: a review of recent advances. *Hypertension Research,* 35**,** 695.

Zhang, D., Cheng, Y., Guo, Q., Xu, T., Yang, Y., Li, J., Sheng, C., Huang, Q., Wang, J. & Li, Y. 2018. A1495 Subtypes of Masked Hypertension and Their Associations with Target Organ Damage in Untreated Chinese Patients. *Journal of Hypertension,* 36**,** e121-e122.

Zhang, D., Shen, X. & Qi, X. 2016. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *Cmaj,* 188**,** E53-E63.

Zhang, L., Li, Y., Wei, F.-F., Thijs, L., Kang, Y.-Y., Wang, S., Xu, T.-Y., Wang, J.-G. & Staessen, J. A. 2015. Strategies for Classifying Patients Based on Office, Home, and Ambulatory Blood Pressure MeasurementNovelty and Significance. *Hypertension,* 65**,** 1258-1265.

Zhang, Z., Cogswell, M. E., Gillespie, C., Fang, J., Loustalot, F., Dai, S., Carriquiry, A. L., Kuklina, E. V., Hong, Y. & Merritt, R. 2013. Association between usual sodium and potassium intake and blood pressure and hypertension among US adults: NHANES 2005–2010. *PloS one,* 8**,** e75289.

Appendix 1: Ethics Clearance Certificate

R14/49 Mr Nyundu Franswell

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170416

NAME: (Principal Investigator)	Mr Nyundu Franswell
DEPARTMENT:	School of Physiology Hypertension Clinic
PROJECT TITLE:	Masked Hypertension and Cardiovascular Outcomes in People of African Descent
DATE CONSIDERED:	05/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr M.J. Maseko
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/07/2017

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 in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised 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 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 review April and will therefore be due in the month of April 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: Turnitin Plagiarism Report

Turnitin Originality Report

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Cardiovascular diseases (CVDs) which include diseases of the heart, cerebrovascular diseases, and peripheral vascular diseases have become endemic globally. According to the World Health Organisation (WHO), CVDs are now indisputably a leading cause of preventable mortality and morbidity worldwide. They are accountable for over 17.3 million deaths per year (Zhang et al., 2016). Their occurrence is no longer limited to economically developed countries only, but the prevalence of these diseases is escalating even in low income and developing areas such as those in Sub-Sahara-Africa (SSA). Majority (82%) of premature deaths due to CVDs are occurring in low income countries (Puska et al., 2011). The increase in the prevalence of CVDs in low-income areas is parallel with the forecast of the WHO, which predicted that in a 10-year period from 2006 to 2016, deaths due to non-communicable diseases would increase by more than 24% in Africa. In South Africa, non-communicable disease, counting CVDs are responsible for an estimated 43% of total adult deaths and CVDs account for almost a fifth of these deaths (Bradshaw et al., 2003, Sliwa et al., 2008). Typically, infectious diseases have been the main cause of death in low-income areas. However, the epidemiological transition (ET) has fuelled CVD risk factors such as dyslipidaemia, diabetes, obesity, hypertension (HT), metabolic and endothelial dysfunctions and consequently hastening mortality rates in low-income areas. These risk factors promote the progression of CVDs because they share some form of interrelation and interaction through one pathophysiological mechanism or another (Mozaffarian et al., 2008, Murray et al., 2003). While all of these risk factors contribute to the progression of CVDs, HT is an acknowledged and most prominent established risk factor for CVD (Okpechi et al., 2007). So what is the evidence to support that HT contributes to a significant percentage of CVD mortality and morbidity in a population? Out of ~17 million deaths due to CVDs worldwide, 7.5 million deaths and 57 million disability adjusted life years are attributed to poorly controlled HT. In Africa, this burden is rising at a faster rate as compared to other parts of the world (Adeloye and Basquill, 2014). The fraction of the worldwide burden of disease attributable to HT has increased considerably from about 4.5% in the year 2000 to 7% in 2010, and is still rising (van de Vijver et al., 2013). Apparently HT was virtually absent in African in the first half of the twentieth century, however, estimates now show that over 40 percent of adults in most parts of Africa have HT (Addo et al., 2007). Epidemiological data demonstrates that the prevalence of HT has amplified significantly over the years and that in the year 2000; ~80 million adults had HT in SSA. Predictions based on the current data suggest that the number will increase to ~150 million by the year 2025 (Opie and Seedat, 2005). Further, to support the suggestion that HT has become the single most important cause of mortality and morbidity in areas of Africa, evidence shows that complications of HT, particularly stroke and heart failure have also become progressively more common in areas where HT is on the rise (Mensah, 2008, Walker et al., 2000). In line with this information, a recent systematic review has shown that in the last 10 years, systolic BP has risen highest in east, west, central and southern Africa more than in any other region of the world (Ogah and Rayner, 2013). As highlighted earlier, the prevalence of CVDs and their risk factors such as HT have increased as a manifestation of the ET in the SSA region as observed in other parts of the world (Dalal et al., 2011). The ET is a result of changes in economic