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Isolated nocturnal hypertension and target organ damage in a population of African descent



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

by

Edgar Matome Phukubje

(1578771)

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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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG 100 1922 2022 | FACULTY OF HEALTH SCIENCES

Declaration

I, Edgar Matome Phukubje, declare that this thesis, submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, is my own work. Work by other scholars has been acknowledged and referenced accordingly. The body of work contained within this thesis has not been previously submitted for any degree to the current or any other institution.

I certify that the assessments contained in this thesis have the approval of the Committee for Research in Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg. The ethics approval number is **M170214**.



Edgar Matome Phukubje, 1578771

Date: 28 October 2024

I certify that the above statement is correct:



Associate Professor Muzi Maseko

(Supervisor)

Date: 28 October 2024

Dedication

"Kodumela moepathutse, ga go lehumo le letjwago kgauswi".

I dedicate this thesis to my family: my mother, my grandmother, and my three sisters. I am grateful for your continued support throughout this journey. No matter the circumstances, you have always allowed me to be a dreamer. Lastly, this is to the memory of my late grandfather.

Acknowledgements

Gratitude goes to the **most-high God**, for You are the strong tower that kept me safe to this day, receive the Glory and Honour. I would like to extent my fervent gratitude to my supervisor, **Associate Professor Muzi Maseko**. This milestone would not have been possible without your brilliant guidance and expertise. Not to mention your patience and how you always found a way to help me see the bigger picture, no matter the hurdle. Moreover, I would like to thank **Mrs Mokgadi Maseko**, for allowing me to be your "last-born" son through this academic journey at Wits. Your constant check-ups and messages really meant a lot to me. Thank you for your love and patience, even when we did not see eye-to-eye. Thank you, **Dr. Thamsanqa Nyundu**, for always encouraging me, even when I was doubtful. Likewise, **Dr. Monare Thulo**, you have been there through every step of this PhD journey, I am truly grateful for your unwavering support and for your strategic advice. I would further like to extend my gratitude to my colleagues from the **Human Nutrition Research Laboratory** (HNRL), no matter the arguments; we always achieved what we set out to do. I would like to acknowledge the constant encouragement from **Dr. Carol Hartmann**; thank you for being a great "Boss" and for allowing me time-off when needed, to focus on this thesis. I would like to thank **Rachel Babaganov** (Germany) and **Amani Jamal** (Yemen) for the constant motivation and support. You may have been across the globe, but our Zoom meetings made me feel like you were with me every step of the way; you have been an incredible team to work with during our EARTHS time together. I have received a lot of support and "check-ins" from other colleagues and friends, I appreciate ALL of you. There would not be data that culminated this thesis without **participants of the South African Hypertension and Diet Study** (SAHDS), a huge thank you goes to you for your voluntary participation in this research. Lastly, I would like to appreciate the financial support that afforded this degree, support received from the **National Research Foundation (NRF), the German Academic Exchange Service (DAAD)**, and the University of the Witwatersrand's post-graduate office (PMA), the Faculty of Health Sciences' FRC. Finally, I would like to express my deepest gratitude to the ECAD program and its organisers; this is for "fuelling" the last lap of this journey.

Abstract

The use of ambulatory blood pressure monitoring (ABPM) has revolutionised the approach to hypertension diagnosis and management. The ability to monitor blood pressure over a 24-hour period has enabled researchers to monitor blood pressure profile away from the doctor's clinic, which has led to the diagnosis of various hypertension phenotypes like masked hypertension, isolated nocturnal hypertension (INH) and isolated daytime hypertension (IDH), and others. Previous studies have shown that night-time blood pressure is more closely related to target organ damage compared to daytime blood pressure. Since more studies indicate that people of African ancestry have elevated night-time blood pressure compared to other population groups, nocturnal blood pressure monitoring in this population group is crucial. However, there are few studies that have investigated the prevalence of INH, and their results are inconclusive. Hence the impact of INH on cardiovascular target organ damage is not well understood in this population group. It has been reported that dietary salt intake (DSI) has more severe cardiovascular outcomes in African populations compared to non-African populations groups because they are said to be salt sensitive. However, there are no studies that have investigated the relationship between 24-hour urinary salt excretion and 24-hour dipping patterns in populations of African ancestry. In addition, the impact of INH on target organ damage has never been compared to that of IDH. Hence, current intervention strategies primarily rely on daytime blood pressure to diagnose and treat hypertension. The relationship between age and blood pressure is well understood, but current studies have mainly focused on daytime blood pressure. The impact of age on nocturnal blood pressure is not well understood in this population group, and it is also unclear whether the age-related changes in nocturnal blood pressure translate to any cardiovascular target organ changes. Therefore, the aim of this study was to determine the relationship between INH and cardiovascular target organ damage in a South African population of African ancestry.

A total 1600 participants above 18 years were recruited. These form part of the ongoing South African Hypertension and Diet Study in the Human Nutrition Research Laboratory. Office blood pressure was measured conventionally and through SpaceLabs ambulatory oscillometric monitors for 24-hours. Target organ function was determined through echocardiographic measurements and applanation tonometry using the sphygmocor device. 24-hour urine samples were collected to determine electrolyte excretion rates. Blood was collected when the participants visited the clinic. Only data with complete 24-hour ABPM matched with complete urinary collections were included for data analysis and the final sample was 796 participants.

Findings from the current study showed that 11% of the participants had INH, 13% had 24-hour sustained hypertension and 4% had IDH. The three groups had different dipping patterns. The sustained hypertensive group were non-dippers, IDH group were dippers, and the INH group had two dipping patterns: non-dipping (IND) and reverse dipping (IRD). Urinary electrolyte concentrations were significantly higher in IDH, and lower in INH. The INH group and 24-hour sustained hypertensives were the oldest cohort, while the NT and IDH were youngest. Pulse wave velocity (PWV) was significantly higher in the IND and IRD. The NT and IDH group had the lowest PWV. PWV in the INH was similar but not significantly different to the 24-hour sustained HT group. These findings indicate that the two INH subtypes (IND and IRD) damage large arteries to a similar effect as 24-hour sustained hypertension, while IDH does not cause any damage. The ABPM results were used to show changes in blood pressure with age. Different age group ranges were used, in increments of 10 years. Increased nocturnal blood pressure was associated with being older. Additionally, age-related changes in nocturnal blood pressure were associated with pre-clinical diastolic dysfunction. The current findings further show that blood pressure related cardiovascular target organ damage occurs during night-time in this population group. Urine analysis showed increased excretion in IDH and sodium retention in INH. Aldosterone levels were significantly higher in the INH, compared to 24-hour sustained HT group. Low aldosterone and salt retention increased nocturnal BP in the INH group. This means the current rise in the prevalence of cardiovascular disease in people of African descent despite increased efforts to diagnose and treat hypertension, is driven by INH, which remains undiagnosed because of the over reliance on conventional blood pressure measurement.

Conference presentations

Edgar Phukubje, Muzi Maseko. *Isolated nocturnal hypertension predicts target organ damage above isolated daytime hypertension in a population of African ancestry*. 50th Congress Anniversary of the Physiology Society of Southern Africa (PSSA), University of Limpopo, 25-28 August 2024. Oral presentation.

Edgar Phukubje, Muzi Maseko. *The association between increasing age and blood pressure*. PSSA 49th Congress, Stellenbosch, 4-7 September 2022. Oral presentation.

Edgar Phukubje, Muzi Maseko. *The prevalence of isolated nocturnal hypertension and its association with arterial stiffness in an African population*. AAPS-PSSA Virtual conference. 12-15 September 2021. Oral presentation.

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Edgar Phukubje, Grace Tade, Muzi Maseko. *The sodium-to-potassium ratio determines arterial stiffness independent of blood pressure in hypertensive people of African ancestry*. 10th Wits Cross Faculty Postgraduate Symposium. 03-04 September 2019. Oral presentation.

Edgar Phukubje, Muzi Maseko. *The sodium-to-potassium ratio determines arterial stiffness independent of blood pressure in hypertensive people of African ancestry*. Molecular Biosciences Research Thrust. Postgraduate research day. 29 November 2018. Oral presentation.

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List of Abbreviations

24-Hr BP	24-hour blood pressure
AASK	African American Study of Kidney Disease and Hypertension)
ABPM	Ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
BMI	body mass index
BP	Blood pressure
BPM	Blood Pressure Monitoring
CAD	Coronary Artery Disease
CBPM	Conventional Blood Pressure Monitoring
CHF	Congestive Heart Failure
cIMT	Intima Media Thickness
CVDs	Cardiovascular diseases
DAAD	The German Academic Exchange Service
DASH	Dietary Approaches to Stop Hypertension
DBP	Daytime Blood Pressure
DD	Diastolic Dysfunction
DHF	Diastolic Heart Failure
DSI	Dietary Salt Intake
EAH	The European Society of Hypertension
EF	Ejection Fraction
ESC	European Society of Cardiology
FRC	Faculty of Health Sciences Research Committee
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HNRL	Human Nutrition Research Laboratory

HT	Hypertension
IHD	Ischemic Heart Disease
INH	Isolated nocturnal hypertension
m/s	metres per second
MAP	Mean Arterial Pressure
mm Hg	Millimetres of Mercury
Na^+	Sodium
NBP	Night-time/Nocturnal Blood Pressure
NRF	National Research Foundation
OSA	Obstructive Sleep Apnoea
PAMELA	Pressioni Arteriose Monitorate e Loro Associazioni
PMA	Postgraduate Merit Award
PWV	Pulse Wave Velocity
RAAS	Renin-Angiotensin-Aldosterone System
SAHDS	South African Hypertension and Diet Study
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
TOD	Target Organ Damage

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Chapter 1

Introduction

1.1 Preview of thesis

The work presented in this thesis is made up of seven chapters. The first chapter give the brief background into the overall study, including the rationale. Chapter two gives the literature review related to the overall topic. It pieces together supporting literature around blood pressure with its many facets and complexities to date; and culminates to the justification and purpose of the overall study. In summary, the chapter introduces BP in cardiovascular diseases and how it leads to hypertension. The definition of hypertension is provided and the two ways that it can be monitored and diagnosed. The circadian rhythm of BP is described, together with insights between daytime and night-time BP. The regulation of BP is presented, along with various systems that determine said regulation. Finally, isolated nocturnal hypertension is introduced. Its association with nocturnal BP decline and how they relate to cardiovascular target organ damage is presented as well.

The third chapter encompasses all the methodological approaches from the thesis. It gives details on Ethical considerations for the study, and then the study design as approved by the ethics committee. All the assessments and equipment employed in the study are described in detail, and finally the statistical software and tests employed in order to logically present the findings from the above assessments are described. Chapter four starts by giving background literature to introduce the overall focus and aim in the chapter. It gives background literature on BP and arterial stiffness, and their association with cardiovascular target organ changes. After assessments the chapter gives findings related to INH. The prevalence in a South African black population. The discussion then focuses on lifestyle and behavioural factors that are associated with INH. It further describes differences in target organ changes in INH and sustained 24-hour hypertension.

The fifth chapter introduces another hypertension phenotype: IDH. It gives descriptive background and comparison with INH. The findings logically compare these two phenotypes, their risk factors, and confounders; and how they eventually associate with nocturnal BP decline and the vasculature. Chapter six, which is structurally similar to the former, looks at thresholds for BP. There is informative literature, and context is provided regarding its impact on night-time BP and target organ changes. The chapter further describe the impact of ageing, coupled with night-time BP cut-offs and how they impact on the functioning heart. The seventh and last chapter discusses all the pertinent findings from chapter three to five, contextualise their findings. It gives the potential application of key findings in the clinical setting. It lastly

gives propositions on study limitations and potential future work. The final sections include all the cited sources. Also included are the appendices.

1.2 General background

Hypertension is a global challenge. It is associated with damage to other body systems or organs, leading to its increased mortality when compared to other diseases (Deere and Ferdinand, 2020). Hypertension has various risk factors, and it is reported that it can present differently in different population groups based on genetic and other lifestyle or environmental factors (Yusuf *et al*., 2020; Payne, 2012). It is reported that people of African descent have a higher prevalence. Their prevalence has been attributed to genetics more than other factors such as environmental and lifestyle (Aronow, 2017). Hypertension remains underreported and undertreated in most communities. Yet there has been improved efforts to increase its awareness, and control measures (Ferdinand *et al*., 2020). The lack of improvement in hypertension diagnosis and treatment, starts with its monitoring. Currently, there is high reliance on conventional methods of blood pressure measurement, the clinic or office blood pressure measurement. However, it has its own shortfalls (Ettehad *et al*., 2016; Lewington *et al*., 2003). For a long time, office/clinic blood pressure measurements have been associated with the white coat effect. Reports have shown that the stress or anxiety of visiting the doctor or health facilities was associated with increased blood pressure. This creates a two-fold challenge. Patients who may be under the "white-coat effect" could be wrongfully diagnosed (Kronish *et al*., 2018). The second challenge is that daytime or office blood pressure monitoring does not account for the diurnal changes in blood pressure (Kario, 2005).

It is reported that blood pressure follows a circadian rhythm. It is expected that blood pressure decreases during night-time by about <10% of its daytime values. This introduced the dipping phenomenon. With dipping, reports have shown that a lack of dipping (non-dipping) has been associated with severe cardiovascular damage (Casagrande *et al*., 2020). The introduction of dipping emphasises that blood pressure monitoring should not be limited to daytime measurements or clinic measurements. Including a 24-hour blood pressure monitoring is key in uncovering different types of hypertensions, that may also persist under different conditions. Twenty-four blood pressure monitoring has been used in conjunction with other investigations to study associated risks that lead to lack of dipping. There are conditions that increase blood pressure at night, thus leading to non-dipping (Douma and Gumz, 2018). Among the black populations, one the risk factors for hypertension are DSI. It is reported that they metabolise

dietary salt different to other ethnic groups, like Europeans (Elijovich *et al*., 2016). They are reported to be salt sensitive and retain salt. Salt sensitivity implies that they experience an increase in their blood pressure following DSI (Mishra *et al*., 2018). Whereas salt retention means that members of African descent may not excreted urinary sodium when compared to non-African counterparts. While these are on opposite site, they are associated with how black people are genetically designed to handle DSI (Lindhorst *et al*., 2007). Nonetheless, studies show that these are some risk factors that increase night-time blood pressure, contributing to non-dipping or even reverse dipping. All which are detrimental to the overall cardiovascular health (Elijovich *et al*., 2016). Therefore, using 24-hour ambulatory blood pressure monitoring is key in uncovering hypertension phenotypes or blood pressure patterns, since some of these are associated with severe cardiovascular target organ damage. Isolated nocturnal hypertension is one of the blood pressure or hypertension phenotype associated with target organ damage (Ogedegbe *et al*., 2013). It can only be diagnosed through 24-hour blood pressure monitoring.

1.3 Justification of study

Isolated nocturnal hypertension (INH) is a condition in which night-time blood pressure is elevated even though daytime BP is normal. The Jackson study indicates that there is a high prevalence of INH in black communities (Ogedegbe *et al*., 2013). However, these studies have been conducted in African American communities and to date this condition remains undiagnosed in black communities of South Africa. Furthermore, no studies have been conducted to determine whether INH is associated with TOD in these communities. One of the limitations of community-based South African studies is that they employ conventional BP measurements, a method that has several limitations, including the inability to diagnose hypertension phenotypes like INH. Consequently, there may be many people who may be at risk of suffering cardiovascular events like strokes or myocardial infarctions even though they present with a normal conventional BP, whilst other risk factors may only be uncovered through 24-hour ABPM. Therefore, there is a critical need for studies to use ambulatory BP monitoring in black South African communities to diagnose and treat hypertension and its phenotypes. The longitudinal nature of these studies could help determine if INH is associated with TOD, and whether the mechanisms that govern the progression of INH are similar to international studies.

1.4 Rationale

The definition and classification of nocturnal hypertension, notably in its isolated form, has different clinical implications (Li and Wang, 2013). The prevalence and the severity of INH denote its importance in the management of hypertension; and frequent use of ABPM express clinical relevance in this regard (Abdalla *et al*., 2015; O'Brien, 2009). Previous studies conducted in South Africa indicate that there is a rise in hypertension-related cardiovascular events (Alberts *et al*., 2005). Since INH confers cardiovascular risks, and currently remains undiagnosed, the current observed epidemiological transition from infectious to cardiovascular diseases may be partly due to many underlying factors, one of which may include INH. Thus, the diagnosis of INH may be critical in the control of HT and may be pivotal in the alleviation of the cardiovascular disease burden in black South African communities. The current limited use of ABPM could be masking INH in health care settings and communities. The cross-sectional nature of the studies conducted so far across the globe has its own limitations in determining the association of INH with TOD within a South African context. This current study investigated whether INH is a clinical entity that that requires intervention in South Africa, based on whether it is associated with TOD or not.

1.5 Purpose of the study

To determine the prevalence of INH and investigate its association with (TOD), the following objectives were derived to:

i. Determine the prevalence of isolated nocturnal hypertension in South Africa.
ii. Determine the association between isolated nocturnal hypertension and target organ changes using echocardiography, pulse wave analysis.
iii. Establish whether isolated nocturnal hypertension and isolated daytime hypertension have similar progression and similar risk factors.
iv. Determine and compare cardiovascular target organ changes between isolated nocturnal hypertensives, isolated daytime hypertensives, sustained 24-hour hypertensives and normotensives.
v. Use 24-hour urinary sodium excretion rates and plasma aldosterone concentrations to assess whether dietary mineralocorticoids play a role in the development of isolated nocturnal hypertension.

Chapter 2

Literature Review

2.1 The role of blood pressure in cardiovascular diseases

Cardiovascular diseases (CVDs) are undoubtedly the largest contributors to total mortality and disability worldwide (Gaziano, 2022). By virtue of their name, CVDs affect the overall vasculature, the heart, and related organs like the kidneys, the eyes and the brain. They can present in various forms, and include, but are not limited to, ischemic heart disease (IHD), coronary artery disease (CAD), cardiac arrest, peripheral vascular disease, stroke, and hypertensive heart disease, which can ultimately result in heart failure (Jagannathan *et al*., 2019; Roth *et al*., 2015; Yusuf *et al*., 2014). CVDs have various risk factors that are associated with adverse end organ changes. These risk factors can be grouped as modifiable and non-modifiable risk factors (Wood, 2001). Modifiable risk factors include dietary habits, sedentary lifestyle and substance use such as tobacco smoking or alcohol consumption (Yusuf *et al*., 2020). Modifiable risk factors are further labelled as behavioural risk factors (Piepoli *et al*., 2016). Non-modifiable risk factors include family history, gender, age, and ethnicity (Payne, 2012). These risk factors, regardless of category, exacerbate the rate at which CVDs progress and the severity thereof. Among these risk factors, studies show that age is a strong predictor of cardiovascular outcome as ageing is related with the development of CVDs (Rapsomaniki *et al*., 2014). There is, nonetheless, a shift regarding the effects of age on CVDs, because younger populations are steadily presenting with CVDs at earlier ages (Lakatta, 2002). Nonetheless, baring from the effects of these traditional risk factors, elevated blood pressure remains a major contributor to CVDs and their progression. There is a direct association between elevated BP increase and CVDs, and it is associated with risk factors for heart failure and kidney disease, more so when elevated BP leads to hypertension (Fuchs and Whelton, 2020).

2.2 Hypertension

Various mechanisms contribute to high blood pressure (BP) and how it ultimately progresses into hypertension (HT). Neural and renal processes elevate BP (Hart and Charkoudian, 2014; Conway *et al*., 1984). Cardiac output and peripheral vascular resistance are the main contributors to elevated BP (Jordan *et al*., 2018). Other predispositions that contribute towards the development of HT include race and genetics (Luft *et al*., 1991; Grim *et al*., 1984). Poor awareness in other ethnic groups may contribute to the severity of HT and thus should not be ignored (Deere and Ferdinand, 2020). Furthermore, environmental, and behavioural risk

factors that are associated with CVDs can be translated into the causal mechanisms for HT (Kokubo *et al*., 2019). In 2015 over one billion people were diagnosed with HT globally, ~45% of which were adults. With advancing age, the prevalence of HT increases. In the adult population a more sedentary lifestyle could be the leading cause (Guedes *et al*., 2010). However, it has been reported that the transition and adoption of more westernised lifestyles are increasing the HT prevalence irrespective of income status (Gheorghe *et al*., 2018). These transitions further come with changing dietary and behavioural habits such as increased alcohol intake, smoking; coupled with increased sedentary lifestyles these lead to body weight changes that may increase the risk of HT (Aronow, 2017). HT risk factors and mechanisms are common, whether it presents as essential HT or has secondary causes (Onusko, 2003). Although it is reported that the latter form of HT may affect ~10% of the hypertensive population, this may have increased over the years. Risk factors for secondary HT may have reversible damage if diagnosed early. However, since there is a shift in the age of presentation, with an increasing prevalence in the younger population, HT diagnosis and management has is becoming more challenging (Charles *et al*., 2017; Vongpatanasin, 2014). Although the aetiologies for HT may vary, there may be common causes with co-prevalence (Goodfriend, and Calhoun, 2004). Renovascular hypertension is one such cause that may be present in patients with atherosclerosis (Textor and Lerman, 2010). Renal disease, in the form of elevated serum creatinine level or proteinuria is another associated cause of HT; although, it can be both a cause and consequence of HT (James *et al*., 2014). Within the function of Renin-Angiotensin-Aldosterone System (RAAS), excessive production of aldosterone is associated with HT. Its association is independent of the RAAS as it also increases BP (Mosso *et al*., 2003). Obstructive sleep apnoea (OSA), although common in older, obese people of the male gender, is associated with HT (Brown *et al*., 2022). A disrupted normal circadian BP rhythm is associated with elevated BP and HT. Lastly, salt retention affects the overall BP profile (Baguet *et al*., 2005; Logan *et al*., 2001). Regardless of the cause, elevated BP is mostly reported in the context of overall cardiovascular risk. The haemodynamic shift that leads to HT may vary between individuals. Within the context of diagnosing HT, elevated daytime BP is the first line of diagnosis. Notwithstanding, there could be other factors that affect the vasculature without elevating daytime BP and yet causing some cardiovascular damage. Therefore, separating the normotensive and hypertensive population could be misleading since different populations may have differing BP profiles that may still render the overall vasculature susceptible to adverse changes (Brown and Haydock, 2000).

2.3 The diagnosis of hypertension

2.3.1 Determining blood pressure through conventional methods

The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) recommend that the threshold values for diagnosing HT is 140/90 mm Hg when measured through conventional methods. The classification of BP is further categorised below in Table 2.1 to indicate various HT grades (Williams *et al*., 2018). Hypertension thresholds have been used as the standard for HT diagnosis and prevalence among the old and the young, and in different ethnic groups (Howard *et al*., 2018). It is crucial to properly monitor BP and identify individuals that may be at risk of developing adverse outcomes. The long-standing method of monitoring BP is office BP, the mercury sphygmomanometer, and conventional automated machines. For the purpose of this thesis, these methods were grouped as conventional blood pressure monitoring (CBPM). These methods often require multiple measurements or visits to a health care facility to establish a diagnosis (Egan and Forman, 2018). Monitoring BP conventionally has been the gold-standard for decades due to its long-established practice. Furthermore, there have been great efforts in improving CBPM through increased training to reduce potential observer bias, intra-observer variations or differences in techniques (Veiga *et al*., 2003; Armstrong, 2002). Nonetheless, it is still reported to have shortcomings. Conventional blood pressure monitoring is associated with limited reproducibility, and white coat effect of HT. White coat HT is not regarded as true hypertension, because individuals present with elevated office BP because of anxiety brought about by visiting a health care facility or doctor's office (Nuredini *et al*., 2020). Consequently, such individuals, may be unnecessarily treated with antihypertensive medication. The converse holds true, misclassifying non-elevated office BP implies that patients who require antihypertensive intervention are often overlooked, whereas they may be at risk of HT-related morbidity (Kronish *et al*., 2018).

When measured properly, CBPM should correlate with 24-hour ambulatory BP monitoring (ABPM). This has not been the case in most clinical settings (O'Brien *et al*., 2001). Office or conventional BP readings have been shown to be higher than ABPM readings (Myers, 2016; Lamarre-Cliché *et al*., 2011). CBPM has been used in multiple published research. Its reliability is questioned in non-research environments when there are marked variations due to non-adherence to the measurement guidelines. At times this has led to an overestimation of BP

and variable validity (Graves *et al*., 2003; Gustavsen *et al*., 2003). It is expected that accurate CBPM should correlate to ABPM (Figure 2.1).

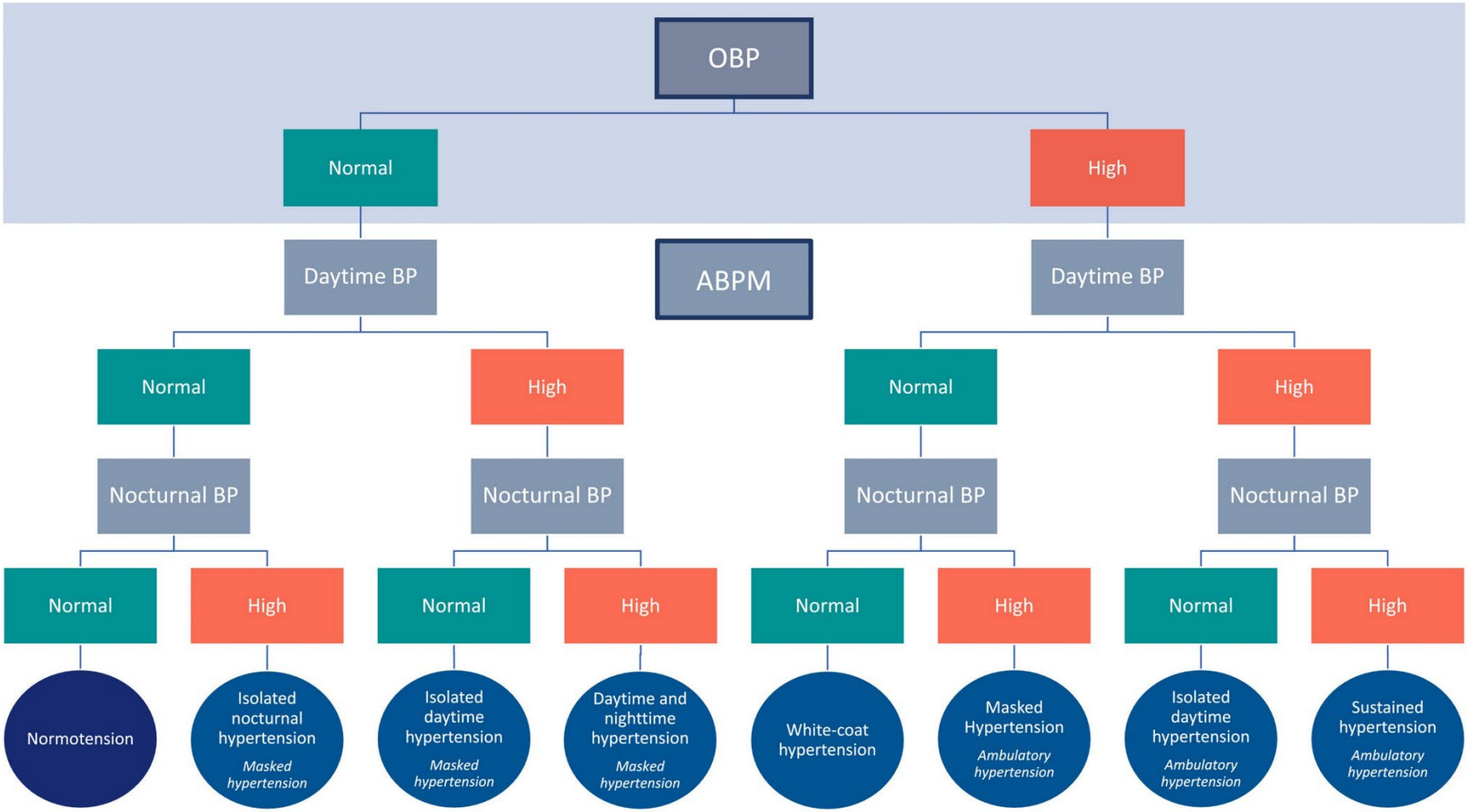


Figure 2.1 Definitions of different types of hypertensions according to office BP in combination with daytime and nocturnal ambulatory BP.
*Adapted from Seeman *et al*., 2022; OBP, Office Blood Pressure; ABPM, Ambulatory Blood Pressure Monitoring.

However, the burden of disease and the conditions of state health care facilities do not always provide an environment where patient monitoring according to the standards of CBPM can be followed on a routine basis, thus leading to differences between in-and out of office BP monitoring (Cloutier *et al*., 2015).

Table 2.1 Classification of office blood pressure and definitions of hypertension grade

Category	SBP **(mmHg)**		DBP **(mmHg)**
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110

[a]Adapted from Williams *et al*. (2018). SBP, Systolic blood pressure; DBP, Diastolic blood pressure; mm Hg, millimetre mercury BP category is defined according to seated clinic blood pressure and by the highest level, whether systolic or diastolic.

2.3.2 Determining blood pressure through ambulatory monitoring

Ambulatory blood pressure monitoring forms part of the out of office BP monitoring interventions and is reported as a better predictor of cardiovascular risk. The oscillometric monitors measure BP while participants are in their own environment and can be used to make a clinical decision and require less patient-clinic visits (Dadlani *et al*., 2019). Oscillometric monitors are widely accepted since they require no specialised training. They present with minimal inter-observer differences since they are automated. Therefore, BP estimates provided by oscillometric monitors are reliable since they need minimal operator involvement and provide standardised 24-hour assessment (Table 2.2) that can be used as reference points for individual BP profile (O'Brien *et al*., 2018). However, they do require patient compliance for proper BP measurements. Using ABPM involves patients keeping diary records of sleep and awake periods, mealtimes, or medication intake. This information is used to correlate BP disturbances to daily activities and to further highlight the transition periods between the evening and mornings (Li *et al*., 2005). Thus, using ABPM shows a 24-hour BP profile, that

considers resting and non-resting periods, and clinical information that is known to affect BP. This is important since BP can be volatile in that it is influenced by various factors that can either elevate it or decrease it. Being able to determine a BP profile and simultaneously being able to isolate or correct for factors that can influence BP makes ABPM a superior method of BP monitoring (O'Brien *et al*., 2013). Since it is essential to properly diagnose HT so that appropriate intervention methods can be initiated, using ABPM further allows the stratification of BP phenotypes in hypertensive cohorts and risk stratification in normotensive cohorts (Ben-Dov *et al*., 2007). This could improve intervention methods in the management of HT. Through ABPM, other HT phenotypes can be diagnosed and with frequent monitoring perhaps even early on in their progression. Ambulatory blood pressure monitoring is also aimed at advancing HT diagnoses without the white coat effect or masked HT. It attenuates the white coat effect because measurements are away from the clinical settings (Myers *et al*., 2009). It is further essential in diagnosing masked HT. Masked HT can be seen as the opposite of white-coat HT since patients present with normal office BP but have an elevated BP out of the clinic setting (Pickering *et al*., 2007). Ambulatory BP monitoring allows the stratification of the daytime and night-time BP determination in addition to the overall 24-hour BP profile. It further allows for their effects on end organ damage to be determined in isolation (Fan *et al*., 2010; Hansen *et al*., 2007; Boggia *et al*., 2007).

Table 2.2 Classification of ambulatory blood pressure and definitions of hypertension grade

Ambulatory blood pressure monitoring (mm Hg)		
Optimal	**Daytime**	**<120 and <80**
	Night-time	**<100 and <65**
	24-hours	**<115 and <75**
Normal	**Daytime**	**<135 and <85**
	Night-time	**<110 and <70**
	24-hours	**<130 and <80**
Hypertension	**Daytime**	**≥135 or ≥85**
	Night-time	**≥120 and ≥70**
	24-hours	**≥130 and ≥80**

[a]Adapted from Mancia *et al*. (2013). Blood pressure thresholds are given in mm Hg. Consensus classification proposed by the 2013 European guidelines.

2.4 The treatment of hypertension: conventional vs ambulatory blood pressure monitoring

In the management of HT, there are various goals that must be met. For this reason, research efforts have investigated how lowering BP may help subvert its impact on CVDs, since modest increases in BP present with adverse effects on CVDs outcome (Ettehad *et al*., 2016; Lewington *et al*., 2003). It has been reported that reducing BP reduces the risks attributable to CVDs, even in established vascular disease that does not present with extreme BP (Williamson *et al*., 2016). Nonetheless, Roth *et al*. (2015) reported that lowering BP in patients without vascular disease does not show consistent patterns of improved CVD-risk. Perhaps the regulation of BP without vascular disease may be subject to different mechanisms. Another effect to the lack of consistency may be BP monitoring methods during interventions. In estimating the impact of BP on CVDs, BP should be monitored at clinical settings and away from clinical settings. Thus, allowing BP monitoring under various conditions while monitoring the effects of the interventions. Monitoring BP in this way could alleviate underestimations of the effects of reduced BP in the presence or absence of vascular diseases and other anomalies (Joseph *et al*., 2017; Murray and Lopez, 1999).

For decades CBPM has been accepted as the standard measure of BP and the mean BP was used as the basis for any BP-related interventions (Howard *et al*., 2018). However, subject to error readings and measurement techniques, intervention methods were inappropriately initiated. Other methods were explored, and ABPM later became the gold-standard for BP monitoring and treatment (Myers, 2010; Dolan *et al*., 2005). As mentioned above, using CBPM has a few factors that may lead to increased BP averages when compared to ABPM. According to Myers *et al*. (2006), when there are differences in CBPM measurements, it could have implications for detecting target organ damage (TOD). Further studies have shown that CBPM, on average, shows higher BP profile than ABPM (Beckett and Godwin, 2005; Graves *et al*., 2003; Gustavsen *et al*., 2003). Despite numerous reports to improve the quality of BP monitoring, to properly measure office BP, it would require more than 15 minutes per single patient. In busy and under resourced health care facilities, this practice may not be effectively implemented (Sala *et al*., 2006).

ABPM can be used for initiating and following up on HT interventions. It can be used as a screening tool to determine whether BP elevation is indeed sustained or a consequence of the white coat effect or whether there are masked BP changes (Siamopoulos *et al*., 1996). ABPM can be repeatedly used to monitor the efficacy and response to antihypertensive treatment. It can further be used even when there is evident TOD, thus evaluating the efficacy of the intervention on both BP reduction and target organ changes (O'Brien *et al*., 2013). As a superior method of monitoring BP, ABPM has been associated with better outcomes regarding target organ changes. ABPM further aided in adjusting or changing antihypertensive treatment regimens as needed when compared to CBPM. ABPM presents with lower overall BP profile when compared to CBPM. The threshold for CBPM is 140/90 mm Hg while that for ABPM is 135/85 mm Hg (Myers *et al*., 2010). This means that interventions could be prematurely implemented when using CBPM (Staessen *et al*., 2016). Using ABPM can be crucial when considering that CBPM has yielded trivial BP control rates (Kario *et al*., 2023). Including ABPM in HT treatment can improve and widen population control in HT management (Banegas *et al*., 2015). This does not only lead to better lifestyle on the side of patient care but also carries a financial advantage towards the health care system that is battling with varied issues such as other chronic diseases or malnutrition. Proper antihypertensive initiatives or interventions could mean that financial resources can be spared for other purposes (Lovibond *et al*., 2011; Verberk *et al*., 2007).

ABPM is crucial in the diagnosis and control of white coat and masked HT, since they both cause damage similar to sustained 24-hour HT (Tomiyama *et al*., 2006). To date, patients that are suspected of having white coat response during CBPM are advised to have BP monitored over 24-hour (Bland and Altman, 2010). Ambulatory BPM allows such interventions through its ability to measure and isolate daytime BP from night-time BP (NBP). Regarding treatment goals, this can be of particular importance towards managing the effects of NBP, since it has been reported to be a better predictor of worse TOD and future CVD events (Myers, 2010). On average, ABPM can more closely predict TOD than CBPM (Beckett and Godwin, 2005). Although 24-hour, daytime and night-time BP monitoring can predict cardiovascular morbidity, there is however, a stronger relationship between CVDs outcome and NBP (Fagard *et al*., 2008). This emphasises using 24-hour ABPM in BP control since it can show the differences in BP regulation between the changes in daytime and night-time BP during interventions.

2.5 Blood pressure follows a circadian rhythm

The overall 24-hour BP pattern varies between daytime and night-time, with daytime BP usually higher than night-time BP (Kario, 2005). This is a natural phenomenon of BP rhythm; however, its dysregulation is associated with increased risk of CVDs. It is influenced by regulatory factors that can be intrinsic and extrinsic (Douma and Gumz, 2018). Extrinsic factors can be in the form of environmental influences and personal/ behavioural habits that affect basal BP. The physical environment in which people reside in can affect BP changes between daytime and night (Nwankwo *et al*., 2020; Huang *et al*., 2018). Dietary and lifestyle habits such as alcohol consumption, cigarette smoking, and salt intake affect the circadian changes in BP (Lampert *et al*., 2005; Pickering and James, 1993). Intrinsic factors in the form of neural, endocrine, and endothelial changes affect BP rhythm (Hermida *et al*., 2007; Guasti *et al*., 2005; Furlan *et al*., 1990). Studies show that sympathetic tone and changes in RAAS can alter the day and night BP pattern (Grassi, 2009; Narkiewicz *et al*., 2002). Decreased vagal activity, reduced sympathetic dominance, increased levels of atrial natriuretic peptide and nitric oxide influence the vasodilatory factors during circulation and affect the overall 24-hour BP rhythm (Hermann *et al*., 2006; Flickinger *et al*., 1995). Other changes in BP rhythm between day and night can cause unfavourable changes that are associated with cardiovascular risks. The dysregulation of the circadian rhythm of BP, such as reduced vascular compliance, left ventricular hypertrophy, increased incidences of stroke, increased risk of cardiac dysfunction

and cerebrovascular changes affects BP rhythm (Kusunoki *et al*., 2019; Soylu *et al*., 2009: Routledge *et al*., 2007). Using 24-hour ABPM, researchers have been able to correlate the above anomalies with changes during either daytime or night-time. Investigating the prognostic significance of daytime and night-time BP regarding CVDs risks shows that changes in the vasculature and haemodynamics indeed correlate with the diurnal changes in BP (Khattar *et al*., 2001).

2.6 The difference between daytime and night-time blood pressure regulation

Since the diurnal pattern of BP is well established (Wu *et al*., 2021; Asayama *et al*., 2018; Ernst and Bergus, 2002), both daytime and night-time BP have been associated with CVDs risk factors (Roush *et al*., 2014; Fagard *et al.,* 2008). Daytime BP is associated with adverse cardiovascular events and contributes to cardiovascular anomalies (Banegas *et al*., 2018). It can significantly and independently predict all-cause mortality (Dolan *et al*., 2005). Daytime physical activities may increase daytime BP (Coccina *et al*., 2020). Alcohol intake and tobacco smoking impact on BP and are some daytime activities that could support the acceptance of daytime BP as a predictor of cardiovascular risk (Jaubert *et al*., 2014; Pannarale *et al*., 2008). Daytime BP has negative contributions towards cardiovascular disease pathogenesis. During 24-hour ABPM, daytime duration is longer than night-time. This means that daytime BP could display the highest risk because this pattern exposes patients to a greater cardiovascular load each day. This implies daytime BP has an important role in the pathogenesis of cardiovascular disease and its prognostic value could be increased in that regard (Roush *et al*., 2014). However, the prognostic value of daytime BP decreased when adjusted for NBP and the relationship between daytime BP and adverse cardiovascular events may change based on several factors (Fagard *et al*., 2008).

Being able to isolate the differences between daytime and night-time BP pattern has likewise allowed much focus on night-time BP which is associated with more adverse cardiovascular outcomes compared to daytime BP (Yano and Kario, 2012). In this thesis night-time BP and nocturnal BP are used interchangeably and are both abbreviated as NBP. As stated earlier, NBP predicts adverse cardiovascular outcome above and independent of daytime BP (Li *et al*., 2017). Fagard *et al*. (2008) reported that NBP adds significant prognosis to daytime BP whereas daytime BP does not translate the same findings for NBP. When included in the same prediction model, NBP can predict all-cause mortality above daytime BP. It was further

reported that night-time systolic BP is another predictor of fatal and non-fatal cardiovascular outcome; although, it has not been currently well explained why NBP predicts adverse cardiovascular outcomes better than daytime BP (Ben-Dov *et al*., 2007). Perhaps intermittent BP measurement may not fully capture true daytime averages since BP can be variable during the day. Daytime activities are known to affect BP measurements. Perhaps the stability of NBP is what gives it the superiority over daytime BP and in making NBP a representative resting average BP (Leary *et al*., 2000). Night-time BP is not subject to the same environmental factors that increase daytime BP since some of these are not prevalent at night, therefore, this can be added support that NBP can be a better predictor of adverse CVD outcome. It is further accepted that since NBP is not interrupted by daytime activities during monitoring it increases its prognostic value above daytime BP (Fava *et al*., 2004; Vinck *et al*., 2001). Night-time BP has been shown to consistently predict adverse cardiovascular events (Hansen *et al*., 2011). Therefore, NBP could be standardised to identify mechanisms that underlie BP regulation, especially where TOD is concerned (Fargard *et al*., 2008).

Considerably, there could be other factors that increase NBP. Night-time BP regulation can be influenced by the autonomic nervous system, salt-sensitivity, nocturia and sleep disorders (Kario, 2018). Deleterious changes in the sympathetic activity, pressure natriuresis and sleep apnoea are some of the factors that are known to increase NBP when they are limited to night-time hours (Iwashima *et al*., 2022). Other factors such as decreased arteriolar tone might contribute to TOD as the small arteries are subjected to increased BP at night (Korolev *et* al., 2022; Coccagna *et al*., 1971). Age is another factor that can affect NBP. It is reported that older participants have high NBP when compared to daytime BP in younger populations (Xing *et al*., 2021). It has been reported that genetic influences that regulate BP may have differing effects on daytime and night-time BP. There may be a genetic component that contributes to the difference in NBP profile, increasing the prognostic value of NBP (Wang *et al*., 2005). This reiterates that NBP plays an important role in BP-related morbidity (Roush *et al*., 2014). Undoubtedly population studies have reported on the importance of daytime and night-time BP. They both have significant contribution to fatal and non-fatal cardiovascular events (Fagard *et al*., 2008). Where some studies report NBP as a superior predictor, others report that they carry the same prognostic value (Kario *et al*., 2020). The differences can be attributed to study methodology, research designs and demographic differences. Therefore, this warrants a focused approach into the determinants of BP since the mechanisms that increase NBP, and its associated risk factors can be subjected to various controls.

2.7 Determinants of blood pressure

Night-time BP has a strong predictive value regarding cardiovascular events; however, the rise and fall of BP does not have one identifiable cause but is subject to many influences (Kario *et al*., 2020). It results from the interaction between multiple risk factors. Many of which affect the functioning of the systems that regulate BP (Shahoud and Aeddula, 2019). The complex and multifaceted physiological control of BP includes the workings of the cardiovascular, neural, renal, and endocrine systems (Ahmed *et al.*, 2019; Guyton *et al*., 1981). An important part of normal physiological function is that arterial pressure should remain within relatively narrow limits, any deviation from the normal range inflicts insidious effects (Chopra *et al*., 2011). Below are few humoral and other systems that are known to influence BP, and whether they have a regulatory role in nocturnal BP or TOD.

2.7.1 Renin-Angiotensin-Aldosterone System (RAAS)

This renal endocrine-hormonal mechanism is responsible for acute BP regulation and electrolyte homeostasis during normal physiological and disease states. It is a potent modulator of BP, and it regulates BP through the action of the hormones that increase blood volume and peripheral resistance (Johnston, 1992). It is supressed in periods of excess sodium intake or when arterial pressure increases (Nakagawa *et al.*, 2020). Conversely, during low levels of salt intake RAAS stimulates renal sodium reabsorption and conservation of body fluid volumes and BP (Coffman and Crowley, 2008). When there is overactivation of the RAAS, there is a proclivity towards sustained alterations in arterial pressure because of the negative shift in pressure natriuresis. During conditions that reduce BP or deactivate sympathetic nervous system (SNS) activity, RAAS commences a sequence of events beginning with renin release from the juxtaglomerular cells and end with the production of angiotensin-converting enzyme (ACE) from the endothelium. Angiotensin II, as the final product of this cascade causes vasoconstriction and attempts to increase BP. Furthermore, it causes sodium reabsorption and increases blood volume and arterial pressure (Shahoud and Aeddula, 2019). Therefore, any dysregulation of the RAAS may result in increased BP that becomes a risk for HT and TOD (Le and Coffman, 2008; Coffman and Crowley, 2008). When blood volume is low, arterial cells in the kidneys secrete renin directly into circulation. Plasma renin then carries out the conversion of angiotensinogen into angiotensin-I. Angiotensin-I is subsequently converted to angiotensin-II by ACE. Angiotensin-II causes blood vessels to contract and elevates BP. It stimulates the secretion of aldosterone from the adrenal cortex (Wadei and Textor, 2012).

Another hormone from RAAS is aldosterone, it regulates BP through electrolyte and fluid homeostasis (Booth *et al*., 2002). Its secretion is promoted by Angiotensin-II and it is the final signal to regulate sodium reabsorption. It causes conservation of extra cellular sodium and is under negative feedback mechanism. This is because it responds positively to decreased BP and negatively to its increase (Lifton *et al*., 2001; Fuller and Young, 2005; Funder, 1997). In the vascular system, aldosterone is known to modulate vascular tone, possibly by increasing the pressor response to catecholamines and impairing the vasodilatory response to acetylcholine or by upregulation of angiotensin-II receptors (Taddei *et al*. 1993; Wang *et al*. 1992; Jazayeri & Meyer 1989; Schiffrin *et al*., 1985). Aldosterone stimulates sodium and water reabsorption in the distal tubule. Urine output is reduced and circulating blood volume is increased. Increased blood volume leads to elevated BP as the heart generates more pressure (Samuel *et al*., 2018).

Aldosterone further has the potential to cause vascular damage independent of BP changes (Griffin *et al*., 2003). It induces actions that are similar to the functioning of angiotensin-II in inducing endothelium-dependent vasodilatory or constrictor effects (Virdis *et al*., 2002). Moreover, aldosterone causes vasoconstriction when it activates phospholipase C, thereby causing nitric oxide release to combat vasoconstriction (Arima *et al*., 2004). It affects blood vessels and may thus be implicated in some cases of vascular stiffness because it can cause vasoconstriction by modulating membrane receptors of agents that sensitize the vasculature (Schiffrin, 2006). The association between aldosterone and TOD is based on its regulation of vascular tone and impairing vasodilatory response (Schiffrin *et al*., 1985). When the renal system has excess salt, the activation of aldosterone perpetuates stiffness in the vessels and kidneys because it sensitizes the cardiovascular system to inflammatory effects (Libby, 2012; Park and Schiffrin, 2002). Increased oxidative stress is mediated by aldosterone during such states (Virdis *et al*., 2002). It further promotes excess collagen and therefore negatively affects vascular compliance. Additionally, these changes can occur independent of BP changes (Rocha *et al*., 2002; Funder, 2004).

2.7.2 Leptin and blood pressure

Leptin has been associated with central adiposity, high body mass, and excess body weight. High BP has also been established in said association (Zheng *et al*., 2019). Although not completely understood, there may be pathophysiological mechanisms involved (Hall *et al*., 2001). Leptin is a peptide hormone that plays a role in food intake and inhibits fat accumulation.

The inhibition of fat deposition by leptin is innervated by sympathetic nervous system activation (Rahmouni, 2010). In relation to elevated BP, there may be a leptin-mediated sympathetic nervous system activation that can be attributed to obesity-associated high BP. The sympathetic system can regulate leptin production in white adipose tissue (Lu *et al*., 2020). In animal studies, overexpressing leptin leads to HT, whereas in human studies, the direct influence could be masked by excess weight and other measures of body fat. High leptin levels are associated with excess body weight, while the sympathetic sensitivity of adipose tissue to leptin is reduced (Paolisso *et al*., 2001; Aizawa-Abe *et al*., 2000). When leptin becomes unresponsive in obese people, its regulatory role in the cardiovascular system can be reduced as well (Enriori *et al*., 2011). These effects are attributable to chronic levels of high leptin. Animal studies further report that mean arterial pressure is increased with increasing leptin levels (Kuo *et al.,* 2001; Shek *et al*., 1998).

Human studies on the association between leptin and BP have been inconsistent. It is suggested that sustained high levels contribute to HT in obese people (Izquierdo *et al*., 2019). Additionally, some hypertensive participants only exhibit high leptin levels at night (Ficek *et al*., 2002). There is still a lack of association regarding the cause-and-effect relationship between leptin and elevated BP. This can be impacted by age, gender, and other demographic characteristics (Correia *et al*., 2001; Kuo *et al*., 2001). Women are generally expected to have higher leptin levels, however there is an increasing trend in overweight older men (Ryan *et al*., 2003; Kennedy *et al*., 1997). Agata *et al*. (1997) reported that people with essential HT had higher leptin levels, these were correlated with high BP. Moreover, the association between HT and leptin levels can be independent of body mass index (BMI) and age (Hirose *et al*., 1998). Contrary, Kokot *et al*. (1999) found that leptin levels in hypertensive people were not significantly different to normotensive people and could not show the correlation with BP. Narkiewicz *et al*. (1999) further reported that BP monitored over 24-hour did not show any correlation. Clinical evidence on the role of leptin in BP elevation is not unanimous, however, leptin has peripheral physiological effects that suggest it may be a link in the triad between obesity and HT. In addition to these inconsistencies, activation of the sympathetic nervous system within the renal and vascular system has a close relationship (Hodge *et al*., 2001). Albeit Oda *et al*. (2001) argued that the sympathetic nervous system may have its own shortfalls in fully explaining the hypertensive effects of leptin. Since endothelin-1 may be stimulated by leptin levels, there may be vascular remodelling and proliferation of vascular smooth muscles, all of which are associated with HT (Ghosh *et al*., 2005; Quehenberger *et al*., 2002).

Additionally, there is consistent reports on fat distribution. High and low leptin concentrations have been associated with high BP in overweight participants. This implies that leptin may be involved in body weight changes coupled with BP increase (Masuo *et al*., 2001). There is a large independency on body mass and abdominal adiposity in elevated BP where leptin is concerned. It can increase sympathetic nervous activity and resultantly increase BP (Haynes, 2000). Comparing lean and overweight individuals is another endeavour that allowed the demonstration of elevated leptin levels with high BP. High leptin levels and high adiposity are linked with high BP. However, interindividual differences in sympathetic tone could elicit some differences (Enriori *et al*., 2011). Schorr *et al*. (1998) reported that young men that generally had lean body weights had high leptin levels. Albeit it was not determined whether genetic predisposition to HT could have led to increased leptin levels. There may be possible leptin resistance with excess central adiposity, this could render leptin unable to reduce fat deposition (Barba *et al*., 2003; Bray, 2000). Where genetic predisposition is concerned hyperleptinemia may precede HT (Makris *et al*., 1999). Although the findings are scanty, dietary habits in the form of salt intake and urinary excretion may be associated with leptin levels that increases BP, especially since it is metabolised in the kidneys (Barba *et al*., 2003; Kokot *et al*., 1998).

2.7.3 The kidneys and blood pressure

The kidneys have an integrated function to balance fluid volume and sodium homeostasis. Long-term and greatest BP control is generated by the kidneys, while other bodily systems elicit acute BP regulation (Joyner *et al*., 2008). Renal function is complex because it is innervated by neuro-hormonal mechanisms, which ultimately affects BP regulation. The kidneys play a major role in BP regulation through sodium-based renal mechanisms. This function regulates circulating blood volume and arterial function (Wadei. and Textor, 2012; Sam *et al*., 2011). The renal-body fluid feedback mechanism has long been believed to regulate arterial pressure through volume homeostasis. Maintaining arterial circulation and blood pressure is closely linked to renal control because extracellular volume and renal perfusion pressure are also regulated by the kidneys. For instance, when arterial BP rises, the kidneys excrete sodium and water; therefore, decreasing blood volume and consequently decreasing arterial pressure (Wadei. and Textor, 2012). The kidneys are specialised to adapt to sodium intake through transient increases in arterial pressure (Suckling *et al*., 2012). When renal function is impaired, it plays a crucial role in elevated BP, whether directly or indirectly. It

follows then that defects in renal excretory function would lead to a sustained chronic increase in intra-arterial pressure (Granger *et al*., 2002). Regardless of the cause, the prevalence of HT correlates to kidney function and circadian disturbances in renal sodium handling are associated with the pathogenesis of HT (Burnier, 2008). However, individual differences, genetic and environmental factors affect the adaptability of the kidneys to sodium intake and how they regulate BP (Graudal *et al*., 2012).

The kidney-fluid mechanism for BP control is under the control of the RAA system. The system is suppressed when arterial BP increases. This inhibition reduces vasoconstriction as the effects of angiotensin-II wear off. It further causes sodium retention as its reabsorption is decreased (Wadei and Textor, 2012). Through the RAA system, the kidneys maintain a steady state between sodium intake and excretion. During increased sodium intake BP is elevated to balance arterial pressure. This requires decreased angiotensin-II to wean off its vasoconstrictive effects (Wang *et al*., 2000).

Other factors that regulate sodium reabsorption is activity of the sympathetic nervous system (SNS), since it has been established to contribute to arterial BP regulation (Chiolero *et al*., 2001). Signalling by the nervous system elevates BP and subsequently triggers sodium and water excretion through renal nerve stimulation (Kopp, 2018). Furthermore, within the kidneys, afferent sympathetic impulses can regulate BP by modulating the SNS (Dunn and Donnelly, 2007; Phillips, 2005). During night-time periods, an intrinsic system regulates BP without the physical and mental activities that regulate daytime BP. Afferent arteriolar tone is the lowest at night and any dysregulation can increase NBP. From sympathetic nervous system innervation, damaged sympathetic modulation of night-time BP increases BP (Dodt *et al*., 1997). Disturbed daytime natriuresis shifts sodium excretion during resting periods and increases NBP. The capacity for sodium excretion by the kidneys provides a compensatory system to oppose processes such as increases in peripheral vascular resistance, which would increase BP (Fukuda *et al*., 2004). Volume overload or impaired baroreflex sensitivity may increase NBP. When NBP increases, it is transmitted to the glomerulus, which increases intraglomerular hyperfiltration. There could be latently decreased renal function which may result in hypertension-induced kidney damage (Redon *et al*., 2002).

2.7.4 Sodium and night-time blood pressure

Sodium intake and urinary excretion regulates BP in many ways. Various body systems are involved in increased BP during sodium intake and including those involved in keeping BP within normal limits (Soliman and Pollock, 2021). Ideally, it is accepted that sodium intake increases BP through increased extracellular volume. To restore BP to normal intervals, renal sodium excretion is crucial to balance sodium concentrations (Shin *et al*., 2014). However, daytime, and night-time increase in BP may be differently impacted by sodium excretion. Elevated daytime BP is reported to correlate with daytime urinary sodium excretion whereas low daytime excretion is associated with a reduced ability to concentrate sodium in the urine (Fukuda *et al*., 2006). Increased urine concentration may reduce the capacity of the kidneys to excrete sodium. Therefore, daytime urinary sodium excretion and increased urinary sodium concentrations elevates NBP to balance sodium excretion because of blunted daytime excretion (Bankir *et al,* 2008). This means that any disturbances in daytime excretion may lead to elevated NBP since the excess sodium would be excreted during resting hours. Night-time BP is sensitive to blunted daytime sodium excretion since reduced daytime excretion is associated with elevated NBP so that excess sodium can be excreted to maintain 24-hour sodium balance (Sica and Wilson, 2001). In this regard this shows that NBP and nocturnal sodium excretion can be determined by daytime excretion rates (Burnier *et al*., 2007; Sachdeva and Weder, 2006; Obarzanek *et al*., 2003).

The association between sodium and NBP has clinical implications, however, the exact mechanisms that disrupts daytime sodium excretion have not been clearly defined. Age, genetics, ethnicity, and disease state are factors that can affect sodium handling and how it affects BP (Kim *et al*., 2012; Park *et al*., 2010). Additionally, reduced renal function such as low glomerular filtration rate or increased tubular sodium reabsorption such as during primary aldosteronism may cause blunted sodium excretion (Yahalom *et al*., 2014; Pimenta *et al*., 2013). Hypertension has shown some strong correlation as well. It has been reported that hypertensive people may present with blunted daytime sodium excretion rates that may correlate with elevated NBP (Blagonravov *et al*., 2017). Moreover, between the young and elderly hypertensive patients there may be differences in BP response to sodium intake (Intersalt, 1988). This means that sodium excretion and its effects on BP may also be impacted not only by age but by disease state, including HT itself. This requires robust BP measurements that exclude the effects of confounders to determine its correlation with NBP. The effects of

sodium intake and excretion needs to be well defined, even in circumstances where BP effects can be masked at night. It is therefore important to definitively describe the renal-body fluid control system and its regulation of NBP. This is essential because high sodium intake has prognostic value where CVDs are concerned and can lead to negative outcomes (Kario *et al*., 2019).

2.7.5 Pressure natriuresis

The renal-body fluid feedback control system regulates BP through pressure natriuresis. This is described as increasing arterial pressure to promote sodium excretion and decrease blood volume (Evans *et al*., 2005). Sodium excretion decreases with a fall in BP and blood volume. The process of salt excretion and retention is thus dependent on pressure natriuresis mechanism. This is influenced by excess or reduced sodium intake and fluid volume feedback (Granger *et al*., 2002). Sodium plays a role in fluid volume balance, and any abnormality in its metabolism leads to a compensatory increase in arterial pressure (Hall *et al*., 1986). Since BP is primarily influenced by intravascular volume, when it increases, renal arterial pressure increases as well. The effects cause the kidneys to excrete more sodium. The converse holds true for when BP decreases, salt is retained due to decreased renal arterial pressure when tubular sodium reabsorption is decreased (Granger *et al*., 2002). Therefore, sodium retention increases arterial pressure. For this reason, when there is sodium retention, increased arterial pressure is essential to allow the kidneys to excrete excess sodium. During prolonged states of sodium retention, pressure natriuresis is essential to maintain sodium balance (Granger *et al*., 2002; Hall *et al*., 1984). This means that in conditions where the kidneys are subjected to an underlying condition that causes sodium retention, the function of pressure natriuresis is crucial in maintaining sodium balance. It is established that renal perfusion pressure influences sodium excretion, although new insights have revealed that it further alters renal handling of sodium and water (Shahoud and Aeddula, 2019; Moreno *et al*., 2001; Granger and Schnackenberg, 2000; Garcia-Estan and Roman, 1989).

The interplay between sodium handling and pressure natriuresis mechanism is a crucial component of the feedback system that controls extracellular fluid volume and arterial pressure (Cowley, 1997). Without any dysregulations, the human renal system excretes salt maximally during the day and minimal excretion occurs at night (Zhang, and Pollock, 2020; Bankir *et al*., 2008). However, blunted daytime sodium excretion elevates NBP to excrete the excess sodium during the night. Since NBP determines nocturnal sodium excretion, decreased NBP correlates

with reduced nocturnal sodium excretion and the converse holds true (Centonza *et al*., 2000). Through this process, the kidneys alter renal excretion of salt and water as arterial pressure changes (Safar *et al*., 2003; Mitchell, 1995). Changes in the renal vascular function might modify the pressure natriuresis mechanism and elevate BP through a primary mechanism involving altered sodium and water excretion by the kidneys (Coffman and Crowley, 2008). When arterial pressure is elevated, activation of the pressure natriuresis mechanism causes sufficient excretion of sodium and water to return systemic pressure to normal (Evans *et al*., 2005).

The pressure natriuresis mechanism is very sensitive to volume regulation. Hypertension influences the pressure natriuresis mechanisms as it is likewise associated with increased nocturnal sodium excretion (Blagonravov *et al*., 2017; Bie and Evans, 2017). As mentioned earlier, reduced, or blunted rates of sodium excretion correlates with increased BP since the body needs to excrete the excess sodium. This leads to increased blood volume and subsequent increases in BP. There is a positive correlation between BP and sodium excretion in hypertensive people and that it could have a hereditary component (Tomson and Lip, 2005). This implies that elevated BP with sodium excretion could be influenced by other factors other than reduced renal capacity to excrete sodium during daytime.

2.7.6 Salt sensitivity

Excess sodium intake affects BP and has been reported to cause deleterious cardiovascular effects (Franco and Oparil, 2006). Some individuals show BP variations following sodium intake while others do not. Such differences, especially ones that increase BP with salt ingestion show a characteristic salt-sensitivity (Flack *et al*., 1991; Sullivan, 1991). Salt sensitivity is defined as an exaggerated change in BP in response to DSI, the increase in BP includes mean arterial pressure (MAP). Salt sensitivity can be determined by genetic factors, ethnicity, and age (Mishra *et al*., 2018). It acts as a precursor to the development and progression of hypertension. It increases the risk of hypertension in normotensive individuals, while hypertensive individuals can become more salt-sensitive than normotensives (Bihorac *et al*., 2000). Being hypertensive acts as an additional risk factor that augments salt-sensitivity. Hypertensive individuals show greater sensitivity to salt than do normotensives (He *et al*., 2001). There has not been a well-defined mechanistic link between salt sensitivity and mortality when comparing normotensive and hypertensive people (Marimoto *et al*., 1997). The most likely association could be when excess salt alters the vascular structure and function as

supported by the effects of salt on the endothelium which modulates the production of transforming growth factor-ß1 (TGF-ß1) and nitric oxide (Sanders, 2009). This implies that being salt-sensitive may have adverse cardiovascular effects as having hypertension. Perhaps, there could be an independent association between salt-sensitivity and cardiovascular events (Morimoto *et al*., 1997).

Salt-sensitivity is reported to have additive genetic effects in the black population. It was reported that about 73% hypertensive African Americans are salt-sensitive, whereas only 36% of the normotensive population is salt-sensitive (Svetkey *et al*., 1996). Salt-sensitivity is considered as a hallmark to hypertension due to its high prevalence in blacks. Since they show some susceptibility to excess salt intake, and as a result salt-sensitivity may have some heritability in blacks (Elijovich *et al*., 2016). Studies by Miller *et al* (1987) and Grim *et al* (1979) determined sodium handling and observed salt-sensitivity correlations in monozygotic than dizygotic twins. According to their findings correlation in monozygotic twins strongly supports genetic influences regarding salt-sensitivity. Notwithstanding, there may be some independent influences since Svetkey *et al*., (1996) reported lower estimates of heritability in their study. Perhaps there may only be a sub-population of black hypertensives that are genetically homogenous and thus could explain the observed differences. Thus, necessitating investigations into multifactorial genetic traits (Lander and Schork, 1994). Therefore, there is a need of the genetic basis of salt sensitivity to be based on heritability estimates in a black population.

Dietary habits are crucial to salt-sensitivity, considering that all these variables (genetics, race, and ethnicity) may affect salt-sensitivity differently among individuals (Barba *et al*., 1996; Svetkey *et al*., 1996). The Guytonian model suggests that a defect in sodium excretion by the kidney is the basis for salt-sensitivity, it supports that impaired elimination of sodium during high salt feeding leads to expanded extracellular fluid volume, which promotes increased BP (Murohy *et al*., 1991). This means that when the kidney's excretory ability is impaired, hypertension develops since sodium excretion requires higher BP (Grillo *et al*., 2019). Findings from the DASH-Sodium trial illustrated that sodium intake alters BP and that reducing sodium intake has a greater effect on decreasing BP when combined with a fruit and vegetable diet (Akita *et al*., 2003). The DASH-Sodium investigators observed increased pressure natriuresis, which perpetuated daytime sodium excretion and resultantly decreased BP. The intervention showed that BP is indeed salt-sensitive since there was a shallow pressure natriuresis curve in

older African American hypertensive participants, thus further emphasising the notion of the genetic effects regarding salt-sensitivity (Akita *et al*., 2003). However, Flack *et al.,* (1991) surmised that there may be a lack of univocal stance regarding the abnormal pressure natriuresis in blacks. Their study hypothesised that there may be an intrinsic factor that induces renal abnormality which may require high BP for natriuresis (Flack *et al*., 1991). Black people have diminished ability to concentrate urinary sodium following salt loading (Wedler *et al*., 1992).

Age as well may affect salt-sensitivity. Over time, older population groups that are salt-sensitive show the highest increases in BP. Weinberger and Fineberg reported that the older and hypertensive populations show progressive increase in salt-sensitivity with age (Weinberger and Fineberg, 1991). This is caused by decreasing glomerular mass with age that decreases the kidney's ability to concentrate sodium in the urine, similar to the effects of chronic kidney disease, and thus perpetuating salt-sensitivity (Aburto *et al*., 2013). Within the black context, the findings suggest that enhanced tubular reabsorption of sodium by the kidneys is responsible for the observed ethnic susceptibility to salt-sensitivity (Chu *et al*., 2008). Nonetheless, moderate salt intake and increased dietary electrolytes that are known to affect BP such as potassium could potentially affect salt loading and suppress salt-sensitivity in blacks (Morris *et al*., 1999). However, with the potential deficient potassium in the black population (Swanepoel *et al*., 2016) this could blunt the pressor effects of the electrolytes and thus explain the racial variation in hypertension and ultimately salt-sensitivity in blacks.

Neuro-hormonal status such as renin concentration influences salt-sensitivity (Giner *et al*., 2000). The RAA system plays an important role in the regulation of sodium excretion, and it is sensitive to alterations in sodium intake (Rasmussen *et al*., 2003; Sandgaard *et al*., 2000). People of African ancestry have been reported to have low plasma-renin activity when compared to other racial groups. The RAA system is important in regulating sodium excretion and is thus sensitive to changes in sodium intake and excretion (Bie and Sandgaard, 2000; Graudal *et al*., 1998). It could be that the low activity predisposes people of African ancestry to salt-sensitivity (Sagnella, 2001). While it has been reported that normotensive and hypertensive participants do not show significant differences in renin concentrations, reducing salt intake shows significant plasma renin concentration differences between the two groups, which varies greatly with further salt reduction (He and MacGregor, 2003). Sodium reduction causes a compensatory activation of RAAS, which regulates salt excretion (Franco and Oparil,

2006). Therefore, RAAS could be blunted in hypertensive people and could become less responsive to dietary changes with reduced salt intake, which would therefore be associated with salt-sensitivity (Ibrahim, 2006).

Lastly, understanding the mechanisms and pathophysiology for salt-sensitivity in blacks relies on understanding essential hypertension. Some of the proposed mechanisms for the high prevalence of salt-sensitivity in blacks is that low concentration of electrolytes like potassium and calcium affect the pressor effect (Coruzzi *et al*., 2001; Resnick *et al*., 1994). Black people further present with reduced renal function during hypertension, with higher vascular resistance and reduced renal dopamine regulation after salt-loading (Aperia, 2000). While there may have a high heritability influence, environmental influences have been shown to affect salt-sensitivity (Kelly and He, 2012; Weinberger *et al*., 2001). Other factors like obesity and insulin resistance are high in black people. These increase renin secretion and lead to increased sodium reabsorption. One such indirect effect is the release of the sodium-potassium-ATPase inhibitor during plasma volume expansion. Increased intracellular sodium and calcium, sensitizes the arterial wall to become resistant and thus increase BP (Falck *et al*., 1991). Nonetheless, salt-sensitivity may not be mediated by identical mechanisms that are all triggered by the same effectors. For instance, alterations in salt balance such as impaired natriuresis or expanded plasma volume are not the only characteristics features for salt-sensitivity. Increased BP that leads to hypertension as a response to salt loading could in fact be a counter effect to sustain sodium handling (Elijovich *et al*., 2016). Therefore, all these characteristics, although related pathophysiologically, appear to be different, and they all can modify BP response to salt intake. Thus, the relation of all and any related variables that are associated with salt-sensitivity need systematic evaluation. Moreover, this is not to disregard the body of knowledge that took decades to generate, if anything, such discoveries associated with salt-sensitivity and BP has provided an opportunity to conduct studies with the potential to increase our understanding of hypertension and other phenotypes that have been discovered through ABPM, their impact on TOD and overall cardiometabolic profile.

2.8 Isolated nocturnal hypertension

Isolated nocturnal hypertension (INH) is characterised by a normal daytime BP and an elevated NBP (Li *et al*., 2007). It is a unique hypertension phenotype in that it is only through monitoring BP over a 24-hour period that the characteristic elevated NBP of INH can be uncovered. It is defined through 24-hour ABPM as elevated NBP (>120/70 mm Hg) and normal daytime BP

(<135/85 mm Hg). Isolated nocturnal hypertension presents with a unique challenge in that its associated cardiovascular target organ changes are related to the elevated NBP (O'Flynn *et al*., 2015). It makes INH a high-risk hypertension phenotype because research has shown that an elevated NBP is associated with increased risk of cardiovascular injury independent of daytime BP. Isolated nocturnal hypertension was first described by Li *et al*. (2007) and has a relatively low but varying prevalence among different population groups. Different ethnicities from Asia, South America, Europe, and South Africa have been studied, and they all exhibit differences in their prevalence. These range from 6% to 19% and can all be attributable to race and geographical difference among other methodological differences (Li *et al*., 2007). Isolated nocturnal hypertension has since received a lot of traction and has been investigated to uncover the mechanisms that lead to increased NBP. More details about INH prevalence were discussed in chapter four. The next sub-sections briefly introduced INH and blood pressure dipping pattern, since INH is characterised by elevated NBP, therefore there might be an expected correlation with non-dipping.

2.8.1 Isolated nocturnal hypertension and blood pressure dipping patterns

A non-dipping BP profile is defined as a lack of nocturnal BP fall. Night-time BP is expected to decline by at least 10% of the daytime BP profile. Blood pressure has a circadian rhythm that starts to decline late at night and then rises in the morning (Casagrande *et al*., 2020). Where INH is concerned, this expected decline at night does not occur, rather BP increases (Li and Wang, 2013). Therefore, by virtue of its name there is an expected association between INH and non-dipping. When investigating INH among different racial groups, its prevalence in the black population can probably be attributable to lack of dipping at night. African Americans and by association populations of African ancestry, have a higher nocturnal BP and a blunted NBP decline (Pickering and Kario, 2001). Additionally, they have higher prevalence of 24-hour sustained HT, which is associated with a non-dipping BP profile (Beevers *et al*., 2001). Night-time BP is very crucial because daytime BP does not carry the same prognostic precision. Since NBP is subjected to reduced variability, alterations in its regulation, including a lack of nocturnal decline are associated with increased cardiovascular injury (Li *et al*., 2017).

2.8.2 Night-time blood pressure and non-dipping

Determining the mechanisms that lead to a non-dipping BP pattern is an ongoing endeavour. Although not fully understood, the agreement in literature is that disease states that affect circulation and BP may lead to non-dipping (Dai *et al*., 2019; Rahman *et al*., 2018; Birkenhäger

and Van den Meiracker, 2007). Having some form of hypertension phenotype, diabetes and renal disease is associated with non-dipping (Dubielski *et al*., 2016). Furthermore, sleep disturbances that lead to sleep apnoea may cause non-dipping (BaHammam *et al*., 2021). Since these conditions are known as risk factors towards increased BP and they affect the vasculature to some degree, it could therefore be said that altering the vasulature and BP are contributory towards a non-dipping phenomenon. As a result, elevated BP and non-dipping are associated with some form of cardiovascular target organ changes (Pickering and Kario, 2001). Having an elevated BP seems to accelerate the progression of cardiovascular TOD. Ferrara *et al*. (1998) reported that non-dippers had elevated BP and increased risks of TOD when compared to dipping counterparts (Ferrara *et al*., 1998). However, a lack of NBP decline can lead to TOD independent of sustained BP because normotensive non-dippers showed increased risk of TOD (Hoshide *et al*., 2003). In the context of INH, as it presents with daytime normotension and an elevated NBP, this characteristic increases the risk of TOD independent of daytime BP. This suggests that non-dipping and TOD may occur without sustained elevated BP. Therefore, INH and non-dipping are somewhat connected. Nonetheless, it stands to be elucidated whether non-dipping and TOD in normotension predispose to future sustained elevated BP due to organ alterations or as a consequent of TOD.

Literature on INH and non-dipping is another on-going endeavour, especially where the reproducibility of INH is concerned. Being able to determine INH was only correlated with short-term reproducibility for non-dipping. It is reported that TOD was associated with INH, not non-dipping (Perez-Lloret *et al*., 2008; White and Larocca, 2003). Studies have reported that night-time BP non-dipping is an important risk factor, even above overall 24-hour BP profile, however its clinical use has not yet been fully explained (Hansen *et al*., 2011; Thijs *et al*., 2007). Additionally, while INH may be connected to non-dipping, studies still report that INH causes more adverse effects (Koroboki *et al*., 2015; de la Sierra *et al*., 2014; Yi *et al*., 2014). Perhaps this endeavour could be to the detriment of identifying whether INH and non-dipping could be causing a double impact on CVDs or whether they each affect the vasculature independent of each other since they often present together. Notwithstanding, the diagnostic thresholds for BP, including the cut-off for INH could imply that it is more applicable above non-dipping, however, there is still a need to robustly investigate their association, especially since non-dipping can predict TOD independent on NBP (Tadic *et al*., 2020). This is further supported by de la Sierra *et al.* (2014) who reported that INH and non-dipping may have differences in how they lead to TOD. In their study they reported that advanced disease state

leads to a lack of NBP decline, thus relating clinical evidence of CVDs to non-dipping. Whereas with INH elevated BP at rest promotes TOD (de la Sierra *et al*., 2014). Additionally, while INH is a risk factor for future cardiovascular events, the effects on non-dipping can be blunted, thus making it challenging to isolate their estimated association with CVDs, more so considering that including non-dipping better refines the assessment of BP variability (de la Sierra *et al*., 2012; Redon and Lube, 2008). Therefore, the pathophysiological and clinical significance of INH and non-dipping could be different, yet they each have characteristics that may overlap in how they affect the overall haemodynamic profile (Tsioufis *et al*., 2011).

2.8.3 Night-time blood pressure and reverse dipping

The opposite of non-dipping is when there is an increase in NBP, thus reverse dipping. It is characterised by an increased NBP at a time when NBP is expected to decrease by 10% or more of daytime BP values (Cuspidi *et al*., 2017). Reverse dipping is an abnormal circadian BP rhythm that negatively impacts the vasculature. It presents as a harmful 24-hour BP phenotype because the elevated BP exerts pressure on the vasculature during a time when the body should be regulated for reduced basal BP (Cuspidi *et al*., 2017). Nonetheless, comprehensive reports on the effects of reverse dipping are scanty. From a sample of 1542 participants Okhubo *et al.* (1997) only reported a 3% reverse dipping prevalence. They further associated reverse dipping with a history of cardiovascular diseases, a history of smoking, older age groups and to be prevalent among men (Bombelli *et al*., 2013; Okhubo *et al.,* 1997). Sue *et al.* (2016) reported a 20% reverse dipping in hypertensive patients who presented with diabetes. Afsar *et al*. (2015) reported 36% prevalence of reverse dipping in essential hypertension, although their study participants were on hypertensive treatment. Limuro *et al*. (2013) reported a 15% reverse dipping pattern in patients with kidney disease. Lee *et al.* (2013) investigated sleep disorders and reverse dipping and reported a 13% prevalence. The PAMELA (Bombelli *et al*., 2013) and European study (Fagard *et al*., 2009) reported a 3.5% and 11% reverse dipping, respectively. Being of a Black ancestry descent is a risk factor for reverse dipping. Black people have smaller NBP reductions than other populations and thus could have increased propensity towards reverse dipping (Cuspidi *et al*., 2017). The AASK (African American Study of Kidney Disease and Hypertension) trial reported a 39% reverse dipping in an African American population (Pogue *et al*., 2009). There are differences in the risk factors that could be stratified to contribute to the development of reverse dipping. As is with any population studies, comparisons should be interpreted within the bounds of a few differences such as geographical location, ethnicity, and disease states.

The mechanisms that govern reverse dipping seem to be somewhat associated with a disease state. This means that having some type of anomaly that affects the BP profile causes a shift in NBP pattern. Although the causes may be multifactorial, changes in NBP are associated with changes in the sympathetic activity and peripheral resistance (Cuspidi *et al*., 2017). Furthermore, individuals who are hypertensive, have diabetes or kidney disease are at increased risk of presenting with increased NBP (Limuro *et al*., 2013; Pogue *et al*., 2009). It is reported that the sympathetic drive during hypertension may cause reverse dipping by altering the circadian BP (Grassi *et al*., 2008). Sleep perturbations that increase NBP are associated with increased sympathetic tone and therefore present as risk factors for reverse dipping (Henderson and Macefield, 2016). It is reported that shifting pressure natriuresis to sleep hours because of impaired daytime sodium excretion increases NBP, another common factor that leads to reverse dipping (Kimura, 2008). It is crucial that the body regulate sodium balance, therefore, considering reduced or impaired daytime sodium excretion, a compensatory attempt is by shifting said excretion to sleep hours. Inevitably, this method of preserving sodium balance inadvertently increases NBP (Afsar *et al*., 2016; Uzu, and Kimura, 1999). Notwithstanding, there may be decreased renal function or some form of kidney damage that affects NBP. This would mean that sodium metabolism and excretion would be negatively affected and thus increase NBP.

Reverse dipping and non-dipping are not invariably reported with hypertension. In people with normal daytime and night-time BP, these individuals are then said to have isolated nocturnal hypertension (Cuspidi *et al*., 2017). Reverse dipping and non-dipping are both associated with disease sate and cardiovascular damage. The development and progression of said target organ changes is still somewhat of an enigma. Literature shows that disease state that blunts NBP leads to either non-dipping or reverse dipping and is associated with TOD (Ivanovic *et al*., 2013). Similarly, non-dipping or reverse dipping affects NBP and may be associated with INH which further leads to TOD. The classification of dipping profiles, the relative differences between the ratios that differentiate these dipping patterns, and the contributory effects of BP independent of dipping makes investigating NBP a complex pursuit. It is therefore vitally important to distinguish the causal link between INH, non-dipping, reverse dipping, and the development of TOD. However, INH may offer an opportunity to waive these dipping complexities because even if there may not be any easily discernible signs initially, it is reported that elevated NBP leads to TOD (Li and Wang, 2013).

2.8.4 Isolated nocturnal hypertension and related target organ damage

From its introduction, it appears that increased NBP is intertwined with a blunted nocturnal BP dipping pattern. The link stems from the fact that INH is characterised by elevated NBP when compared to daytime BP and it has adverse effects. Isolated nocturnal hypertension, non-dipping and reverse dipping are associated with increased risk of subclinical cardiovascular events and mortality (Cuspidi *et al*., 2017). While cardiovascular disease events that stem from INH, non-dipping and reverse dipping may not always occur in a sequential order, it cannot be disputed that they have overlapping risk factors that would generally lead to similar outcomes. Based on literature, this next section reports on cardiovascular target organ damage that are associated with INH, related to the aim of the current thesis. Other examples of INH-related TOD are shown in Figure 2.2.

2.8.4.1.1 Kidney dysfunction

Elevated NBP (a feature and risk factor in INH) is associated with blunted renal capacity to excrete sodium. Through the shifted natriuresis to bedtime hours, the elevated NBP, and in some cases coupled with non-dipping, deteriorates renal function (Uzu *et al*., 1997). Where kidney function is concerned, as a disease state kidney disease or dysfunction is more related to the lack of NBP decline, which elevates NBP and thus cause TOD (Kimura, 2008). However, regarding INH prevalence, patients with chronic kidney disease show the highest prevalence (Wang *et al*., 2015). There is another relation to salt-sensitivity, in that nocturnal non-dipping occurs because glomerular filtration capacity is impaired and thus rendering BP salt-sensitive (Fukuda *et al*.., 2011). Nocturnal BP remains elevated when the kidneys have reduced capacity to excrete sodium, which, overtime, deteriorates renal function. Renal function determines the day-night changes in BP. It causes NBP to remain elevated above daytime averages (Fukuda *et al*., 2008). Considerably, renal function can also independently determine NBP (among other factors), therefore renal dysfunction may have a bi-directional association with INH and non-dipping: renal dysfunction causes hypertension, whereas hypertension accelerates renal damage (Kimura, 2008; Lurbe *et al*., 2002; Weinberger *et al*., 2001).

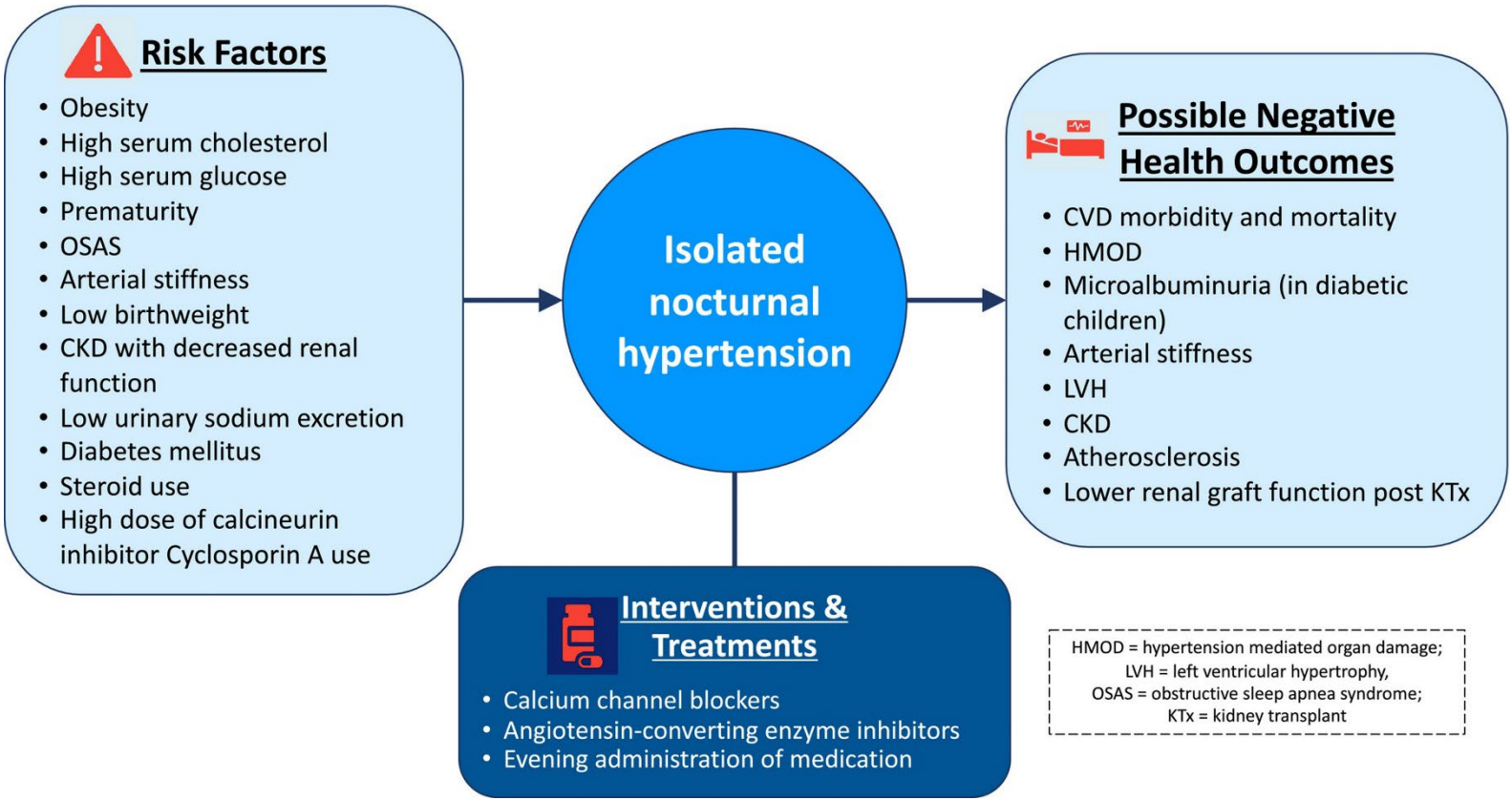


Figure 2.2 Summary of factors that have been shown to be associated with increased risk of isolated nocturnal hypertension.

*Adapted from Seeman *et al*., 2022

2.8.4.1.2 Arterial stiffness

Isolated nocturnal hypertension is associated with elevated indices of arterial stiffness (Li *et al*., 2007). Compared to daytime normotensive people, participants with INH have increased risk of developing arterial stiffness which demonstrates that elevated NBP or blunted NBP decline causes TOD (Fan *et al*., 2010). The initial studies that defined INH, were the first to report that there are higher incidences of arterial stiffness. These are demonstrated through higher PWV, central systolic, mean arterial and pulse pressure (Nolde *et al.*, 2021). Additionally, patients who are normotensive on conventional blood pressure measurement but have unexplained TOD were found to show signs of vascular damage associated with INH when monitored through ABPM (Li *et al*., 2007). Other indices that signal intermediate TOD related to stiffer arteries were determined through pulse wave analysis, augmentation index, brachial-ankle pulse wave velocity and ambulatory arterial stiffness index (Li *et al*., 2008). These reports are consistent with ambulatory determination of arterial stiffness related to NBP (Dolan *et al*., 2005; Lekakis *et al*., 2002; Ohkubo *et al*., 2002). These findings therefore introduce the need to investigate TOD in INH with or without daytime hypertensive status. Furthermore, blunted NBP affects central BP, which increases risk of arterial stiffness (Lekakis *et al*., 2005). This highlights the importance of investigating cardiovascular TOD through ABPM in patients with known or unknown HT.

2.8.4.1.3 Left ventricular function

There are inconclusive findings on INH and left ventricular function. Patients with INH present with markers of TOD including left ventricular hypertrophy. Pais *et al*., (2020) reported that INH predicted left ventricular mass index in patients that were post kidney transplant. Wang *et al*., (2015) reported lower left ventricular mass index in INH patients with chronic kidney disease. Through ECG measurements Lu *et al*., (2008) documented left ventricular hypertrophy in INH. Similar findings were reported by Wijkman *et al*., (2009) in patients with diabetes. However, when correcting for known confounders such as sex, age, BMI and lifestyle behaviour, the relationship showed no statistical significance. Cuspidi *et al*., (2012) reported that non-dippers and dippers with nocturnal HT did not show any significant differences in left ventricular mass. From these studies, it appears left ventricular hypertrophy is not independent of known CVD-confounders. Therefore, the prognosis for Left ventricular mass is yet to be clearly defined in INH. The Jackson Heart study reported that being of African descent and having INH increased the likelihood of thickening of the left ventricular mass (Ogedegbe *et*

al., 2013). Ogedegbe *et al*., (2013) showed left ventricular hypertrophy through two dimensional and M-mode echocardiography after adjusting for age and gender. It is surmised that INH may be leading to left ventricular dysfunction through similar mechanisms as in patients with sustained HT (Kim *et al*., 2022). Although Pais *et al*., (2020) reported severe TOD in sustained HT compared to INH. Despite the varied reports, INH is associated with unfavourable effects on cardiac structure, perhaps these are more reasonably interpreted because of arterial stiffness. Nonetheless, NBP is still a useful parameter and could still be used to identify patients at risk of developing left ventricular hypertrophy (Cuspidi *et al*., 2013). Additionally, it may lead to left ventricular diastolic dysfunction (Kim *et al*., 2022).

2.8.4.1.4 Diastolic dysfunction

Diastolic dysfunction, by definition, means that the heart has difficulty relaxing and filling with blood between contractions. Overtime, it can lead to heart failure (Zille *et al*., 2002). Heart failure (HF) is a progressive condition with complex cardiac adaptations (Braunwald, 1997). Left ventricular remodelling and diastolic dysfunction are associated outcomes of HF (Paulus *et al*., 2007). Patients with HF often present with reduced ejection fraction, to which diastolic dysfunction largely contributes. It is further associated with the presence of increased left ventricular mass (Palatini *et al*., 1998). At times dubbed "diastolic heart failure" it is characterised by the inability of the left ventricle to fill adequately during diastole (Zile and Brutsaert, 2002). Hypertension is still considered a risk for HF, even though it has been suggested that it can predate the condition (Levy *et al*., 1996). Hypertension is associated with structural myocardial abnormalities and impaired left ventricular filling (Tadic *et al*., 2018). When the heart cannot relax properly the left ventricular pressure decline decreases which prolongs the time to allow the heart to relax and it increases isovolumic relaxation time. Consequently, there is a decrease in early diastolic filling, and atrial filing increases to compensate for the shortfall (Mandinov *et al*., 2000). The cardiac involvement during hypertensive disease is different in relation to the NBP profile (Di Raimondo *et al*., 2021). It is hypothesized that elevated NBP impairs left ventricular diastolic function (Tadic *et al*., 2012: Seo *et al*., 2006). However, INH, its effect of cardiac remodelling and the effects of non-dipping or reverse dipping on left ventricular function have not been reported.

2.9 Overall summary

Isolated nocturnal hypertension is a disease masked in the dark. Blood pressure, at night, is elevated and it is associated with adverse cardiovascular effects. Subsequent to the elevated NBP, it therefore creates room for a non-dipping or reverse dipping pattern to occur. Which adds to adverse events. Isolated nocturnal hypertension, with or without blunted nocturnal dipping pattern is associated with severe cardiovascular target organ damage. However, there are several factors that influence the progression of TOD. Since BP and the progression of hypertension is subject to racial, environmental, and behavioural factors, the same factors are at play for INH. It progresses differently in black and non-black populations due to genetic predispositions and variations. One such example is sodium intake and handling. Blacks and non-black populations show difference in sodium handling and how it affects their overall BP profile. Another factor is mineralocorticoids, such as renin and aldosterone. Their regulation further differs in black people compared to non-black counterparts.

These are factors that have crucial role in the progression of INH, and related TOD. However, the use of 24-hour ambulatory BP monitoring is an essential tool that has allowed research to uncover different hypertension phenotypes, their associated TOD. It has further helped distinguish differences in blood pressure profile, including the circadian rhythm and has allowed comparisons between various populations. For that reason, studies can investigate whether INH shows similar patterns in a black population of African descent and compared against the body of data that emanates from international studies. This further allows the investigating whether TOD is similar in the different hypertension phenotypes through ABPM. Additionally, comparisons can be made between these phenotypes, in terms of modifiable risk factors. Lastly, ambulatory BP monitoring further allows comparison of the threshold used to determine TOD related to nocturnal BP when compared to conventional BP monitoring.

Chapter 3

Materials and Methods

3.1 Introduction

This section gives a detailed description of the methodological aspects that were applied throughout the thesis. There are no distinct techniques to each individual experimental chapter. Therefore, this current chapter serves as the global materials and methods of the thesis. Except for data that needed to be collected at the participants' homes, all onsite measurements were performed at the University of the Witwatersrand' Health Sciences Faculty, school of Physiology at the Human Nutrition Research Laboratory.

3.2 Ethics

This research project was approved by the University of the Witwatersrand's ethics committee for research in human subjects (Medical); HREC approval number **M170214** (Appendix 3).



Figure 3.1 A map of distribution of residential areas of study participants.

Map source: https://municipalities.co.za/provinces/view/3/gauteng

3.3 Participant recruitment

The data collected in this current thesis form part of the ongoing South African Hypertension and Diet Study (SAHDS) described by Maseko *et al*., (2018). The details of the study were explained to the participants following which they gave informed written consent (Appendix 4). Study participants were of African origin and recruited from a metropolitan area of Johannesburg (Figure 3.1). The minimum age of the participants was 18 years because BP rapidly increases with age below this value and there was no upper age limit. As this forms part of an ongoing study, three hundred and eighty-one (381) South Africans of black African ancestry were randomly recruited and their data added to the current pool of 1219, to bring the total population to 1600. Participants' recruitment was through word of mouth, to either individual participants, families, or local community members.

3.4 Demographic data collection

A questionnaire designed for the purpose of the current study was administered after recruitment and consent of the participants (Appendix 5). The questionnaire was explained, and assistance was provided when requested because majority of subjects were reasonably proficient in English. An example is illustrated in Figure 3.2, where further details of the study are explained to the participants before asking for written consent. The questionnaire helped document demographic data, level of education, current or past occupational information. Past and/or current medical history were documented. These included the presence of hypertension, diabetes, or kidney disease. The use of any medication prior or at the time of the clinical measurements was documented. Most of the questions simply required ticking the "Yes" or "No" answer box, however, some short answers were required to assess understanding to some questions. In addition, prior and current occupation, level of education, smoking status, and current daily alcohol consumption were recorded. Menstrual history, pregnancies and any contraceptive use was documented in female participants.



Figure 3.2 A picture showing the administration of the study questionnaire and consent form to the participant

The overall objectives of the study are explained during recruitment and again on the day of the clinic visit.

3.5 Anthropometric measurements

Anthropometric measurements were taken according to the international standards for anthropometric assessments (Stewart *et al*., 2011). Participants were dressed in clinical gowns for ease of measurements/ access to measuring body sites. Figure 3.3 illustrates some of the equipment used and the body landmarks for specific measurements. Weight measurements were recorded using an electronic scale (Healthometer Professional, McCook, IL, USA) to the nearest 0.1 kg. Height was measured using a stadiometer (Seca portable stadiometer, Hamburg, Deutschland, Germany) to the nearest 0.1 cm. During measurements the head of the participant was placed in the Frankfort plane with the body standing upright and a sliding headboard was lowered to most superior point of the head. In order to define each participant's nutritional status, participant BMI was computed as weight in kilograms divided by height in metres squared (kg/m^2).

Waist and hip circumferences were determined using a tape measure on the abdominal and thigh regions. Waist circumference was determined at the narrowest width midway between the iliac crest and the lowest rib to the nearest 0.1 cm at the end of a gentle expiration. During

measurements, same sex assistants were assigned to participants if landmarks required close skin contact. The participants stood with their feet close together with their weight equally distributed to each leg and the tape was positioned all around the body in horizontal position. Caution was taken to ensure that the measuring tape was not loosely placed or was too tight around the participants' body. A measurement was deemed tight if the tape made an indent on the skin of the participants or it was too loose if two fingers could fit between the tape measure and skin. A gentle inspiration ensured that the participants were not contracting their abdominal muscles or holding their breath. The hip circumference was measured at the widest part of the hips and largest part of the buttocks to the nearest 0.1 cm. Subsequently, the waist to hip ratio (WHR) was calculated from the waist circumference and the hip circumference to determine central adiposity.

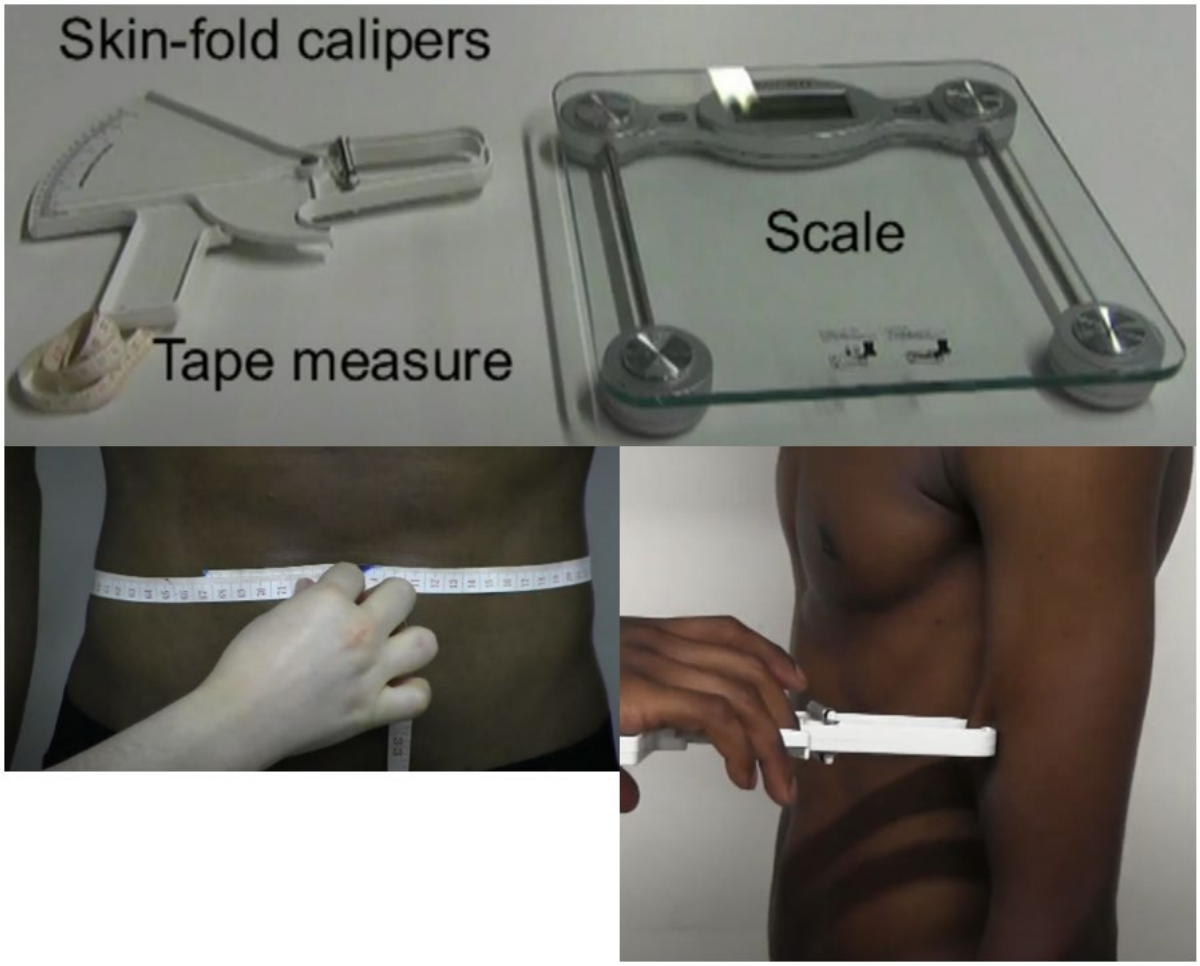


Figure 3.3 A picture showing some measuring tools and the body sites for anthropometric indices

3.6 Blood sampling and assays

Participants were asked to fast overnight prior to clinical visit. Following an overnight fast, venous blood of about 18 ml was drawn from the median cubital vein of the participants' arm for the analysis of the full and differential blood count, to exclude possible underlying subclinical conditions. The samples were taken to Central Laboratory Services (CLS) to analyse for renal, hepatic, or haematological disorders. Blood glucose assessed with participants using insulin and oral hypoglycaemic agents and or with an HbA1C value ≥ 7% being deemed diabetic. Serum mineral (Ca^{2+}, K^{+}, Mg^{2+}, and Na^{+}) and hormone (aldosterone, leptin and insulin) concentrations were determined.

3.7 Determination of the 24-hour urinary electrolyte excretion rates

Participants were issued large specimen bottles to collect 24-hour urine samples. Collection bottles were labelled appropriately including date of urine collection and time urine collection started and ended. For anatomical reasons, female participants were issued beakers to use and then transfer the urine into the specimen bottles. Subsequently, these specimen bottles were collected from the participants after 24-hours, a 24-hour urine volume less than 500 ml/day was considered incomplete. Urine samples were collected parallel with 24-hour ABPM; therefore, the start and finish times of the collection period were similar to that of the BP monitoring. The ‘‘first-pass urine’’ was discarded, and all urine passed thereafter was collected in the container provided, including the first urine of the following morning. Figure 3.4 illustrates examples of the large specimen bottles used to collect 24-hour urine samples. These are later transferred to 6ml specimen bottles which were sent to a clinical laboratory for analysis. Excess samples were then frozen in at minus 80°C. Urine samples were analysed for determination of 24-hour, daytime, and night-time urinary electrolyte excretion at CLS. Twenty-four-hour urine Na^{+} excretion rate was calculated as the product of urine volume and urine Na^{+} electrolyte concentration. Based upon the 95% confidence intervals for each group, a 24-hour urine sample was considered acceptable, if 24-hour urine creatinine was above 3.5 and below 35 mmol/24 hours for males and above 3.5 and below 30 mmol/24 hours for females. Creatinine clearance was determined from the product of urine volume and urine creatinine concentrations divided by plasma creatinine concentration.



Figure 3.4 A picture showing Twenty-four-hour urinary sample collection bottles and performance of fresh spot urine test.

Spot analysis was performed on the day of the clinic visit using urinary dipsticks, whereas urinary electrolytes were determined at the CLS laboratory, in Braamfontein.

3.8 Determination of clinic conventional blood pressure

Blood pressure was measured as previously described by O'Brien *et al*. (2003). Brachial blood pressure of the participants was measured using an automated sphygmomanometer (Omron HBP-1300 (OMRON Healthcare Europe B.V) with the participants seated on a chair with a back and armrest (Figure 3.5). Participants were requested not to cross their legs, and they rested the arm at which the BP was measured on a table that was set beside the chair at an elevation close to the heart level. Caution was taken by using a cuff suitable to the arm circumference of each participant. Cuff sizes included 22 x 12 cm, 30 x 13 cm and 31 x 14 cm and higher. Without interruptions, participants rested for ten minutes before commencing with initial measurements. Five consecutive BP measurements were taken at one-minute intervals and were then averaged to determine the participants' systolic and diastolic BP in mm Hg and resting heart rate. Participants who received anti-hypertensive treatment or had elevated BP as noted during clinical measurements were classified as hypertensives.

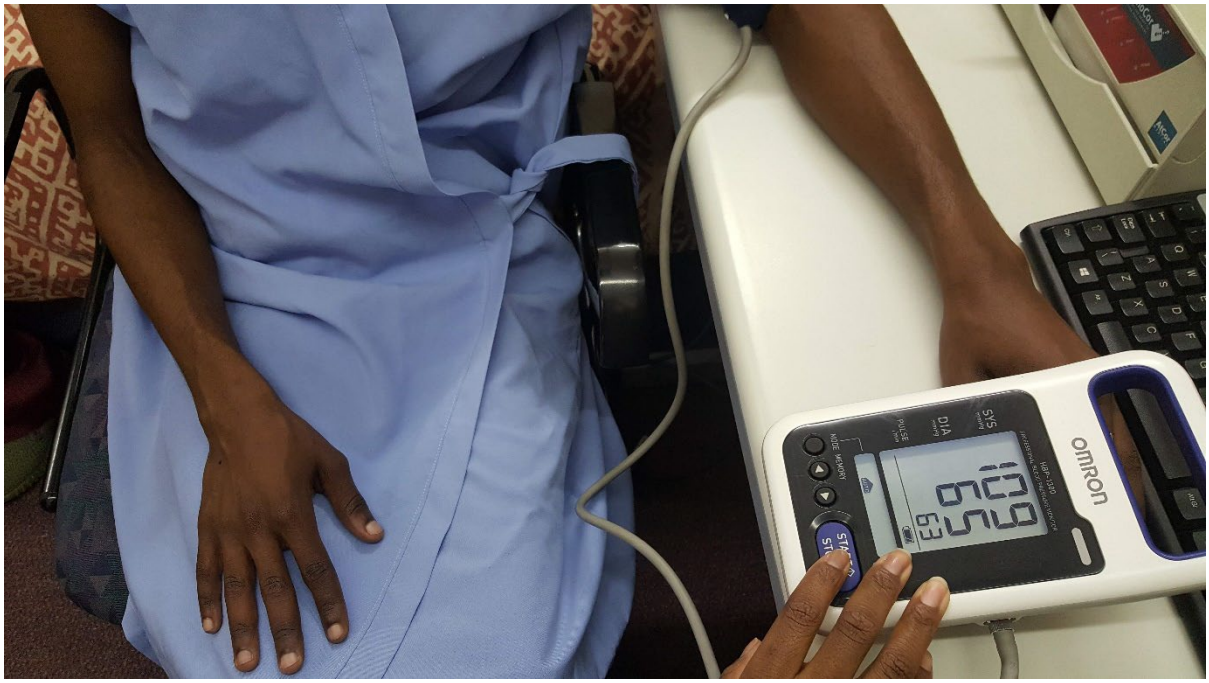


Figure 3.5 A picture illustrating Conventional BP measurements using an automated sphygmomanometer

3.9 Determination of 24-hour ambulatory blood pressure

ABPM was measured on the day of the clinic visit over a 24-hour period using oscillometric monitors as described by O'Brien *et al*., (2013). Suitable BP cuff sizes as described above, were used. The oscillometric monitors were programmed to measure daytime BP from 06:00 to 22:00 at 15 minutes time intervals; and night-time measurements from 22:00 to 06:00 at 30 minutes interval. The participants kept diary cards to record their bedtime and awakening times. Awake and sleep times were used to determine and define the participants' sleep and awake periods. The time intervals were used to eliminate the transition periods between evening and morning during which there are rapid BP changes in most participants. Furthermore, each participant kept a record of their night-time meal and any oral intake including medication or any kind of beverages taken and smoking activities during the 24-hour BP monitoring. Participants were asked to continue with their normal daily activities but to keep the cuff arm steady when the monitor is taking readings, to avoid motion disturbances or error readings. Additionally, they listed any physiological distress during the monitoring period. Following the 24-hour monitoring data was uploaded onto a computer for analysis. The 24-hour average systolic and diastolic BP was determined; the night-time BP percentage decrease was determined according to the difference between day and night BP and the ratio for day-to-night

BP. The 24-hour ABPM with less than 20 hours of recording, less than 20 daytime readings, or 10 night-time readings were excluded from analysis. A day–night decrease in systolic BP of <10% was used to characterize non-dippers from dipping participants. Figure 3.6 illustrates a standard ABP oscillometric monitor with its tubing. Monitors have a standard pouch and a strap for the waist or belt loop. The left of the image shows expected BP threshold (dotted lines) during day and night-time monitoring.

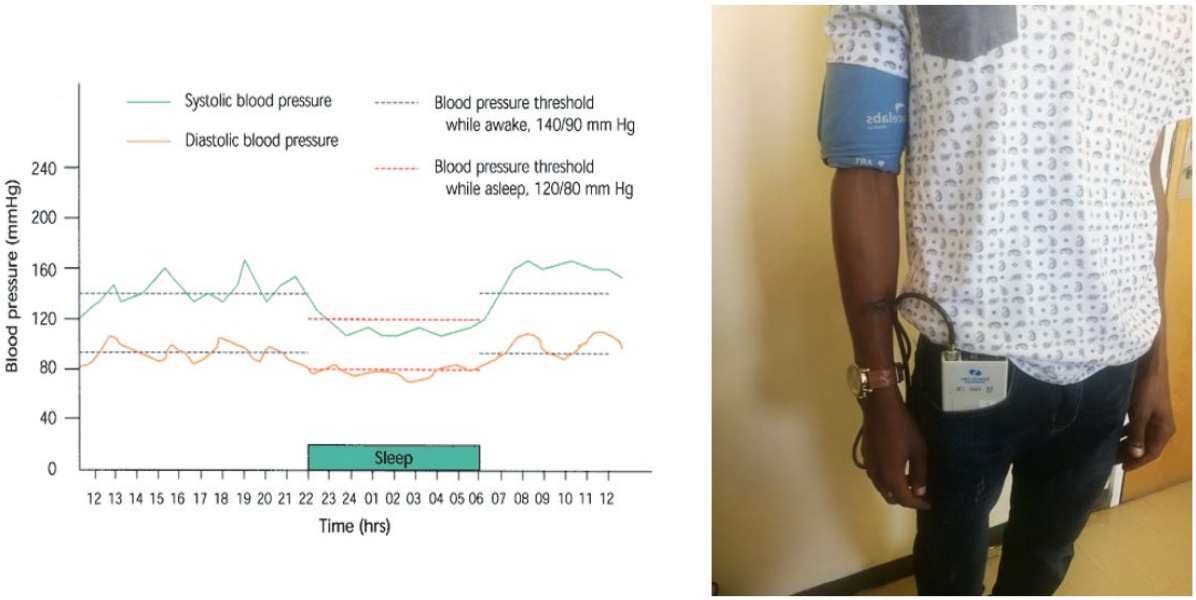


Figure 3.6 An example of the measurement of 24-hour ambulatory blood pressure.

3.10 Measurement of arterial stiffness

Measurements of arterial stiffness were performed as described by Shiburi *et al*. (2006). Arterial stiffness was measured using a high fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas), interfaced with a computer employing SphygmoCor software version 9.0. The participants rested in the supine position for 15 minutes before commencing with measurements. BP measurements from the above sections were inputted into the software for calibration. Before measuring pulse wave velocity, distances from the suprasternal notch to the carotid sampling site (distance A), and from the suprasternal notch to the femoral artery (distance B) were measured. The radial pulse wave velocity was measured at the participants' non-dominant arm. The carotid-femoral pulse wave velocity was measured non-invasively by applanation tonometry at an 8-s period. Two pressure waveforms generated

by an inbuilt transfer function were recorded simultaneously with pressure-sensitive transducers placed on the common carotid artery and the femoral artery. The pulse wave transmit time is the duration of the pulse wave from the carotid to the femoral site, and it is the difference in the time taken to generate the femoral and carotid pulse waveforms. The pulse transmit time was determined from the average of 10 cardiac cycles. A three-lead electrocardiogram was performed concurrently with pulse waveform sampling to assess the differences in time of the generation of the femoral and carotid pulse waveforms. Therefore, pulse wave velocity was calculated as the ratio of the distance, in metres, to the transit time in seconds between the common carotid artery and the femoral artery. For quality control measurements where the variability of the consecutive waveforms between the systolic or diastolic measurements were below 5% or >80 mV pulse wave signal amplitude was accepted. Figure 3.7 illustrates the different sites of measurements of the pulse wave. 3.7 (a) was the radial pulse, whereas 3.7 (b) was the carotid pulse. 3.7 (c) illustrated ECG trace that was matched with site A (radial) and site B (carotid) when determining the pulse wave velocity. Three sites were used to determine PWV, radial, carotid pulse and at the femoral region. The femoral region and waves were not shown in the picture and the resultant outcome.

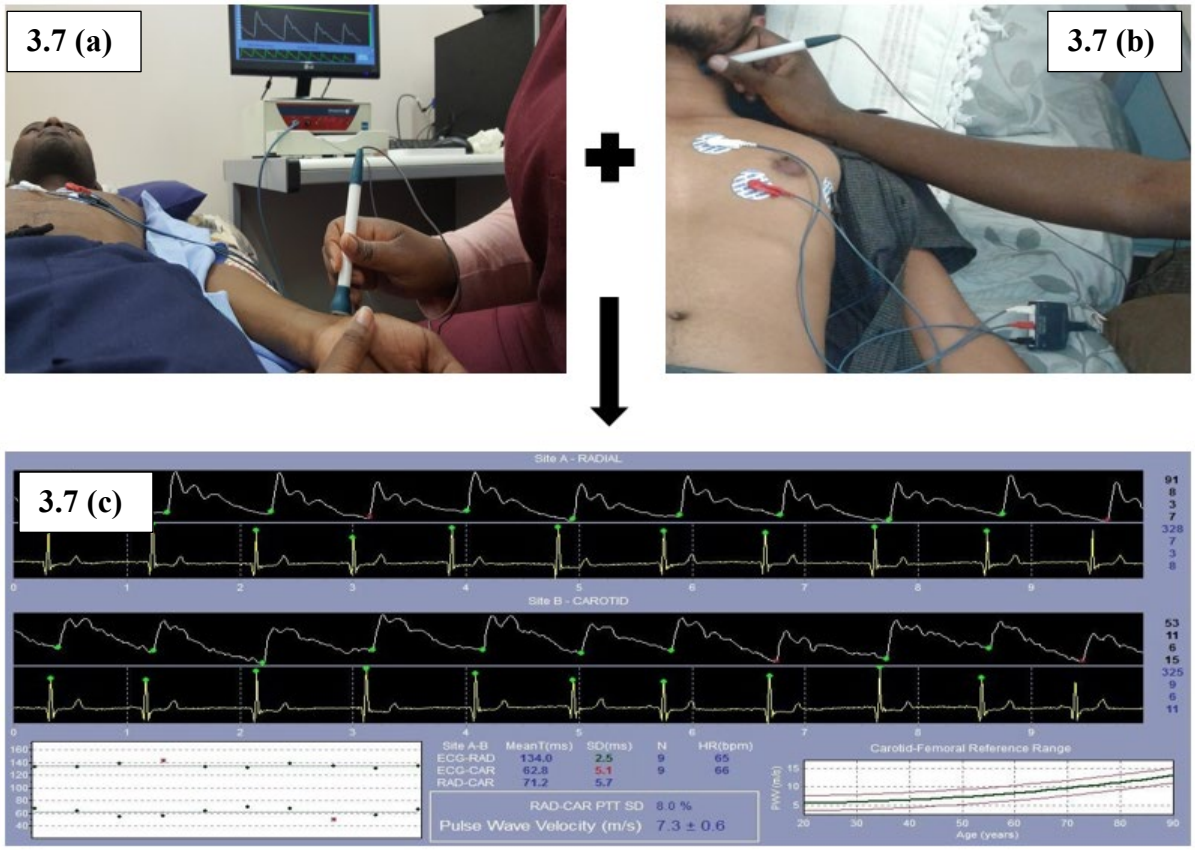


Figure 3.7 An Illustration of the arterial stiffness analysis measured through Pulse Wave Velocity.

3.11 Echocardiographic measurements

Echocardiographic measurements were performed using a Sonosite M-Turbo ultrasound (Sonosite Inc., Bothell, Washington, USA) device as previously described by Millen *et al*., (2014). Participants assumed the partial left decubitus position during the measurements. Measurements included assessing whether the participants had mitral valve abnormalities using two-dimensional and colour Doppler imaging. The two-dimensional directed mode was used to determine left ventricular dimensions in the short-axis view, the recordings were analysed according to the American Society of Echocardiography convention (Sahn *et al*., 1978). Images of the dimensions were captured during the measurements for later offline analysis. Only M-mode images of acceptable quality were analysed. For this reason, dimension included for analysis had appropriate visualization of both the right and left septal surfaces; additionally, the endocardial surfaces of the septal and posterior wall needed to be clearly visible at the optimal angle of incidence. Left ventricular mass (LVM) was determined using a standard formula as described by Devereux *et al*., (1986) and indexed (LVMI) to height $^{2.7}$. Left ventricular ejection fraction was calculated using the biplane Simpson method presented as

[(left ventricular end-diastolic volume − left ventricular end-systolic volume) / left ventricular end-diastolic volume] × 100. Figure 3.8 illustarates assessment of left ventricular end systolic (LV ESD), end diastolic internal diameters (LV EDD), the intraventricular septal wall thickness during systole (IVST S), diastole (IVST D), and the posterior wall thickness during systole (PWT S) and diastole (PWT D). These values were used for the calculation of ejection fraction and LV mass.

Tissue Doppler indices was used to determine left ventricular diastolic function at rest through the pulsed-wave Doppler examination as previously described by Quiñones *et al* (2002). Pulse-wave Doppler recordings of transmitral velocity were obtained with the sample volume at the tip of the mitral valve in the apical four-chamber view. Transmitral velocity measurements were obtained during the early (E) and late atrial (A) period of left ventricular diastolic inflow. Figure 3.9 illustrates images that were obtained to assess transmitral flow patterns; where the "E" was illustrating early diastolic filling velocity, and "A" late diastolic filling velocity. To perform tissue Doppler indices, the velocity of myocardial tissue lengthening at the level of the mitral annulus was recorded in the apical four-chamber view. The sample volume was positioned at the septal and lateral corners of the mitral annulus. Left ventricular diastolic dysfunction was evaluated as mild (impaired relaxation when E/A $\leq$0.75), moderate (pseudonormal, in which E/A > 0.75 < 1.5), and severe (in which E/A $\geq$1.5).

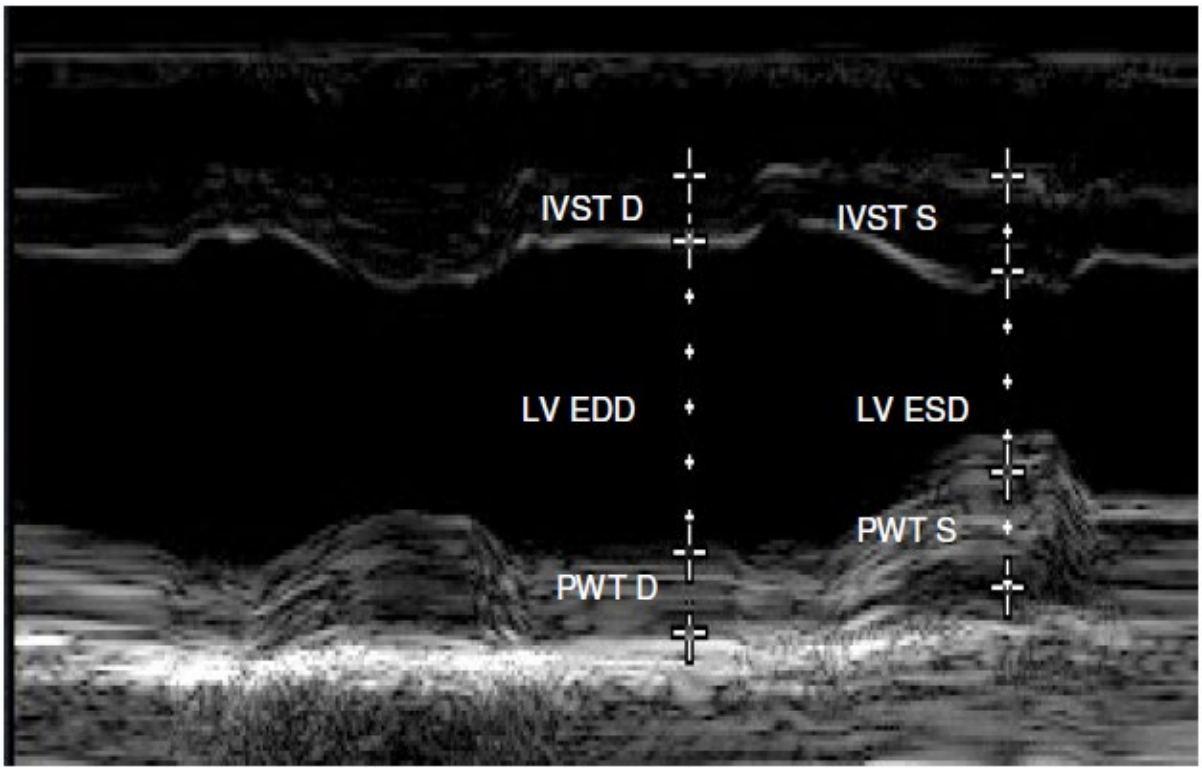


Figure 3.8 An example of an M-Mode echocardiographic image of the left ventricle.

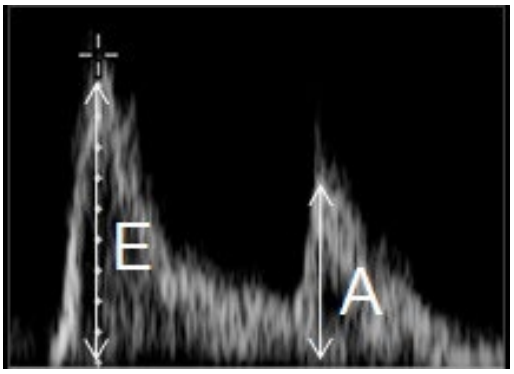


Figure 3.9 An example of a pulse waved Doppler echocardiographic image of the left ventricle.

3.12 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). For continuous variables, data were expressed as mean ± standard deviation (SD). Categorical variables were expressed as absolute or relative frequencies or as percentages. A P-value of less than 0.05 was accepted as the indicator of

statistical significance performed to determine relationships between variables. Of the 1 600 participants enrolled in the study, 397 were excluded from the analysis because they failed to meet the pre-specified quality criteria for ABP recordings. 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. Additionally, because 24-hour ABP was monitored parallel with 24-hour urinary collection, incomplete measurements for either ABPM or urinary electrolyte excretion to the count of 298 were thus disregarded for analysis. Some participants that were overweight/obese had unacceptable femoral pulse waveforms, for that reason 109 PWV measurements were therefore discarded. Other exclusion criteria included existing cardiovascular disease and use hypertensive medication.

The five readings obtained from CBPM in all chapters were averaged to obtain a single systolic and diastolic BP reading. ABPM data were expressed as 24-hour, daytime, and night-time average systolic and diastolic pressures. Night-time BP dipping was expressed as the ratio of daytime to night-time BP. Departure from normality of continuous variables was evaluated using Shapiro-Wilk's statistic and skewness by the computation of the coefficient of skewness for categorical variables. The normal distribution was used to determine the significance of the coefficient of skewness. Confounders, which included age, smoking, alcohol use, diabetes, body height, body weight, heart rate, BMI, waist circumference, Waist-to-Hip ratio, indices of adiposity and hypertension treatment along with use of medication, were included in the regression model and in the multivariate regression model to see if they were independent correlates of TOD. These confounders were corrected for because they may contribute to cardiovascular damage. Although sex differences may influence the manifestation of cardiovascular pathologies; in the current study sex was not included in the model for data analysis since the study focus was not sex specific. Multivariate regression analysis was used to determine association between 24-hour ABPM parameters, urinary Na^+ excretion, hormone concentrations and other markers of organ changes, including pulse wave velocity. ABPM data were expressed as average daytime (awake), average night-time (sleep) or average 24-hour systolic and diastolic BP. 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. Additionally, the models were used to determine association between dipping and general demographic parameters. Urinary electrolyte excretion rates were assessed in

models separate from those used for Na^+ to Creatinine ratios and subsequently assessed for probability values.

To determine BP dipping patterns (chapter four) the study participants were grouped according to BP. The state of hypertension was defined and used to categorise participants into NT, sustained 24-hour hypertension and INH. Traditional confounders were corrected for, in the regression model for the effects of BP, urinary Na^+ and renin on TOD. Renin concentrations were not normally distributed and were therefore expressed as log renin. Comparisons between dipper and non-dipper groups were done using independent Student's t-test or one-way analysis of variance (ANOVA).

In comparing TOD caused by INH and IDH (chapter five), the effects of cofounders were corrected and using regression models, renal function was assessed using the Na^+, microalbumin and creatinine. Comparisons between dipper and non-dipper groups were done using independent Student's t-test or one-way analysis of variance (ANOVA). Multiple and simple regression was used to determine the relationship between TOD in dippers and non-dippers according to defined hypertensive states. In chapter six, data was arranged into four groups according to defined 24-hour systolic BP quartiles. Multiple regression was used to determine the relationship between ambulatory blood pressure parameters and age. Simple regression analyses were used to determine association urinary Na^+ excretion and plasma aldosterone. Logistic regression analyses were used to determine association diastolic function and quartiles of systolic ABP.

In determining diastolic heart function (chapter six) multiple linear regression analysis was performed to determine effects of indices of 24-hour BP on measures of diastolic function. Diastolic BP in the E/A ratio models was employed as described by Libhaber *et al.,* (2014). Indexes of diastolic LV function were adjusted for several confounders associated with diastolic function. The parameters age, sex, regular alcohol or tobacco use, the presence or absence of diabetes mellitus or the use of antihypertensive agents, and pulse rate were included in the regression models since they were established to be associated with indices of left ventricular diastolic dysfunction in unadjusted regression analysis. To compare the relative impact of 24-hour BP indices on indices of diastolic dysfunction, standardized β-coefficients were determined.

To define the state of hypertension the following were used to categorise participants. Normotension on ABP was defined as daytime systolic BP <135 mm Hg and night-time blood

pressure <120 mm Hg, whereas on auscultatory measurements it was <120 mm Hg SBP/<80 mm Hg DBP. Sustained hypertension on 24-hour ABP was defined as overall systolic BP ≥130 mm Hg and night-time systolic blood pressure ≥ 120; yet from auscultatory measurements it was ≥140 mm Hg SBP or 90 mm Hg DBP. High-normal BP was considered if SBP was between 130 – 139 mm Hg or 85-90 mm Hg of DBP. Pre-hypertension on CBP was defined as measurements of 120-139 mm Hg SBP/ 80-90 mm Hg DBP. Therefore, optimal BP was <120/80 mm Hg. The cut-off values for isolated nocturnal hypertension were daytime systolic blood pressure < 135 mm Hg and night-time systolic blood pressure ≥ 120 mm Hg. Isolated daytime hypertension was defined as a systolic diurnal BP ≥135 mm Hg or 85 mm Hg diastolic. The presence of hypertension was further identified if subjects were either receiving antihypertensive medication or had an elevated auscultatory BP value obtained in a clinic environment that was above optimal threshold BP (Carey and Whelton, 2018; Williams *et al*., 2018; Cifu and Davis, 2017; Parati *et al*., 2014; Chobanian *et al*., 2003). Blood pressure dipping was recorded as day-night ratio between 10% and 20% of the day-night BP values. Non-dipping was defined as BP dipping was recorded as day-night ratio <10%. A riser profile or reverse dipping was defined as negative dipping ratio or actual BP night-time BP increase above daytime values. 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 ≥7%.

Chapter 4

Dietary Salt Intake and Blood Pressure Dipping Pattern in Isolated Nocturnal Hypertensives

4.1 Abstract

Isolated nocturnal hypertension (INH) is an anomaly in which nocturnal blood pressure is elevated despite normal daytime blood pressure. The determinants of INH have not been well established. Importantly, the role of dietary salt intake (DSI) on the pathophysiology of INH is currently unknown. In an earlier study conducted in this population it was shown that urinary sodium excretion is blunted. Since the relationship between DSI and blood pressure has been demonstrated in several studies, a possibility exists that attenuated urinary sodium excretion in this population may be the main determinant of INH. Furthermore, DSI may determine the nocturnal blood pressure dipping pattern in isolated nocturnal hypertensives. The first objective of this current study was to establish whether isolated nocturnal hypertensives have a non-dipping or reverse dipping blood pattern and/ or both. The second was to investigate whether DSI determines the dipping pattern. From a total sample of 1600 individuals, 796 participants were selected because they had complete 24-hour ambulatory blood pressure monitoring results and corresponding 24-hour urine collections. Pulse wave velocity was measured using applanation tonometry. Using the twenty-four-hour blood pressure results, the population sample was divided into three groups: normotensives (NT), 24-hour sustained hypertensives (HT), and isolated nocturnal hypertensives (INH). The isolated nocturnal hypertensives were further divided into non-dippers (IND) and reverse dippers (IRD). The urine samples were used to determine 24-hour urinary sodium and potassium excretion rates. The results show that 72% (n=570) of the participants were NT, 13% (n=105) were HT and 11% (n=90) had INH. In the INH group, less than 2% were dippers, 51% were IND and 47% were IRD. Despite the normal 24-hour and daytime blood pressure, the INH group had elevated night-time blood pressure. Renal sodium handling was different between the HT and INH when compared to the NT. The 24-hour HT excreted more sodium when compared to the IND group; however, the IRD group retained salt. Compared to the NT, the HT and INH group had a significantly lower plasma renin and a higher sodium-to-creatinine ratio. PWV of both the IND and the IRD was significantly higher than that of the NT group and similar to the HT group. These findings indicate that the two INH subtypes (IND and IRD) are as damaging to the large arteries as HT. These findings show that INH is similar to HT because both forms of hypertension are a low renin hypertension phenotype and are mediated by DSI as indicated by the high sodium-to-creatinine ratio in both groups. Moreover, both groups are associated with an increased PWV, an index of arterial stiffness. However, the nocturnal blood pressure dipping patterns are completely different in the two groups. The 24-hour hypertensives have a nocturnal systolic

blood pressure that is above the threshold of 120 mm Hg, but it remained lower than daytime BP; whereas the INH group had a night-time systolic blood pressure that was not only above the threshold of 120 mm Hg, but it was higher than the daytime systolic blood pressure. In conclusion, findings from the current study show that even though both HT and INH are associated with increased DSI, their dipping pattern were different. The HT group showed a non-dipping pattern while INH had a reverse dipping pattern. Both forms of hypertension were associated with an increased PWV. This implies that although the reverse dipping pattern observed in INH is limited to night-time, its impact on target organ damage is similar to 24-hour sustained hypertension.

4.2 Introduction

Blood pressure (BP) follows a circadian rhythm that is characterised by daytime BP that is higher than night-time BP in a 24-hour cycle. However, in a condition known as isolated nocturnal hypertension (INH), the circadian BP profile is characterised by a normal daytime BP and an elevated nocturnal BP (NBP) (Li *et al*., 2007). This unusual BP pattern imposes a serious challenge on the diagnosis and control of BP in third world countries with limited resources. The main challenge is that in these countries diagnosis of hypertension is dependent on conventional BP measurements, which is more affordable compared to 24-hour ambulatory BP monitoring. This creates a crisis because people with INH have normal BP during the day and only present with elevated BP at night (Fan *et al*., 2020). Since conventional BP monitoring is only performed during the day, and in the clinical settings, INH remains undiagnosed or misdiagnosed as normotension in these settings. Due to this discrepancy, there is no conclusive data on the impact of INH on target organ damage (TOD).

There is sufficient evidence that shows that elevated BP is associated with severe end organ damage (Zhou *et al*., 2020; Verbrugge *et al*., 2020; Mancia and Parati, 2003). Studies that focus on INH could provide an opportunity to determine whether TOD related to elevated BP through the sustained effects of BP over a 24-hour period is similar when BP is only elevated at night. This could expand knowledge on the scope of the effects of elevated nocturnal BP independent of daytime BP. Knowledge about the effects of elevated nocturnal BP could create a paradigm shift from diagnosing BP based on daytime BP only to a thorough diagnosis that is based on both day and night BP. Findings on the negative effects of elevated BP, could reveal that TOD may not necessarily be limited to people who are hypertensive, but that people classified as normotensives can be at risk of TOD if they present with elevated nocturnal BP. Tadic *et al.* (2020) postulated that TOD in people with INH may eventuate to ventricular remodelling that leads to hypertrophy. This highlights that INH may be more dangerous than hypertension because it may be undiagnosed through CBPM. Through CBPM, patients present with normal daytime BP hence they are misdiagnosed as normotensive whereas they may be presenting with elevated nocturnal BP or presenting as non-dippers.

The nocturnal BP dipping pattern of nocturnal hypertensives has not been studied. Currently three abnormal nocturnal BP patterns have been identified, non-dipping, reverse dipping, and extreme dipping. In non-dipping, night-time BP decreases by less than 10% of the daytime BP values (de la Sierra *et al*., 2010), in reverse dipping, night-time BP increases above day-time

BP (Cuspidi *et al*., 2017) and in extreme dipping, night-time BP decreases by more than 20% of the daytime BP values (Kario and Shimada, 2004). Studies have shown that all three types of dipping patterns are associated with TOD (Yano and Kario, 2012; Tsioufis *et al*., 2011). Of these three abnormal BP patterns, extreme dipping cannot be classified as part of the INH subtype. These individuals are characterised by an exaggerated decrease in night-time BP while INH is an abnormally elevated nocturnal BP (Li *et al*., 2007). There is currently no knowledge of whether individuals with INH are non-dippers (nocturnal BP decreases by less than 10% of daytime BP) or reverse dippers (nocturnal BP increases above daytime BP values). As stated earlier, both dipping and reverse dipping are associated with cardiovascular TOD (de la Sierra *et al*., 2014); however, there is currently no data on whether TOD persists even when daytime pressures are normal since only night-time BP is elevated (≥ 120mm Hg) while daytime BP is normal (> 135 mm Hg). Nonetheless, these dipping subtypes have an elevated nocturnal systolic BP that is above the threshold of 120 mm Hg (Li *et al*., 2007). In addition, despite the differences in these patterns, they play a role in INH which requires investigation.

The prevalence of INH is influenced by several factors. These vary between population groups because of the effects of geographical and ethnical differences (Ogedegbe *et al*., 2013). Overall, INH seems to have a low prevalence in most populations and ethnicities; however, during investigations the differences in each population are further affected by population size, their nocturnal BP fall, and disease state and comorbidities that are prevalent in each population (Tadic *et al*., 2020). For instance, the Asian population has a higher prevalence of INH than the European and African populations, which underlines the differences in ethnic presentation of INH, and thus, leads to a hypothetical pathophysiological mechanism of INH (Li *et al*, 2008). To demonstrate this, in their study Li and Wang, (2013), only reported a 10% prevalence of INH in South African black participants in comparison with other ethnicities: Chinese (11%), Japanese (10%), and Eastern Europeans (8%) and Western Europeans (6%). However, Li *et al* (2007) had a small sample size of 200 South Africans; therefore, their findings of a 10% prevalence are inconclusive. With a 26% HT prevalence in South Africans (Maluleke *et al*., 2013), the incidence of INH may be higher in this group compared to other population groups.

Notwithstanding, the cardiovascular risks of both INH and non-dipping are worth noting. They both predispose to pathological disease and TOD. Adverse cardiovascular events like heart failure (HF) and TOD like kidney dysfunction are some of the common presentations (Fan *et al.*, 2010; Hoshide *et al*., 2003). The determinants of INH and non-dipping are similar and most of the risk factors are associated with increased BP during the night. Other risk factors include

daytime and night-time activities that blunt nocturnal BP decline (Wang *et al*., 2015; Li *et al*., 2007). There are neuro-hormonal factors that impact on the cardiovascular system and dimmish the NBP fall (Kario, 2018). Moreover, INH and non-dipping have an increased propensity to be impacted by environmental conditions, co-morbidities such as obesity and diabetes, race, and excess salt intake (Wijkman *et al*., 2009; Kimura, 2008). Excess salt intake seems to induce several cascades of events that lead to TOD. Not to mention that when daytime salt excretion is blunted and pressure natriuresis shifts to night-time hours, increased circulating volume increases NBP as the kidneys excrete salt (Kimura, 2008; Uzu *et al*., 1997). Moreover, increased blood volume is a risk factor for increased left ventricular load and further leads to renal dysfunction as intraglomerular pressure and hyperfiltration become eminent. It is possible that not all non-dippers or reverse dippers are isolated nocturnal hypertensives, but all nocturnal hypertensives may be either non-dippers or reverse dippers. A possibility exists that since DSI influences night-time BP, it may further determine whether isolated nocturnal hypertensives have a non-dipping or a reverse dipping pattern.

A major structural change that occurs resulting from the blunted BP regulation is arterial stiffness (Nolde *et al*., 2021). Stiffening of the arteries mostly relates to a change in the compliance and distensibility of large arteries. It affects vascular function and when there is less compliance and reduced distensibility, this is considered a cardiovascular risk because of the negative effects (Oliver and Webb, 2003). As the arteries stiffen overtime there is an augmentation of the pressure waves when there is less elastic recoil. Furthermore, this augmentation of the aortic pressure and peripheral vascular resistance can cause negative BP changes (Bhandari *et al*., 2020; Payne and Webb, 2006). Arterial stiffness has many determinants, and diurnal BP has received a lot of attention in recent years regarding its correlation with an ageing vasculature. This is because the diurnal changes of BP can determine arterial stiffness overtime. Moreover, since the structural and functional changes that come with stiffening of the arteries can at times precede the effects of BP anomalies, it can be said that the determinants of diurnal changes in BP and arterial stiffness share commonality (Lithovius *et al,* 2018).

According to Castelpoggi *et al* (2009), the association between NBP and arterial stiffness is under-reported. One of the postulates between vascular stiffness and NBP is that changes in endothelial function have a positive correlation with arterial stiffness. When monitoring NBP, studies show that increased pro-inflammatory activity and endothelial dysfunction are associated with vascular changes that are consistent with increasing stiffness (Higashi *et al*.,

2002; Chappell *et al*., 1998; Lacolley *et al*., 1995). Elevated NBP subjects the arterial tree to increased distending pressure, overtime, this elevated pressure damages the endothelium, and promotes arterial stiffness (Payne and Webb, 2006; Asmar *et al*., 1996). Moreover, the perpetual state in elevated NBP leads to arterial damage and vascular remodelling because arterial distensibility becomes reduced overtime (Zakopoulos *et al*., 2005; Zanchetti *et al*., 2001). One of the underlying determinants of arterial stiffness with NBP is the lack of nocturnal BP fall (Lekakis *et al*., 2005). When investigating vascular changes, research shows that dipping has a negative correlation whereas non-dipping has a positive correlation with arterial stiffness (Shinohata *et al*., 2008; Jerrard-Dunne *et al*., 2007). Since NBP and non-dipping are predictors of adverse cardiovascular outcome, perhaps arterial stiffness is one of the underlying mechanisms in the prognosis of adverse cardiovascular outcomes (Boggia *et al*., 2007; Ohkubo *et al*., 2002). There still exist some disagreements to the effects and extent of a lack of nocturnal BP decline and arterial stiffness, more especially considering that the reproducibility of dipping and non-dipping can be challenging (Tsioufis *et al*., 2005; Cuspidi *et al*., 2003; Grandi *et al*., 2002). Therefore, the underlying association between NBP, dipping and arterial stiffness remains to be fully elucidated. Notwithstanding, there are possible explanations, including methodological differences between studies and patient demographics, which affect the nocturnal decline from daytime BP, dipping and non-dipping status.

The nocturnal decline from daytime BP is multifactorial. Although it is a normal phenomenon that occurs to all individuals, it can have dire consequences when the nocturnal decline is disrupted (Anyfanti *et al*., 2020). Furthermore, it can have worse outcome in hypertensive patients or patients with disease states such as renal damage, wherein impaired Na^+ handling can increase NBP dysfunction (Fagard *et al.*, 2008). Several studies have shown that increased salt intake reduces the decline in NBP (Sachdeva and Weder, 2006; Fujii *et al*., 1999; Uzu *et al.*, 1997). Moreover, the decline is further impacted when there is an impairment in salt excretion (Del Giorno *et al*., 2020). It is commonly expected that salt excretion is a daytime activity, and less salt is excreted during the night. Therefore, when there are any disruptions and daytime excretion shifts towards night-time hours, it subsequently leads to increased NBP, as a compensatory mechanism to excrete excess salt and maintain Na^+ balance (Sachdeva and Weder., 2006). Since excess salt intake is one of the proposed effects of increased NBP, it can be accepted that eminent pressure natriuresis during sleep is an attempted compensatory mechanism to excrete daytime Na^+. Nonetheless, this increases NBP and perpetuates a non-dipping BP pattern (Staessen *et al.*, 1993).

Besides impaired handling of salt and excess intake, there is still a racial component that affects NBP. Racial factors may contribute to impaired Na^+ handling because there is a predisposition that certain ethnicities are prone to increased BP with low renin and aldosterone (Koolen *et al*., 1983). Nonetheless, the response to excess salt intake may vary between populations (Weinberger *et al*., 1886) and excess dietary salt may cause inactivation of hormonal and neural mechanisms that regulate night-time Na^+ excretion and consequently increase NBP (Bankir *et al.,* 2008). It is reported that impaired Na^+ handling contributes largely to the prevalence and effects of INH within different racial groups (Kimura, *et al*. 2010). This implies that INH could be a major problem in people of African ancestry because their bodies handle Na^+ differently. Although there are some disagreements regarding salt-handling, it has been shown to be a major problem in this ethnic group (Ji *et al*., 2014; Ergul, 2000; Svetkey *et al*., 1996). Although the effects of salt may be genetic, it is exacerbated by lifestyle habits such as excessive salt intake, which is further compounded by an intrinsically reduced Na^+ excretion together with dysregulation in NBP mechanisms (Kimura *et al.*, 2010). There is a postulate that elevated NBP compounded by insufficient tubular Na^+ reabsorption is due to salt retention (Sachdeva and Weder, 2006). This is based on observed BP changes during excess DSI and decreased excretion.

It is established that when there is an impaired mechanism that regulates daytime urinary Na^+ excretion night-time BP becomes elevated as Na^+ excretion shifts towards night-time (Del Giorno *et al*., 2020). This means that renal perfusion pressure and blood volume increases as the kidneys attempt to excrete Na^+ (Bankir *et al*., 2008). Therefore, excess Na^+ intake without subsequent daytime excretion can be caused by blunted Na^+ handling which interacts with renal handling to elevate night-time BP (Uzu *et al.*, 1998). Blood pressure increases as a result and pressure natriuresis shifts to sleeping hours to accommodate night-time salt excretion (Choi *et al*., 2015; Kusche-Vihrog and Oberleithner, 2012; Guyton, 1991). This introduces an association between salt retention and NBP. Uzu *et al* (1998) further reported that salt retention is associated with nocturnal hypertension regardless of the absence of other causative factors. The association between excess Na^+ intake and nocturnal hypertension implies that salt retention may cause renal dysfunction; because glomerular capillary pressure increases in individuals with reduced salt excretion (Kimura *et al.*, 2010). Therefore, the effects of salt retention, which causes renal dysfunction, could likewise cause the associated renal and cardiovascular events that are caused by nocturnal hypertension. Although the exact mechanism for salt retention is still unknown, it is associated with vascular and structural end

organ damage (Fukuda *et al.,* 2012). Moreover, reduced vascular reactivity may be related to salt retention through the disruption of the endothelium that affects arterial compliance when the sustained elevated BP adversely affects kidney function (Elias *et al*., 2014).

Notwithstanding, there is still no univocal mechanism that defines the relationship between salt retention and the development of nocturnal hypertension. Nonetheless, it has been suggested that hypertension may be an underlying link to salt retention (Svetkey *et al.*, 1996), whereas Uzu *et al* (1996) proposed that salt retention and nocturnal BP are interlinked (Uzu *et al*., 1996). Kimura (2008) identified a dysregulation in NBP profile in people that present with impaired Na^+ excretion (Kimura, 2008). This further supports the postulate that there is a link between NBP and impaired Na^+ excretion. Moreover, there is a hypothesis that the prevalence of hypertension in the black population may be an underlying link to salt retention (Svetkey *et al.*, 1996), whereas it could be argued that salt retention may be a surrogate of a non-dipping BP profile (Uzu *et al.*, 1996). Regardless, the degree of disagreement between salt retention and the NBP profile still does not present a univocal conclusion. Therefore, the objective of this study was to investigate the association between INH and target organ changes in a population that may present with impaired sodium excretion.

4.3 Results

Table 4.1 shows the general characteristics of the study participants. The study participants were stratified according to BP into various groups and these groups were compared. They were categorised according to hypertension status; normotensives (NT), sustained 24-hour hypertensives (HT) and isolated nocturnal hypertensives (INH). Normotensive participants had overall 24-hour systolic BP of 111.1 mm Hg over 68.7 mm Hg of diastolic BP. The HT group had overall 24-hour systolic BP of 146.3 mm Hg over 88.6 mm Hg of diastolic BP. Lastly, the INH group had overall 24-hour systolic BP of 127.1 mm Hg over 76.9 mm Hg of diastolic BP. The full haemodynamic profile of the study participants is shown in Table 4.2. The total study population was predominantly female at 64%. Even when separated according to BP, each group was comprised of more than 50% of the female cohort, 66% in the NT group, 58% and 57% in the sustained 24-hour HT and INH group, respectively. The mean age of the total population was 44 years and there was a significant difference in the ages of the three groups. The NT were the youngest (mean age of 29 years), followed by the HT (mean age of 55 years) and the INH group were the oldest (mean age of 57 years). The total population sample had an

overall overweight BMI of 28.90±7.62 kg/m^2. None of the subgroups were in the normal BMI range. The average BMI values of the NT, HT and INH were 27.9 kg/m^2, 31.7 kg/m^2 and 31.1 kg/m^2, respectively. There was a higher prevalence of diabetes in the HT group. The prevalence of diabetes was 18% and 14% in the HT and INH group respectively, whereas only 6% of the NT group had diabetes. Participants with sustained 24-hour HT smoked tobacco more than people without hypertension or those with INH. The prevalence of tobacco smoking was 18% in the HT group, whereas the NT and INH group had a prevalence of 14%. Notwithstanding, alcohol intake was the lowest in the HT group. The results show that only 17% of the sustained 24-hour HT group consumed alcohol; whereas the NT showed a prevalence of 20% and the highest prevalence was in the INH group at 27%.

Table 4.1 General characteristics of all, normotensives, sustained 24-hour hypertensives, and isolated nocturnal hypertensive participants.

	All Participants	NT	HT	INH
Number	796	570	105	90
Age (years)	44.19±18.30	29.18±16.73	55.34±15.91 [a]	57.02±17.42 [ab]
BMI (kg/m^2)	28.90±7.62	27.91±7.06	31.69±7.56 [a]	31.14±8.83 [a]
% Female	64	66	58	57
% Diabetic	9	6	18	14
% Tobacco smokers	15	14	18	14
% Alcohol intake	21	20	17	27

NT, normotensives (day time systolic BP < 135 mm Hg or daytime diastolic BP < 80 and night time systolic BP < 120 mm Hg or night-time diastolic BP < 70 mm Hg); **HT**, sustained 24-hour hypertensives (daytime systolic blood pressure ≥ 135 mm Hg or daytime diastolic BP ≥ 85 mm Hg and night-time systolic blood pressure ≥ 120 mm Hg or night-time diastolic BP ≥ 70 mm Hg); **INH**, isolated nocturnal hypertensives (night-time systolic blood pressure of ≥ 120 mm Hg systolic or night-time diastolic BP ≥ 70 mm Hg and daytime systolic BP < 135 mm Hg or daytime diastolic BP < 85 mm Hg). **BMI**, body mass index. [a] significantly different from NT; [b] significantly different from HT. P value <0.05.

Table 4.2 shows the 24-hour ambulatory BP profile of the study population. The total study population had normal average 24-hour BP of 118.3/72.6 mm Hg. The NT group had a mean 24-hour BP 111.1/68.7 mm Hg of systolic over diastolic BP. The HT group showed an average 24-hour systolic BP of 146.3 mm Hg over diastolic BP of 88.6 mm Hg. The INH group was further divided into the non-dipping (IND) and reverse dipping (IRD) cohorts. The IND group showed an average 24-hour systolic BP of 127.1 mm Hg over 76.9 mm Hg of diastolic BP. The IRD group showed mean 24-hour BP of 126.5/78.8 mm Hg. By comparison, there are significant differences in the overall 24-hour BP changes between group cohort, respectively. Daytime BP changes of the four cohorts showed significant differences among them. The NT had daytime BP that was slightly higher than the mean 24-hour BP; 116/70 mm Hg of systolic over diastolic BP. The HT had mean daytime BP that was higher than the overall 24-hour at 149.1/92.8 mm Hg of systolic over diastolic BP. Continuing in the same trend was the IND group that showed mean daytime BP of 129.5/80.7 mm Hg of systolic over diastolic BP. However, the IRD group showed a daytime BP average that was lower than the mean 24-hour BP. Their daytime BP was 122.6/78.9 mm Hg of systolic over diastolic BP. Additionally, Night-time BP changes were also distinct among the four cohorts. The normotensive group showed lower nocturnal BP averages, with 103.3/60.5 mm Hg. The sustained 24-hour HT also showed decreased mean night-time BP compared to daytime values, at 141.6/81.6 mm Hg. The non-dipping group of the INH cohort showed lower nocturnal BP values compared to daytime; their average night-time BP was 123.5/71.4 mm Hg. Lastly, the reverse dippers showed elevated mean nocturnal BP when comparing with daytime values. Their night-time BP increased to 131/77.8 mm Hg.

Table 4.2 Haemodynamic characteristics (mm Hg) of the population sample classified according to hypertension and dipping status.

	All Participants	NT	HT	IND	IRD
Number	796	570	105	46	42
SBP24	118.3±15.0	111.1±7.8	146.3±13.0 [a]	127.1 ± 3.2[ab]	126.5 ± 7.3[ab]
DBP24	72.6±10.2	68.7±6.8	88.6±10.9 [a]	76.9 ± 6.3[ab]	78.8 ± 7.0[ab]
SBPD	122.5±14.7	116.0±8.5	149.1±11.5 [a]	129.5 ± 2.9[ab]	122.6 ± 7.6[abc]
DBPD	77.6±10.4	70.0±7.5	92.8±11.1 [a]	80.7 ± 6.7[ab]	78.9 ± 7.9[ab]
SBPN	111.3±17.2	103.3±8.7	141.6±16.9 [a]	123.5± 3.1[ab]	131.0 ± 9.3[abc]
DBPN	65.0±11.7	60.5±8.0	81.6±12.1 [a]	71.4 ± 7.2[ab]	77.8 ± 8.7[abc]

SBP24, twenty four-hour systolic blood pressure; **DBP24,** twenty four-hour diastolic blood pressure; **SBPD**, daytime systolic blood pressure; **DBPD**, daytime diastolic blood pressure; **SBPN**, night-time systolic blood pressure; **DBPN**, night-time diastolic blood pressure; **NT**, normotensives (day time systolic BP < 135 mm Hg or daytime diastolic BP < 80 and night time systolic BP < 120 mm Hg or night-time diastolic BP < 70 mm Hg); **HT**, sustained 24-hour hypertensives (daytime systolic blood pressure ≥ 135 mm Hg or daytime diastolic BP ≥ 85 mm Hg and night-time systolic blood pressure ≥ 120 mm Hg or night-time diastolic BP ≥ 70 mm Hg)**; IND**, isolated nocturnal hypertensive non-dippers (daytime systolic blood pressure < 135 mm Hg, daytime systolic blood pressure ≥ 120 mm Hg and night-time BP and nocturnal BP decline < 10%); **IRD**, isolated nocturnal hypertensive reverse dippers (daytime systolic blood pressure < 135 mm Hg, night-time systolic blood pressure ≥ 120 mm Hg and night-time and nocturnal BP decline < 0%). [a] significantly different from NT; [b] significantly different from HT; [c] significantly different from IND. P value <0.05 accepted as significant.

Table 4.3 shows the urinary electrolytes excretion rates and plasma hormone concentrations. Compared to the other groups (NT, HT, and IND) the lowest excretion rates were observed in the IRD group (mean Na^+ = 72 mmol/day). Whereas the highest excretion rates, among the groups, were observed in the IND group (mean Na^+ = 120 mmol/day). The NT and HT groups had relatively normal urinary Na^+ excretion rates, presenting with mean Na^+ excretion rates = 105 and 100 mmol/day, respectively. Similarly, urinary K^+ excretion rates were lower in the IRD group (mean K^+ = 18.9 mmol/day) when compared to the NT, HT, and IND. However, the IND and NT group had relatively similar excretion rates, with mean K^+ = 28.4 mmol/day and 29.8 mmol/day, respectively. Magnesium concentration in the IRD group was different from the NT, HT, and IND groups. This excretion was lower than all three groups, with a mean Mg^{2+} = 1.1 mmol/day. All the remaining groups, the NT HT and groups showed similar Mg^{2+} excretion rates, mean Mg^{2+} = 2.4 mmol/day for NT and 2.1 mmol/day for both HT and IND. Plasma renin concentrations differed among the four groups. Plasma renin in the IRD group was higher (mean renin = 15.1 ng/dl); which was significantly different from the IND groups (mean renin = 41.2 ng/dl). Whereas the HT group had the lowest plasma renin (average renin = 26.0 ng/dl) when compared to the rest of the groups. The lowest observed aldosterone was in the IND, mean aldosterone =168.9 ng/dl. This was significantly different when compared to the IRD group (mean aldosterone =257.2 ng/dl).

Table 4.3 Urine electrolytes excretion rates and plasma hormones concentrations of the population sample classified according to hypertension and dipping status.

	NT	HT	IND	IRD
Number	570	105	46	42
Na^+ (mmol/day)	105.2 ± 76.5	100.8 ± 74.4	120.9 ± 92.9	72.8 ± 44.2[ac]
K^+ (mmol/day)	29.8 ± 23.3	24.2 ± 18.1[a]	28.4 ± 15.8	18.9 ± 15.0[ac]
Mg^{2+} (mmol/day)	2.4 ± 1.9	2.1 ± 2.1	2.1 ± 1.4	1.1 ± 0.9[abc]
Renin (ng/dl)	39.4 ± 79.9	26.0 ± 41.9[a]	41.2 ± 59.9	15.1 ± 18.7[ac]
Aldosterone (ng/dl)	192.6 ± 156.3	208.8 ± 165.2	168.9 ± 160.2	257.2 ± 218.9[ac]
Aldost/Renin	21.3 ± 33.3	56.3 ± 103.6[a]	19.4 ± 38.1[b]	48.2 ± 61.3[ac]

NT, normotensives (day time systolic BP < 135 mm Hg or daytime diastolic BP < 80 and night time systolic BP < 120 mm Hg or night-time diastolic BP < 70 mm Hg); **HT**, sustained 24-hour hypertensives (daytime systolic blood pressure ≥ 135 mm Hg or daytime diastolic BP ≥ 85 mm Hg and night-time systolic blood pressure ≥ 120 mm Hg or night-time diastolic BP ≥ 70 mm Hg); **INH**, isolated nocturnal hypertensives (night-time systolic blood pressure of ≥ 120 mm Hg systolic or night-time diastolic BP ≥ 70 mm Hg and daytime systolic BP < 135 mm Hg or daytime diastolic BP < 85 mm Hg). **Na^+**, Sodium; **K^+**, Potassium; **Mg^{2+}**, Magnesium; **Aldost/renin**, aldosterone-to-renin ratio. **[a]** significantly different from NT; **[b]** significantly different from HT. **[c]** significantly different from IND. P value <0.05 accepted as significant.

Figure 4.1 shows the nocturnal BP dipping pattern of the NT, HT and INH group according to different age categories, the young adults (age < 35 years), middle-aged adult group (ages 35 to 49 years), adult group (ages 50 to 65 years) and the elderly (age ≥ 65 years). In the INH group, night-time BP pattern showed non-dipping that is prevalent above 35 years. The group continue to show non-dipping throughout their middle age until they reach the adult age group 50 to 65 years, where their non-dipping percentage is at zero. This showed that nocturnal BP in the elderly group of the study population does not decline. In the elderly years (>65) they start showing negative dipping values, thus becoming reverse dippers, meaning nocturnal BP is increasing. In sustained 24-hour HT, the dipping pattern in the adult years (>35 years) showed non-dipping. The group continues as non-dippers through middle-age, adult age and into their elderly years. On the other hand, the NT group present when they are young adults (<35 years). They remain as dippers, and only become non-dippers when they are in their elderly years, ≥ 65 years. These results show that age affects the BP profile in all groups; young adults (age < 35 years), middle-aged adult group (ages 35 to 49 years), adult group (ages 50 to 65 years) and the elderly (age ≥ 65 years), although the non-dipping pattern only becomes reverse dipping in people with INH.

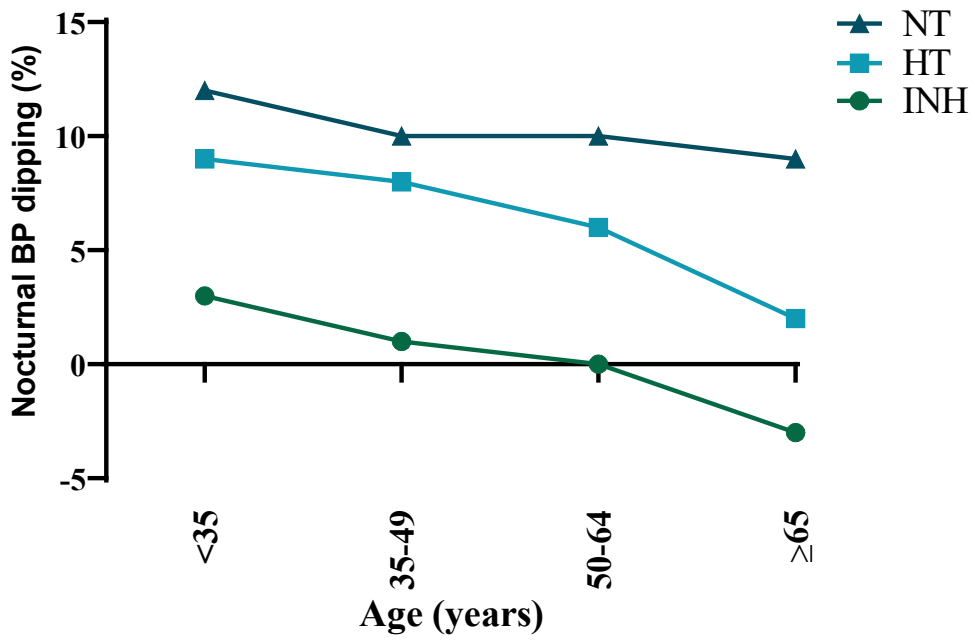


Figure 4.1 Age related changes in dipping status in normotensives (NT=570), sustained 24-hour hypertensives (HT=105), and isolated nocturnal hypertensives (INH=90).

Figure 4.2 represents the night-time BP dipping profile. Participants that were normotensive had normal nocturnal BP decline of 11%. The sustained 24-hour HT group and the IND group showed similar dipping patterns. Both were non-dippers, and both only showed 5% decline in night-time BP. Whereas the IRD group showed they had a reverse dipping pattern. Instead of declining, their night-time BP increased above daytime BP, hence they showed a -7% dipping pattern.

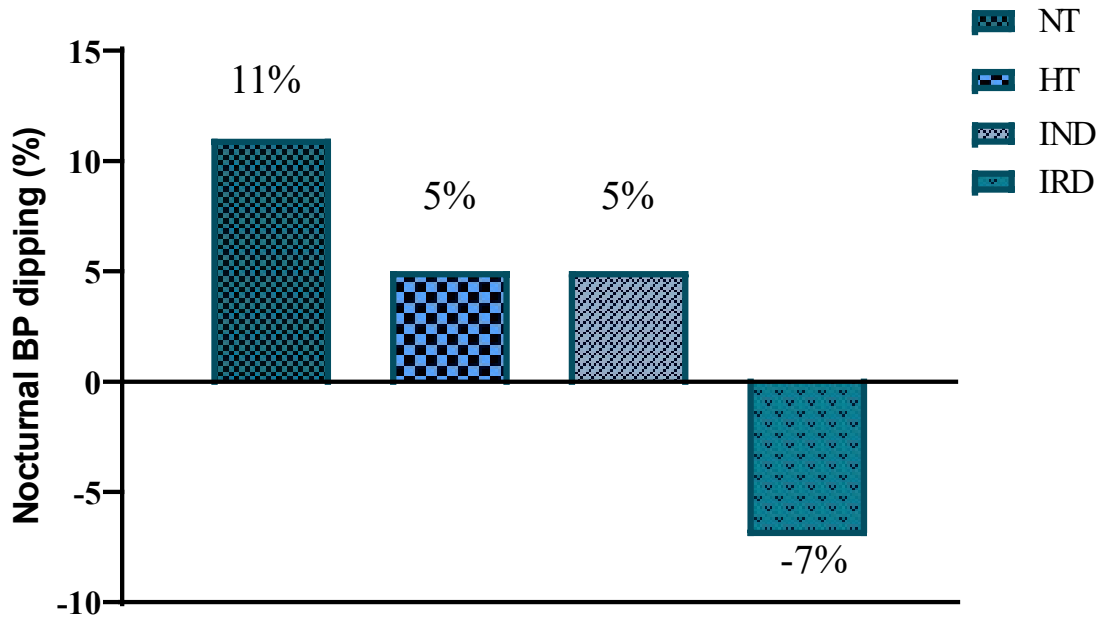


Figure 4.2 Nocturnal dipping pattern of the normotensives (NT=570), sustained 24-hour hypertensives (HT=105), isolated nocturnal hypertensive non-dippers (IND=46), and isolated nocturnal hypertensive reverse dippers (IRD=42).

Figure 4.3 illustrates pulse wave velocity (PWV), an index of arterial stiffness, in the different groups. The normotensive group showed lower PWV when compared to the HT, IND, and IRD groups. Participants with sustained 24-hour HT, IND and IRD showed similar PWV. There was no significant difference in the PWV of the sustained 24-hour HT, IND, and IRD, which implies similar changes in arterial stiffness among these three groups. Although these three groups showed marked difference in their BP profile.

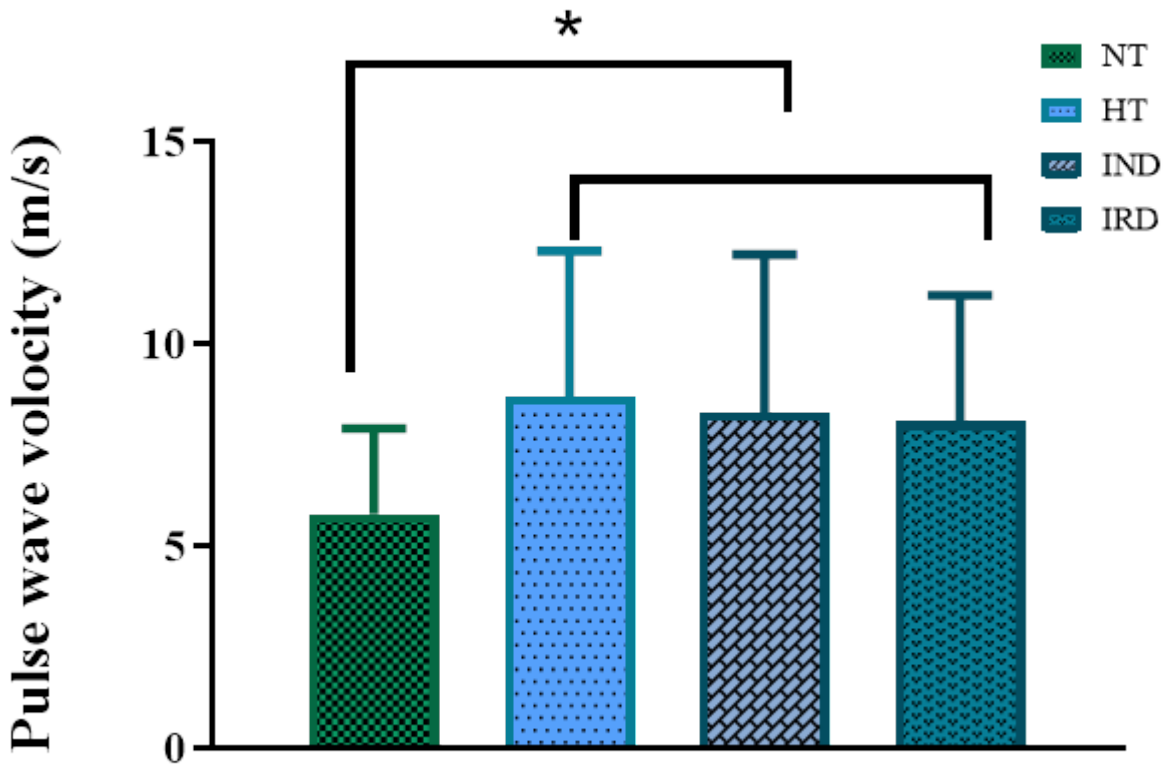


Figure 4.3 Pulse wave velocity (m/s) of the normotensives(NT=570), sustained 24-hour hypertensives (HT=105), isolated nocturnal hypertensive non-dippers (IND=46), and isolated nocturnal hypertensive reverse dippers (IRD=42).

*P value <0.05 accepted as significant for the NT group compared with the sustained 24-hour HT, IND and IRD group.

The Sodium-to-Creatinine ratio in Figure 4.4 showed Na^+ handling. There was no significant difference in the Na^+/Creatinine ratio of the NT, HT, and IND group. Only the IRD group showed a higher Na^+/Creatinine ratio.

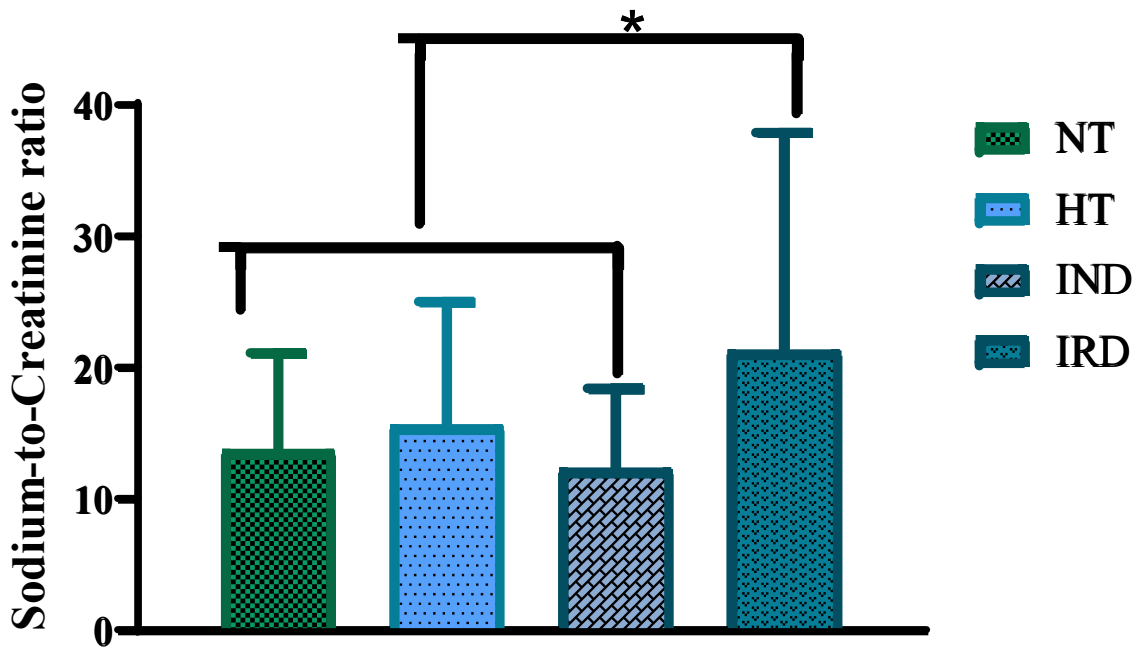


Figure 4.4 Sodium-to-Creatinine ratio of the normotensives (NT=570), sustained 24-hour hypertensives (HT=105), isolated nocturnal hypertensive non-dippers (IND=46), and isolated nocturnal hypertensive reverse dippers (IRD=42).

*P value <0.05 accepted as significant for the NT group compared with the HT, IND and IRD group.

4.4 Discussion

The results show that 11% of the current study population do not experience a decline in nocturnal BP, but rather that their night-time BP increased during sleep. The prevalence of INH has been previously reported in other population groups. A low prevalence of INH in a black population has been previously reported (Li *et al*., 2007). Another study conducted in an African American population showed a high INH prevalence of 30% (Rhee *et al*., 2021). These studies, including the current study, indicate that INH is a common phenomenon that exists in most populations. However, the uniqueness of my findings is that ours is the first to show that INH has two different nocturnal BP dipping patterns, a non-dipping pattern, and a reverse dipping pattern. Therefore, based on the nocturnal BP dipping pattern, isolated nocturnal hypertensive individuals can be categorised into two subtypes, isolated nocturnal hypertensive non-dippers (IND) and isolated nocturnal hypertension reverse dippers (IRD).

Our findings show that age plays a significant role in nocturnal BP dipping patterns (Figure 4.1). As the current study population grows older, the regulation of dipping seems to be affected differently in the current study cohorts. There was a gradual change in the dipping pattern, and these varied in all the cohorts. Figure 4.1 showed that the change in the dipping had a similar onset at the age of 35 years among the four groups. In the normotensive group nocturnal BP dipping decreased slightly from the 30th decade to the 50th decade; and it remained relatively stable. It did not drop below 10%. The average percentage dipping in the NT group was 11% (Figure 4.2). Dipping (or rather lack thereof) is usually reported in hypertensives or people with other disease risk factors (Gavriilaki *et al*., 2020; Fargard, 2009; Palatini, 2004). Dipping status in a normotensive cohort is not widely reported. Albert *et al* (2016) reported that in middle-aged men who were overweight, but normotensive (60%) were non-dippers (and dipping was reported at 40%). There is no current data that showed the effects of age on dipping in a normotensive cohort. The average age in the Albert study was 45 years in the dippers and 48 years in the non-dippers (Albert *et al*., 2016). This is different from the current study, the normotensive cohort remained as dippers, even above the 50th decade. The measured variables between the current study and Albert's show no significant differences when comparing BP and BMI; however, Albert showed a 21% risk of obstructive sleep apnoea (OSA), whereas sleep results were not included in the current study. It is reported that OSA has a 23% prevalence in the South African population (Raine, 2020). This would imply a huge burden of sleep-disordered breathing that could be associated with cardiovascular risk. Another study

showed that normotensives who were also diabetic, became non-dippers (Hassan *et al*., 1993); however, the current only showed a 6% prevalence of diabetes. Data in the current study indicates that normal BP is associated with non-dipping irrespective of age. Therefore, the control of BP to targeted normal values could prevent cardiovascular risk factors associated with nocturnal BP non-dipping.

Contrary to the NT group, at a similar age (>35 years); the sustained 24-hour HT group were already presenting as non-dippers. The non-dipping pattern further decreased with age, and the current study only reported 3% non-dipping above the age of 65 (Figure 4.1). The non-dipping pattern continued throughout their adult life reaching an average percentage dipping of 2% in the elderly group (≥65 year). The average percentage dipping in the whole hypertensive group was 5% (Figure 4.2). This indicates that hypertensive individuals have a non-dipping nocturnal BP pattern throughout life. Since hypertension and non-dipping are two different cardiovascular risk factors, it means non-dipping hypertensives are at an even higher risk of developing cardiovascular related health complications. A study by Staessen *et al* reported on non-dipping patterns in a European population. Like the current study, they showed a curvilinear correlation between non-dipping and age in a hypertensive cohort (Staessen *et al*., 1997). The rate at which the hypertensive group showed the non-dipping pattern showed a faster progression in the older population, when compared to the younger population. Even though the attenuation of nocturnal BP decline begins at the age of 30 years in hypertensive individuals, it continued to progress throughout life. By the age of 60 years, it had significantly been reduced. In another study conducted in people of European ancestry, it was reported that there is a 0.7 mm Hg decline in nocturnal BP dipping with each decade of life (Elser *et al*., 1989). Similar trends supporting these studies have been reported in Asian populations (Elser, 2000; Guyton, 1990). However, the same has not been conducted in people of African ancestry, therefore, the current study reports on the first age-related changes in nocturnal BP in an African population.

Another uniqueness of the current study is that it compares dipping patterns between 24-hour sustained hypertensive and isolated nocturnal hypertensive individuals. The findings show that the dipping pattern of the INH group is below that of the 24-hour sustained hypertensive (Figure 4.1). It is below 3% in the younger group (>35 year) and in the 50th decade of life it drops to 0% dipping. It eventually declines to negative dipping, in the older age group (≥65 years), which is called reverse dipping. Thus, showing two different percentage dipping

patterns in INH: non-dipping and reverse dipping. It was then imperative to compare the percentage dipping of the HT, IND and IRD (Figure 4.2). The results showed a non-dipping pattern in the IND group similar to the sustained 24-hour HT group, each were 5% respectively. Being hypertensive disrupts the normal NBP decline because of the sustained elevated BP (Fagard, 2009). Although the sustained 24-hour HT and IND groups have similar non-dipping percentages, their haemodynamic characteristics were different. This implies that there is some mechanism that causes non-dipping in IND in a similar manner to the 24-hour sustained HT group. One of the long-standing postulates is that reduced daytime Na^+ excretion could be associated with a blunted NBP decline, despite a hypertensive state. This is based on the understanding that nocturnal Na^+ excretion increased blood volume and subsequently BP (Van Beusecum and Inscho, 2015; Guyton *et al*., 1972). This could potentially explain the non-dipping in these two groups. However, the sustained 24-hour HT group and IND showed varied Na^+ excretion rates, respectively.

Further investigation showed that on average the IND group showed higher Na^+ excretion rates (120.9 mmol/day), compared to the reverse dippers (IND), who had lower Na^+ excretion (72.8 mmol/day). Being a nocturnal phenomenon there is possibly some mechanism that disrupts NBP dipping. Low Na^+ excretion could mean that the IRD group is not ingesting these electrolytes in large amounts, which would translate into excreting less amounts. However, the current study did not include dietary questionnaire to ascertain this, making this associated decreased intake a postulate. In the IND group, a possible cause for their differences in dipping patterns could be that increased salt intake results in increased plasma osmolarity, which in turn affects NBP (Meneton *et al*., 2005). Nonetheless, the excretion rates of Na^+ in these groups affect circulating blood volume, which ultimately affects BP. Hormonal concentrations were included because they help regulate electrolyte excretion rates. The IRD group had the lowest renin concentrations and the highest aldosterone concentrations, compared to the IND group. Since it is known that aldosterone can cause Na^+ absorption, there is an association between NBP in this group and the effects of aldosterone on Na^+. The secretion of renin and aldosterone are influenced by Na^+ balance. Generally, there is an expected inverse relationship between renin and increased BP because high levels of renin disrupt Na^+ homeostasis and disturb the circadian BP profile (Fagard *et al*., 1977). However, it is the effects of the observed low renin in the IRD group which could be the stimuli that increased excess aldosterone. Having observed the increased NBP in the IRD group, therefore blunted renal Na^+ excretion could not be ruled out. When daily salt excretion is disturbed, it is excreted at night, for this to happen BP must

increase to allow for volume expansion by the kidneys (Kimura *et al*., 2010). For that reason, the low Na^+ excretion in the IRD group (72 mmol/day) is further indicative that this group is retaining salt during the day. As a compensatory mechanism to excrete the excess Na^+, this is carried to night-time period and resultantly increased NBP, making them reverse dippers. Black people present with low renin and high levels of aldosterone (Rayner *et al*., 2001). Although, low-renin hypertension is not uncommon, it is common in essential or secondary hypertension, but not in INH (Athimulan *et al*., 2019). Since the IRD group presented with low Na^+ excretion and increased NBP, this was ascertained this to Na^+ retention, which subsequently increase NBP. Furthermore, sustained high aldosterone levels can lead to renal injury, with related haemodynamic changes that can be associated with increased NBP. Therefore, excess aldosterone, low Na^+ excretion and low renin may have combined effects leading to IRD (Pimenta *et al*., 2013).

Additional to Na^+ the IRD group further showed low K^+ excretion (18.9 mmol/day) compared to the IND group (28.4 mmol/day). However, since K^+ in the IND group was relatively higher, the current study cannot ascertain that the lack of NBP decline in this group is entirely attributable to Na^+ excretion. This is based on the report that increased K^+ intake is associated with increased Na^+ excretion. Furthermore, urinary K^+ excretion and the ratio of Na^+ to K^+ affects BP. The converse of this is true, that reduced K^+ intake is associated with increased BP (Filippini *et al*., 2020). To further support this, studies have shown that the African American population generally consume less K^+ when compared to other counterparts (Stamler *et al*., 1991). Data on the association between K^+ and nocturnal dipping are scarce. Therefore, the low levels of K^+ in the IRD group is another factor that could cause night-time BP to increase, coupled with the Na^+ retention that was observed. This happens because low K^+ further contributes to a blunted ability to handle Na^+, therefore contributing to its retention. Hence, the increasing BP at night that leads to reverse dipping. It has further been reported that day-to-night ratio of K^+ excretion is negatively related to changes in night-time BP, causing it to increase (Liu *et al*., 2023). Potassium is a vasodilator, its levels affect intracellular ion concentration, which affects the Na^+ -K^+ pump. This transport system then affects cells in the blood vessels (Haddy *et al*., 2006). Additionally, K^+ affects the contractile state of vascular smooth muscles, thus ultimately affecting BP (Haddy, 1983). Although there exists some mutual dependency between Na^+ and K^+, they are under complex regulation; and other factors such as hormone concentration are associated with the observed differences in the IND and IRD group. Moreover, the timing and amplitude of BP rhythm is affected by intrinsic factors,

such as neurohormonal regulation (e.g., sympathetic nervous system and renin–angiotensin–aldosterone system).

So far, the current study had been observing that the entire study cohort was showing a nocturnal BP percentage dipping that was decreasing. The differences in the current cohorts were that the NT were dippers, and the sustained 24-hour HT non-dippers. Regardless, of the percentage decrease, nocturnal BP was decreasing in the NT and HT group. There was a non-dipping pattern in INH, and reverse dipping when they became elderly. Non-dipping in the sustained 24-hour HT group is associated with their hypertensive state and Na^+ excretion, and this could be the same cause in the IND group since they have Na^+ excretion that is higher than the 24-hour sustained HT. It has been reported that people with hypertension present with a blunted NBP decline, which is a risk factor for non-dipping (Fagard, 2009). Therefore, these differences show that non-dipping is not only associated with sustained elevated BP, but that even when daytime BP is normal, there is the inability to reduce NBP below 10% of the daytime values. Perhaps other lifestyle habits beyond Na^+ intake can be attributed to these differences. Shown in the current study, alcohol intake and tobacco smoking varied between the sustained 24-hour HT and INH group. These differences could be affecting NBP and leading to the differences in the dipping patterns. Tabacco smoking and alcohol consumption are known to increase peripheral resistance and cardiac output, thus increasing BP (Omvik, 1996). However, the timing of tobacco smoking and alcohol consumption, and other daytime and night-time activities should be considered. Such is important since smoking and alcohol can have acute effects on BP, and their effects are removed following cessation of said activities (Venkataraman *et al*., 2013; Thuy *et al*., 2010). However, there are inconclusive reports with their chronic use (Hering *et al*., 2010: Groppelli *et al*., 1992). Furthermore, the day-night differences regarding the impact of alcohol intake are still not conclusively shown (Linden *et al*., 2008). It has been reported that alcohol could reduce NBP. Perhaps the non-dipping pattern in INH could be an associated outcome, since they had the lowest percentage intake (Kawabe *et al*., 2007). Furthermore, daytime, and night-time consumption needs to be stratified to determine the causal links that could elevate NBP and cause differences in the dipping status (Rakic *et al.,* 1998).

What was intriguing in the INH group, was the sudden increase in NBP as this cohort gets elderly. The differences between the IND and IRD group could imply that the pathophysiology of INH could be driven by more than one mechanism. The current study has shown that the

IRD group had high aldosterone levels. They were the oldest cohort in this study. With ageing, normal function of several physiological systems starts to decline. This affects the RAA system, influencing renin and aldosterone levels. Aldosterone secretion increased with increasing age. It has been shown that increased aldosterone leads to increased salt retention (Nanba *et al*., 2018). Being the oldest of the cohort, and having the highest aldosterone concentration, which was associated with the observed Na^+ retention, these changes lead to the reverse dipping pattern in the IRD group.

From the above, the differences in percentage dipping patterns were imminent, I then determined whether these differences had any impact on vascular changes. Using PWV as a measure of arterial stiffness (Figure 4.3), the current study showed vascular changes in the sustained 24-hour HT, IND and IRD groups. The three groups had increased PWV above the NT group, but most importantly there was no significant differences among the three. Arterial stiffness in sustained 24-hour HT has been previous reported (Yin *et al*., 2021; Zhang *et al*., 2020; London *et al*., 2019; Oh, 2018). There are associations between arterial stiffness and INH. Moreover, non-dipping and reverse dipping have reportedly been associated with vascular damage. It has been reported that reverse dipping may even present with worse damage than non-dipping (Cuspidi *et al*., 2021). However, what is unique in the vascular changes in the current study is that a non-dipping and reverse dipping pattern causes increased PWV to almost a similar effect as having sustained 24-hour hypertension. Since the hypertensive group experiences sustained hypertension over a 24-hour period, the expectation was that PWV would be higher than that of the INH group (IND and IRD). However, contrary to this expectation, the PWV of the two groups was similar. Considering these similarities between sustained 24-hour HT, IND and IRD group, it is therefore worrisome that a high-normal BP profile can cause vascular stiffness that is comparable to people who experience sustained daytime and night-time high BP. In addition, there were differences in the night-time BP between the IND and IRD group, subsequently leading to the non-dipping and reverse dipping pattern. The sustained 24-hour HT group were also non-dippers. This means they are at a higher risk of developing worse target organ changes. Non-dipping in sustained 24-hour HT could cause more cardiovascular damage and is associated with increased arterial stiffness (Ohkubo *et al*., 2002). Moreover, the high PWV, which leads to vascular damage in the IND and IRD group is attributed to the differences in NBP. Non-dipping and reverse dipping can cause intermediate TOD; arterial stiffness is one such indication of said vascular damage. Non-dipping and reverse dipping cause damage to the vasculature because of the effects of the

elevated NBP. Moreover, they induce damage that is linear and above the one caused by sustained 24-hour HT. The effects of non-dipping are caused by the persistent pressure overload that is expected to decline at night, but does not (Kanbay *et al*., 2008). It was reported that a 5% nocturnal dipping in sustained 24-hour hypertension increased mortality risk by 20% (Ohkubo *et al*., 2002). Whereas reverse dipping may deteriorate arterial elasticity and accelerate TOD. This places emphasis that any BP change not within the margins of NBP regulation (more than 10% of daytime values) is indeed detrimental to the vasculature. Having an elevated NBP means it is above the normal margin of baseline BP at night and thus is subjecting the arterial walls to increased pressure. This perpetuates arterial wall remodelling which causes stiffening of arteries (Zhou *et al*., 2018). Therefore, the current study has shown that TOD associated with INH is attributable to elevated night-time BP. For this reason, the vasculature in IHN participants (IND and IRD) in the current study is being subjected to the effects of night-time BP, which is elevating their PWV, leading to arterial stiffness. This showed that arterial damage is not only related to the effects of extreme BP, but that elevated NBP is as detrimental even when daytime BP values are normal. This further postulate that arterial stiffness in INH could indeed predate sustained 24-hour hypertension. Therefore, it is important to manage NBP to ward off the vasculature from its adverse effects. Thus, the association between IND and IRD with worse TOD could stem from effects of uncontrolled NBP (Li *et al*., 2018). Furthermore, the current study results show that disturbances in the NBP regulation can cause damage to the same effects as sustained 24-hour hypertension, since the IND group only presented with elevated NBP and IRD group had high-normal NBP.

Important to note is that the NBP profile and its association with PWV in the current study presents differently to other studies on INH (Li and Wang, 2013; Spruill *et al*., 2009; Li *et al*., 2007). Li *et al*. reported that INH is associated with an elevated nocturnal BP without daytime hypertension and caused increased arterial stiffness (Li *et al*., 2007). A Swedish study reported higher cardiovascular risk with a 9 mm Hg systolic NBP increase when compared to daytime values (Ohkubo *et al*., 1997). In the current study, comparing NBP between the IND and IRD groups showed the importance of NBP and how changes in night-time BP can have adverse effects. Furthermore, the premise that arterial stiffness may antedate hypertension is shown in the current study. Hypertension and arterial stiffness do not have a clearly defined causal mechanism because they are confounded by many similar variables (Oh, 2018). The association between hypertension and arterial stiffness rests upon the effects of high pulsatile pressure on arterial walls. Sustained high pressure accelerates elastin degradation, therefore it

could be considered an accelerated form of vascular damage (Cecelja and Chowienczyk, 2009). The sustained 24-hour HT group had vascular damage because they have sustained 24-hour hypertension. It has been shown that in a hypertensive state the heart is overworked, and this accelerates the degeneration of arterioles that leads to arterial stiffness (Cecelja and Chowienczyk, 2009). However, there are some incidences where arterial stiffness predates hypertension. In such incidences arterial stiffness is considered as a reinforcer of hypertension in later years, than being a consequence of said hypertension (Mitchell, 2014). This introduces an enigma when trying to determine the causal link between hypertension and arterial stiffness. Therefore, arterial stiffness and high pulsatile pressure may present with a bidirectional association. This seems to hold more water when arterial stiffness is established in younger participants, and it leads to pre-hypertension (O'rourke and Hashimoto, 2007). Nonetheless, in this study the sustained 24-hour HT and INH only showed an age difference of two years. Therefore, the age differences in these groups could not be used as an attributable factor to the PWV but the differences in the dipping pattern. This means that increased PWV in the sustained 24-hour HT group, the IND and IRD group have different causal mechanisms. There could be other possible factors, including the observed smoking habit and urinary Na^+ excretion as possible factors that disturbs the NBP decline. However, non-dipping remains detrimental to target organ function even without known traditional risk factors that are associated with cardiovascular mortality in sustained 24-hour hypertension (Verdecchia *et al*., 1994).

Reverse dipping has not been previously reported in INH. However, as a phenotype of NBP, it is particularly harmful and is associated with worse cardiovascular outcome (Cuspidi *et al.*, 2017). It is worth mentioning that although the IRD group only presented with elevated 24-hour ABP (126 mm Hg SBP), their NBP profile was high (131 mm Hg SBP). An elevated NBP is detrimental because it elicits effects that are opposite to the physiologic rhythm of BP. At night, NBP needs to be regulated within certain limits so that there is minimal BP needed for adequate organ perfusion. Therefore, when NBP is above these limits, the pressure experienced overwhelms the cardiovascular system. Consequently, the entire vasculature becomes susceptible to damage overtime (Hernandez *et al*., 2012). There are possible mechanisms that increase NBP. Even though there is lacking comprehensive data, incidences of cardiovascular injury are more pronounced in reverse dippers who are older (Cuspidi *et al*., 2017; Kario *et al*., 2001). Perhaps the riser effect of IRD can be associated with poor health as the current study population grows older. Fagard and De Cort reported at baseline and without any major cardiovascular events, that IRD showed prognostic significance in elderly participants (Fagard

and De Cort, 2010). It has been shown that age and smoking habits are associated with IRD (Dada *et al*., 2014; Pogue *et al*., 2009; Ohkubo *et al*., 1997). The current study has now interestingly showed that alcohol is associated with INH, and this could perhaps be the distinguishing cause between non-dipping and reverse dipping in INH. The kidneys play a pivotal role. Salt retention can impair renal function. When there is a propensity towards blunted daytime Na^+ excretion, natriuresis shifts towards night-time hours. There is an adaptive mechanism by the kidneys that elevates nocturnal BP to excrete excess Na^+ resultantly, NBP increases, and reverse dipping ensues, as is shown in the current study. Additionally, high aldosterone leads to Na^+ retention; these Na^+ concentrations cause adverse effect on microcirculation and can lead to the development of stiffer arteries (Kanbay *et al*., 2011; O'Rourke and Safar, 2005). Boggia *et al*. reported that reverse dipping had the highest incidences of total mortality, followed by cardiovascular morbidity (Boggia *et al*., 2007) and these incidences are double fold when compared to non-dippers (Cuspidi *et al*., 2017). Therefore, since high NBP has adverse outcomes because it overloads the cardiovascular system, this would mean that IND and IRD in the current study may be subjected to worse outcomes (Redon and Lurbe, 2008).

To this end, there were observable differences in the excretion rates of Na^+ among the different groups. The IND group had high Na^+ excretion with an elevated NBP, whereas the IRD group had lower Na^+ but high NBP. There were differences in the concentration of aldosterone and renin between the groups. These differences in urinary electrolytes excretion and hormone concentrations and how they impact BP has many postulates. To rule out conjecture, the ratio of sodium-to-creatinine (Na^+ /Crt) was determined. This was done to ascertain Na^+ excretion in the sustained 24-hour HT, IND and IRD group. There was a higher sodium-to-creatinine ratio in the IRD group, compared to the IND, sustained 24-hour HT and NT group. This therefore confirms that the low Na^+ excretion rate observed in Table 4.2 is not an indication of reduced intake, but that the IRD group was indeed retaining salt. According to Huang *et al.* evaluating Na^+ /Crt ratio allows the determination of Na^+ intake without factors that may blunt excretion rates. Using the Na^+/Creatinine ratio is useful in estimating the study population's salt intake (Huang *et al*., 2016). Since a decreased Na^+ excretion and an increased Na^+ /Crt ratio indicates that the IRD group is indeed ingesting salt and excreting only smaller concentrations, it showed that NBP can be affected by salt intake and thus has an association with INH. An increased Na^+/Crt ratio has prognostic value in determining the effects of Na^+ retention in the current study because it provides the opportunity to ascertain that the IRD group was indeed

ingesting salt and retaining it, which led to the low excretion concentration. Therefore, Na^+ excretion in the IRD group indicates that there could be Na^+ deposition in the body and that people with INH have a diminished ability to excrete salt as they get older. This is contrary to the study by Ogedegbe *et al* (2013). They showed no significant difference in salt ingestion in people with INH (Ogedegbe *et al*., 2013). Whereas the current study demonstrated that the IRD group retains salt and that it affects NBP. Additionally, the IRD had the highest aldosterone levels and low renin. This could be caused by an adaptive renal defect that unfortunately perpetuates the development of INH. It is important to balance Na^+ and its excretion because excess Na^+ causes vascular damage by removing the protection against Na^+ overload and may heighten the progression of vascular damage (Ohashi *et al*., 2017; Kusche-Vihrog *et al*., 2012).

The current study reported differences in Na^+ excretion. The results further showed that there is an association between age, hormone levels and Na^+ excretion in the IND and IRD groups. Cuspidi *et al.* suggested that to some degree, INH could be attributed to a blunted Na^+ handling (Cuspidi *et al*., 2017). Li *et al*. reported that INH is associated with decreased urinary Na^+ excretion (Li *et al*., 2008). Therefore, in the IRD group, the elevated NBP is a result of Na^+ that is reabsorbed because aldosterone levels are very high. As the IRD group is older, it has been shown that aldosterone levels increase with age. Since they cause Na^+ retention, daytime Na^+ excretion is shifted to the night-time hours. Resultantly, NBP is elevated as an adaptive mechanism by the kidneys to excrete excess Na^+. Furthermore, Na^+ retention is associated with volume expansion, which increased BP. The compensatory response is increased nitric oxide (NO) to prevent BP increase. Albeit Impaired NO production would impose the negative effects of NBP on the vasculature (Kanbay *et al*., 2011; Tolins and Shultz, 1994). Sodium consumption and Na^+ renal handling has a dual effect on nocturnal HT (Li, and Wang, 2013), therefore, reduced excretion rate is a risk factor to the observed increased PWV in the IRD group. This could further constrain the vasculature through high pulsatile strength caused by increased vascular load at night and lead to severe TOD (Scholze *et al*., 2007). Perhaps there is a genetic disposition in the current study population regarding Na^+ handling. The current study further showed that there is salt retention as measured through the sodium-to-creatinine (Na^+/Crt) ratio. Therefore, the contributory role of Na^+ handling in INH needs to be further investigated. This is particularly important because black people generally present with a higher nocturnal BP profile compared to other ethnicities (Eksteen and Mungal-Singh, 2015; Booth III *et al*., 2018; Hyman *et al*., 2000). High salt intake that is followed by decreased excretion leads to increased NBP (Blaustein *et al*, 2006); and induces a series of complex

events. It leads to adverse vascular changes (Sanders, 2009). It is further associated with cellular events that impair nitric oxide production, which affects endothelium remodelling (Rudic *et al*., 1998). Reduced vascular compliance and stiffness in population groups with known excess salt ingestion is one of the known adverse changes due to endothelial dysfunction. These events lead to changes in BP and are known as negative regulators in the progression of hypertension (Davies, 1995). For this reason, reverse dipping, salt retention and INH may be areas that require further elucidation to determine the causal link. However, these findings should be explored within the scope of and the effects of reverse dipping, the withdrawal of the sympathetic drive and the hormonal mechanisms that regulate Na^+ handling and vascular damage in INH. Furthermore, there is a need to conduct further investigations by separating the daytime and night-time urinary Na^+ excretion to ascertain if indeed there is increased night-time excretion in the INH group. Additionally, high Na^+ concentrations cause adverse effect on microcirculation and can lead to the development of arterial stiffness (Kanbay *et al*., 2011; O'Rourke and Safar, 2005). These results allow the postulation that possible categorical mechanisms may be responsible for INH, and that high aldosterone and a blunted Na^+ handling could have a contributory role that led to the differences between the IND and IRD group. Contrary to what Li *et al* (2007) suggested, that higher urinary excretion rates may lead to the progression of INH, the current results show different excretion rates which led to the stratification of the IND and IRD group.

From the overall results of this study, PWV in these groups could be elevated by different mechanisms. Reasonably one of the major factors for these discrepancies is the fact that the current study was conducted in people of African descent while the studies from abroad included participants of either European or Asian descent. Racial diversity plays an important role in INH progression. This is important because studies that reported high NBP in INH patients determined that these patients presented with worse TOD, as determined through PWV (Düzova *et al*., 2019; Wijkman *et al*., 2009; Li *et al*., 2007). They included indices of TOD, such as central BP and other markers of arterial stiffness (Ogedegbe *et al*., 2013). Therefore, the same would hold true when interpreting the vascular changes in the current study because members of African ancestry could be subjected to worse TOD. Therefore, as demonstrated by the PWV that was similar between the sustained 24-hour HT, IND and IRD group, it is shown that even modest NBP elevation in a black population may cause severe vascular damage, without hypertension. Albeit reverse dipping concurrent with INH have not been previously reported in a black South African population.

In conclusion, the findings in this chapter showed target organ damage in the form of elevated PWV, that causes vascular damage in people that have isolated nocturnal hypertension. Pulse wave velocity in the isolated nocturnal hypertensive non-dippers and isolated nocturnal hypertensive reverse-dippers was similar to the sustained 24-hour hypertension group. Sustained 24-hour HT and INH are characterised by a high day-night pressure and elevated NBP respectively, however, in the INH group, the IND group had lower NBP compared to the IRD group. Therefore, TOD in INH that is similar to sustained 24-hour HT showed the detrimental effects of elevated NBP without high daytime BP. These differences show that the physiological mechanisms of renal Na^+ handling and excretion through the influence of aldosterone is of paramount importance to a black South African population. They handle and excrete Na^+ differently compared to other ethnic groups. They further show increased aldosterone levels as they grow older. There is a risk of adverse cardiovascular outcome when daytime Na^+ excretion is retained. Salt excretion affects NBP and has adverse effects. Generally, salt retention is associated with non-dipping; however, the current study showed a reverse-dipping profile, that may be a predisposition to and associated with INH. Although the mechanisms of INH are still mostly speculative, there is enough evidence showing significant damage to end organ function. This warrants further attention because INH causes TOD to a similar magnitude as sustained 24-hour HT. There is therefore a need for studies to explore the physiological variant of converting reverse dipping and by association non-dipping in the current study population and its clinical implications.

Chapter 5

Isolated nocturnal hypertension predicts target organ damage above isolated daytime hypertension in a population of African ancestry.

5.1 Abstract

Ambulatory BP monitoring provides a better profile of the different types of hypertensions including the variability between day and night pressures. This is important because changes in BP variability are associated with indices of cardiovascular damage; thus, monitoring BP over a 24-hour period uncovers these changes. Since hypertension-related cardiovascular target organ damage (TOD) occurs throughout, monitoring BP over 24-hours provides a unique opportunity to distinguish between daytime and night-time cardiovascular TOD. In a black population, it has not been clearly established whether TOD is more severe during the day or during the night. Therefore, this study investigated whether hypertension-related TOD is different or similar during daytime and night-time by looking at blood pressure-related pre-clinical vascular damage. Pulse wave velocity (PWV) was measured in 796 participants who had complete 24-hour ABPM and 24-hour urine collections. Based on 24-hour ambulatory BP results, participants were either categorised into isolated daytime hypertensives (daytime SBP ≥135 mm Hg and night-time SBP <120 mm Hg) or isolated nocturnal hypertensives (daytime SBP <135 mm Hg and night-time SBP ≥120 mm Hg). The current results show that sustained 24-hour hypertension (HT), isolated nocturnal hypertension (INH) and isolated daytime hypertension (IDH) prevalence were 13.7%, 11.8% and 4.0% respectively. PWV in INH was similar to HT but significantly higher than the NT (normotensive) and IDH, while the latter groups had significantly lower PWV. These findings indicate that INH was associated with vascular damage when compared to IDH. The mechanisms that determine these vascular changes may be mediated by sodium retention-induced attenuated nocturnal blood pressure decline in INH. The results further showed INH had a non-dipping pattern while IDH presented with dipping. These findings indicate that nocturnal blood pressure dipping in IDH may be protective, delaying the progression of TOD that is associated with increased BP. IDH further presented with decreased pulse rate. Lastly, sustained 24-hour HT and INH had elevated night-time pulse rate which indicated that an elevated nocturnal BP or non-dipping is associated with vascular damage, but not in IDH. Finally, the current results indicate an increasing IDH prevalence in a South African black population. Although any blood pressure elevation is detrimental, the current findings indicate that there may be protective features in IDH. These include pulse rate and a dipping BP profile. These could delay the progression of related cardiovascular TOD that are commonly associated with increased BP.

5.2 Introduction

Elevated BP, at any time, is known to negatively impact the vasculature as it overloads the cardiovascular system during periods when the arteriolar tone should be lower (Kikuya *et al*., 2005). This therefore impacts the vasculature, damages to arteries, the heart, the kidneys, and other organs like the brain. Damage to the arteries results in arterial stiffness, which causes an increase in pulse pressure and consequently an increase in BP (Mancia, 2007). Hence, the bi-directional relationship between elevated BP and arterial stiffness. Elevated BP negatively affects conduit arteries, and the overall vasculature, whereas stiffening arteries and reduced distensibility are known to increase BP due to reduced compliance. Furthermore, vascular damage may be predictive of future BP-related TOD. This bidirectional relationship results in a cause-and-effect vicious cycle (AlGhatrif and Lakatta, 2015).

There is a high incidence of hypertension in the South African population of African ancestry. Earlier studies conducted in this population indicated that the prevalence of hypertension is between 21 and 37% (Mphekgwana *et al*., 2020; Maimela *et al*., 2016; Alberts *et al*., 2005). Considering the bi-directional association between BP and arterial stiffness, the high incidence of hypertension presents an even greater risk of arterial stiffness in this population. Therefore, 24-hour BP variation and its association with vascular changes ought to be thoroughly investigated in communities of African ancestry. The constant changes in BP may be physiological and important in maintaining homeostasis. However, excessive increases or decreases in BP can cause vascular damage (Hansen *et al*., 2010). Since these changes in BP occur over a 24-hour period, some occur during the daytime, while others are limited to the night-time. Hence the need to use appropriate monitoring tools to help uncover these changes as they occur during these times. These further help in identifying different hypertension phenotypes. Using the 24-hour ABPM has allowed researchers to be able to categorise other BP phenotypes that are influenced by changes in BP at different times. This has allowed investigations concerning the correlation between daytime, night-time and 24-hour ABP and cardiovascular events (Mancia *et al*., 2006; Dolan *et al*., 2005). Isolated nocturnal hypertension (INH) and isolated daytime hypertension (IDH) are some of these BP phenotypes that are uncovered through 24-hour ABPM.

The 24-hour ABPM allows the determination of the effects of decreased night-time BP even when daytime BP is elevated (Fagard *et al*., 2009). This phenomenon is called isolated daytime hypertension (IDH). According to Li *et al* (2007), IDH is characterised by a daytime systolic

BP of ≥135 mm Hg or daytime diastolic BP ≥85 mm Hg. Although patients with IDH present as night-time normotensives, it is reported that IDH remains predictive for cardiovascular events compared to normotensive status due to the elevated daytime BP (Düzova *et al*., 2019). The IDACO study has shown that daytime BP can be used to predict fatal cardiovascular events (Boggia *et al*., 2007) and the PAMELA study suggested that IDH has detrimental effects on the vasculature (Cuspidi *et al*., 2017). Contrary to IDH, individuals with INH have raised NBP despite normal daytime BP. Nonetheless, just like IDH, INH is likewise associated with target organ damage (Cuspidi *et al*., 2017).

In South Africa, the conventional BP measurement technique is the most widely used method to diagnose hypertension (Maseko *et al*., 2011). The biggest limitation of this technique is that it does not distinguish between other hypertension phenotypes including IDH and INH. The once-off measurement is assumed to represent the BP profile of the individual and it does not account for the BP changes that occur throughout a 24-hour period, but further assumes that BP remains the same. In the current study population, it is currently unknown, which of these two hypertension subtypes, (IDH or INH) is more damaging to the vasculature. There is no evidence of whether they predict vascular damage independent of each other. Moreover, there is no published data available on whether they predict vascular damage similar to sustained 24-hour hypertension. Therefore, in this study ABPM was used to diagnose hypertension and separate participants into four groups, 24-hour normotensives (NT), 24-hour sustained hypertensives (HT), isolated nocturnal hypertensives (INH) and isolated daytime hypertensives (IDH). The current study further aimed at determining the impact of the different hypertension subtypes on arterial stiffness.

5.3 Results

Table 5.1 represents findings from the total study participants and were further characterised into groups according to BP profiles. These show different population characteristics according to NT, HT, INH and IDH). Among the 796 participants, the prevalence of sustained 24-hour HT was reported as 13.7%, INH and IDH were 11.8% and 4.0%, respectively. Compared to the NT participants, participants that had sustained 24-hour HT and INH were much older (55 and 57 years, respectively), had an overweight BMI (31.69±7.56 kg/m^2 and 31.14±8.83 kg/m^2, respectively) and had a higher diabetic proportion (18% and 14%). Participants that presented with IDH, on the hand, were younger (49 years) and reported frequent alcohol intake (29%) compared to other groups (17% and 27% for sustained 24-hour HT and INH). They had high daytime Na^+ excretion rates (151.8 mmol/day) than the other groups (100.8 mmol/day and 99.4 mmol/day for sustained 24-hour HT and INH). They had low concentrations of leptin (20.9 ng/mL).

Table 5.1 General characteristics of all, the normotensive, hypertensive, isolated nocturnal and isolated daytime hypertensives.

	All Participants	NT	HT	INH	IDH
Number	796	570	105	90	31
Age (years)	44.19±18.30	29.18±16.73	55.34±15.91[a]	57.02±17.42[ab]	49.9±17.8[abc]
BMI (kg/m^2)	28.90±7.62	27.91±7.06	31.69±7.56[a]	31.14±8.83[a]	30.6±9.5[a]
% Female	64	66	58	57	55
Alcohol intake (%)	21	20	17	27	29
% Diabetic	9	6	18	14	3
Na^+ (mmol/day)	105.6±78.4	105.2±76.5	100.8±74.4	99.4±78.6	151.8±116.3[abc]
Leptin(ng/mL)	24.2±24.3	23.0±24.4	28.5±22.8[a]	28.2±26.9[a]	20.9±17.8[bc]

[a] significantly different from NT; [b] significantly different from HT; [c] significantly different from INH. P value <0.05 accepted as significant. **NT**, normotensives (daytime blood pressure systolic <135 mm Hg and night-time blood pressure <120 mm Hg); **HT**, sustained 24-hour hypertensives (daytime systolic blood pressure ≥135 mm Hg and night-time systolic blood pressure ≥120 mm Hg); **INH**, isolated nocturnal hypertensives (night-time blood pressure of ≥120 mm Hg systolic or 70 mm Hg diastolic and a daytime blood pressure <135/85 mm Hg); **IDH**, isolated daytime hypertension (daytime blood pressure of ≥135 mm Hg systolic or 85 mm Hg diastolic and a night-time blood pressure <120/70 mm Hg). **Na^+**, sodium; **BMI**, body mass index.

Figure 5.1 shows smoking habits in the four groups (NT, HT, INH and IDH). Among the four groups, the highest smoking prevalence was shown in the IDH (35%) and HT groups (18%), respectively. There was a lower smoking prevalence in the NT and INH at 14% each. The differences in smoking prevalence showed an association between daytime smoking habits and possibly increasing daytime BP, since smoking is mostly daytime activity; however, the effects may not only be limited to daytime BP.

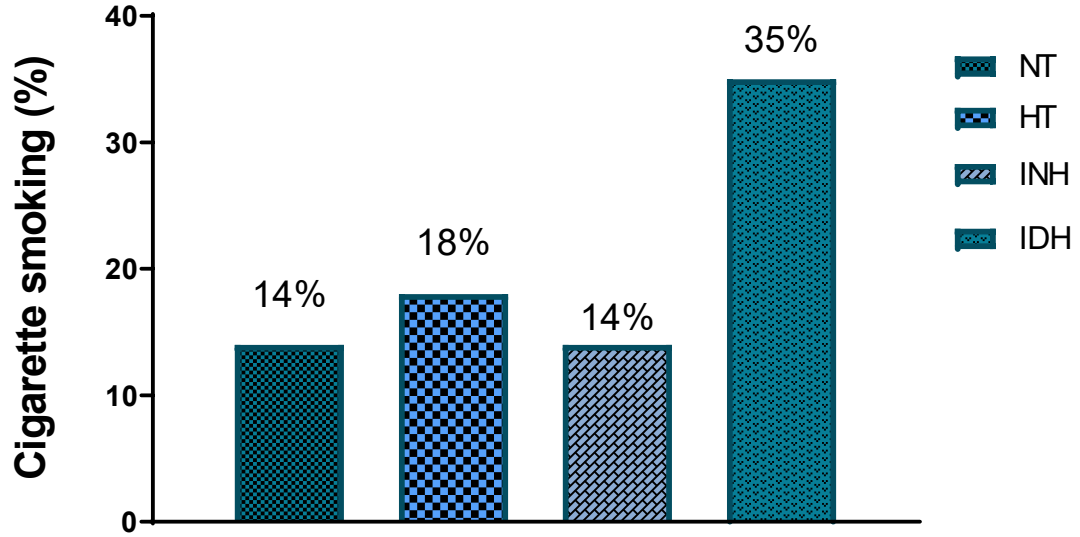


Figure 5.1 The figure showing proportion of cigarette smokers in the normotensive (NT=570) group, sustained 24-hour hypertensives (HT=105), isolated nocturnal hypertensives (INH=90) and isolated daytime hypertensive (IDH=31) group.

Blood pressure was measured to identify variables that differentiated the four sub-groups from the total population; these are shown in Table 5.2. The results in the HT group showed high BP during the daytime (149.13±11.52 mm Hg), night-time (141.63±16.89 mm Hg) and over a 24-hour period (146.34±12.95 mm Hg). Those categorised as INH presented with a slight increase in mean NBP (126.99±7.73 mm Hg), when compared to the daytime BP (126.31±6.61 mm Hg); but they had a relatively unchanged pre-hypertensive state across the 24-hour period (overall mean 24-hour BP 126.86±5.46 mm Hg). The IDH group presented with daytime hypertension (140.9±4.9 mm Hg). However, they had a high-normal mean 24-hour BP (130.2±4.2 mm Hg) and were normotensive at night (111.7±7.3 mm Hg).

Pulse rate was measured between day and night among the four groups. The highest pulse rate at night was observed in the INH group (71±12.6 bpm), and it was similar to the sustained 24-hour HT group (70.9±10.4 bpm). The IDH group had a lower pulse rate (66.2±9.8 bpm), even lower than in the NT group (68.9±8.5 bpm). In order of highest to lowest, daytime pulse rate was higher in the NT group (83.11±11.1 bpm) and the least was in the IDH group (80.3±9.5 bpm).

The differences between night-time and daytime pulse rate were determined. These were used to highlight the differences in the change between day and night pulse rate. The NT and IDH group show a difference of ~14 bpm, whereas the sustained 24-hour HT and INH group showed a difference of ~11 bpm. Comparing the dipping ratio showed that each group had its own unique dipping pattern. The NT group showed a dipping pattern on systolic, with a 0.89 dipping ratio (11 % dipping) and diastolic 0.82 dipping ratio (18% dipping). The sustained 24-hour HT were systolic non-dippers, with a 0.95 dipping ratio (5% dipping) and diastolic dippers at 0.88 dipping ratio (12% dipping). The INH group were reverse dippers because their systolic dipping ratio was 1.01 (-1% dipping) and diastolic non-dippers with a ratio of 0.93 (7% dipping). Lastly, the IDH were extreme dippers on both systolic and diastolic dipping ratio, they showed 0.79 (21% dipping) and 0.73 (27% dipping).

Table 5.2 Haemodynamic characteristics (mm Hg) of total, normotensive, hypertensive, isolated nocturnal and isolated daytime hypertensive participants.

	All Participants	NT	HT	INH	IDH
n	796	570	105	90	31
SBP24	118.3±15.0	111.1±7.8	146.3±13.0[a]	126.9±5.5[b]	130.2±4.2[abc]
DBP24	72.6±10.2	68.7±6.8	88.3±10.9[a]	77.8±6.6[ab]	77.3±8.1[ab]
SBPN	111.3±17.2	103.3±8.77	141.6±16.9[a]	126.9±7.7[ab]	111.7±7.3[abc]
DBPN	65.0±11.7	60.5±8.0	81.6±12.1[a]	74.5±8.5[ab]	62.6±9.2[bc]
SBPD	122.5±14.7	115.9±8.5	149.1±11.5	126.3±6.6[ab]	140.9±4.9[abc]
DBPD	77.6± 10.4	70.0±7.5	92.8±11.1[a]	79.7±7.4[ab]	85.9±8.8[abc]
PRD	82.7±11.0	83.1±11.1	82.2±10.7	81.7±11.2	80.3±9.5
PRN	68.7±10.7	68.9±8.5	70.9±10.4[a]	71.0±12.6[a]	66.2±9.8[bc]
DPR	14.0±0.4	14.2±2.6	11.3±0.3[a]	10.7±1.4[a]	14.1±0.3[bc]
RSBP	0.91±0.08	0.89±0.07	0.95±0.08[a]	1.01±0.08[ab]	0.79±0.06[abc]
RDBP	0.84±0.10	0.82±0.09	0.88±0.08[a]	0.93±0.09[ab]	0.73±0.08[abc]

NT, normotensives (daytime blood pressure systolic <135 mm Hg and night-time blood pressure <120 mm Hg); **HT**, sustained 24-hour hypertensives (daytime systolic blood pressure ≥135 mm Hg and night-time systolic blood pressure ≥120 mm Hg); **INH**, isolated nocturnal hypertensives (night-time blood pressure of ≥120 mm Hg systolic or 70 mm Hg diastolic and a daytime blood pressure <135/85 mm Hg); **IDH**, isolated daytime hypertension (daytime blood pressure of ≥135 mm Hg systolic or 85 mm Hg diastolic and a night-time blood pressure <120/70 mm Hg); **SBP24**, 24-hour systolic blood pressure; **DBP24**, 24-hour diastolic blood pressure; **SBPN**, night-time systolic blood pressure; **DBPN**, night-time diastolic blood pressure; **SBPD**, daytime systolic blood pressure; **DBPD**, daytime diastolic blood pressure; **PRD**, daytime pulse rate; **PRN**, night-time pulse rate; **DPR**, day-night pulse rate difference; **RSBP**, systolic blood pressure dipping ratio; **RDBP**; diastolic blood pressure dipping ratio. [a] significantly different from NT; [b] significantly different from HT; [c] significantly different from INH. P value <0.05 accepted as significant.

Figure 5.2 shows the differences between daytime and NBP, values are presented as integers (rounded off). The results show that BP decreased at night in only three groups: the NT, HT and IDH; and it increased in the INH group. In the order of decreasing magnitude, the greatest difference was in the IDH group (29 mm Hg), followed by the NT group (13 mm Hg) and the sustained 24-hour HT group (8 mm Hg). Whereas the INH group instead increased by (-1) mm Hg.

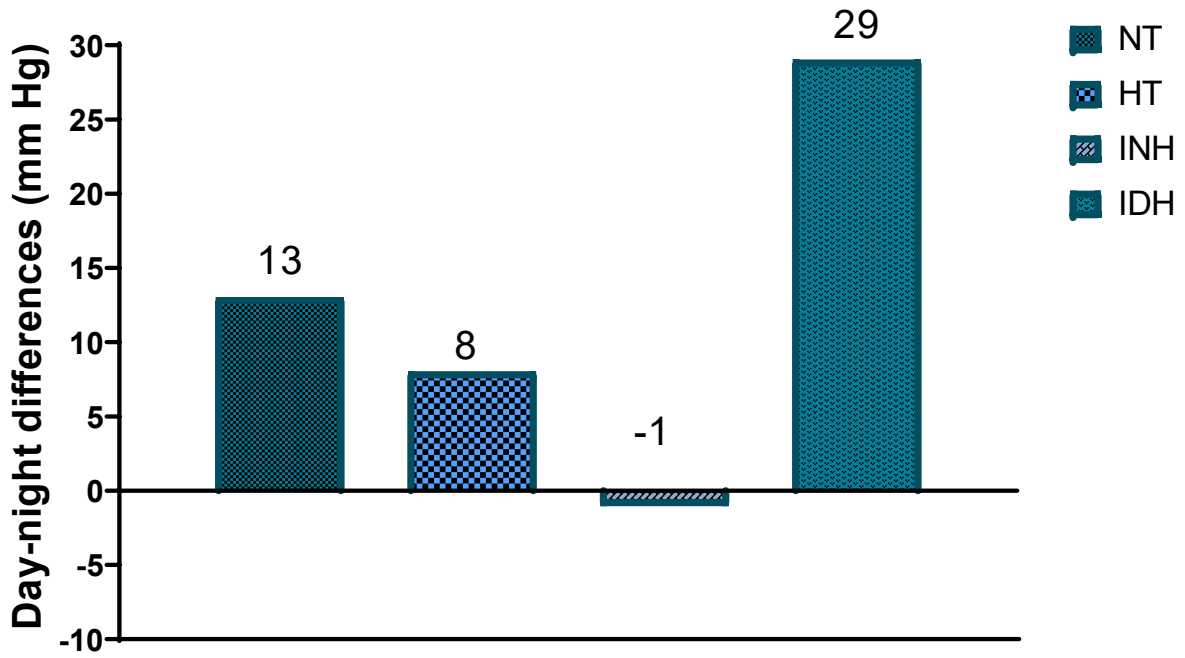


Figure 5.2 The day-night blood pressure differences (mm Hg) between the normotensive (NT=570), sustained 24-hour hypertensives (HT=105), isolated nocturnal hypertensives (INH=90) and isolated daytime hypertensive (IDH=31) participants.

Figure 5.3 shows an associated change in vascular function as indexed by PWV. The results show no significant differences in the PWV between the NT group and those with IDH. These two groups had lower PWV when compared to the sustained 24-hour HT and INH group. The sustained 24-hour HT and INH group had the highest PWV. When comparing the sustained 24-hour HT and INH group, there was similar PWV despite significant differences in their overall BP profiles.

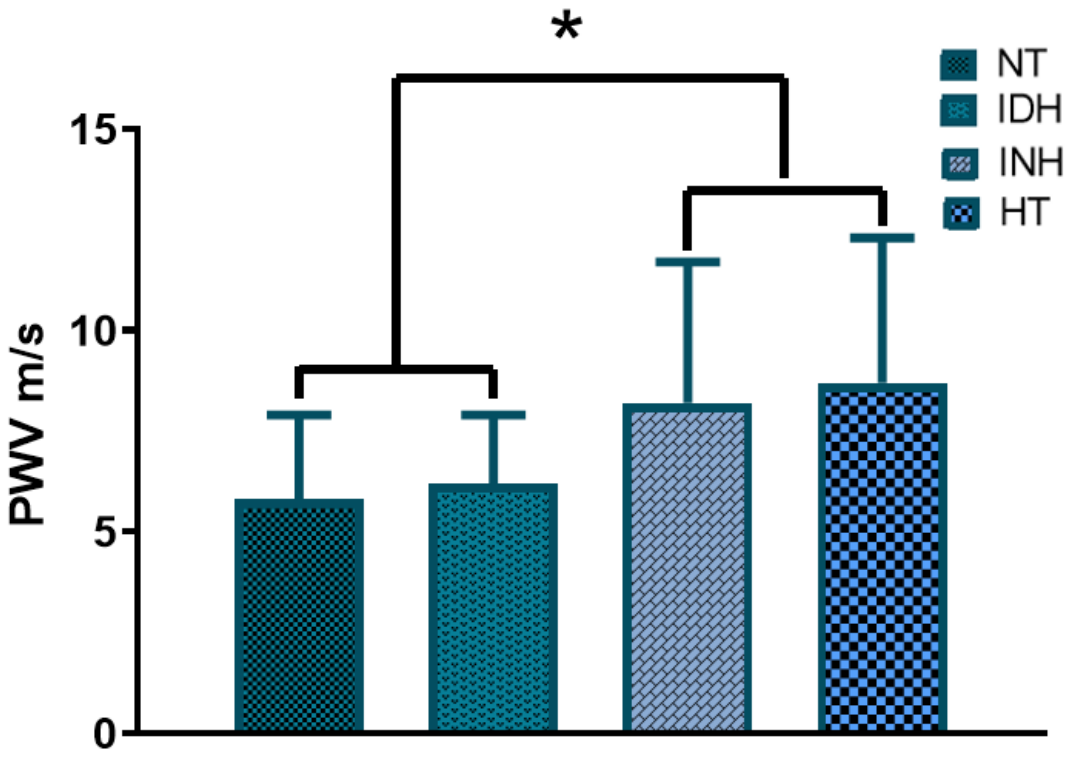


Figure 5.3 Pulse wave velocity (m/s) of the normotensive (NT=570), sustained 24-hour hypertensives (HT=105), and isolated nocturnal hypertensives (INH=90) and isolated daytime hypertensive (IDH=31) participants.

* P<0.05 was considered significant. P value is for NT vs IDH participants and sustained 24-hour HT vs INH participants**.**

Table 5.3 The relationship between PWV (m/s) and the difference in daytime and night-time BP (DND) in mm Hg using different models of cofounding variables

	R^2	Confidence interval	P-values
DND vs PWV			
Model 1	- 0.18	-0.25 to -0.11	<0.0001
Model 2	-0.18	-0.25 to -0.10	<0.0001
Model 3	-0.16	-0.24 to -0.09	<0.0001
Model 4	-0.14	-0.21 to -0.06	0.0004

R^2 , partial r –squared; **Model 1**, uncorrected for risk factors; **Model 2**; corrected for gender as a non-modifiable risk factor; **Model 3**; corrected for gender plus other modifiable risk factors including BMI, alcohol intake and cigarette smoking; **Model 4**, corrected for all the covariates in Model 3 plus diabetes as a disease of lifestyle.

In continuous analyses examining the index of arterial stiffness of the four sub-groups, the models were initially unadjusted for confounding variables (model 1) and then adjusted for cofounders including sex (model 2), gender and modifiable risk factor (model 3) and disease state and lifestyle factors (model 4). The analysis revealed that participants who had IDH did not present with significantly increased PWV, much like the NT group; both groups had a normotensive night-time ABP (Table 5.2). However, the analysis showed a risk of increased PWV in the INH group who presented with pre-hypertensive daytime BP that increased at night (Table 5.2). Their PWV resembled a similar pattern to the participants that had sustained hypertension on 24-hour, daytime, and night-time ABPM. Pulse wave velocity differences between the INH and sustained 24-hour HT group remained significant even after excluding anti-hypertensive treatment.

5.4 Discussion

In this study, using 24-hour ABPM, participants were stratified according to the four BP categories: normotensive (NT), sustained 24-hour hypertensive (HT), isolated nocturnal hypertensive (INH) and isolated daytime hypertensives (IDH) groups. The current results show that the prevalence of sustained 24-hour HT, INH and IDH were 13.7%, 11.8% and 4.0% respectively. The current results only show a 4.0% IDH prevalence, which is lower that reported by Li *et al* (2007). Their study reported an overall ~4.9% IDH prevalence in a study comprising of population groups of African (from South Africa), Japanese, and Asian origin. Their study showed a lower IDH prevalence (6.0%) in the South African population when compared to the European (13%,) and Japanese (6.6%) but higher than the Asian participants (4.9%). Although the IDH prevalence reported by the current study is comparable (4.0% vs 6.0%), the study sample characteristics were quite different from sample populations in Li *et al.* (2007) studies. Perhaps the frequency of IDH and its prevalence may be masked by sustained 24-hour HT and INH. Despite the lack of extensive information, IDH is reported to contribute to cardiovascular morbidity (Düzova *et al*., (2019). However, this study was in a Chinese children population that had kidney disease. Li *et al.* (2007) only had 33 adults in their investigation. Notwithstanding, its association needs to be determined alongside the prognostic effects of INH regarding TOD.

The previous experimental chapter reported on prevalence of INH in a black population sample. However, Düzova *et al*., 201 reported that IDH and INH have a combined prevalence that is ~10% (Düzova *et al*., 2019). Very few studies have compared IHN and IDH (Li *et al*., 2007; Li *et al*., 2008; Li and Wang, 2013; Abdalla *et al*., 2016). Most of these report on INH and its prognostic value, but do not compare vascular damage between INH and IDH. In a 2019 report based on the ESC/ESH guidelines, the prevalence of INH and IDH were reported at 8.6% and 17%, respectively (Salazar *et al*., 2018; Williams *et al*., 2018). Rhee *et al*. (2021) reported a 3.5% IDH prevalence in people of Korean descent not taking any antihypertensives treatment. Ogedegbe *et al*. (2013) reported a 3.8% IDH prevalence from noninstitutionalized African American adults. In another study with 8711 participants from 10 populations, Fan *et al*. (2010) reported a 6.6% IDH prevalence. Most of these studies report low IDH prevalence, despite differences in sample characteristics, these studies reported low IDH reproducibility, even with repeated ABPM. Two issues could arise from such findings: the low IDH prevalence could be an under report the true prevalence, therefore contributing to its reported adverse

effects (Li *et al*., 2007). Secondly, the focus on IDH over INH could be motivated by adverse cardiovascular TOD that is associated with increased night-time BP (Kusunoki *et al*., 2019; Soylu *et al*., 2009: Routledge *et al*., 2007). This necessitates more investigations into IDH on its own. Although IDH is considered another form of masked hypertension phenotype, it has not been extensively reported when comparing it against data available on INH. Nevertheless, it develops earlier in life when compared to INH (Li and Wang, 2013).

According to the ESC/ESH report, IDH ensues earlier in life, with a mean age of 42 years (Li *et al.*, 2007). The Korean study by Rhee *et al*. (2021) showed a similar age (45 years). The JHS study by Ogedegbe *et al*. (2013) reported a mean age of 51 years, comparable with the study by Fan *et al*. (2010) at 55 years. In the current study, even though the IDH group had a higher mean age compared to these reports, they were the youngest (49 years). Other comparable baseline characteristics are variable. The IDH groups from the Korean study, the JHS and the IDACO studies presented with diabetes prevalence higher than compared to the current study at 6.1% and 6.3% respectively' while the current study population only showed 3.0%. However, the current cohort had a higher diabetes prevalence when compared to the ESC/ESH report, 2.2%. In addition to diabetes, these studies had relatively non-obese groups. The Chinese study and the JHS had normal BMI, 23.3 Kg/m^2 and 24.8 Kg/m^2, respectively; whereas the IDACO study had high BMI 26.2 $Kg.m^2$, the ESC/ESH had an overweight IDH cohort, with BMI of 27 $Kg.m^2$ whereas the current study cohort was overweight/obese, 30 Kg/m^2. Lifestyle habits like tobacco smoking was also higher in the current study (35%) when compared to the ESC/ESH report and JHS study, 13% and 6.3% respectively. Notwithstanding, it was comparable to the Chinese study, 30.3% (Li *et al*., 2007), the Korean study, 32% (Rhee *et al*., 2021) and the IDACO study with 33% (Fan *et al*., 2010).

Although IDH in the current study and the ones above may have differences and some comparable characteristics, these reports had relatively higher sample sizes to when compared to the current study. The ESC/ESH report had 1344 patients, the Korean study had 1128 participants and the JHS only included 425 participants in their analysis, whereas the current study only included 796 participants, of which 31 had IDH. Furthermore, the racial difference in these studies supports the differences in results outcome when comparing the current study with above studies. However, the studies cited above were not race specific, while my current study only compared a black population sample. Only Li *et al*. (2008), reported a 6% IDH prevalence in a South African cohort of African ancestry from a multi-ethnic study.

Additionally, some of these reports are from participants that were referred from hypertensive clinic based on their BP profiles, whereas in the current study a certain category of participants in South Africa that resided in a specific area were chosen. Therefore, the differences in the prevalence of IDH when compared to other studies can be attributed to environmental and ethnic differences. Studies have reported that BP is under genetic control. This means different racial groups will show differences in BP patterns (Padmanabhan *et al*., 2012). Renal physiology, more especially the RAAS, in conjunction with high DSI and blunted excretion in black people, could account for the differences (Goldblatt, 1947). Additionally, endocrine factors such a low renin are associated with increased HT prevalence in black people (Coffman and Crowley, 2008). Since these factors affect BP and HT prevalence, further investigation into their association with IDH is needed. This highlights the importance of 24-hour ABPM with regards to the effects of IDH in the current study population because there may be lifestyle factors that affects the BP profile. (Boggia *et al*., 2007). In the current study there were differences in alcohol intake and smoking prevalence among our groups. Their effects are expanded on in the below sections.

Now, comparing INH and IDH in the current study showed that the INH group were the oldest (57 years), followed by the sustained 24-hour HT group (55 years) and the IDH group was the youngest (49 years). As already reported in chapter four, ageing is associated with changes in the mechanisms that regulate BP. The vasculature changes with age. It loses some of its elastic properties and compliance, thus perpetuating the development of HT (Staessen *et al*., 1997). Findings from the current study show that DH developed earlier than INH in the study population. The observed early IDH potentiates significant adverse effects because sustained elevated BP can lead to increased cardiovascular risk as it has already been demonstrated that IDH is associated with significantly increased adverse cardiovascular events (Fan *et al*., 2010). The physiological mechanisms responsible for the development of these two hypertension subtypes are different. A significantly higher percentage of smokers in the IDH group (35%) was observed, compared to the INH group (14%). The smoking prevalence in IDH may account for the high daytime BP in the IDH group. Smoking, which is usually a daytime activity, affects the vasodilatory function and leads to BP increase (Irfan *et al*., 2017). The exact components of smoking and the mechanisms related to cardiovascular dysfunction are largely unknown. However, it is reported that nicotine in cigarette smoke plays a major role in smoking-related increases in cardiac output, heart rate, and blood pressure (Ambrose and Barua, 2004). Studies have shown that smoking increases BP by sympathetic excitation, it impairs the arterial

baroreflex function and reduces arterial compliance (Hering *et al*., 2006; Grassi *et al*., 1994). It has deleterious effects on the endothelial function and can cause inflammation (Virdis *et al*., 2010). Oakes *et al*. (202) reported that nicotine exposure leads to systemic endothelial dysfunction through reduced endothelium-dependent vasodilatory response to acetylcholine. According to Cavusoglu *et al*. (2004) smoking can cause direct endothelial damage, and impairment of endothelium dependent coronary vasodilation. However, there is still the endeavour regarding the effects of smoking only on daytime BP increases. It has been reported that the daytime effects of smoking may coincide with peaks in catecholamines and BP and resultantly increase daytime BP (Linsell *et al*., 1985). It is further accepted that nicotine increases heart rate and blood pressure. However, the effects could be acute. Therefore, people who smoke may present with elevated daytime heart rate but normal at night (Benowitz *et al*., 2002). According to Adan *et al*. (1995), there are differences in the effects of smoking on BP elevation when diurnal BP is considered, and that the outcomes are not always consistent. On the other hand, Sabha *et al*. (2000) reported that the haemodynamic effects of smoking could be attributed to the habituation of smoking. This is supported by low BP following the cessation of smoking (Omvik, 1996). However, there are transient BP increases during the daytime, leading to smokers presenting with a higher mean daytime BP on ABPM (Bang *et al*., 2000). These studies contended that diurnal BP monitoring showed elevated daytime BP in smokers. Groppelli *et al*. (1992) showed that smoking following night-time abstinence increased BP. The effects can be long-lasting due to a possible pressor response. This would elevate BP persistently, making daytime BP higher. These effects consequently elevate daytime BP, even when the smokers have normal overall BP profile. This is important since chronic or continuous smoking could present with normal BP when measure conventionally, while NBP may be elevated.

There were observable differences in 24-hour renal Na^+ excretion rate; these were associated with high NBP in the INH group compared to the IDH group. Urinary Na^+ excretion in the INH group was 99.4 mmol/day which is significantly lower than the 151.8 mmol/day in the IDH group. Dietary Na^+ has a much wider range of effects in the body and plays an important role in cardiovascular outcomes because it can chronically increase BP and cause detrimental changes to the vasculature (Grillo *et al*., 2019; Guyton, 1992). Excess DSI impairs endothelial function through reduced nitric oxide bioavailability (Robinson *et al*., 2019). It further increases circulating endothelin-1 and arginine vasopressin; vasoconstrictors that are associated with increased BP (Dickinson *et al*., 2014; Spinelli *et al*., 1987). Lower Na^+

excretion in the INH group may be due to the significantly higher leptin concentration (20.9 ng/mL) in this group compared to the IDH (28.2 ng/mL). Leptin plays a role in pressure and volume regulation. Leptin stimulates the SNS by altering the secretion of various neuromodulators which regulate SNS activity and lead to elevated arterial BP (Guha *et al*., 2018). Generally, leptin is associated with adiposity and increased risk of hypertension, especially in an overweight or obese population (Rahmouni, 2010). Contrary, in the current study there were no significant changes in BMI amongst the four groups. In addition to being associated with overweight/obesity, leptin has been reported to be elevated in hypertensive patients (Agata *et al*., 1997). As part of the salt-regulating hormones, leptin has natriuretic potential and regulates Na^+ handling and excretion. It contributes to the Na^+-volume balance by increasing urinary Na^+ and water excretion (Bełtowski, 2010; Bełtowski *et al*., 2002). In the current study population and any changes in leptin concentration may have a great impact of Na^+ excretion. The natriuretic effect of leptin inhibits tubular Na^+ reabsorption. Leptin has a physiological role in Na^+ control and balance; however, the effects are influenced by dietary Na^+ intake. For the current study population, the INH group was retaining salt because of the effects of leptin. Additionally, the Na^+ excretion differences between the IDH and INH group showed that leptin has a functional role in renal biology, in that leptin's net effect on renal Na^+ metabolism may reflect direct natriuretic actions (Patel *et al*., 2008; Varela *et al*., 2004; Villarreal *et al*., 2000; Jackson and Li, 1997). Therefore, the blunted natriuretic effects of leptin cannot be ignored in the current study. This is because leptin can blunt salt excretion through stimulation of the sympathetic nervous system or enhanced efferent renal sympathetic activity (Haynes *et al*., 1997). From the current study, inference can be made that low leptin further leads to Na^+ retention in the INH group.

Since the INH group was retaining salt, this led to elevated NBP. When salt natriuresis is blunted during the daytime, there is a shift in salt excretion during hours of rest at night (Bankir *et al*., 2008). For the current study, salt retention in the INH group led to an elevated NBP as the renal mechanism excreted salt during sleep hours. Therefore, when there is a blunted excretory function during the day, elevated NBP can be seen as a consequence of nocturnal salt excretion. It has been reported that NBP correlates with sodium excretion during sleep hours (Staessen *et al*., 1991). Although blunted salt excretion can be multifactorial (Uzu *et al*., 1998); however, the current study has demonstrated that hormonal effects are relevant, and lead to daytime salt retention, which consequently increased NBP as a compensatory mechanism to excrete the excess salt. This is accompanied by increased blood volume, which further

perpetuates high BP during the night. Since the night-time salt excretion in hypertensives has had contrasting results (Sachdeva and Weder, 2006; Kawano *et al*., 1990), the elevated NBP in the INH group can be attributed to salt-retention and postulate that as they excrete salt at night, elevated BP is a consequent and a determining factor to allow salt to be excreted.

In the current study, the daytime and nighttime among NT, HT and IHN were similar. The IDH had a much lower night-time pulse, in comparison to the HT and INH. However, the difference (Table 5.2). These differences show that the 24-hour circadian pattern in IDH is characterised by a nocturnal decline which may decrease the pressure load on the vasculature during the day or through sustained 24-hour elevation. Increased pulse rate increases central haemodynamics and is associated with damaged large arteries (Palatini *et al*., 2018). Additionally, daily activities can increase pulse rate, therefore a night-time measurement could be useful the effect of daily activities are weaned off (Tochikubo *et al*., 2001). The current study did not include daily activities; however, the smoking prevalence was high in the IDH. Perhaps increased daytime pulse could be attributable to the acute effects of daytime smoking. When these wear off at night, they could lead to a reduced night-time pulse rate. Including 24-hour pulse rate measurement is important because its variability can be affected by physical, environmental, and other factors which ultimately increase BP (Kekes *et al*., 2020). For instance, considering daytime activities that impact on pulse rate and BP, their effects may be removed during resting period as pulse rate decreased (Cuspidi *et al*., 2017; Zhu *et al*., 2012). Essentially this change may influence the heart and arterioles. Therefore, a nocturnal reduction may confer some protection. Night-time pulse rate is further important since it removes the white-coat phenomenon of daytime or clinic measurements because since daytime observations may serve as the basis of elevated pulse rate and incorrectly be used as a marker of adverse outcomes (Palatini *et al*., 1998). Therefore, the inclusion of 24-hour monitoring extends the reliance on the overall mean pulse rate and allows stratification of the daytime and night-time effects. Additionally, this can correct for the masking effects of an overall pulse rate in predicting cardiovascular outcomes. Results from the current study allows the concession that reduced night-time pulse rate may be protective in the IDH group because there is a circadian pulse rate pattern that drops at night. This renders the adverse effects of elevated daytime pulse rate in this group moot, removing the possible sub-clinical organ damage that is associated with elevated pulse rate. Lower sympathetic activity is associated with vasodilation, which leads to decreased BP. This may further be associated with improved arterial compliance and

distensibility. It therefore can help in explaining the observed night-time hypotension in the IDH group.

On the other hand, the INH group had a relatively higher night-time pulse rate, which could indicate higher sympathetic activity at night in this group, it further implies decreased sympathetic tone (Palatini *et al*., 1997). The autonomic nervous system's influence on the heart propels its activity towards adverse target organ changes, hence it is important that sympathetic activity is regulated. Considering that it may be mediated through the autonomic nervous system, not only does it affect the BP profile, but it may cause overactivation of the autonomic nervous system and lead to adverse cardiovascular incidences (Gordan *et al*., 2015). Determining the 24-hour pulse rate in the current study offered better estimates of the cohort's regular pulse rate. However, it is plausible that night-time pulse rate is a better measure of the effects of pulse rate and can be a stronger predictor of all-cause mortality. It has been reported that sympathetic neural influence can increase NBP because autonomic nervous system helps mediate intrinsic circadian BP change (Okutucu *et al*., 2011; Grassi *et al*., 2008). The cyclic components of BP change over 24-hours are modulated by sympathetic neural factors. The difference between daytime and night-time BP therefore can be influenced by sympathetic activation (Dell'Oro, 2003; Narkiewicz *et al*., 2002). Moreover, overactivation of the sympathetic activity does not exhibit a decrease in NBP, instead BP is elevated. It has been suggested that the differences in daytime and night-time BP are caused by sympathetic modulation of NBP, which may be different in normotensive and, in patients who do not exhibit a declining NBP (Grassi, 2009). It may be associated with reduced renal function, which could affect excretory function and increase NBP (Jeong *et al*., 2020; Grassi *et al*., 2010). There may be a link between sympathetic overactivation and high NBP. Studies have endeavoured to determine the exact mechanism by which sympathetic activation contributes to NBP increase and have suggested that systemic activation may be through adrenergic influences that modulate vasomotor tone and vascular resistance (Grassi, 2009). Lastly, from a pathophysiological viewpoint, the possible influences of genetic factors on sympathetic activation in INH should be investigated as genetic differences in sympathetic activity have been reported (Greenfield *et al*., 2009).

Having established that IDH and INH are mediated by different physiological mechanisms, the current study further sought to establish whether their impact on target organ is comparable. It has been reported that INH and IDH carry a substantial risk regarding TOD and cardiovascular

mortality, when compared to NT and sustained 24-hour HT (Booth *et al*., 2016). Nonetheless, there is currently no data that distinguishes between these hypertension subtypes in relation to their impact on target organs in this population. The current study measured PWV, as an index of arterial stiffness, since pre-clinical cardiovascular pathology first manifests in the arteries before other organs are impacted (Shirwany and Zou, 2010; Zieman *et al*., 2005). The current results show that PWV of INH group was significantly higher than that of the IDH group but similar to the sustained 24-hour HT group (chapter four) while that of the IDH group was not statistically different from the NT group. The vascular changes observed in this chapter, especially in the IDH group, were contrary to that observed by the PAMELA study. Their study reported that hypertension phenotypes diagnosed through ABPM are associated with sub-clinical damage. They further reported that the progression of the end organ damage in IDH is similar to INH (Cuspidi *et al*., 2017). The current study results show that the effects of elevated NBP in INH carry the same magnitude of vascular damage as sustained elevated 24-hour HT and not in isolated elevated daytime BP. The IDH group showed a decline in NBP and no significant vascular changes. These findings indicate that in the current study, INH is as detrimental as sustained 24-hour HT while IDH has no significant impact on vascular changes. For the INH group, such findings are worrisome since research has shown elevated systemic vascular resistance and heightened vascular constriction in response to sympathetic nervous system activation at night in people of African ancestry (Sherwood *et al*., 1995).

As mentioned above, the prevalence of IDH and INH have been previously reported. Studies have reported adverse cardiovascular outcomes in INH patients (Ogedegbe *et al*., 2013; Hoshide *et al*., 2007; Lurbe *et al*., 2002). Based on the current findings, worse adverse effects are a result of the effects of elevated NBP in INH due to salt retention. This is based on the premise that people with normal daytime BP may regard this as an indication of good health whereas vascular damage progresses unnoticed. Additionally, even when monitored through conventional methods, such individuals would present with daytime BP that is below the traditional threshold for hypertensive monitoring or treatment (Salazar *et al*., 2020; Lawes *et al*., 2006). Although the JHS did not report on vascular damage, contrary to the current study they reported higher urinary Na^+ excretion rates in the INH vs IDH group. They further reported that increased urinary Na^+ excretion could be an adaptive mechanism for pressure natriuresis which can increase NBP associated with INH (Ogedegbe *et al*., 2013). The IDACO study did not determine PWV but reported higher pulse rate in the INH vs IDH group. As a result, their INH group had higher CVD events (Fan *et al*., 2010). The current study showed that IDH itself

presented with high daytime BP but low pulse rate whereas INH on the other hand presents with normal daytime BP and increased pulse rate. These findings demonstrated that the INH group and not the IDH group are at risk of adverse cardiovascular damage because they have elevated PWV. Li *et al*. (2008) reported that brachial PWV in the IDH group was higher than the INH group. Contrary, the current study showed that INH and sustained 24-hour HT group had higher PWV than the IDH group and similar PWV that was higher than the IDH group. This is contrary to the findings by Cuspidi *et al*. (2017). In their analysis of the isolated diurnal and nocturnal BP elevation, they determined that IDH causes similar degree of cardiac damage to nocturnal hypertension when patients with IDH and INH present with comparable overall 24-hour BP profile (Cuspidi *et al*., 2017). Reports on IDH and vascular damage, although limited, may be attributable to and masked by elevated NBP in INH and sustained 24-hour HT. For the studies reporting on higher PWV and vascular damage in IDH, they surmise that BP elevation, regardless of time of day, is detrimental to target organ function (Düzova *et al*., 2019; Li *et al*., 2007). Contrary, the current study only showed similar findings in the INH and the sustained 24-hour HT group. Perhaps in the current study, these finding in the IDH group can be attributable to pulse rate and nocturnal BP decline, as shown in Table 5.2. It appears that despite elevated daytime BP, nocturnal BP decline and restored pulse rate at night are protective in IDH, whereas, in INH, elevated NBP despite normal daytime causes vascular damage. Furthermore, urinary Na^+ excretion seems to play a crucial role in determining vascular damage. For that reason, participants who presented with blunted urinary Na^+ excretion (the INH group) had some degree of vascular damage; whereas enhanced urinary Na^+ excretion, as seen in the IDH group, may be protective when reported with other haemodynamic parameters. Perhaps ethnic diversity in diurnal blood pressure patterns must be considered in the above studies. Profant and Dimsdale (1999) reported that black people had higher daytime and night-time BP, with greater differences at night. Li *et al*. (2008) reported that their African cohort presented with a higher IDH prevalence than the INH group. Rhee *et al*. (2021) reported that the ethnic diversity of diurnal BP is probably responsible for the differing cardiovascular outcome in comparing IDH and INH. Although this highlights that the black population may present with higher BP profile due to their ethnicity and possibly through lifestyle habits such as salt intake, it still is contrary to the current study findings. The current study did not show any adverse effects in the IDH group, as the group did not show elevated PWV.

The findings of this study indicate that elevated NBP has a negative impact of the vasculature even if daytime BP is normal, whereas raised daytime BP has no impact on target organs if night-time BP is normal. In the current study this is contrary to other studies. For the current study, these differences raise a critical question, why is NBP detrimental to the vasculature despite normal daytime BP while the opposite is not true? To answer this question, the current study investigated the difference between daytime and night-time BP in the current study population (daytime minus night-time BP). The current study results indicate that all the daytime blood pressures are significantly higher than the night-time blood pressures (Figure 5.2). A stepwise regression analysis indicated that day–night difference in BP (DND) is independently associated with PWV (Table 5.3). This relationship was negative, demonstrating that as the difference between day and night BP increased, PWV decreased. The biggest DND was in the IDH group (29 mm Hg) followed by the NT group at 13 mm Hg, then the sustained 24-hour HT group at 8 mm Hg. Contrary to the other three groups, the DND was negative in the INH group, implying that NBP is higher than daytime BP in this group (in keeping with the reverse dipping in Chapter 4). The differences in DND between the INH and IDH is indicated in the way they impact PWV (Figure 5.3). In the INH group, even though daytime BP was normal, the low (and negative) DND translates to an increased PWV that is similar to that of the sustained 24-hour HT group. On the other hand, despite the high daytime BP, the high DND in the IDH group translates to a low PWV that is similar to the NT group. This means DND impacts arterial stiffening independent of daytime BP. However, this requires further investigation. Why does the drop in BP from daytime to night-time causes significant changes to normal arterial function? During daytime, arteries have adapted to high pressures because of increased perfusion required by organs during a busy day schedule. Hence an increase in BP during the daytime period leads to an insignificant change in arterial compliance (Bodlaj *et al*., 2007; Westhoff *et al*., 2007; Cornelissen, and Fagard, 2005). However, during night-time, most organs require minimal perfusion because this is a period of reduced activity. Hence, even arteries have adapted to function under low pressures during this period since NBP represents the minimal BP needed for adequate organ perfusion (Boggia *et al*., 2007). A normal daytime BP which is increased at night causes adverse cardiovascular outcomes beyond the effects of increased daytime or overall sustained elevated BP. Moreover, in the INH group, NBP that is higher than daytime pressure leads to increased vascular damage, through increased PWV.

Since the dipping pattern of the INH and IDH group were different, it warranted further investigations. The DND in the IDH was higher, when compared to INH. Increased DND in

the IDH group translated into increased percentage dipping in this group while the negative DND in the INH group translates to reverse dipping. Therefore, not only does the IDH group present as night-time normotensives, but they have a NBP decline (dipping) that is significantly different. Conceivably, a nocturnal dipping profile in IDH could further offer a protective mechanism because a lack of nocturnal BP dipping is associated with target organ dysfunction. It is reported that daily activities and sleep patterns affect nocturnal dipping (Iwashima *et al*., 2022). Generally, dipping is affected by circadian rhythm of BP, activities of the autonomic nervous system, and sodium regulation (Fabbian *et al*., 2013). Furthermore, decreased night-time pulse rate, and decreased cardiac output are associated with dipping (Birkenhäger and Van den Meiracker, 2007). The dipping pattern in IDH of the current study is intriguing for an IDH cohort because different types of secondary hypertension are associated with a non-dipping NBP profile (Triantafyllidi *et al*., 2021; Viera *et al*., 2011; Mochizuki *et al*., 1998; O'Brien, 1998). Perhaps the low leptin levels, coupled with increased urinary Na^+ excretion and pulse rate are further protective in this regard. Although research showed that a non-dipping profile negatively affects cardiovascular outcomes beyond BP values (Redon and Lurbe, 2008), this is not the case from the PWV results in the IDH group. The group had high daytime BP and other parameters as has been described above, but no adverse PWV increase due to dipping. On the other hand, the INH group showed a reverse dipping profile and indications of arterial stiffness. Although the mechanisms governing the differences in nocturnal BP between sub-types of hypertensions are not fully understood, Sherwood *et al*. (2002) determined that the day-to-night differences in sympathetic nervous system activity affects the magnitude of night-time BP dipping (Sherwood *et al*., 2002). Since there were differences in PWV in the IDH and INH group but similar between the NT group and IDH group, it showed that participants that present with elevated daytime BP, but normal NBP are not subjected to similar TOD as individuals who have elevated NBP but normal daytime BP. This is clinically important because BP does not have a threshold for cardiovascular events, resultantly, BP-related deaths are not only reported in hypertensives but there is an increased prevalence in BP related mortality in normotensives (Whelton *et al*., 2020; Stamler, 1991). The lack of threshold for adverse cardiovascular events does not, however, alleviate another challenge in IDH. The group does not present with vascular damage, however due to their high daytime BP, current guidelines would recommend pharmacological intervention, whereas the current results show that they do not present with increased risk of vascular damage.

The association between reverse dipping and arterial stiffness in the INH group, could be in part attributed to the higher NBP. Although reverse dipping has been reported as an independent risk factor for cardiovascular morbidity, data on arterial stiffness is lacking and the pathophysiological mechanism needs investigation. Since the arteries have adapted to function under low pressures during the night, elevated PWV in INH may be a result of higher blood mechanical forces that damage the vascular integrity as they act on endothelial cells (Boos *et al*., 2006). Moreover, the high NBP could compromise baroreceptor sensitivity and perpetuate vascular damage (Nagai and Kario, 2013). Another possibility is that reverse dipping can lead to aortic wall remodelling and reduced compliance (Lacolley *et al*., 1995). It is reported that vascular damage may increase BP; albeit, in the current study, the INH group presented with normal daytime BP. This removes the associated closed loop between arterial stiffness and BP but focuses attention on the effects of elevated NBP and reverse dipping; in that they result in detrimental vascular changes at the level of the larger arteries without increased mean BP but only NBP. Furthermore, the elevated PWV in INH implies that normotensives who succumb to cardiovascular morbidity, as reported by Whelton *et al*. (2020) could have had elevated nocturnal BP that was undetermined and all the while precipitating organ damage leading to their demise. In animal models, reduced arterial distensibility, increased collagen content and density in arterial walls are associated with a change in BP variability without mean increase in sustained 24-hour BP (Sasaki *et al*., 1994). Therefore, at any population level, especially one that is prone to the effects of blunted Na^+ excretion, there is a need to prospectively isolate mechanisms of elevated PWV, NBP and reverse dipping to further explain the observation in the current study. Since the current study has shown that NBP can be used as a tool to determine TOD independent of daytime BP. This indeed has prognostic value since elevated NBP is correlated with and vascular damage (Ogedegbe *et al*., 2013).

It has been over a decade since INH was first reported, yet to some extent its pathophysiology remains an enigma. In chapter four, I reported on the prevalence of IHN and that its feature characteristic, elevated NBP. INH is subject to a few mechanisms that results in a higher PWV, resulting in vascular damage. Two mechanisms associated with INH and vascular damage are Na^+ handling and increased sympathetic activation. Their regulation elevates nocturnal BP, subjecting cardiovascular system to high pulsatile pressure during periods when there should be low pressure (Guyton, 1980). In the current experimental chapter INH was compared to IDH and sustained 24-hour HT, with unique key findings pertaining INH. The INH group in

the current study presented with salt retention, reverse dipping, and increased PWV. Despite normal daytime BP, any dysregulation of the mechanism that control NBP precipitates to arterial stiffness in an INH cohort, even more so, it is similar to the effects of having 24-hour sustained hypertension. Sodium retention led to night-time natriuresis and increased NBP as the kidneys try to eliminate excess Na^+. Excess Na^+ is detrimental to the large arteries and is a risk factor as it increased NBP. It further leads to vascular damage through an increased NBP loop, because elevated NBP causes adverse changes to vascular function. This results in damage to the conduit arteries and increased PWV. Nonetheless, what was more interesting was that using the day-night difference in BP (DND) PWV was elevated in the INH group that was independent of BP changes. With a negative relationship, the current study findings illustrated that high PWV, even though it can still be perpetuated by elevated NBP, can independently cause vascular damage. Lastly, regarding IDH and INH, the current study concludes that elevated daytime BP is not as detrimental if there are parameters that favour a decline in NBP, such as dipping, and pulse rate; in fact, it confers some protection in IDH. The opposite holds true for the INH group, that normal daytime BP with an elevated NBP that is coupled with reverse dipping, and increased pulse rate causes vascular damage that is similar to the effects of sustained day and night hypertension.

Chapter 6

Age Related Increases in Nocturnal Blood Pressure and Diastolic Heart Function

6.1 Abstract

Findings shared in chapters four and five demonstrated that nocturnal blood pressure is a better predictor of pre-clinical vascular damage compared to daytime BP especially in people of African ancestry. The experimental findings showed that nocturnal hypertension has two BP phenotypes: non-dipping and reverse dipping. Risk factors for nocturnal hypertension include elevated nocturnal BP and a non-dipping BP pattern. Likewise, age is a risk factor and one of the strongest predictors of hypertension. The current experimental chapter sought to determine the role of age in the pathogenesis of nocturnal hypertension. Importantly, I wanted to determine the age at which pre-clinical cardiac pathology begins to manifest. I further wanted to establish whether guidelines for diagnosing nocturnal BP at <120 mm Hg systolic BP and <70 mm Hg diastolic BP are applicable to the current study population. For this investigation, conventional BP and 4-hour ambulatory BP were measured in 796 participants of African ancestry from a southwestern township in the Johannesburg metropolitan. Plasma aldosterone and urinary Na^+ concentrations were determined. Diastolic function, measured using echocardiography, was determined. Findings were stratified according to night-time systolic BP (SBPN) and categorised as SBPN 1 <100 mm Hg, SBPN 2 ≥100 and <110, SBPN 3 ≥110 and <120, and SBPN 4 ≥120 mm Hg. Age was positively associated with both daytime and night-time systolic BP. However, the age-related increase in nocturnal BP was higher than daytime BP. Nocturnal BP increased at an average age of 30 years and continued to increase until 70 years. Beyond the age of 70 years, nocturnal BP increase became similar to daytime BP. The age-related increase in both nocturnal and daytime BP were driven by plasma aldosterone concentrations, which was increased in the elderly population (≥70 years). The results showed an inverse association between plasma aldosterone concentration and urinary sodium excretion (Na^+). As plasma aldosterone concentrations increased, urinary Na^+ excretion decreased. Therefore, increased night-time and daytime BP was attributable to decreased urinary Na^+ excretion (i.e., urinary Na^+ retention. However, urinary Na^+ affected night-time BP more than daytime BP. Night-time BP increased faster than daytime BP, when comparing young adults (40-49 years) with the elderly study population (60-69 years). The current study results showed that the effects of sodium on BP only transpire until about 50 years of age, since there were steady increases in earlier age groups. After the age of 50 years, the effects of aldosterone on BP occur independent of urinary Na^+ excretion. Urinary Na^+ excretion only decreased until the age of 50 years, after that its excretion rate was similar in the remining age groups, up to 70 years. Investigations into TOD showed that a night-time BP range from 110

mm Hg to 119 mm Hg was associated with pre-clinical diastolic dysfunction. This nocturnal BP range showed pre-clinical diastolic dysfunction akin to what was observed in the fourth quartile (nocturnal BP ≥120 mm Hg). This implied early onset diastolic dysfunction between 110 mm Hg to 119 mm Hg. In conclusion, the findings of the current study showed that the current threshold for diagnosing nocturnal HT (<120 mm Hg of systolic BP) must be revised to BP <110 mm Hg, since pre-clinical diastolic dysfunction was observed at lower BP, when compared to the recommended BP. Pre-clinical diastolic changes were associated with the effects of plasma aldosterone and age. Aldosterone-induced changes were independent of urinary Na^+ excretion from the age of 50 years. Furthermore, age-induced BP changes were more pronounced when determined through nocturnal BP monitoring compared to daytime BP monitoring. Findings from this current study can advise treatment and management plans for elevated BP in people of African ancestry. Due to the age-associated changes observed from this current stud, perhaps after the age of 50 years, there must be a shift from Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers as the first line of therapy to aldosterone antagonists. However, extensive investigations are required to confirm this hypothesis confirmation.

6.2 Introduction

Diastolic dysfunction (DD), which occurs when the heart fails to fill up or pump as expected, can lead to heart failure. The type of dysfunction, whether filling or contraction determines the type of heart failure (HF). HF can further be categorised according to weakened perfusion to the body or the lungs (McDonagh *et al*., 2021). HF characterised with preserved ejection fraction (HFpEF) results from high filling pressure but with normal ejection (HFpEF) (Kapłon-Cieślicka *et al*., 2022). Caruna *et al*. (2000) contended that patients with HF that present with preserved ejection fraction (EF) are in diastolic heart failure (DHF). To confirm the diagnosis, Doppler imaging is performed to visualise heart chambers, and changes in the functioning of the left ventricles (Acil *et al*., 2005). Changes in diastolic function are believed to be a major contributor in such HF cases. However, given the complexities of HF, it is challenging to clearly isolate diastolic dysfunction as the sole cause of HF (Rusconi, 2000). As a result, DHF is accepted as a syndrome of clinical HF, characterised by normal left ventricular systolic function (Aziz *et al*., 2013).

DHF is prevalent in the elderly and mostly hypertensive population (Zile and Brutsaert, 2002). However, its symptoms may have delayed presentation. Accordingly, the delayed symptomatic manifestation of DHF may present with irreversible structural alterations (Tsuyuki *et al*., 2001). DHF is more marked when the left ventricle cannot accommodate blood volume during diastole at low filling pressure and therefore presents with low or normal end-diastolic volume. Elevation of the left ventricular end-diastolic pressure, and delayed isovolumic relaxation or increased passive stiffness are commonly associated with the DHF (Litwin and Grossman, 1993; Grossman, 1990). DHF predominantly presents with recurrent heart failure symptoms, including preserved EF and increased diastolic pressure. Thus, it has close relation to the clinical manifestation of DD. Moreover, DHF presents with impaired left ventricular filling which means that there is a decreased end-diastolic volume and stroke volume (Paulus *et al*., 1998; Ruzumna *et al*., 1996; Brutsaert *et al*., 1993). Diastolic performance is regulated by various confounding factors such as changes in the structures within the extracellular matrix neurohumoral and cardiac endothelial activation. This regulation poses a challenge towards proper diagnosis of DHF because it relies on the proper identification of diastolic haemodynamic abnormalities (Aurigemma, and Gaasch, 2004; Zile and Brutsaert, 2002; Mandinov *et al*., 2000). Nonetheless, Vasan and Levy (2000) reported that defining DHF should include evidence of congestive heart failure (CHF), normal left ventricular systolic

function, and objective evidence of DD. DHF has no specific treatment, therefore pharmacological interventions target associated conditions such as hypertension, coronary artery disease and HF itself to delay DHF-induced adverse effects (Paulus and Tschöp, 2013; Dahlström, 2005; Zieman *et al*., 1999; Paulus *et al*., 1988). There is increased DHF morbidity in patients with heart diseases and hypertrophic or restrictive cardiomyopathy (Mandinov *et al*., 2000; Zabalgoitia *et al*., 1997; Marantz *et al*.,1994).

Since research is perpetually highlighting the importance of monitoring nocturnal BP in uncovering severe cardiovascular events, there is a need therefore to report on the association between HF and DD and ambulatory BP parameters. ABPM can help uncover subclinical changes, even when the patients present with BP thresholds that are below hypertensive states (Messerli *et al*., 2017). The use of ABPM has allowed effortless assessment and the uncovering of BP-related anomalies more than conventional or clinic measurements (Verdecchia *et al*., 1994). Monitoring 24-hour ambulatory BP provides a complete BP profile and variability over a 24-hour cycle. Unlike isolated and intermittent clinic BP measurements it has furthermore allowed researchers to uncover the deleterious effects of nocturnal blood pressure towards TOD (Verdecchia, 2000; Ohkubo *et al*., 1997; Muiesan *et al*., 1996).

Monitoring BP during sleep hours is essential because there is an expected decreased arterial blood BP and heart rate at night and higher cardiac parasympathetic modulation (Fagard *et al*., 2008). This explains the associated increased risk between elevated NBP and indices of TOD, including left ventricular mass index and common carotid intima–media thickness in patients with known and unknown cardiovascular risks (Lindroos *et al*., 2016; Van de Borne *et al*., 1994). The general consideration is that NBP reflects basal BP because its determination coincides with sleeping period. Barring daytime activities that affect BP, NBP may help uncover other BP phenotypes that are blunted during daytime measurements (Hansen *et al*., 2011; Waeber *et al*., 2010). This implies that NBP is better standardized than daytime BP. NBP is a better predictor of TOD and of cardiovascular outcomes over daytime BP changes in various anomalies that adversely affect the vasculature (Draman *et al*., 2015; Minutolo *et al*., 2011; Boggia *et al*., 2007). Elevated NBP is affected by altered sympathetic modulation of night-time BP (Codt *et al*., 1997), disturbed baroreflex sensitivity (Vaile *et al*., 1996) and night-time pressure natriuresis in the elimination of excess Na^+ (Sachdeva and Weder, 2006; Staessen *et al*., 1993). Other studies include home NBP, and 24-hour ABPM to determine the effects of NBP on TOD. These studies univocally report that the predictive value of NBP is beyond daytime BP changes, systolic NBP is a better predictor of cardiovascular outcome and has a

stronger correlation (Whelton *et al*., 2018; Andreadis *et al*., 2016; Lindroos *et al*., 2016; Hansen *et al* 2011).

Based on NBP, hypertension is defined as the mean nocturnal BP of at least 120 mm Hg systolic over 70 mm Hg of diastolic BP; however, values higher than 125/75 mm Hg are deemed abnormal (Shimamoto *et al*., 2014; Mancia *et al*., 2013). These values correspond with the conventional BP guidelines for office BP ≥ 140 mm Hg/ 90 mm Hg (Kikuya *et al*., 2007). Elevated NBP can lead to nocturnal hypertension. Regardless of optimal daytime BP control, NBP increases cardiovascular risk and is further associated with increased TOD (Sawamura *et al*., 2017; Salwa *et al*., 2014; Vij, and Peixoto, 2009). Monitoring NBP is integral because it is well known that a lack of the night-time BP dipping, sometimes characterised by elevated NBP, is associated with various risk factors (Crinion *et al*., 2019; Fagard *et al*., 2008). Risk factors include among many, the physical environment, dietary and lifestyle habits such as alcohol consumption, cigarette smoking, and salt intake (Nwankwo et al., 2020; Huang et al., 2018); or intrinsic factors in the form of neural, endocrine, and endothelial changes that affect BP rhythm (Hermida et al., 2007; Guasti et al., 2005). Moreover, assessing TOD related to night-time BP changes shows better prognosis than daytime BP when determining the risk of fatal and non-fatal cardiovascular events (Kario *et al*., 2003). Elevated NBP independently predicts future cardiovascular risk factors and morbidity in patients that present with HFpEF (Punjabi, 2008; Peppard *et al.,* 2000).

Nocturnal BP can be used to evaluate and predict cardiovascular risks. Nonetheless, factors such as altered BP variability are more predictive of adverse effects, than other lifestyle risk factors (Lampert *et al*., 2005; Pickering and James, 1993). Granted, although there are other risk factors, age remains a major factor in how the vasculature changes and consequently leads to changes in NBP (O'Rourke *et al*., 2011). ABPM allows the differentiation between the night-to-day BP ratio and helps determine cardiovascular outcomes according to the day-night variability. Regarding the effects of age on the vasculature, it significantly increases the day–night differences in systolic and diastolic BP. Additionally, patients above the age of 60 years have increased risks of developing severe cardiovascular outcomes (Musameh *et al*., 2007; Boggia *et al*., 2007). Notwithstanding, normal aging can exert changes in diastolic function (Boyd *et al*., 2011). These changes may occur earlier in life due to various pathology; however, mild dysfunction commonly ensues above the age of 50 years. The underlying pathophysiology has not yet been fully reported (O'Rourke *et al*., 2011; Tokushima *et al*., 2001; Klein *et al*., 1994). Interestingly, normal aging only results in mild degrees of diastolic impairment

(Pritchett *et al*., 2005; Tsang *et al*., 2002). Barring from the usual causal factors, being younger, combined with reduced left ventricular compliance and relaxation are areas that require investigations, especially when the haemodynamic profile is variable. To control the effects of BP variability age should be considered during prescribed interventions. Currently interventions are not based on age, but on BP profile (Whelton *et al*., 208). Perhaps different guidelines for various age groups could be introduced, along with measures of diastolic dysfunction. Kane *et al.*(2011) described diastolic grading parameters using a four-point ordinal scale: (i) normal; (ii) mild diastolic dysfunction = abnormal relaxation without increased left ventricular end-diastolic filling pressure {decreased E/A ratio <0.75}; (iii) moderate diastolic dysfunction = abnormal relaxation with increased left ventricular end-diastolic filling pressure {E/A 0.75 to 1.5, deceleration time >140 ms, plus two other Doppler indices of elevated end-diastolic filling pressure}; (iv) severe diastolic dysfunction = advanced reduction in compliance with restrictive filling {E/A ratio of >1.5, deceleration time <140 ms, and Doppler indices of elevated left ventricular end-diastolic filling pressure}. Additionally, exact cut-off values should be adopted for different age groups and the measured diastolic parameters, than to what is currently available. Therefore, this study sought to determine the effects of different quartiles of 24-hour systolic BP and how BP changes within these quartile affects TOD, including diastolic function.

6.3 Results

The general characteristics of the study population are represented in Table 6.1. Data was divided into four quartiles using 24-hour systolic night-time BP, labelled SBPN 1 to 4. The results showed that systolic night-time BP increased with age through all the four quartiles. SBPN 1 was associated with a younger age (36 years), and SBPN 4 was associated with a much older age (56 years). Based on age, BP was different between quartile one to four, it increased as the increased. There was an association with increased age and weight increments and therefore increased BMI. Participants in quartiles 1 through to 3 fell into the overweight category while those in in quartile 4 were obese. There was an association between increasing BMI and increasing SBPN. The state of hypertension changed with each quartile as SBPN increased from the first to the fourth quartile. The proportion of hypertension was 15%, 20% and 31% from the first to the third quartile and 52% in the fourth quartile. Nonetheless, a higher smoking proportion (27%) was reported in the second quartile. Alcohol intake was higher in the first and third quartiles at 35% and 26%, respectively.

Table 6.1 General characteristics of the study population according to the 24-hour systolic night-time blood pressure quartiles

	SBPN 1	SBPN 2	SBPN 3	SBPN 4
	<100	≥100 – <110	≥110 – <120	≥120
n	199	243	159	195
Age	36.3 ± 15.7	40.2 ± 16.8[a]	45.6 ± 7.3[ab]	56.0 ± 16.6[abc]
BMI	26.8 ± 7.3	28.4 ± 7.1	29.1 ± 7.2 [a]	31.5 ± 8.1[ab]
% Females	75	65	55	57
% Hypertensive	15	20	31	52
% Diabetes	5	5	9	16
% Smokers	14	27	20	16
% Alcohol intake	35	19	26	22

SBPN 1, night-time systolic BP < 100 mm Hg; SBPN 2, night-time systolic BP ≥ 100 and < 110; SBPN 3, night-time systolic BP ≥ 110 and < 120; SBPN 4, night-time systolic BP ≥ 120. All data expressed as mean ± SD. [a] Significantly different from SBPN 1, [b] Significantly different from SBPN 2, [c] Significantly different from SBPN 3. BMI, Body Mass Index.

Table 6.2 Haemodynamic characteristics (mm Hg) of the study population according to 24-hour systolic night-time blood pressure quartiles

	SBPN 1	SBPN 2	SBPN 3	SBPN 4
	<100	≥100 – <110	≥110 – <120	≥120
n	199	243	159	195
SBPC	115.6 ± 14.9	122.2 ± 15.7[a]	128.6 ± 14.7[ab]	148.7 ± 21.4[abc]
DBPC	77.8 ± 9.2	81.1 ± 10.1[a]	84.4 ± 10.6[ab]	92.4 ± 12.1[abc]
SBP24	104.3 ± 6.2	112.8 ± 5.7[a]	120.9 ± 6.2[ab]	137.3 ± 14.5[abc]
DBP24	64.7 ± 5.6	69.4 ± 6.2[a]	74.3 ±6.7[ab]	83.4 ± 10.6[abc]
SBPN	93.9 ± 4.9	104.4 ±2.8[a]	114.8 ±3.1[ab]	134.8 ± 15.3[abc]
DBPN	54.7 ± 5.8	60.9 ± 6.4[a]	67.4 ± 7.4[ab]	78.3 ± 11.1[abc]
SBPD	110.8 ± 8.2	117.7 ± 8.1[a]	124.5 ± 9.6[ab]	138.6 ± 14.8[abc]
DBPD	71.2 ± 6.8	74.7 ± 7.5[a]	78.8 ± 8.3[ab]	86.9 ± 11.4[abc]

n = sample size; SBPN 1, night-time systolic BP < 100 mm Hg; SBPN 2, night-time systolic BP ≥ 100 and < 110; SBPN 3, night-time systolic BP ≥ 110 and < 120; SBPN 4, night-time systolic BP ≥ 120. SBPC, conventional systolic BP; DBPC, conventional diastolic BP; SBP24, 24-hour systolic BP. DBPN, 24-hour diastolic BP; SBPN, night-time systolic BP; DBPN, night-time diastolic BP; SBPD, daytime systolic BP; DBPD, daytime diastolic BP; All data expressed as mean ± SD. [a] Significantly different from SBPN 1, [b] Significantly different from SBPN 2, [c] Significantly different from SBPN 3.

The results in Table 6.2 shows that BP on conventional monitoring increased as 24-hour night-time SBP increased. There was a significant increase in BP between quartile two and three and were associated with prehypertension. Increased BP in quartile four was associated with severe hypertension and was significantly higher compared to that of quartiles 1 through to 3. These findings showed stage one hypertension on overall 24-hour BP in quartile four. Daytime BP was increased among all four quartiles: SBPN 3 showed pre-hypertension and SBPN4 showed stage one hypertension. Lastly, night-time BP was increased among all four quartiles: SBPN 4 showed night-time hypertension and SBPN 1 through to 3 showed normotension.

Age-related changes in daytime and night-time BP changes are illustrated in Figure 6.1. Daytime and night-time BP increased as the population grew older. At 40 years and above 70 years, findings from the current study showed a shift in NBP towards a pattern that exemplified daytime BP. Above age 70, daytime and night-time pressure were the same. Figure 6.1 below showed increased daytime and night-time BP. Night-time regulation above age 70 was impaired; elevating NBP similar to daytime BP.

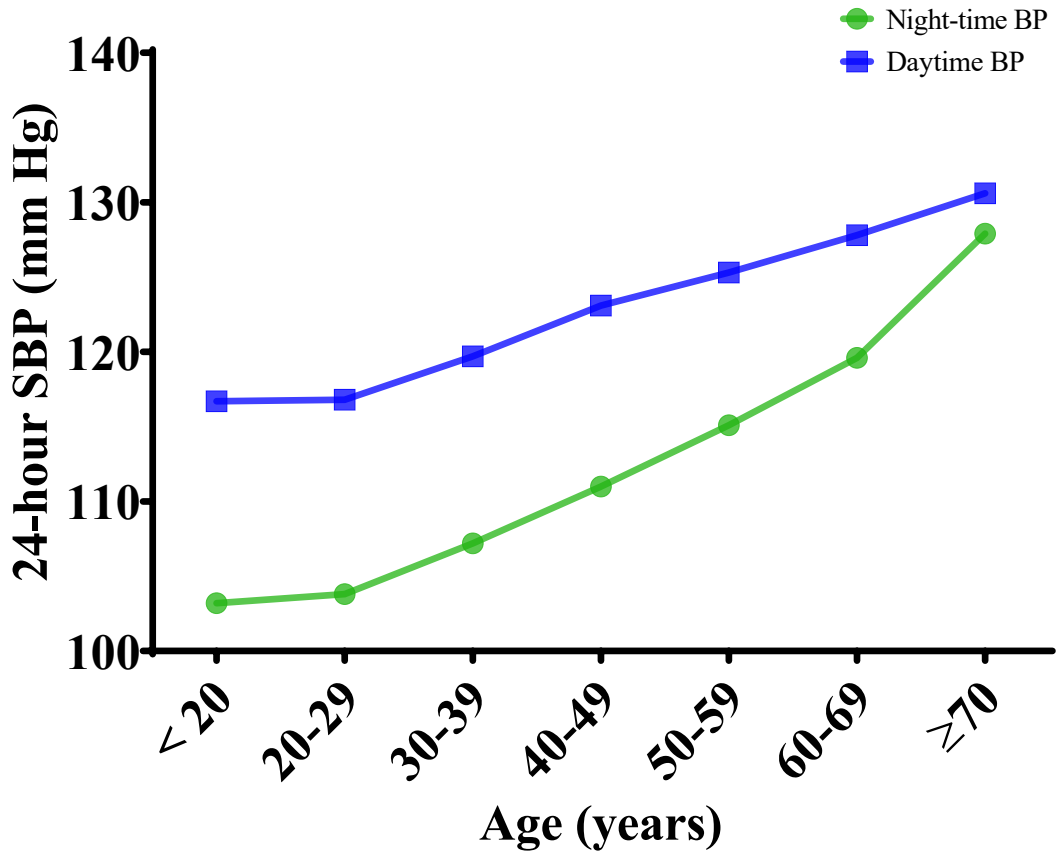


Figure 6.1 Age related increases in night-time and daytime systolic blood pressure.

Plasma aldosterone concentrations showed a direct association with age (Figure 6.2). There was a steady increase between ages 20 and 40 years. Above age 40, plasma aldosterone increased significantly. Urinary sodium excretion, which was inversely related to plasma aldosterone concentration, decreased with age. The excretion rates show no significant differences from ages 50 to 70 years and above. Figure 6.2 below showed converse association between plasma aldosterone, urinary Na^+ excretion and age. Plasma aldosterone and urinary

Na^+ have different SI units; they represented on the same legends to highlight their differences and association with age in the current study.

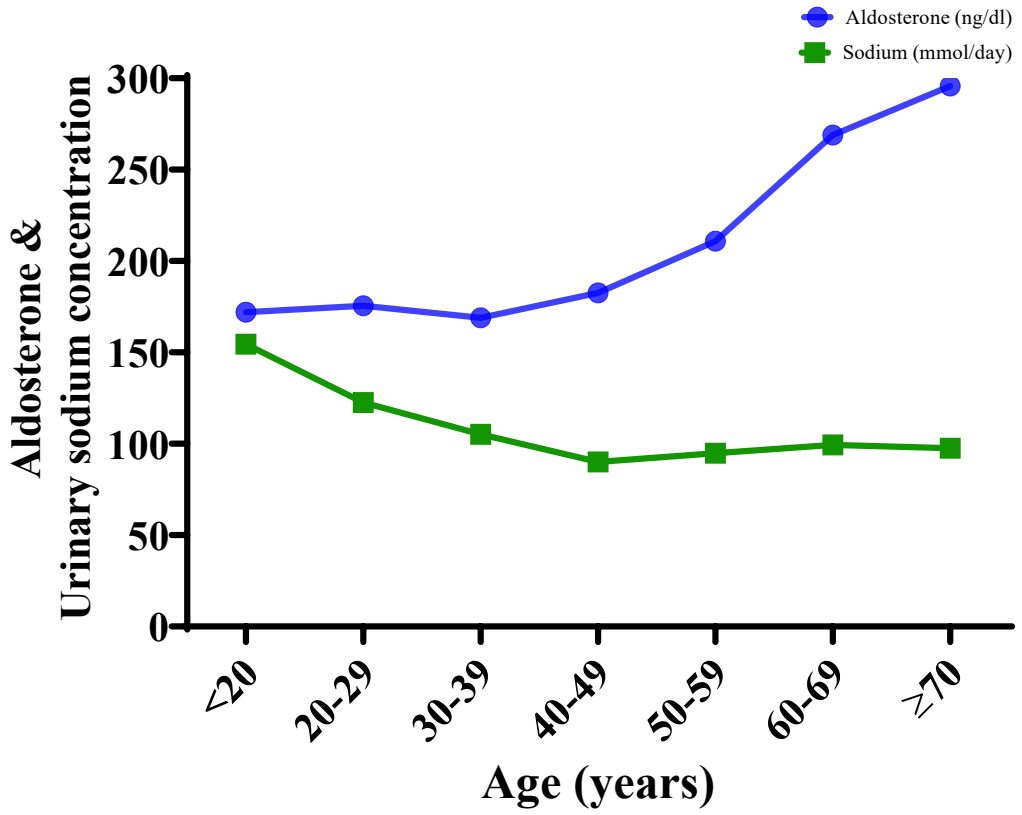


Figure 6.2 Age related changes in plasma aldosterone and 24-hour urinary sodium excretion.

Diastolic filling pressure decreased with increasing SBPN. The findings in quartiles one and two were not associated with adverse changes in diastolic filling. SBPN 1 (<100 mm Hg) did not show marked changes in relaxation. However, SBPN 2 (≥ 100 and < 110) there were signs of delayed filling. The effects of SBPN 1 showed compromised diastolic filling. Ventricular filling in early diastole was delayed in quartiles 3 and 4 (≥ 110 and < 120 mm Hg and ≥ 120 mm Hg, respectively). As SBPN increased diastolic function decreased characterised by increased early diastolic filling. Figure 6.3 below showed decreased diastolic filling, that was associated with increased SBPN.

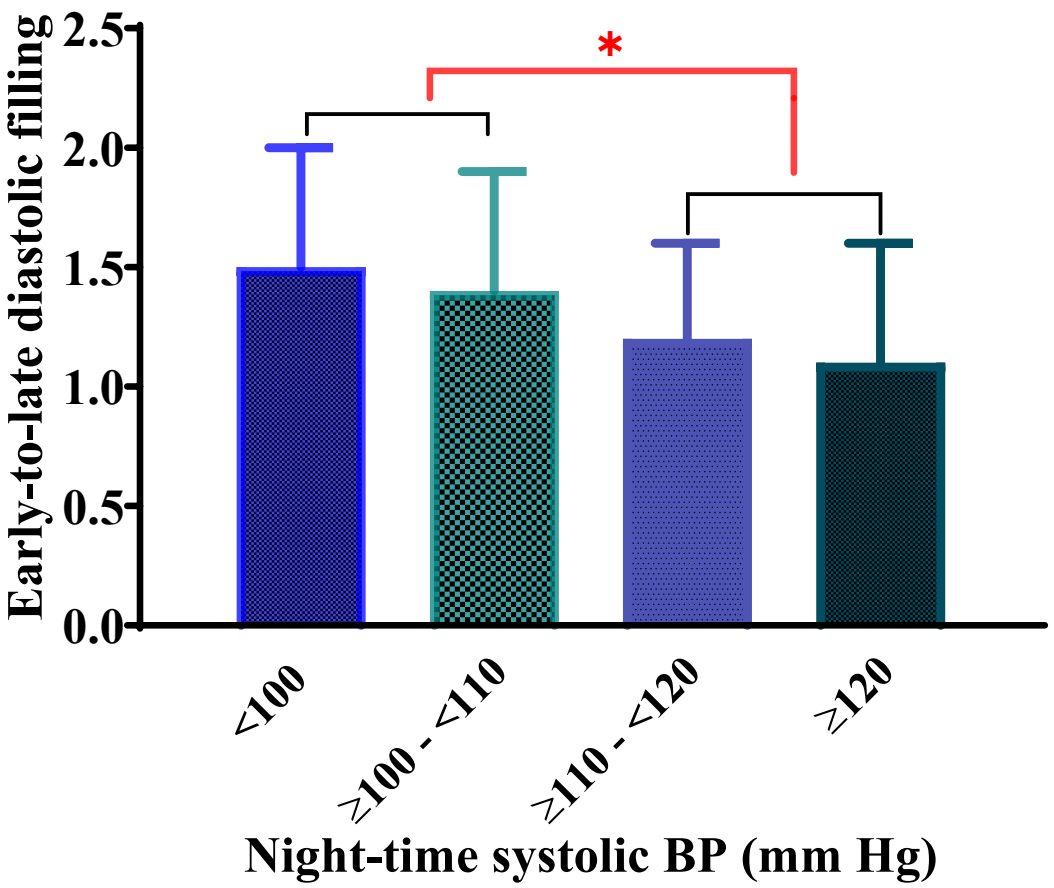


Figure 6.3. Night-time systolic BP induced changes in early-to-late diastolic filling.

SBPN 1, night-time systolic BP < 100 mm Hg; SBPN 2, night-time systolic BP ≥ 100 mm Hg and < 110 mm Hg; SBPN 3, night-time systolic BP ≥ 110 mm Hg and < 120; SBPN 4, night-time systolic BP ≥ 120 mm Hg.

6.4 Discussion

In this study, the sample (study) population was separated into four quartiles according to 24-hour night-time systolic blood pressure (SBNP) due to the propensity for increased SBP and a decreased ability to respond to abrupt haemodynamic changes (Izzo *et al*., 2000). Findings from this study showed that BP increased with age, predisposing to early development of BP-related TOD. The haemodynamic profile was affected by the changing vasculature as the population advanced in age. Sustained elevation of BP causes harmful changes that may lead to heart remodelling and ventricular stiffness because with age the vasculature changes in structure and function (Wang and Shah, 2015). Furthermore, it can be speculated that the observed increase in BP with advancing age could have been mediated by age-induced arterial changes that lead to arteriolar resistance. Since arteriolar resistance is synonymous with stiffness, the added effects of advanced age can presumably contribute to ventricular hypertrophy and consequently distort diastolic function (Bruno *et al*., 2017; Shipley and Muller-Delp, 2005). It was therefore integral to determine quartiles of night-time BP and the cut-off values at which increasing age caused notable vascular damage since the current study findings had demonstrated a trend of increased SBP with advanced age.

The current study further showed that as the population ages, BMI increased. From the SBPN 1 to SBPN3 participants were overweight and for the SBPN 4 participants were obese. The differences in BMI between the groups are associated with increased risk towards the ageing vasculature and the effects on BP (Figure 6.1). There is an increased cardiovascular risk with increasing BMI in an adult population. Advanced age is associated with reduced energy expenditure, leading to accumulation of adiposity (Seals and Bell, 2004). Accumulation of adiposity is associated with SNS activation via release of hormones that regulate BP and energy balance (Van Gaal *et al*., 2006). Additionally, adiposity accumulation has been reported to be activated with advanced age (Seals and Esler, 2000). It is reported that the age group between 30 and 75 years are susceptible to vascular changes as vasculature traits change with increasing age (Dua *et al*., 2014). Nonetheless, from the current study an overweight BMI was observed at the age of 56 years, with an average SBPN above 120 mm Hg. This indicates a decline in the relative risk associated with BMI, age, and increased BP. The Intersalt study reported that increased BMI and BP predisposed to adverse CVD outcome (Dyer and Elliott, 1989). Additionally, it was predominantly overweight and obesity that were associated with an increased risk of developing hypertension (Drøyvold *et al*., 2005). Therefore, the differences

in BMI between the SBPN 3 and 4 showed that regulating body weight could slow the progression of age-induced BP increase. This is further supported by the prevalence of hypertension (≥120 mm Hg) shown in the SBPN 4 at 52%. Participants in the fourth quartile showed an obese profile whereas all the lower quartiles had lower BMI and a low hypertension prevalence 15%, 20% and 31% in SBPN1, SBPN2 and SBPN3, respectively. Indeed, studies report that high BMI is a risk factor for increased BP. However, the studies associated increased risks with BP >130 mm Hg of SBP (Jiang *et al*., 2016; Mertens and Van Gaal, 2000). Contrary, separating the current study population into BP quartile showed that the effects may have an early onset, with at least BP levels between ≥110 and <120.

The current study showed that effects of lifestyle could cause BP changes later in life. Smoking and alcohol have BP-increasing effects (O'Keefe *et al*., 2014; Virdis *et al*., 2010; Bang *et al*., 2000); however, their effects may wear off at night, decreasing BP as a result (Minutolo *et al*., 2007). In the current study, the highest smoking prevalence (35%) was reported in the first quartile participants, who were the youngest cohort (36 years). The highest alcohol intake was recorded in the second quartile (27%). Yet none of these two groups presented with potentially harmful SBPN. Their SBPN was ≥ 100 mm Hg and < 110 mm Hg unlike the high SBPN 4 participants who were at higher risk of BP-related CVD events despite the lowest alcohol intake (22%) and smoking (16%) frequency. There is a propensity that participants could modify lifestyle behaviour like smoking cessation and reduced alcohol intake; however, the effect and damage could manifest at an older age as ageing affects the vasculature. These results imply that early lifestyle habits with the potential to increase BP could manifest in later years. Diabetes (16%) and hypertension (52%) were higher in the fourth quartile, and these are known risk factors that negatively impact the vasculature, mediating increases in BP (Assar *et al*., 2016; Prenner and Chirinos, 2015; Harvey *et al*., 2015).

In each quartile (Table 6.1) the observed low night-time SBP does not imply that the population is free of the cardiovascular risk because there was an associated lower SBPN 3 and 4 with reduced diastolic function (Figure 6.3). Therefore, stratifying the study participants according to night-time BP allows the effects of basal BP to be determined without the masked effects of daytime activities that could increase BP since there is an expectation that the effects of daytime activities wear off at night (Boggia, 2007). The average BP showed a steady increase occurring after the age of 40 years and this increase was different for conventional BP compared to 24-hour ABPM. Blood pressure on CBPM in participants that were 40 years and above was high, with systolic BP of 122.2 mm Hg and 128.6 mm Hg in the second and third quartile,

respectively. Albeit the mean systolic 24-hour ABP for the same cohort was normal 112.8 mm Hg and 120.9 mm Hg, respectively. Additionally, the fourth quartile showed differences in CBP and 24-hour ABP. The participants presented with severe hypertension on CBP (systolic BP of 148.7 mm Hg); yet, they had stage one hypertension according to mean 24-hour ABP (137.3 mm Hg of systolic BP). Since the participants in the fourth quartile were above 50 years, their change in BP is in support of findings that BP increases with age (Franklin *et al* 1997).

The current study results show that BP monitored using office CBP and 24-hour ABP varies in the same group of participants as they grow older. The revised new BP guidelines indicate that hypertension is diagnosed at 130 mm Hg of SBP (Williams *et al*., 2018). However, the current study brings in a new perspective with the stratification according to SBPN using 24-hour ABPM. From the current results high BP corresponded with SBPN ≥ 120 mm Hg, it implies that the revised guidelines are excluding other members in the same population, according to the stratification used in the current study. This means early management of hypertension-related cardiovascular outcomes should consider BP on both CBPM and ABPM. Additionally, the nocturnal BP fall was different between SBPN 1, 2 and 4. SBPN 1 and 2 cohort were dippers, whereas SBPN 4 were non-dippers. Moreover, non-dipping in the fourth quartile presented with hypertension because 52% of this cohort was hypertensive. Reiteratively, this emphasises that BP intervention should be cognisant of NBP changes because of the risk of cardiovascular mortality associated with nocturnal hypertension (Fan *et al*., 2010).

Figure 6.1 further showed that NBP posed an increasing risk as the population grows older. Understandably, SBP increased with age, with a higher increase in NBP. This meant the elderly presented as non-dippers, but showing a prevalence of a “riser” profile above 50 years of age. This showed an increased overall NBP with advanced age. This meant they were non-dippers, presenting with increased night-time BP. Above the age 50 years, there was severe hypertension and stage one hypertension on CBPM and 24-hour ABPM respectively. Sustained elevated BP was a risk for worse cardiovascular outcomes. These findings are worrisome for a population that is susceptible to vascular stiffness because of ageing. A blunted NBP decrease with advanced age implies that the mechanism that regulate night-time BP may be impaired with age (Albert *et al*., 2016). Including NBP therefore carries some clinical significance because daytime BP in Figure 6.1 was <130 mm Hg of systolic BP on 24-hour ABPM. This BP implies normal BP profile and a healthy population. However, the current findings showed risk of HT-related outcomes. Moreover, elevated NBP, if not monitored, could lead to

detrimental target organ changes. NBP predicts cardiovascular risk better than daytime BP, consequently, an increasing NBP could cause TOD that could predate hypertension (Cai *et al*., 2017).

The 2017 ACC/AHA Hypertension Guidelines reported that NBP ≥110 mm Hg/65 mm Hg corresponds to stage one hypertension on CBPM (≥130/80 mm Hg) (Whelton *et al*., 2018). Kikuya *et al*., (2007) reported that severe hypertension on CBPM (140/90 mm Hg) corresponds with 120/70 mm Hg on ABPM. These reports did not define the cut-off values for NBP. Since the recommendation for BP management has changed for CBPM, there is a need to revise nocturnal BP thresholds. Without defined NPB thresholds, studies that employ the same criteria for daytime BP could underreport the effects of NBP (Asayama *et al*., 2014; Shimamoto *et al*., 2014; Mancia *et al*., 2013). Additionally, the notion of normotensive non-dippers (reported in chapter five) supports the adoption of lower NBP threshold to determine end organ changes. The current findings offer support for early monitoring, and implementing prevention strategies, even if hypertension is not eminent. Including nocturnal dipping adds prognostic value through the night-to-day BP ratio independent of the 24-hour BP average (findings from chapter five). This implies that if NBP is poorly monitored, the same would translate for nocturnal BP dipping, which could lead to cardiovascular TOD (Floras, 1988).

Contrary to direct association between BP and age, urinary Na^+ excretion and aldosterone showed an inverse association. Aldosterone levels increased above the age of 40 years. High aldosterone levels are pathological; therefore, increased levels may predispose to early organ damage (Brown *et al*., 2014). Aldosterone increases the risk of cardiovascular morbidity by promoting vascular damage (Duprez *et al*., 2000). Additionally, ageing leads to an impaired aldosterone stimulation mechanism that eventuate into vascular damage. Brown *et al* (2014) reported that increasing age and aldosterone have a negative association. The study reported high aldosterone in participants with a mean age of 54 years (Brown *et al*., 2014), whereas aldosterone in the current study increased beyond the age of 60 years, and thus it consequently carries a disposition for future TOD. Aldosterone can be pathological even when participants do not present with any co-morbidities (Tomaschitz *et al*., 2010). Aldosterone levels in the current study add to the progression of hypertension and could perpetuate TOD, combined with dipping patterns in the different quartiles.

The average adult aldosterone concentration levels are less than 30 ng/dL in an upright position or more than 16 ng/dL in a supine position (Pagan and Pagan, 2017; Fischbach and Dunning, 2009). The average aldosterone levels in the current study, were very high. The younger cohort

had low levels (172 ng/dL) and the cohort above the age of 50 years had high concentrations (210 ng/dL). Contrary, studies have reported that black populations have low aldosterone levels, when compared to other counterparts (Lindhorst *et al*., 2007; Sagnella, 2001; Rayner *et al*., 2001). These studies report that low plasma-renin activity and the dysregulation of RAAS in black population leads to low aldosterone levels. Furthermore, excess Na^+ intake could cause aldosterone dysregulation. Combined high dietary Na^+ intake and aldosterone dysregulation lead to adverse cardiovascular outcome (Bentley-Lewis *et al*., 2007; Ferri *et al*., 1999). Nonetheless, there is no definitive correlation about the effects of excess and controlled Na^+ intake. Some studies reported no significant effects of Na^+ intake when comparing RAAS activity and aldosterone levels (Barlow *et al*., 1986; He *et al*., 1998). In the current study there was a direct effect of aldosterone on Na^+ absorption. Since aldosterone regulates Na^+ metabolism, it affects BP as well. Therefore, black populations may have different stimulatory pathways affecting aldosterone levels, independent of Na^+ intake (Spence, and Rayner, 2018; Verrey, 1999).

Ordinarily, high aldosterone concentrations cause salt retention that is excreted during sleep hours, consequently this increased NBP. Since high aldosterone causes Na^+ reabsorption, decreased Na^+ observed in the current study population could account for the observed BP difference using age and SBPN. Salt retention has deleterious effects on the heart, kidneys, and blood vessels. It increases extracellular fluid volume and impacts the progression towards hypertension and other related cardiovascular outcomes (Murro *et al*., 2013; Briet and Schiffrin, 2010). The current study is cognisant that Na^+ retention is a phenomenon of interest in a black population (Sagnella, 2001), and its effects cannot be ignored because it is a marker for TOD. High aldosterone concentrations can perpetuate salt retention and decreasing Na^+ excretion as a result. Age is a prominent risk factor for renal vascular disease and declining renal function, therefore in a population that ingests excess Na^+ intake, high aldosterone will promote TOD (Hannemann*et al*., 2011; Epstein, 2006; Duprez *et al*., 2000; Lindeman and Goldman, 1986). Therefore, high salt and high aldosterone perpetuates cardiovascular damage. However, an independent association between high levels of aldosterone and TOD without elevated BP exits. The combined effects of high aldosterone and salt retention sensitises the vasculature, causing systemic vascular resistance (Lim *et al*., 2015). In isolation, high aldosterone levels are associated with impaired vascular function, hence the current study surmise that coupled with high dietary Na^+ intake, ageing exacerbates TOD because there may be a limited responsiveness to increased aldosterone concentrations (Vaidya *et al*., 2013;

Bankir *et al*., 2008). Lastly, high aldosterone may contribute to cardiac remodelling predisposing heart failure, since age is associated with age-related increases in cardiac stiffness (Kim *et al*., 2018; Young, 2008; Leopold, 2011).

Finally, Figure 6.3 confirms that diastolic function deteriorates with increasing BP and age. Increased BP was associated with a delay in left ventricular filling, and the peak flow velocity rate in early diastole was higher than late diastole. These changes were not only associated with increasing SBPN but with age as well. Age-related changes in the left atrium which signifies reduced function have previously been reported (Boyd *et al*., 2011). Hypertension and ageing are some of the few traditional risk factors associated with decreasing left ventricular function (Nagueh *et al*., 2016). The early and late trans-mitral velocities are used to indicate reduced diastolic function. Additionally, because quartiles 3 and 4 were in the pre- and severe-hypertensive state, respectively, the increased BP is an added risk that causes left atrial enlargement. Consequently, as the trans-mitral velocities decreased, filling pressure from the left side of the heart increased (Nagueh *et al*., 2016).

The SBPN 1 cohort showed a prehypertensive state, a predisposition to early TOD. This emphasises the need for rigorous ABPM in this group of participants. Additionally, SBPN 4 presented with sustained 24-hour hypertension, even during sleep hours. Therefore, the effects of NBP on TOD was delayed ventricular filling. This supports studies reporting that diastolic dysfunction is an early marker of TOD when BP increases (Solomon *et al*., 2010; Redfield *et al*., 2003). Ageing and related increased pulsatile pressure caused by vascular stiffness leads to further deterioration of diastolic function, as evidenced by the increasing E/A ratio. What was worrisome is that the current study population showed preserved EF, therefore delayed ventricular filing was indicative of intermediate HF in the current study population. This is not disregarding that the degree of BP change, in particular to filling pressure, has adverse effects on diastolic function. Sundqvist *et al*., (2020) reported that age and hypertension adversely affects diastolic function, moreover, with increasing age the adverse effects remain, even after correcting for hypertension. For this reason, the current study emphasises that increasing age has sizable association with diastolic dysfunction, and that non-dipping could be a marker of TOD without hypertension. The current study reports that the threshold for TOD should be evaluated to account for lack of NBP decline, because this predisposes severe cardiovascular damage that may predate other known pathologies that further affect the functioning of the heart like kidney dysfunction, obesity or even diabetes.

Chapter 7

SUMMARY and CONCLUSION

7.1 Conclusions

The key findings and inferences drawn from this study that investigated INH and TOD in a population of African descent are presented below. Furthermore, limitations to the current study are highlighted and recommendations for future studies are made.

Findings from the current study showed an 11% INH prevalence in a South African population of African descent. This is different from the 6% INH previously reported by Li *et al*., (2007). Several factors may account for the observed differences: genetic makeup, dietary Na^+ intake or alcohol consumption, etc. Regardless, INH remains a cardiovascular disease risk factor that results in vascular damage. Vascular damage leads to arterial stiffness in INH. Impaired urinary Na^+ excretion was associated with elevated PWV, that leads to vascular damage in INH. INH was associated with lower urinary Na^+ excretion compared to sustained 24-HT. Low excretion pointed to blunted daytime sodium excretion which translated to increased nocturnal BP as the kidneys attempted to excrete sodium at night. This impact thus led to a reverse-dipping profile. Reverse dipping is harmful (Cuspidi *et al.*, 2017); however, regarding INH there is limited data that support this. The observed reverse dipping suggests that this population experiences daytime pressure overload that remains elevated at night. Findings from the current study reported salt retention as a risk factor towards INH. The premise is that there is a disturbed daytime Na^+ excretion that is shifted to the night-time hours. Therefore, there is an adaptive mechanism by the kidneys that elevates nocturnal BP to excrete excess Na^+ in the current INH group. Findings from the current study showed that the sodium-to-creatinine ratio was higher in INH, and this confirmed sodium retention and suggested that possible categorical mechanisms may be responsible for INH. The shift from day to night-time Na^+ excretion that is commonly associated with nocturnal HT can have a role in the progression of INH. Li *et al* (2007) suggested that higher urinary excretion rates may lead to the progression of INH Contrary, the current findings showed salt-retention, which is not in line with what Li *et al* (2007) postulated. Therefore, during pressure natriuresis, sustained elevated nocturnal BP leads to INH. For this reason, reverse dipping and INH may be areas that require further elucidation to determine the causal link. Vascular damage in INH was similar to sustained 24-hour HT. Vascular damage is associated with high nocturnal BP. The mean daytime and night-time BP in IHN were 126 mm Hg systolic BP. Studies report that unrecognised elevated nocturnal BP without daytime hypertension is associated with arterial stiffness (Li *et al*., 2007). The current study showed that vascular damage was associated with elevated nocturnal BP, without

daytime hypertension. More importantly, elevated NBP perpetuated reverse dipping, which elevated PWV, leading to vascular damage.

Vascular damage is associated with diabetic nephropathy; however, the current study reported a lower diabetes prevalence in INH. Therefore, the current study showed that reverse dipping causes independent of traditional vascular risk factors such as diabetes. Moreover, night-time BP predicts TOD above daytime BP. Vascular damage and TOD may ensue independent of known traditional risk factors. These results emphasise the use of ABPM in any population. ABPM can measure nocturnal BP variability, findings which will lead to early interventions to against deleterious effects of elevated nocturnal BP or reverse dipping.

It was important to include another BP phenotype, IDH since it is reported to cause severe TOD. The IDH group had similar BP profile compared with the NT. Even when investigating their nocturnal and dipping BP profile, the similarities remained, while INH and HT showed reverse dipping and non-dipping respectively. For that reason, findings from PWV measurements were not associated with vascular damage with IDH and NT. Non-dippers and reverse dippers are characterised by elevated nocturnal BP; and there is a further inference of high systemic vascular resistance (Sherwood *et al*., 2002). Elevated systemic vascular resistance and heightened vascular constriction are associated with sympathetic nervous system activation at night (Sherwood *et al*., 1995). Vascular disturbances lessen vascular relaxation that would favour BP dipping, this explains non-dipping and reverse dipping in HT and INH in the current study. The current findings were contrary to the PAMELA study which reported that phenotypes of ambulatory hypertension are associated with sub-clinical cardiac damage and that the progression of the end organ damage in IDH is similar to INH. Findings from the current study showed that the effects of elevated night-time BP carry the same magnitude of vascular damage as sustained 24-hour HT.

The lack of vascular damage in IDH was intriguing because different types of secondary hypertension are associated with a non-dipping nocturnal BP (Mochizuki *et al*., 1998). Conceivably, a nocturnal dipping profile in IDH could be attributable to the low leptin levels in this group and could offer a protective mechanism, since a lack of nocturnal BP dipping is associated with TOD (O'Brien, 1998). Non-dipping negatively affects cardiovascular outcomes beyond BP values (Redon and Lurbe, 2008), it could be deduced from the current results that the IDH group may not be at risk because they are dippers. The mechanisms governing the differences in nocturnal BP between sub-types of hypertensions is not fully understood, albeit the effects of the sympathetic nervous system on BP regulation may affect

nocturnal BP (Sica, 1999). Conjointly, Sherwood determined that the day-to-night differences in sympathetic nervous system activity affects the magnitude of night-time BP dipping, therefore a high DND that was observed in IDH could have been a result of normal SNS activity at night, that lead to dipping. Daytime activities and daytime urinary Na^+ excretion was also associated with DND in IDH.

Blood pressure does not have a set threshold for cardiovascular TOD; moreover, BP-related deaths are not only reported in HT but there is an increased prevalence in BP related mortality in NT (Stamler, 1991). Elevated PWV in INH proved that normotensives who succumb to cardiovascular mortality could have had elevated nocturnal BP that was not detected on CBPM and all the while precipitating organ damage leading to their demise. Furthermore, INH presented as daytime pre-hypertensives, and therefore did not meet the required criteria for pharmacological interventions (Appel, 2003). On the contrary, in IDH, high daytime BP warranted BP intervention, whereas the IDH group did not present with vascular damage. PWV results in IDH were similar to the NT group. Both groups were night-time dippers and had reduced night-time pulse rate, these parameters could be protective. Nocturnal BP dipping is influenced by daytime activities, although different factors may be dominant at different times and each may affect nocturnal BP differently (O'Shea, and Murphy, 2000). The current study showed increased daytime urinary Na^+ excretion and night-time dipping in IDH. Diurnal BP regulation is impacted by urinary Na^+ excretion; therefore, daytime excretion in IDH led to nocturnal dipping. Daytime urinary Na^+ excretion and dipping in IDH showed that urinary Na^+ excretion attenuates autonomic pathways that facilitates nocturnal BP dipping. Findings from the current study supports the role of the circadian rhythm of Na^+ excretion on BP dipping. However, dipping could not only be attributed to urinary Na^+ excretion, but other mechanisms could also be at play. This was evident when comparing dipping status between sustained 24-hour HT and INH. Both groups showed similar urinary Na^+ excretion rates, but and different dipping patterns. Non-dipping may be caused by various disturbances such as relative nocturnal volume overload or baroreflex or autonomic dysfunction and Na^+ handling (Redon and Lurbe, 2008). Nonetheless, the different Na^+ excretion patterns in the current study could help determine groups that may be at risk of detrimental cardiovascular outcomes because of the effects of urinary Na^+ excretion on night-time BP dipping. This could offer some clinical relevance considering the effects of Na^+ metabolism in a black population (Elijovich *et al*., 2016; Akita *et al*., 2003; Wedler *et al*., 1992). Therefore, night-time BP can be used as a tool to determine target organ damage independent of daytime BP.

The current findings support that the use of ABPM was not only crucial in uncovering hypertension phenotypes but showed that age played an important contribution in BP phenotypes. Different HT phenotypes were associated with advanced age: IDH = 49 years, sustained 24-hour HT = 55 years and INH = 57 years. Sustained 24-hour hypertension is associated with advanced age (Dada *et al*., 2014; Pogue *et al*., 2009; Ohkubo *et al*., 1997); however, the INH group was the oldest. Furthermore, above 60 years the current study population showed increased NBP. This was associated with non-dipping, and reverse dipping in NT and INH respectively. The effects of age on HT phenotypes could be associated with lifestyle behavioural changes. Alcohol intake and smoking had higher prevalence in younger cohorts. Alcohol intake and smoking were also associated with NT and IDH. This implied that people could make behavioural changes as they grow older, such as smoking cessation and reduced alcohol intake. Alcohol intake and smoking were observed in IDH and INH; and associated with age. However, the IDH group were younger and the INH older. In older participants, impaired mechanism of urinary Na^+ handling is associated with TOD (Young *et al*., 1995).

Urinary Na^+ excretion and aldosterone showed an inverse association, with advanced age. Rayner *et al*., (2001) reported that black normotensives have lower aldosterone levels and Charlton *et al*., (2005) reported that South Africans are excreting less Na^+. Eksteen and Mungal-Singh (2015) supported that the same population ingest excess Na^+, whereas Bertram *et al*. (2012) ascertained that they mostly retain Na^+ and excrete it at night. In the current study, the sodium-to-creatinine ratio was used to ascertain Na^+ retention. However, without a quantifiable dietary recall questionnaire that would include measurements of salt intake, it was challenging to definitively make the conclusion that the current study participants were ingesting a lot of salt and retaining it based on the decreased urinary Na^+ excretion. The inverse relationship between aldosterone and dietary electrolytes could be influenced by the interplay between ionic transport mechanisms, renal epithelial Na^+ channel, the RAAS and vasoactive substances (Lindhorst *et al*., 2007). Lastly, age-related aldosterone increase may lead to diastolic dysfunction because there is attenuation in the age-related increases in cardiac stiffness (Kim *et al*., 2018; Young, 2008; Leopold, 2011).

In conclusion, investigations carried out in this thesis resulted in several key unique findings within a black South African context. INH is associated with arterial stiffness (through elevated PWV), but the damage was similar to having sustained 24-hour HT. This implied there might be a population that presents with normal daytime BP but are reverse dippers since they have

elevated NBP. Combined, elevated nocturnal BP and reverse dipping cause vascular damage to the same effect as sustained 24-hour HT. Lifestyle factors such as dietary Na^+ intake, smoking and alcohol consumption impacts on overall BP profile and were associated with changes that perpetuated vascular damage. Nonetheless, there may be some protective effects that is drawn from daytime urinary Na^+ excretion and pulse rate. The IDH cohort presented as dippers because they had increased daytime urinary Na^+ excretion and pulse rate, compared to night-time rates. Finally, advanced age affects BP profile. By stratifying nocturnal BP into four quartiles age was associated with increased E/A ratio, and preserved EF, which indicated decreased diastolic function. These effects can progress independent of hypertension; but were associated with reverse dipping in INH. For this reason, the threshold for TOD should be described to account for NBP and dipping profile. It is important to actively include ABPM in health care settings. It will improve early diagnosis of INH and other related HT phenotypes.

7.2 Study limitations and future perspectives

Findings of the current study should be interpreted within the context of potential limitations. The study was cross-sectional, and it precluded conclusions about causal relationships. The ratio of male to female participants was unbalanced, this was common with most cross-sectional studies. Familial settings and socio-economic statuses impact hugely on gender-based participation in studies of this nature. A balanced gender-based analysis of the current findings would deem useful in stratifying the current findings. The study was conducted with a population of exclusively black people of African Descent therefore the results of the present thesis should not be theorised to other ethnic groups. The outcomes of this study should be interpreted within the perspective of its confines. Although IHN, IDH and sustained 24-hour HT status was determined by a single ABP measurement, it should be considered that ABPM is more reliable and reproducible, therefore repeated measurements were not required to determine their true prevalence. In the indices of urinary electrolytes, spot urine analysis was not performed. Determining if the same results from 24-hour urinalysis could be observed from spot analysis may add further statistical power to studies this nature. In addition, the urine collection did not separately include daytime and night-time urine; such a protocol would have shed more light on the diurnal and nocturnal pattern of urinary electrolyte excretion and its relationship with ambulatory blood pressure parameters: daytime vs night-time BP changes. Findings of the present thesis have important implications for the diagnosis and treatment of

INH within the black communities of South Africa. The results indicated that there are more complex mechanisms that exist in the development and progression of INH, this requires further investigation. Sleep apnoea which is usually associated with blunted nocturnal BP decline was not investigated. It may have been a confounder in the multivariate relationships in determining TOD. It is not known if genetic predisposition plays a role in the development of INH, therefore future studies are needed to investigate if a genetic component is involved in its development. Lastly, to identify the possible causes of INH from a clinical perspective, routine medical check-ups and the use of ABPM is encouraged. Early diagnosis may culminate modifiable risk factors that have been implicated, thus assist in delivering solid resolutions on reducing CVD burden related to INH.

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Appendix 1: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Edgar Matome Phukubje (Student number: 1578771) am a student registered for the degree of Doctor of Philosophy (Physiology) in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 28 October 2024

Appendix 2: Turn-It-In Plagiarism report

ORIGINALITY REPORT

16%	12%	12%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	wiredspace.wits.ac.za Internet Source	3%
2	Submitted to University of Witwatersrand Student Paper	2%
3	hdl.handle.net Internet Source	1%
4	docksci.com Internet Source	1%
5	Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics, 2016. Publication	<1%
6	hyper.ahajournals.org Internet Source	<1%
7	academic.oup.com Internet Source	<1%
8	Tomáš Seeman, Mairead Pfaff, Christine B. Sethna. "Isolated nocturnal hypertension in pediatric kidney transplant recipients", Pediatric Transplantation, 2021 Publication	<1%

Appendix 3: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

14 January 2019

Phukubje Matome
School of Physiology

Sent by email to: ephukubje@gmail.com

Dear Phukubje Matome

Re: **Protocol Ref No: MM170214**
Protocol Title: Isolated nocturnal hypertension and target organ damage in a salt sensitive African population.
Principal Investigator: Phukubje Matome
Protocol Amendment: Modification and extensions of experiments

This letter serves to confirm that the Chairperson of the Human Research Ethics Committee (Medical) has approved the amendment for the above-mentioned protocol, as detailed in your letter, dated 10 December 2018.

The following documents were received:

- Summary Letter
- Application form
- Clearance certificate
- Amended Protocol

Thank you for keeping us informed and updated.

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
14 JAN 2019
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Yours Sincerely,

.....
Mr Joshua Ndlangamandla
Administrative Officer
Human Research Ethics Committee (Medical)

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 304, Corner York Road and 29 Princess of Wales Terrace, Parktown, 2193 Private Bag 3, Wits 2050 | T+27 (0)11-717-1234/2656/2700/1252 E: Bhulani.Mkansi@wits.ac.za | Office E HREC-Medical.ResearchOffice@wits.ac.za |Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

R14/49 Mr Edgar Matome Phukubje et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170214

NAME: (Principal Investigator)	Mr Edgar Matome Phukubje et al
DEPARTMENT:	School of Physiology Hypertension Clinic, School of Physiology University of the Witwatersrand
PROJECT TITLE:	Impact of Fasting on Cardiovascular Parameters
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Muzi Maseko
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/06/2017

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 February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 30/06/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 4: Consent form

D#: _____

Human Nutrition Research Laboratory

South African Hypertension and Diet Study (SAHDS)

Study title: Isolated nocturnal hypertension and target organ damage in a population of African descent

Written consent form

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

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

Name of participant: _____

Participant code : _____

Signature : _____

Date : _____

To be filled by the principal investigators

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

Name :_____

Signature : _____

Date : _____

Appendix 5: Standard questionnaire

Human Nutrition Research Laboratory

South African Hypertension and Diet Study (SAHDS)

Standard Questionnaire

Participant Identification

Surname: _____

Full Name: _____

Date of birth:_____

Sex:_____

Residential Address: _____

_____

Postal code: _____

Cell phone number:_____

_____

HOW TO COMPLETE THE QUESTIONNAIRE?

You may complete the questionnaire yourself. However, you may also request help from the investigators. All information provided will be treated confidentially and will be used anonymously in the statistical analysis.

[***The first page of this questionnaire will be stored separate from the remainder of questionnaire****.]*

SECTION A

D#: _____

1. Specify your current marital state.

Single ☐ Married ☐ Divorced ☐ Widow or widower ☐

2. What is your highest academic qualification:_____

3. What is your current occupation:_____

3.1 For employed professionals, how long have you been in this occupation:_____

_____

3.2 If you are presently not working, please answer the below questions.

- Have you ever been employed before Yes ☐ No ☐
- Are you retired? Yes ☐ No ☐
- Other reasons:_____

SECTION B: Medical history

1. Are you currently in good health? Yes ☐ No ☐

2. Have you ever taken pain-killers on a regular basis, for instance against headaches, tooth pain, painful periods, etc.? Yes ☐ No ☐

3. Did you take medicines during the past 2 weeks? Yes ☐ No ☐

- If yes: please, specify:_____

4. Are you on any medical treatment? Yes ☐ No ☐

D#: _____

If Yes, please specify:_____

5. Please name any medical condition you have or had in the past:

_____

6. Do you have a history of non-communicable diseases?

Hypertension Yes ☐ No ☐

Heart disease Yes ☐ No ☐

Diabetes Yes ☐ No ☐

Chronic kidney disease Yes ☐ No ☐

Chronic lung disease Yes ☐ No ☐

7. Have you ever been told by a health professional that you have an elevated blood pressure?

Yes ☐ No ☐

- If yes, when was the diagnosis established for the first time: _____
- Have you received treatment for the elevated blood pressure?

Yes ☐ No ☐

If Yes, describe the regimen:_____

8. Please, specify whether some of your relatives currently suffer (or have suffered) from high blood pressure (hypertension).

Please, tick <u>one</u> box for each relative.

- Your father Yes ☐ No ☐ Unknown ☐
- Your grandfather (father's side) Yes ☐ No ☐ Unknown ☐
- Your grandmother (father's side) Yes ☐ No ☐ Unknown ☐
- Your mother Yes ☐ No ☐ Unknown ☐

D#: _____

- Your grandfather (mother's side) Yes ☐ No ☐ Unknown ☐
- Your grandmother (mother's side) Yes ☐ No ☐ Unknown ☐

- Your own children Yes ☐ No ☐ Unknown ☐
- Your grandchildren Yes ☐ No ☐ Unknown ☐
- Your own brothers or sisters Yes ☐ No ☐ Unknown ☐

9. Do you currently smoke? Yes ☐ No ☐

-If yes, explain the frequency, type and amount per day**:**_____

_____

10. Did you smoke in the past? Yes ☐ No ☐

- Please, specify the reason(s) why you stopped smoking:_____

_____

11. Do you currently consume alcoholic beverages? Yes ☐ No ☐

- If yes, explain the frequency, type and amount per day:_____

_____

12. Did you consume alcoholic beverages in the past? Yes ☐ No ☐

- Please, specify the reason(s) why you stopped:_____

_____

13. Do you drink coffee or caffeine-containing beverages (cola) on a regular base?

Yes ☐ No ☐

- If yes, give details:_____

14. Do you practice any sports activities on a regular basis?

D#: _____

Yes ☐ No ☐

If yes, explain the type, frequency and intensity:_____

_____

SECTION C FOR WOMEN ONLY

1. Did you already have your periods? Yes ☐ No ☐

2. Have you ever taken "The Pill"? Yes ☐ No ☐

- If yes, explain the regimen:_____

_____

3. Are you pregnant at present: Yes ☐ No ☐

4. Have you been pregnant before: Yes ☐ No ☐

For women older than 30 years

5. Do you still have your periods? Yes ☐ No ☐

5.1 At present are your periods suppressed by taking "the pill"?

Yes ☐ No ☐

5.2 If No, explain: _____

The End