AMBULATORY ISOLATED SYSTOLIC HYPERTENSION AND TARGET ORGAN DAMAGE IN A SOUTH AFRICAN POPULATION

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine

Johannesburg, 2020

Declaration

I Bongubuhle Wanelisile Mlambo declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

I certify that the assessments contained in this dissertation have been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. The ethics approval number is **M180201**.

Bongubuhle Wanelisile Mlambo

Signed on the 18th day of September 2020 in Johannesburg

We the undersigned declare that the above statement is correct.

Prof M.J. Maseko
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Date: 18/09/2020

Dedication

To my son Nathaniel Musa Mlambo.

You are my sunshine and I will always love you.

In loving memory of my loving father

Victor Moyo

1947-2005

Abstract

Isolated systolic hypertension is a major contributor to renal and cardiovascular disease morbidity and mortality worldwide, however, its prevalence in the adult population of African ancestry in South Africa is unknown. Moreover, the existence and effects of ambulatory types of this condition on vital organ systems have not been fully investigated. The aim of this study was to determine prevalence of, and target organ changes associated with, conventional and ambulatory subtypes of Isolated Systolic Hypertension. A total of 549 participants underwent general clinical and ambulatory blood pressure measurements by whose outcome they were divided into four Isolated Systolic Hypertension subtypes (Conventional, Daytime, Night-time and 24-hour Isolated Systolic Hypertension) and two control groups (Systolic-Diastolic Hypertensives and normotensives). Participants further underwent measurements of Pulse Wave Velocity, Left Ventricular Mass Index and Microalbuminuria to determine the extent of arterial stiffness, left ventricular hypertrophy and renal dysfunction associated with the subtypes of Isolated Systolic Hypertension, respectively. The prevalence of Conventional Isolated Systolic Hypertension, 24-hour Isolated Systolic Hypertension, Night-time Isolated Systolic Hypertension and Daytime Isolated Systolic Hypertension was 7.5%, 7.1%, 7.7% and 7.5% respectively. All subtypes of the condition emerged as strong predictors of Pulse Wave Velocity, Left Ventricular Mass Index and Microalbuminuria. Furthermore, similarly increased Pulse Wave Velocity was observed in the 24-hour Isolated Systolic Hypertension subtype and hypertensives. Greater Left Ventricular Mass Index was observed in the Conventional Isolated Systolic Hypertension subtype compared to hypertensives, whereas microalbuminuria was clinically present in the Night-time Isolated Systolic Hypertension group significantly more than it occurred in the hypertensive control group. Overall, this study revealed that Isolated Systolic Hypertension is prevalent in both clinical and ambulatory sub-types in this populations, and that it is associated with arterial stiffness, increased left ventricular mass and renal dysfunction equal to or exceeding the detrimental effects of hypertension on the arteries, heart and kidneys.

Acknowledgements

My utmost gratitude goes to my supervisors, Prof. Muzi Maseko and Dr Thamsanqa Nyundu for their guidance and support throughout the pursuit of this degree. Your love for research and teaching has been an inspiration like no other. I would also like to thank Mrs Mokgadi Maseko for her warm hugs and supportive prayers through the toughest times of this journey. I am grateful to her and Ms Delene Nciweni for their selfless assistance and skills transfer in collecting data for this research. To my colleagues at the Human Nutrition Research Laboratory, thank you for all your support, for the relationships we have built and for all the memories we have made together that will be treasured for a lifetime. Many thanks to the Head of School Prof Willie Daniels and the Wits School of Physiology Staff and colleagues for creating an environment that nurtures the love for life and science. My deepest thanks to my dear husband Maqondisa Mlambo, for seeing and supporting my vision, and for the sacrifices he endured to get to this point. I extend my deepest appreciation to my special helper, Siphathisiwe Mathuthu for mothering my son when I could not; there is no fit reward for your love and kind-heartedness, but our Father in heaven will reward you Himself. Thanks to my mother for your prayers and encouragement, and to family and friends for their love and support. I am grateful to all the participants in this research study, without whom this work would not exist. A heartfelt thank you to the Wits Financial Aid Office, the Faculty of Health Sciences' Research Committee and Postgraduate Office for their financial and administrative support throughout this endeavour. Above all, **blessed *and* worthy of praise be the God and Father of our Lord Jesus Christ, who has blessed *me* with every spiritual blessing in the heavenly realms in Christ.**

Table of Contents

List of tables

List of figures

List of Abbreviations

ABPM	Ambulatory Blood Pressure Monitor(ing)
ACC	American College of Cardiology
AGE	Advanced Glycation End-products
AHA	American Hypertension Association
ASE	American Society of Echocardiography
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CVD	Cardiovascular Disease(s)
DBP	Diastolic Blood Pressure
DBPC	Conventional Diastolic Blood Pressure
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HREC	Human Research Committee
IDH	Isolated Diastolic Hypertension/Isolated Diastolic Hypertensive(s)
ISH	Isolated Systolic Hypertension/Isolated Systolic Hypertensive(s)
ISH24	24 hour Isolated Systolic Hypertension
ISHC	Conventional Isolated Systolic Hypertension
ISHD	Daytime Isolated Systolic Hypertension
ISHN	Night-time Isolated Systolic Hypertension
IVSTD	Interventricular Septal Thickness in Diastole
LVH	Left Ventricular Hypertrophy
LVIDD	Left Ventricular Internal Diameter at end-Diastole

LVM	Left Ventricular Mass
LVMI	Left Ventricular Mass Index
M:C	Microalbumin:Creatinine Ratio
MMP	Matrix Metalloproteinases
MUAC	Mid-Upper Arm Circumference
NHANES	National Health and Nutrition Examination Survey
NO	Nitric Oxide
PP	Pulse Pressure
PWTD	Posterior Wall Thickness in Diastole
PWV	Pulse Wave Velocity
RAAS	Renin-Angiotensin-Aldosterone System
ROC	Receiver Operating Statistic
SA	South Africa
SBP	Systolic Blood Pressure
SBPC	Conventional Systolic Blood Pressure
SDH	Systolic-Diastolic Hypertension
SHEP	Systolic Hypertension in the Elderly Program
TGF	Transforming Growth Factor
US	United States
VSMC	Vascular Smooth Muscle Cells
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

In recent years, non-communicable diseases including cardiovascular diseases (CVDs) have overtaken infectious diseases to become a leading cause of mortality globally (WHO, 2013). The number of deaths caused by CVDs far exceeds that of deaths caused by cancer (Townsend et al. 2015) and accounts for almost a third of total deaths worldwide (WHO, 2013). Cardiovascular diseases are also a leading cause of morbidity and increasing healthcare costs worldwide (Celemajer et al. 2012; Owolabi et al. 2014). The trend persists in Europe where CVDs remain the most common cause of death, claiming over 4 million lives annually (Townsend et al. 2015). This trend is becoming more and more apparent in Africa (Celemajer et al. 2012; Owolabi et al. 2014).

Growing changes to lifestyle and diet associated with urbanisation have been suggested as contributors to the increase in CVDs in Africa, along with genetic variation, demographic transitions and other socioeconomic factors (Celemajer et al. 2012; Owolabi et al. 2014). In order to work towards alleviating this burden in the African continent, an in depth understanding of behavioural and associated clinical risk factors of CVDs (Steyn et al. 2004); as well as the sub-clinical conditions and resultant target organ damage in African populations is of paramount importance (Owolabi et al. 2014).

There are several risk factors for CVDs, namely age, overweight/obesity, smoking, hypercholesterolaemia, diabetes mellitus and hypertension to mention a few (Steyn et al. 2004; Celemajer et al. 2012). These are common in most populations, but differ in the degree of significance and association to CVDs. Of all of the factors, diabetes mellitus and hypertension have been consistently shown to be among the most important risk factors regardless of ethnicity (Celemajer et al. 2012). Over half of the 17 million deaths due to CVDs annually arise from complications of hypertension (WHO, 2013). Indeed, hypertension has emerged as a major risk factor for CVDs (He et al. 2005; Celemajer et al. 2012; Williams et al. 2018).

Hypertension is recognised as a global health problem (Park et al. 2015). About 40% of the world's adult population above the age of 25 had been diagnosed with the condition in the year 2008 (WHO, 2013), a cause for concern considering that an additional number of adult hypertensive individuals below the age of 25 may have remained undiagnosed at the time. A recent analysis of pooled worldwide data revealed that the prevalence ranges from 4% to 78% confirming a marked increase in the prevalence of hypertension in the last decade (Salem et al. 2018). Hypertension tends to affect populations in low and middle income countries of the world (which often have poor health and socio-economic systems) to a far greater extent as compared to those in high

income countries which are able to implement strong public healthcare policies to reduce the burden of hypertension (Salem et al. 2018; WHO, 2013).

The prevalence of hypertension is high across Asian countries and is associated with increased risk of CVDs and stroke (Park et al. 2015). A Vietnamese study of hypertension conducted by Hien et al. (2018) in older adults yielded a hypertension prevalence of 44.8%. Although there has been a decrease in the prevalence of hypertension within the United States (US) over the last fifteen years or so, the figure still remains high (45.4%). The absolute burden of hypertension in that country has in fact increased to 108.2 million according to analysis of 2015-2016 data from the National Health and Nutrition Examination Survey (NHANES) (Dorans et al. 2018).

The highest prevalence of hypertension worldwide has been recorded in Africa where 46% of the population over the age of 25 is hypertensive (WHO, 2013). There is strong evidence to believe that genetic and socio-economic factors such as urbanisation, poverty, unavailability and unaffordability of effective healthcare, as well as educational status are all involved in the dynamics of CVDs and indeed hypertension in the African continent (Seedat, 1999; Seedat et al. 2018; Gomez-Olive et al. 2017). An investigation into hypertension prevalence in a Nigerian community revealed that 21% of the subjects were hypertensive (Erhun et al. 2005), while another study in a separate Nigerian community yielded a prevalence of 51% (Ademolu et al. 2017). In rural Malawi, 13.6 % of the population was hypertensive, while the prevalence of hypertension in urban Malawi was 14.7 % (Price et al. 2018). Kenyan scholars have reported the age standardised prevalence of hypertension to be 24.5% in their country (Mohamed et al. 2018). Research carried out in Nigerian, South African, Tanzanian and Ugandan populations revealed that 25.9% of the overall participants were hypertensive after standardising for age (Guwatudde et al. 2015).

In another recent study of 40 to 60 year olds carried out in six study sites spread out over four Sub-Saharan countries, sites located in West African countries had a relatively low hypertension prevalence (Burkina Faso 15.1% and Ghana 19.3%). Nairobi, a site in Kenya had a prevalence of 21.9% and 28.7% in men and women respectively. The remaining three study sites located in South Africa (SA), however, had the highest prevalence values encountered in the study; 42% in a village called Digkale, 47% in a semi-rural township called Agincourt and 54.1% in the Soweto township. These figures are undoubtedly a cause for much concern (Gomez-Olive et al. 2017). In a demographic survey carried out in SA in 1998, Steyn et al. (2001) reported that an estimated 6 million South Africans were hypertensive by World Health Organisation (WHO) standards. The hypertension problem in SA is grossly amplified amongst the elderly where the prevalence is as high as 77% (Peltzer and Phaswana-Mafuya, 2013).

Evidence suggests that there is an increasing risk of hypertension and a deteriorating global cardiovascular disease risk factor profile for South Africans (Charlton et al. 2005; Celemajer et al. 2012). There are valid and growing concerns that hypertension in its different forms and categories, may soon become a major public health problem in both urban and rural SA (Seedat et al. 2014; Ntuli et al. 2015).

1.2 Definitions and categories of hypertension

By definition, hypertension is a chronic condition characterised by persistent elevated blood pressure (BP) (Egan et al. 2015; Seedat et al. 2014). Traditionally, the term hypertension has been used to describe a condition in which systolic BP (SBP) is above 140 mm Hg and/or a diastolic BP (DBP) above 90 mm Hg (Williams et al. 2018). The term Systolic-diastolic hypertension (SDH) is slowly replacing 'hypertension' in this regard as the latter becomes a broader term describing a large number of classes/categories of persistent high BP (Papademetriou et al. 2001; Tin et al. 2002; Sulbaran et al. 2002; Tsimploulis et al. 2017). Thus hypertension can be divided into several types based on several criteria which may or may not overlap. Other categories of hypertension are outside the scope of this dissertation.

Table 1.1 European Society of Cardiology/European Society of Hypertension (ESC/ESH) criteria for the classification of participants according to office (conventional) BP measurement. Adapted from Williams et al. (2018).

Category	**SBP (mm Hg)**	**Condition**	**DBP (mm Hg)**
Normal (Normotensive)	120-129	and/or	80-84
High-Normal (Normotensive)	130-139	and/or	85-89
Hypertensive	≥ 140	and/or	≥ 90
Isolated Systolic Hypertensive	≥ 140	and	≤ 90
Isolated Diastolic Hypertensive	≤ 140	and	≥ 90

The South African Hypertension guidelines concur with the above criteria for conventional BP diagnosis (Seedat et al. 2014). Hypertension can be divided into grades based on the extent of elevation of BP values.

Table 1.2 The ESC/ESH Classification of hypertension by severity. Adapted from Williams et al. (2018).

Grade	SBP (mm Hg)	Condition	DBP (mm Hg)
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

Table 1.3 American College of Cardiology/American Hypertension Association (ACC/AHA) Classification of participants according to office BP measurements (Whelton et al. 2018).

Category	SBP (mm Hg)	Condition	DBP (mm Hg)
Normal (Normotensive)	< 120	and	< 80
Elevated (High-Normal)	120-129	and	< 80
Grade 1 Hypertension	130-139	and/or	80-89
Grade 2 Hypertension	≥ 140	and/or	≥ 90
Isolated Systolic Hypertension	≥ 160	and	≤90, ≤95, ≤110*

**Variable DBP*

The advent of ambulatory BP monitoring (ABPM) has revealed much about other subtypes of hypertension in everyday environments; in fact, some developed countries have called for the application of ABPM as a routine tool in clinical practice (Pang and Brown, 2006; Ommen et al. 2007; Mediavilla García et al. 2011; Bloch and Basile, 2016). The superiority of this technique over office BP measurement has been well documented, particularly with respect to the prediction of cardiovascular events and target organ damage (Staessen et al. 1999; Myers, 2005; Dolan et al. 2009). The use of ambulatory devices to record BP has the advantage of providing a large number of measurements without digit preference (Staessen et al. 1999). According to the ESH and ESC, only ABPM readings with more than 70% of successful recordings can be deemed complete and usable for research and/or clinical applications (Williams et al. 2018). Another benefit of this method is that it minimises the interference of false BP elevations/reductions that may be influenced by clinical settings or other stimuli, as the case may be with white coat hypertension or masked hypertension (Kocemba et al. 1998; Staessen et al. 1999).

The ABPM technique has been instrumental in the understanding of circadian rhythm of haemodynamics, in particular the phenomena of night-time BP dipping or rising, the early morning BP surge (Snincak et al. 2018) as well as BP variability (Kocemba et al. 1998; Mediavilla García et al. 2011). In light of all these advantages, it is not surprising that ambulatory techniques are now

considered the gold standard in hypertension diagnosis and out of office BP measurement (Hodgkinson et al. 2011; Bloch and Basile, 2016). In fact, the ESH and ESC guidelines recommend that wherever possible this method be used as the basis for hypertension diagnosis (Williams et al. 2018).

Table 1.4 The ESC/ESH and ACC/AHA thresholds for hypertension diagnosis according to ABPM (Whelton et al. 2018; Williams et al. 2018).

Category	**SBP (mm Hg)**	**Condition**	**DBP (mm Hg)**
Daytime mean	≥ 135	and/or	≥ 85
Night-time mean	≥ 120	and/or	≥ 70
24 hour mean	≥ 130	and/or	≥ 80

Table 1.5 Hypertension sub-types by home measurement and 24-hour ABPM (Li and Wang, 2013; Williams et al. 2018).

Hypertension sub-type	**Description/Definition**
White Coat Hypertension	An elevated BP that occurs in a clinical setting (in-office) while out of office BP remains normal.
Masked Hypertension	A normal BP in a clinical setting with elevated BP in 'out of office' measurement.
Masked uncontrolled Hypertension	BP that appears controlled 'in-office' but is elevated and uncontrolled 'out of office'.
Isolated Nocturnal Hypertension	Elevated night-time BP with normal daytime measurements
Isolated Diurnal Hypertension	Elevated daytime BP with normal night-time readings
Sustained Hypertension	A BP elevated in both clinical and 'out of office' settings

Both the ACC/AHA and ESC/ESH guidelines are in agreement regarding the hypertension diagnostic thresholds for ABPM (Whelton et al. 2018; Williams et al. 2018). The ACC/AHA guidelines provide more stringent criteria for the classification of hypertension by office BP measurement, however this is not true for Isolated Systolic Hypertension (ISH) whose thresholds are higher (Whelton et al. 2018). On the contrary, ESC/ESH guidelines while seemingly lenient

on other hypertension classes, have a lower threshold for ISH as they consider the existence of the condition in both young adults and the elderly (Williams et al. 2018). In light of this, ESH criteria will be used in this study.

1.3 Isolated Systolic Hypertension

Isolated Systolic Hypertension is a form of hypertension characterized by elevated SBP ≥ 140 mm Hg and often low DBP ≤ 90 mm Hg (Singh, 2012; Egan et al. 2015). As a result of this, ISH is associated with increased pulse pressure (PP), which is the difference between SBP and DBP (Hall, 1999; Singh, 2012; Emeriau and Kalula, 2013). Previous studies of ISH date as far back as 1970 (Colandrea et al. 1970), with interest in the subject increasing around the 1980's (Kannel et al. 1980; Kannel et al. 1981; Curb et al. 1985; Saltzberg et al. 1988). In those days, most studies identified ISH as a disease of the elderly, stemming from the "normal" physiological processes associated with ageing (Kannel et al. 1981; Forette et al. 1982; Saltzberg et al. 1988; Wilking et al. 1988). More recent studies have revealed that ISH does in fact also exist in younger individuals (Grebla et al. 2010; Jangid et al. 2015; Lurbe and Redon, 2016; Eeftinck Schattenkerk et al. 2018). In either age group the condition can have detrimental effects on cardiovascular system and other vital organs (Ming et al. 1993; Kocemba et al. 1998; Lurbe and Redon, 2016; Palatini et al. 2018).

Systolic BP and PP are both increased in ISH, and are major predictors of heart disease. These haemodynamic parameters are associated with increased risk of myocardial infarction, left ventricular hypertrophy (LVH), renal dysfunction, stroke and cardiovascular mortality to a greater extent than DBP (Chobanian, 2007; Emeriau and Kalula, 2013; Egan et al. 2015). Some data from clinical trials suggest that even small elevations of SBP confer a significant risk of coronary heart disease (Cushman, 1998). The low DBP associated with ISH may lead to impaired tissue perfusion, particularly of the heart itself (Chobanian, 2007; Egan et al. 2015). In fact, ISH, which was long believed to be a normal and physiologically harmless state associated with the ageing process (Emeriau and Kalula, 2013; Kannel et al. 1971) has been shown to be a stronger predictor of cerebrovascular and cardiovascular events (Cushman, 1998; Kannel et al. 1971) as well as renal disease (Chobanian, 2007) than DBP. A thorough understanding of the pathophysiology of ISH is necessary in order to manage the condition effectively and possibly reduce its negative effects on target organs.

1.3.1 Pathophysiology of Isolated Systolic Hypertension

As previously mentioned, ISH arises from an increase in SBP coupled with a decreased or normal DBP (Hall, 1999; Emeriau and Kalula, 2013). A number of factors are thought to be responsible for ISH in different groups of people, however there are a number of similarities and overlaps in the underlying mechanisms.

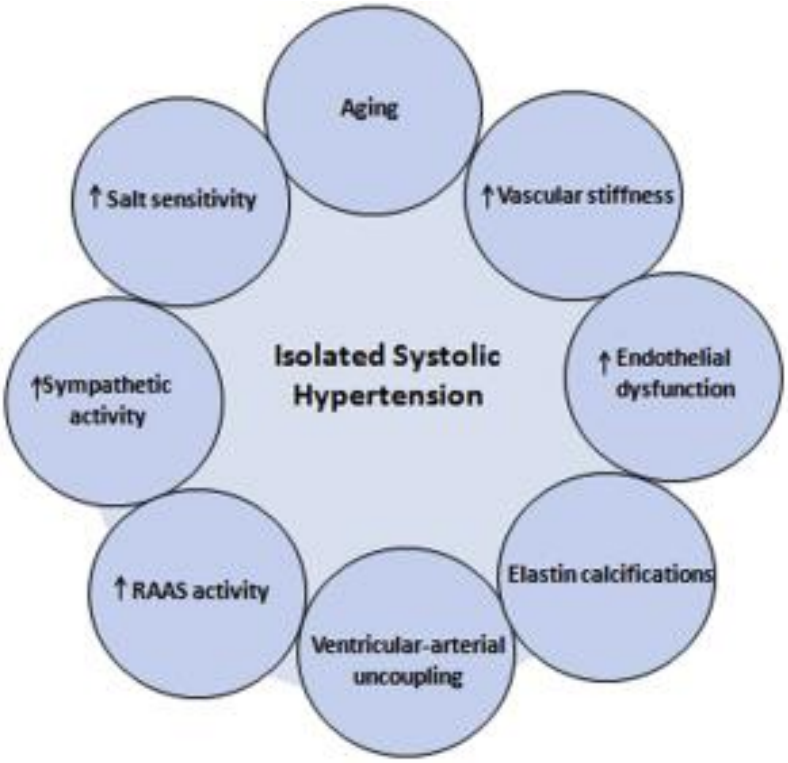

Figure 1.1 Pathophysiological mechanisms linked to the development of ISH. Adapted from Bavishi et al. 2016.

Isolated Systolic Hypertension in the elderly

Systolic BP has been shown to increase with age (Singh, 2012), a phenomenon that has been attributed to "natural" changes occurring in the arterial walls as the body ages. For this reason, most of the physiological mechanisms that are believed to be responsible for ISH are associated with the vascular ageing process (AlGhatrif and Lakatta, 2015). This involves an interplay of several processes typically culminating in increased stiffness of the central arteries (Emeriau and Kalula, 2013; Egan et al. 2015; Park et al. 2015; Bavishi et al. 2016).

As the vascular system ages - usually from about the age of 50 (Emeriau and Kalula, 2013; Gavish and Izzo, 2016), the arterial walls experience fatigue and the elastin fibres therein begin to fragment. This is associated with increased calcium deposition and subsequent media calcification

(Emeriau and Kalula, 2013; Egan et al. 2015). In addition to this, more collagen fibres are deposited into this fragile wall. There is an accumulation of Advanced Glycation End products (AGEs), which progressively and irreversibly interlink with collagen and elastin fragments to form a complex matrix (Steppan et al. 2011; Ecobici and Stoicescu, 2017). Local inflammation occurs, characterised by the release of proinflammatory cytokines and enzymes including some metalloproteases which inhibit the production of Nitric Oxide (NO) an influential vasodilator substance, leading to endothelial dysfunction (Schiffrin, 2004; Steppan et al. 2011; Bavishi et al. 2016).

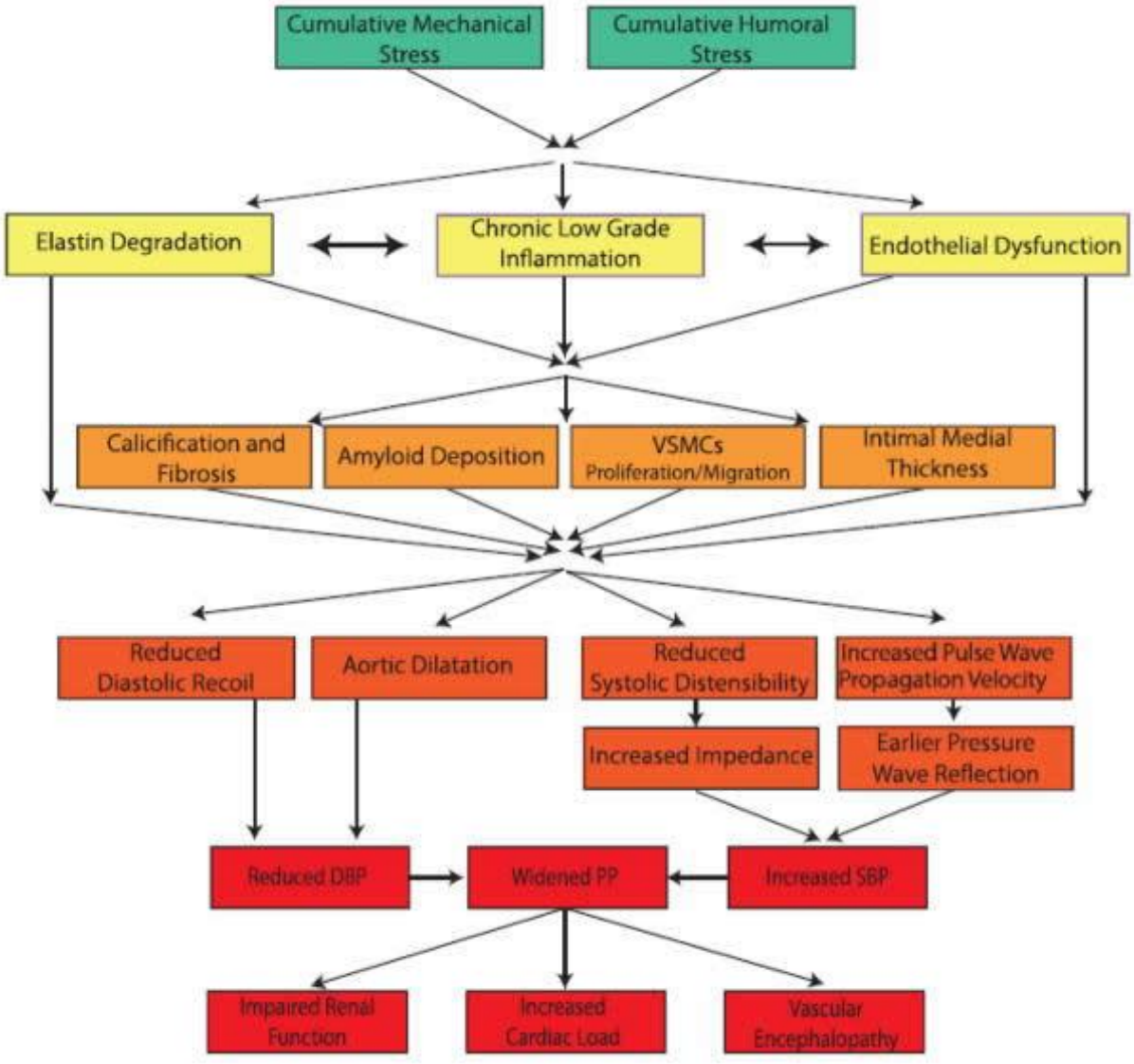

Figure 1.2 The interplay of processes implicated in the age-related pathophysiology of ISH. Ageing arteries are subject to low grade inflammation, elastin degradation and endothelial dysfunction whose combined effects are the stiffening of said arteries leading to haemodynamic changes associated with ISH, and culminating in damage to vital organs. Adapted from BP and Arterial Wall Mechanics in Cardiovascular Diseases, (AlGhatrif and Lakatta, 2015).

Advanced glycation end products speed up inflammation and the release of oxygen free radicals that impair NO function (Stokes et al. 2006; Steppan et al. 2011). Inflammatory products also influence the infiltration of Vascular Smooth Muscle Cells (VSMC's) leading to smooth muscle cell hypertrophy (Steppan et al. 2011; Bavishi et al. 2016). The combined effect of these factors is the thickening and stiffening of arterial walls leading to elevated SBP and widening of PP (Sulbaran et al. 2002; Stokes et al. 2006; Steppan et al. 2011; Singh, 2012; Emeriau and Kalula, 2013; Egan et al. 2015; Bavishi et al. 2016). Arterial stiffness has been shown to have a self-propagating effect (Bavishi et al. 2016), the shear and oxidative stress associated with increased SBP in ISH worsens vascular remodelling and endothelial dysfunction thereby augmenting arterial stiffness.

Excessive salt intake has also been implicated in ISH pathophysiology through the impairment of NO production (Stokes et al. 2006), increased collagen deposition and the salt-related increase in TGF-β1cytokine (Sanders, 2009; Ecobici and Stoicescu, 2017). This cytokine molecule has been shown to promote smooth muscle hypertrophy and production of extracellular matrix proteins while inhibiting the activity of collagen-degrading metalloproteases such as MMP-9 (Sanders, 2009; Ozkayar et al. 2016). Moreover, sodium plays a big role in BP regulation via the Renin-Angiotensin-Aldosterone System (RAAS) particularly in the elderly who tend to become increasingly salt sensitive (Bavishi et al. 2016).

In younger adults, RAAS is thought to be involved in ISH pathogenesis via mechanisms involving smooth muscle cell proliferation, stiffening, diminishing of contractility, increasing thickening and remodelling of the intima (Schiffrin, 2004; Bavishi et al. 2016). The RAAS also mediates ISH pathogenesis via comorbidities such as diabetes mellitus (Ecobici and Stoicescu, 2017).

Isolated Systolic Hypertension in the young

The pathophysiology of ISH in young individuals is thought to differ at least to some extent from the mechanisms described for the older population (Grebla et al. 2010; Palatini et al. 2018). In some young people, ISH develops following a hyperkinetic pre-hypertensive state which is associated with an increase in sympathetic stimulation (Palatini et al. 2018). This is associated with adrenergic activation with the release of norepinephrine (Palatini et al. 2018). In these individuals, an increase in resting heart rate and cardiac output leads to an acceleration of vascular ageing and arterial stiffness with an isolated increase of SBP (Palatini et al. 2018). The findings of McEniery et al. (2005) in a study of individuals between 17 and 27 suggest that indeed aortic stiffness is associated with ISH in young people, having similar pathophysiological implications as it does in the elderly. The cause of such aortic stiffness in the young, however, is not well

understood. Some researchers have shown that an increase in stroke volume in certain young individuals is the major contributor to an elevated PP leading to premature aortic stiffening (McEniery et al. 2005; Lurbe and Redon, 2016; Palatini et al. 2018; Eeftinck Schattenkerk et al. 2018). Increased body fat in obese young adults could also be a contributing factor to isolated elevation of SBP as the former has been shown to be a strong predictor of aortic stiffness (Grebla et al. 2010).

Another type of ISH is observed in young active, particularly athletic adults. In this group, the SBP and PP elevations are often isolated to the peripheral arteries (especially in the upper limbs), while central haemodynamics remain normal (Mahmud and Feely, 2003; Palatini et al. 2018). This phenomenon has been attributed to the effects of exercise-related bradycardia on stroke volume; which is thought to increase PP by exaggerating the amplification of the pressure wave (Mahmud and Feely, 2003; Bursztyn, 2018; Palatini et al. 2018). This type of ISH is arguably considered spurious and somewhat 'non-detrimental' by most researchers (O'Rourke et al. 2000; Hulsen et al. 2006; Krzesinski et al. 2006; Palatini et al. 2018) since most risk is often associated with central rather than peripheral abnormalities (Eeftinck Schattenkerk et al. 2018)

Other causes of ISH

There are several rare secondary causes of ISH that have been documented and these include complete heart block (Kannel et al. 1971), severe anaemia, aortic insufficiency, arteriovenous shunting, thyrotoxicosis (Kannel et al. 1971; Niarchos et al. 1984; Steppan et al. 2011) as well as Paget's disease and beriberi (Singh, 2012). The common factor that is most likely the driver of ISH in these conditions is the increase in cardiac output (Singh, 2012). Other conditions associated with ISH are insulin-dependent diabetes mellitus, osteoporosis associated with vascular calcification, poor elastin formation during foetal growth, repaired coarctation of the aorta and ageing of the proximal aorta (Bavishi et al. 2016). Arterial stiffness is present in nearly all secondary causes of ISH.

The Mechanistic implications

Evidently, reduced compliance of the central arteries is a common denominator in most mechanisms of ISH pathology. Normally, the heart generates a pulse wave during systole, which travels through the vascular tree (Tin and Lip, 2002; Stokes, 2006). As it encounters resistance in the peripheral arteries, a component of the wave is reflected back to the heart and arrives at diastole, augmenting DBP (Tin and Lip, 2002). Under normal circumstances, the wave pattern is a near-symmetric rise followed by a dicrotic notch corresponding to the closure of the aortic valve

at the end of systole (Stokes, 2006). This relieves the ventricular afterload and allows for healthy coronary perfusion (Stokes, 2006).

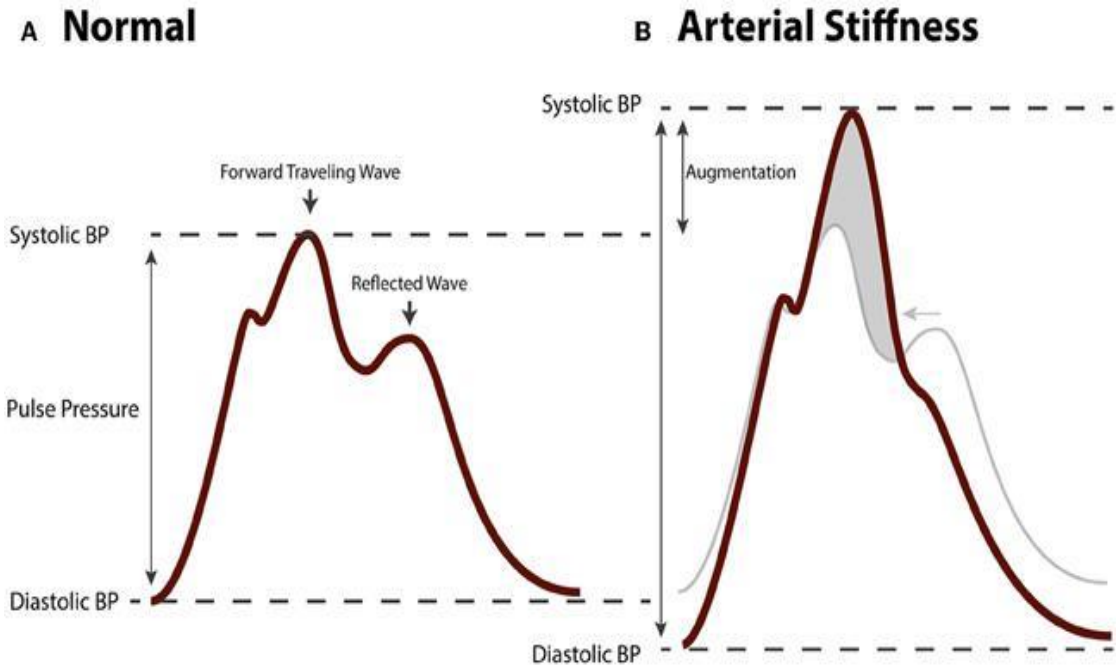

Figure 1.3 Pulse waveforms of an individual with (A) normal and (B) stiffened arteries, showing pulse wave augmentation of systolic BP by the reflected wave in arterial stiffness. Adapted from Van Varik et al. (2012).

When there is increased aortic stiffness, Pulse Wave Velocity (PWV) is increased such that the reflected wave returns prematurely towards the heart, arriving at systole and augmenting the SBP. Diastolic BP is also reduced in cases of poor arterial compliance. Central arteries which normally store a component of stroke volume for subsequent release in diastole (a phenomenon known as the Windkessel effect) fail to do so once they lose elasticity (Bavishi et al. 2016; Gavish and Izzo, 2016). Consequently, PP also widens, ventricular afterload becomes elevated and coronary perfusion is reduced (Nichols and Edwards, 2001: Tin and Lip, 2002; Kannel, 2003; Gavish et al. 2016; Dai and Tan, 2019).

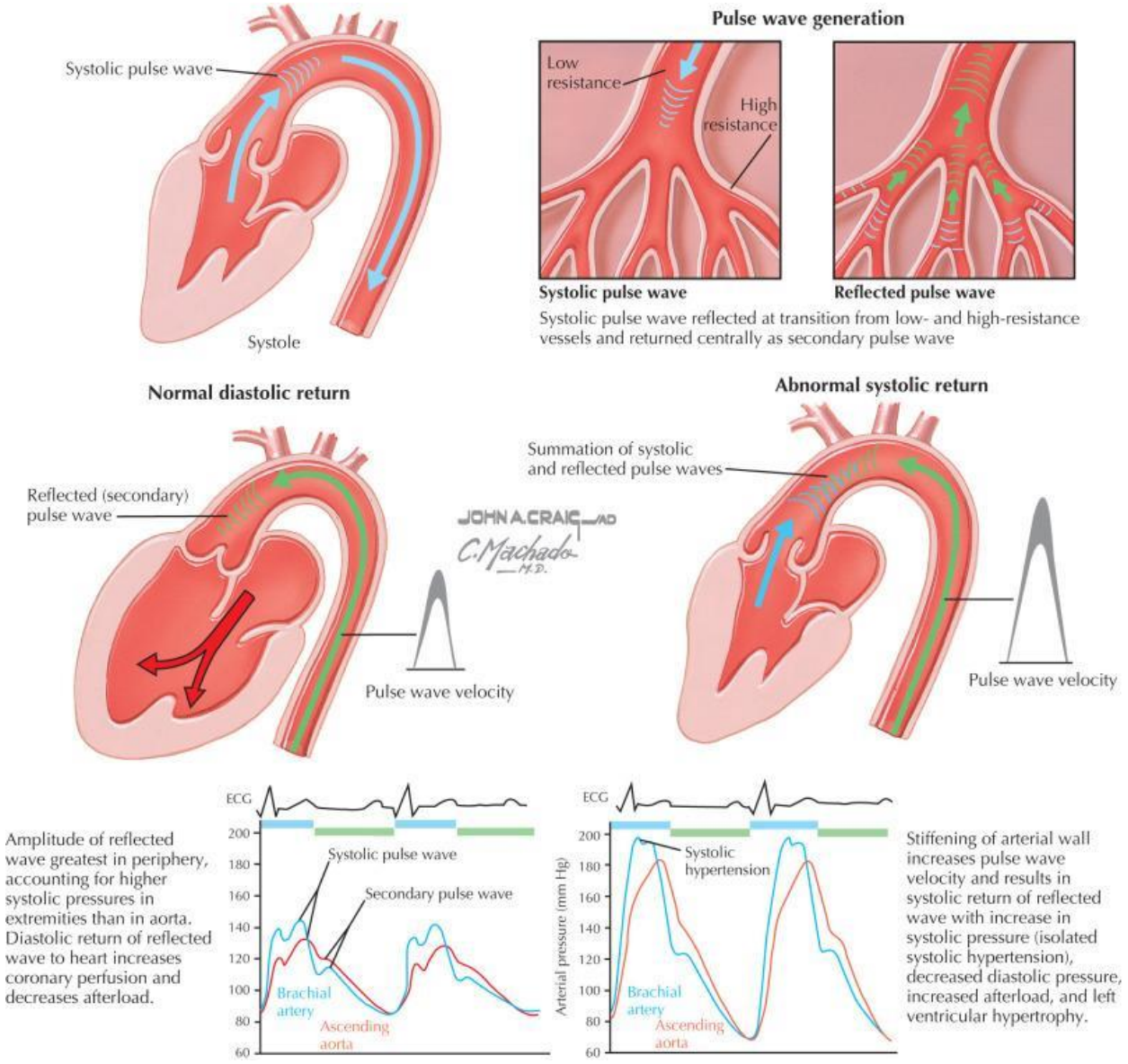

Figure 1.4 Diagrammatic representation of wave reflection in ISH. Stiffening of the central arteries result in elevated SBP and widened PP through pulse wave augmentation. Adapted from Dai and Tan, (2019).

1.3.2 Epidemiology of Isolated Systolic Hypertension

The incidence of ISH worldwide is variable but is increasing; its prevalence has been reported at 4.0 % and 4.4 % in Korea (Kim et al. 2005), 7.6 % in China (Huang et al. 2004) and at 7.78 % in an Indian population (Gupta et al. 2006). Banegas et al. (2002) found a prevalence of 12 % in a Spanish cohort. Studies on ISH in Africa are limited, however, Erhun et al. (2005) reported a 1.4 % prevalence of the condition in the 21-30 age group, and 12.2 % prevalence in the 51-60 age group following a study of the condition in West Nigeria. In SA, Ntuli et al. (2015), have reported

surprisingly high prevalence rates of 21 % in rural Limpopo. It is evident that ISH is becoming a major health problem (Sulbaran et al. 2002; Unni, 2018).

A wide variety of risk factors have been shown to have an influence on the prevalence of hypertension in general, and these include tobacco use, excessive alcohol intake, unhealthy diet, physical inactivity, obesity, elevated blood glucose and abnormal blood lipids (Hien et al. 2018). Hosts of factors have been associated with an increased prevalence of ISH and CVD, and aging is arguably the most paramount of these (Emeriau and Kalula, 2013).

Age as a risk factor for ISH

The existence of ISH in young and middle-aged populations is well documented (Niarchos et al. 1984; McEniery et al. 2005; Gupta et al. 2006; Bavishi et al. 2016; Lurbe and Redon, 2016; Eeftinck Schattenkerk et al. 2018; Palatini et al. 2018; Saladini et al. 2018). However, there is overwhelming evidence that it is the most common form of hypertension in elderly individuals and that its prevalence increases with age (Niarchos et al. 1984; Sulbaran et al. 2002; Papadakis et al. 2018). As such age is considered one of the major risk factors for ISH (Xu et al. 2008; Midha et al. 2010). This relationship between age and ISH is attributable to the aforementioned changes in vasculature that occur with the ageing process, and their impact on cardiovascular haemodynamics. Typically, both BP components i.e. SBP and DBP increase with age until about the 5th decade when DBP reaches a peak and begins to decline while SBP and PP increase due to arterial ageing (AlGhatrif and Lakatta, 2015; Gavish and Izzo, 2016). The haemodynamics surrounding ISH differ according to gender, with women becoming increasingly susceptible with advancing age (Ko et al. 2005).

Female Gender increases the risk of ISH

Findings of several researchers support the identification of female gender as a risk factor for ISH (Martins et al. 2001; Sulbaran et al. 2002; Kim et al. 2005; Gupta et al. 2006). The general short stature of women is associated with a shorter arterial tree, and this facilitates early wave reflection in this gender and is a probable cause of predisposition to ISH (Safar and Smulyan, 2004). The arterial tree length also results in a faster heart rate which causes a more rapid decline in DBP.

In premenopausal women, the activity of female sex hormones, in particular oestrogen, is thought to have a protective effect on haemodynamics (Safar and Smulyan, 2004; Xu et al. 2008). The diminishing activity of these hormones post-menopause is associated with faster ageing of female vasculature and subsequent large artery stiffness causing earlier development of ISH in elderly females compared to elderly males (Safar and Smulyan, 2004). The increased susceptibility of

women to ISH may also be related to obesity, which is often more prevalent in the female gender as compared to males (Case and Menendez, 2009; Lovejoy et al. 2009; Maseko et al. 2018).

Obesity

Obesity has been identified as a risk factor for ISH (Ko et al. 2005; Grebla et al. 2010; Midha et al. 2010). The physiological processes thought to be responsible for this relationship include the increase in sympathetic and RAAS activation, increased sodium retention, hyperinsulinaemia, low-grade inflammation and increased leptin production (Re, 2009; D'Elia and Strazzullo, 2018). It is likely through these mechanisms that obesity is related to an increase in arterial stiffness (Wildman et al. 2003; Grebla et al. 2010; Nordstrand et al. 2011), and so becomes an important risk factor for ISH.

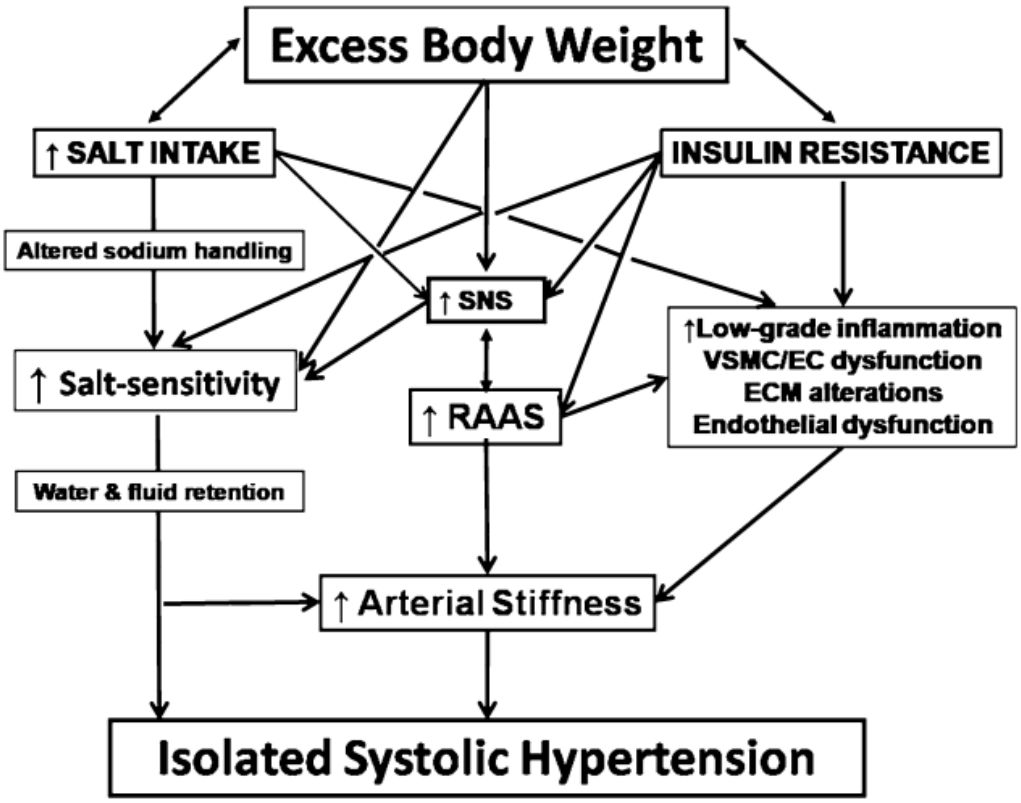

Figure 1.5 A schematic diagram showing the possible ways by which excess body weight in overweight/obese individuals may lead to arterial stiffness and ISH. Adapted from D'Elia and Strazzullo (2018).

There is still much controversy around the suitability of different techniques for categorising obesity in different population groups where ethnicity or genetic factors may affect the trends in fat deposition (Gelba et al. 2008; Schneider et al. 2010). Some scholars support the use of the Body Mass Index (BMI) to determine obesity while others believe that waist circumference, waist to hip ratio or waist to height ratio are more clinically significant measurements (Gelba et al. 2008; Klein

et al. 2001; Wiltink et al. 2013). Despite this, BMI remains the most widely used method for the classification of obesity. It is also the recommended method for reporting on obesity-related research according to the WHO (Sangachin et al. 2018). Obesity has been closely related to diabetes mellitus, which is also a risk factor for ISH.

Diabetes Mellitus

The association between ISH and non-insulin dependent diabetes mellitus (type 2 diabetes) is well documented (Curb et al. 1996; Wang et al. 2000; Kostis et al. 2005; Os et al. 2006; Emeriau and Kalula, 2013). Ko et al. (2005) reported a two-fold risk of developing ISH amongst individuals who suffer from type 2 diabetes, and found that the duration of diabetic illness was an independent predictor of ISH. Diabetes mellitus is associated with insulin resistance, hyperinsulinaemia, and hyperglycaemia (Sowers et al. 1993). The state of hyperinsulinemia is believed to increase arterial stiffness (Schiffrin, 2004) through three mechanisms, namely the promotion of sodium reabsorption by the kidneys, the increase in sympathetic nervous system stimulation as well as proliferation of VSMCs (Wildman et al. 2003; Ko et al. 2005; D'Elia and Strazzullo, 2018).

Under normal circumstances, receptor-bound insulin induces some vasodilation through stimulation of endothelium derived NO in order to balance the increased BP from SNS hyperactivity. With insulin resistance, however, this insulin-related vasodilator activity is diminished and the increased BP may cause shear stress leading to arterial wall damage and ultimately, arterial stiffness (Wildman et al. 2003). Insulin-resistance is also associated with low grade inflammation which, as previously described, causes arterial stiffness mediated by cytokine activity (D'Elia and Strazzullo, 2018). In addition to this, elevated blood glucose levels cause increased glycation of arterial wall proteins, which may lead to atherosclerosis, arterial stiffness and consequently, ISH (Wildman et al. 2003; Nordstrand et al. 2011; Franklin, 2012). In support of this, Ko et al. (2005) suggested that prolonged hyperglycaemia plays a major role in ISH pathogenesis.

Hypercholesterolaemia and ISH

High levels of cholesterol have been reported in ISH patients (Bøg-Hansen et al. 2001; Sulbaran et al. 2002). Existing literature on the relationship between total cholesterol and PWV documents variable results (Kim et al. 2007; Emeriau and Kalula, 2013), however, some researchers have reported a positive association (Schiffrin, 2004). This suggests that arterial stiffness stemming from atherosclerosis may be the main mechanism by which cholesterol contributes to ISH (Bouhanick et al. 2007; Gavish and Izzo, 2016). Plasma cholesterol has been shown to be independently associated with ISH, having also been recognised as an independent predictor of

the condition in diabetic patients (Ko et al. 2005). Ferrier et al. (2002) showed that cholesterol reduction was associated with a reduction in arterial stiffness amongst ISH patients and should be considered as a treatment option for the condition.

Increased dietary salt intake as a risk factor for ISH

The relationship between dietary salt intake and hypertension in any form is a very controversial topic in physiology to date (Hajjar et al. 2001; He et al. 2005; Ha, 2014; Ozkayar et al. 2016). However, the greater weight of evidence leans towards the detrimental effects of increased salt intake and impaired salt metabolism and/or excretion i.e. hypertension and ultimately, target organ damage (He et al. 2005; Ozkayar et al. 2016). Arterial stiffening has been reported as a major consequence of high salt intake, hence SBP is seemingly the most affected BP component (D'Elia and Strazzullo, 2018). It then becomes clear why salt intake has emerged as a risk factor for ISH (Stokes, 2006; Xu et al. 2008; D'Elia and Strazzullo, 2018) and many researchers advocate for salt reduction as a first line therapy for treatment of ISH (Cushman, 1998; He et al. 2005; Singh, 2012; Egan et al. 2015). Systolic Blood Pressure reductions by margins as high as 18 mm Hg accompanied by minimal DBP reduction and unchanged heart rate have been reported in low-sodium intervention studies (Niarchos et al. 1984).

A number of physiological processes have been described as mediators in the salt-related development of arterial stiffness and ISH (Stokes, 2006; Sanders, 2009). These include increased SNS activity and RAAS activation. High salt intake is also associated with impaired NO production (Stokes, 2006; D'Elia and Strazzullo, 2018) and increased production of TGF-β which is known to increase extracellular matrix protein production and VSMC proliferation while inhibiting the formation of collagen-degrading metalloproteases (Sanders, 2009). Since these processes give rise to arterial stiffness and increased SBP, it is not surprising that salt-intake induces greater increase in SBP than in DBP (Niarchos et al. 1984). Salt metabolism in itself may be influenced by other risk factors such as diabetes mellitus, obesity, metabolic syndrome and genetic differences (D'Elia and Strazzullo, 2018). In addition to increased dietary intake of salt, smoking and the consumption of alcohol are linked to ISH.

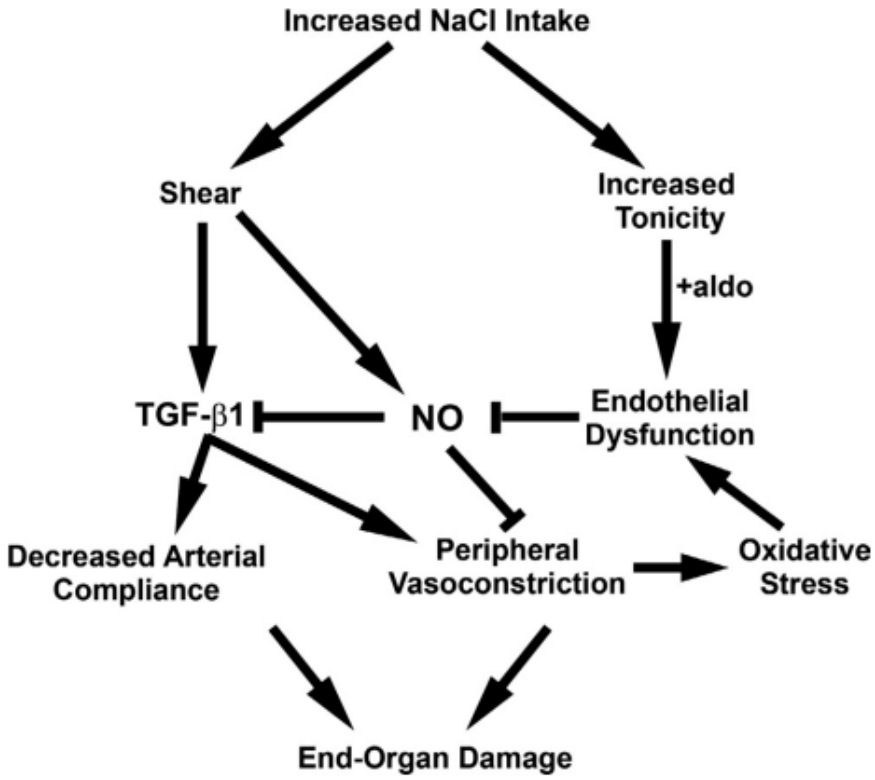

Figure 1.6 A schematic diagram of the physiological mechanisms by which increased dietary salt intake may cause vascular changes leading to ISH and associated target organ damage. Adapted from Sanders (2009).

Smoking and Alcohol consumption

Smoking increases risk of ISH (Wang et al. 2000; Xu et al. 2008; Grebla et al. 2010). A study investigating the influence of smoking and alcohol intake on cardiovascular morbidity and mortality in elderly ISH patients found that smoking was a significant predictor of stroke and death from stroke after correcting for covariates (Wang et al. 2000). Midha et al. (2010) reported that for every non-smoker with ISH, three smokers were afflicted with the condition. Indeed, their study revealed smoking as a significant independent predictor of ISH. The work of Grebla et al. (2010) on ISH in young adults also supports the relevance of smoking as a risk factor for ISH.

The mechanism of this relationship appears to be similar to that of the smoking-hypertension relationship, mediated by smoking-induced SNS activation, inflammation, endothelial dysfunction (Tanaka and Safar, 2005), atherosclerosis and arterial stiffness (Bowman et al. 2007; Virdis et al. 2010; Taha et al. 2013).

Alcohol intake has been shown to be associated with ISH (Xu et al. 2008). A study by Midha et al. (2010) found a four-fold prevalence of ISH in individuals that consume alcohol as compared to those who do not consume alcohol. Alcohol intake was also associated with non-fatal

cardiovascular outcomes including stroke among ISH patients (Wang et al. 2000). The cause of this relationship is not well understood, but some mechanisms of alcohol-induced hypertension may be applicable to the role of alcohol as a risk factor in ISH.

Some studies have attributed the pressor effect of alcohol to an increase in SNS activation (Pickering, 1997; Husain et al. 2014). This is thought to be associated with age-related changes to the sympatho-adrenal response which may alter the response to SNS triggers, resulting in an increased sympathetic outflow and subsequent increase in SBP, heart rate, vasoconstriction and oxidation reactions via the adrenals (Pickering, 1997; Husain et al. 2014). Evidence of increased sympathetic nerve activity following alcohol consumption or infusion has been acquired through direct sympathetic nerve recording (Pickering, 1997; Husain et al. 2014). Increased RAAS activity, impairment of NO synthesis and oxidative damage to the endothelium are other mechanisms that may be mediators of alcohol-induced hypertension (Husain et al. 2014). Oxidative damage of the endothelium results in increased arterial stiffness which causes an increase in systolic BP while the diastolic BP is reduced (Kawano, 2010; Husain et al. 2014). These changes result in an increased pulse pressure associated with ISH. Another aspect of lifestyle that impacts artery health is lack of adequate physical activity.

Reduced physical activity and ISH

Low physical activity is yet another risk factor for ISH (Midha et al. 2010). Regular endurance exercise as simple as moderate walking has been associated with an increase in central artery compliance (Tanaka and Safar, 2005). Research methods used in determining the amount of physical activity have their limitations. Self-reported physical activity is prone to bias and difficulties in standardisation for comparison. The measurement of basal metabolic rate (BMR), as used by Midha et al. (2010) only accounts for physical activity up to 24 hours prior to measurement. Similarly, the prolonged continuous use of electronic activity monitors which may provide more accurate data raises issues of feasibility and participant withdrawal due to annoyance.

Race and genetic factors

The role of genetic variation in disease risk is becoming more and more apparent. Several genes, such as the protein phosphatase-1, catalytic subunits, β isoform (PPP1Cβ), Yotiao (an A kinase anchor protein) and Protein kinase C-β_1 ((PKCβ_1) genes have been associated with the development of arterial stiffness (Schiffrin, 2004) which may cause ISH. While on the matter of genetic differences, certain races have been associated with greater risk of developing ISH than others. In a Chinese study, members of the Mongolian race were more likely to develop ISH than

those of the Han race (Xu et al. 2008). Research by Grebla et al. (2010) reported that people of African ancestry are more likely to develop ISH than those of Caucasian ancestry.

Socioeconomic factors

Like SDH, the incidence of ISH may be affected by socioeconomic factors such as lower educational status, lower household income and lack of health insurance (Midha et al. 2010). Unavailability or poor accessibility to adequate healthcare facilities, unemployment, large number of children, being married are additional factors that have been associated with increased incidence of ISH (Grebla et al. 2010).

1.3.3 Isolated Systolic Hypertension and Ambulatory BP monitoring

Early studies into ambulatory ISH seemed to suggest that ISH was a form of "white coat" hypertension that was not sustained during day to day activities outside a clinical setting (Silagy et al. 1990; Sega et al. 1997). Later research using improved technology for ABPM showed that while this may be true to some extent, sustained and masked forms of ISH are also prevalent, particularly in the elderly population (Franklin et al. 2012).

Over time, ABPM became more useful in investigating ISH from several angles. It has been used to investigate postprandial hypotension in elderly ISH patients (Grodzicki et al. 1998). Saladini et al. (2018) investigated the future risk of sustained hypertension in young, sporty ISH patients diagnosed by ABPM. The work of Staessen et al. (1999) compared the predictive ability of ABPM over conventional BP measurement in older ISH patients, and found that ambulatory SBP was a more superior predictor of cardiovascular risk than conventional SBP. Interestingly, they also found a positive correlation between night-time BP and cardiovascular risk.

Elevated night-time SBP has been implicated as a predictor of vascular events in a separate study (Dolan et al. 2009). Ambulatory BP measurement is also better at estimating PP and PP-related events in elderly ISH patients than conventional BP recording (Staessen et al. 2002; Mediavilla García et al. 2011). In a study, Palatini et al. (2002) found that although ambulatory heart rate had some predictive power with regards to non-cardiovascular mortality in their elderly population, it did not provide any additional prognostic information to that provided by clinical heart rate. The reproducibility of BP measurements is greater in ABPM as compared to conventional clinic measurement (Thijs et al. 1996; Emelianov et al. 1998); moreover, the former method is more strongly correlated with target organ damage and adverse outcomes than the latter (Ming et al. 1993; Staessen et al. 2002)

1.4 Target Organ Damage

Isolated systolic hypertension has been implicated in target organ damage (Unni, 2018). There is overwhelming evidence of its relation to several CVDs. The risk of LVH, myocardial infarction and indeed cardiovascular mortality is increased in patients with ISH (Wildman et al. 2003; Gupta et al. 2006; Stokes, 2006; Egan et al. 2015) more than it is for those suffering from isolated diastolic hypertension (IDH) (Kannel, 2003; Tsimploulis et al. 2017) and SDH (Manios et al. 2016). Similarly, ISH patients have a higher risk of developing coronary heart disease (Franklin, 2012; Egan et al. 2015) or suffering a stroke (Niarchos et al. 1984; Ko et al. 2005; Emeriau and Kalula, 2013). Manios et al. (2016) reported that white coat ISH is associated with carotid atherosclerosis to an extent that is comparable to SDH. This high cardiovascular risk is due to the increased SBP and PP associated with ISH, which have been shown to be stronger predictors of these outcomes than mean BP (Fagard et al. 2002; Wildman et al. 2003; Gupta et al. 2006).

Isolated Systolic Hypertension has been related to dementia, particularly in the elderly (Wildman et al. 2003). Sulbaran et al. (2002) found that the systolic component of ambulatory BP is a strong predictor of dementia. Similarly, Mediavilla García et al. (2011) showed that elevated night time SBP was a significant determinant of impaired cognitive function in their study population. In ISH, an increase in PP and PWV leads to flow–sensitive ischaemia to the brain, which gives rise to white matter lesions, declining cognitive function and possibly dementia (Franklin, 2012; Gavish and Izzo, 2016; Unni, 2018).

Of all the target organs susceptible to hypertension-related damage; the heart, vasculature and kidneys are arguably the most affected by ISH even more than they are affected by IDH or SDH (Kannel, 2003; Stokes, 2006; Egan et al. 2015). Prolonged elevated SBP and PP experienced by these organs is often the reason for their link to increased morbidity and mortality of ISH patients (Franklin, 2012). Three major conditions which often arise from such damage are LVH (Stokes, 2006; Egan et al. 2015), chronic kidney failure (Egan et al. 2015) and arterial stiffness (AlGhatrif and Lakatta, 2015).

1.4.1 Arterial Stiffness

The central role played by arterial stiffness in the pathogenesis of ISH has been established, yet it is important to consider that this relationship can be reversed. There is still a dilemma of causality between arterial stiffness and ISH (Zheng et al. 2015), however, several scholars agree that the relationship is cyclic, i.e. its effects over time are cumulative and self-propagating (AlGhatrif and Lakatta, 2015; Gavish and Izzo, 2016). By virtue of this, Arterial stiffness can well be considered

a form of ISH-related target organ damage in addition to being a cause of ISH (Wallace et al. 2005; AlGhatrif and Lakatta, 2015).

Elevated SBP has been associated with an accelerated rate of PWV increase over time, and this acceleration becomes greater with increasing age (AlGhatrif and Lakatta, 2015). Systolic non-dipping, a nocturnal form of ISH, has also been associated with an increase in arterial stiffness (Syrseloudis et al. 2010). A study by Kollias et al. (2009) supports the occurrence of diurnal changes in arterial stiffness, their subjects exhibited an increase in PWV in the evenings. Arterial stiffening occurring in ISH is more pronounced in central rather than peripheral arteries (Wallace et al. 2007).

Physiologically, there are a number of explanations for this, and their basis is that elevated SBP in ISH causes the same type of damage and effects on the arteries as those that originally caused it. Along with the elevated PP, the increased SBP leads to more shear stress and increases permeability of the endothelium which may lead to atherosclerosis (Unni, 2018), a precursor of arterial stiffness. Increased PP causes endothelial dysfunction characterised by diminished bioavailability of NO, an important vasodilator (Kannel, 2003; Wallace et al. 2007). Furthermore, shear stress also causes low grade inflammation with stimulation of cytokines whose activity facilitates arterial stiffening (Wallace et al. 2007; Sanders, 2009). The increased pulsatility speeds up elastin degradation and arterial stiffening (Kannel, 2003; Zheng et al. 2015). In essence, ISH accelerates arterial ageing. The effects of ISH are not limited to the vascular system, but extend to other vital organs such as the heart, where LVH is a major outcome (Nichols and Edwards, 2001).

1.4.2 Left Ventricular Hypertrophy (LVH) and ISH

Left Ventricular Hypertrophy is characterised by an increase in left ventricular mass (LVM) owing to morphological changes in cardiac myocytes (Lorell and Carabello, 2000) and the proliferation of non-muscle cells within the tissue (Pluim et al. 1999; Nichols and Edwards, 2001). The positive relationship of ISH, SBP and PP with LVH has been reported in several studies (Krumholz et al. 1993; Kannel, 2003). Analysis of data from the Systolic Hypertension in the Elderly Program (SHEP) revealed a higher prevalence of LVH in participants with ISH compared to age-matched normotensives (Ofili et al. 1998). In a study by Staessen et al. (2002), PP emerged as the strongest independent predictor of increased LVM. Nocturnal ISH in the form of night-time non-dipping of the systolic component has been associated with increased LVM in the elderly subjects in the early phase of ISH (Cicconetti et al. 2003).

Premature return of the reflected wave leads to pulse wave augmentation and increased pulsatility in ISH (Nichols and Edwards, 2001; Gavish and Izzo, 2016; Unni, 2018). As a result, the afterload

on the left ventricle is increased (Nichols and Edwards, 2001; Bavishi et al. 2016) and the ventricle experiences remodelling as it exerts itself to meet the demand on cardiac output (Bavishi et al. 2016). The increased force of the afterload on the cardiac myocytes triggers biochemical events which signal changes in gene transcription, culminating in increased production of sarcomeres within the myocytes (Lorell and Carabello, 2000).

Different geometric patterns of ventricle remodelling have been reported in association with ISH. A study by Krumholz et al. (1993) found that increased wall thickness (concentric LVH) and increased chamber size (eccentric LVH) (Ganau et al. 1992) occurred in both male and female patients with uncontrolled ISH. However, concentric LVH was the most common type of hypertrophy observed in, and almost entirely limited to, women. This suggests that gender differences and possibly hormonal influences have a role to play in determining the type of hypertrophy (Krumholz et al. 1993). A later study by Cicconetti et al. (2003) reported eccentric remodelling as the most common type of LVH observed in their cohort.

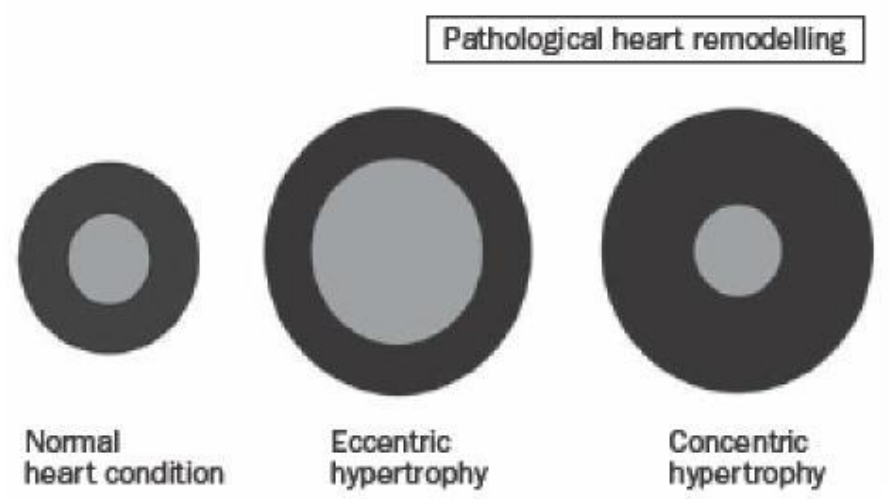

Figure 1.7 A simplified diagram showing cross-sectional views of a ventricle under normal physiological circumstances, following eccentric remodelling or following concentric remodelling, respectively. Adapted from Mihl et al. (2008).

Left ventricular hypertrophy results in reduced diastolic filling and poor diastolic relaxation. The effects of this, along with the effects of arterial stiffness, are transmitted downstream to microvasculature of end organs such as the kidneys, causing damage there (Bavishi et al. 2016).

1.4.3 Renal Dysfunction and ISH

High pulsatility owing to elevated SBP and PP is transmitted to the microcirculation of the kidney where it may cause glomerulosclerosis facilitating leakage of proteins through the glomerulus (Cirillo et al. 2000) and accelerating the progression of renal dysfunction (Kannel, 2003; Unni, 2018).

Several researchers have documented evidence of renal damage associated with ISH (Schiffrin, 2004). The work of Steppan et al. (2011) showed an association between increased PP and renal dysfunction. Microalbuminuria is the earliest indicator of renal damage. Elevated SBP is associated with microalbuminuria, particularly in patients with type 2 diabetes (Mitchell et al. 1997). Even in a population of non-diabetic, middle-aged adults, both pulse pressure and ISH were found to be independent predictors of microalbuminuria (Cirillo et al. 2000). Some studies have shown that there is a diurnal trend in this relationship.

Waking SBP and ISH24 were correlated with poor renal function in an investigation by Ming et al. (1993), while Mitchell et al. (1997), found a strong positive relationship between nocturnal SBP and microalbuminuria. This relationship is affected by non-dipping of the SBP component (Mitchell et al. 1997). Mehta and Drawz (2011) had similar findings in their study, their results showed that elevated nocturnal SBP was associated with a decline in Glomerular Filtration Rate (GFR) and increased risk of developing microalbuminuria.

1.5 Justification

While many may still view ISH as a “natural” and harmless disease of the elderly, the condition presents several challenges. It is evident that ISH is a major contributor to cardiovascular, renal and cerebrovascular deterioration, morbidity and mortality, yet a significant number of untreated ISH patients are asymptomatic (Soltero and Kujubu, 2003; Gupta and Kasliwal, 2004; Ono et al. 2006). Moreover, certain forms of the condition do not present themselves in clinical settings. The danger of this is that prolonged or masked elevated SBP and PP may cause significant organ damage before symptoms emerge and a diagnosis is made.

Current routine hypertension diagnosis in SA makes use of clinical BP measurements, which may not detect ambulatory forms of ISH. Despite evidence of an association between ISH and target organ damage in various populations (Dart et al. 1993; Voyaki et al. 2001; Wallace et al. 2007), there are no studies investigating target organ damage in ISH within a South African population – to the best of our knowledge.

Ambulatory BP Monitoring is better correlated to target organ damage than conventional BP measurement (Mancia, 1990) and there is increasing advocacy for routine clinical use of this technology in hypertension diagnosis and management. Unfortunately, the use of ABPM in SA is still mostly limited to research since the healthcare system has insufficient resources to enable routine use of the technology in day to day patient care (Morar et al. 1998; Majane et al. 2007; Woodiwiss et al. 2009; Bawa-Allah et al. 2018). Even with the existing research there is a gap in understanding with regards to prevalence of ISH and its ambulatory subtypes and corresponding target organ damage in SA.

1.6 Aims and objectives

To determine the prevalence of clinical and ambulatory subtypes of ISH and investigate their association with target organ changes in a South African population.

1.6.1 Objectives

1. To determine the prevalence of Conventional ISH (ISHC), 24-hour ISH (ISH24), Night-time ISH (ISHN) and Daytime ISH (ISHD) in a South African population.
2. To investigate the association between ISH subtypes and arterial stiffness
3. To investigate the association between ISH subtypes and left ventricular hypertrophy
4. To investigate the association between ISH subtypes and renal pathology

CHAPTER 2: METHODS

2.1 Study group

Ethical clearance (Certificate number: M180201) for this study was sought and obtained from the Human Research Committee (HREC) (Medical) of the University of the Witwatersrand. This investigation was carried out in accordance with the Declaration of Helsinki governing the principles of research in human participants.

The study was based in Johannesburg, a metropolitan city in the Gauteng province of SA, with a population of nearly six million (Abrahams and Everatt, 2019). Individuals in and around the city were invited at random by word of mouth to participate in a cross-sectional cohort study. The lower age limit for participation was 18 years and there was no upper age limit. A total of 796 participants were recruited for the study. Of these, only 549 had complete ambulatory and urine collection data, and these were considered as the sample population. The cohort was divided into six groups based on ambulatory and conventional BP measurements, namely ISHC, ISH24, ISHN, ISHD, the hypertensive control group and the normotensive control group. Written consent was sought from the participants following a comprehensive explanation of the aims and requirements of the research study. Thereafter, a medical history, demographic data, as well as information on lifestyle and the use of medications were obtained from these individuals through a standardised, self-reporting questionnaire.

2.2 Anthropometric measurements

Anthropometric measurements were taken as described by Marfell-Jones et al. (2012), while the participants were barefoot and wearing lightweight indoor robes. Weight was measured using a floor scale (Health o meter® Professional, USA) and was recorded to the nearest 0.1 kg. For this measurement, the participant was asked to stand upright on the middle of the scale with their weight distributed evenly between both feet (Marfell-Jones et al. 2012).

Height was measured to the nearest 0.1 m using a wall-mounted stadiometer (Seca®, Germany), with the participant standing upright and his/her head positioned in the Frankfort plane (such that an imaginary horizontal line can be drawn between the orbitale of the eye and the tragion of the ear on the same side as shown in Figure 2.1. In this position, the headpiece of the stadiometer was placed horizontally on the vertex (highest point) of the participant's head and the corresponding reading recorded (Marfell-Jones et al. 2012). Where necessary, the observer stood on a stable stool when taking the height measurement in order to minimise parallax error. Body Mass Index was calculated as weight in kilograms divided by the square of the height in metres. Participants with a BMI $\geq$ 25kg/m2 and < 30 kg/m2 were considered overweight, and those with a BMI $\geq$ 30 kg/m2 were considered obese.

Waist circumference was measured at the end of normal expiration using an inextensible measuring tape aligned parallel to the floor at the narrowest point between the costal margin and the upper iliac crest. Where such a point could not be clearly identified, the measurement was taken at the mid-point between these anatomical markers (Marfell-Jones et al. 2012).

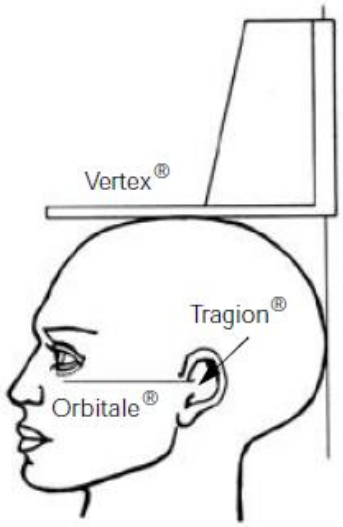

Figure 2.1 Positioning of the head in the Frankfort plane (Marfell-Jones *et al.* 2012).

2.3 Conventional BP Measurement

Participants were allowed to sit comfortably and relax for five minutes before BP measurements were taken. An automatic BP monitor (Omron®, Kyoto, Japan) was used to measure brachial artery BP while the participant was seated with their back supported and legs uncrossed. Standard adult cuffs with an inflatable bladder were used on participants with a mid-upper arm circumference (MUAC) less than 31 cm and larger cuffs for those with a MUAC exceeding 31 cm (Maseko et al. 2006). The cuff was positioned above the cubital fossa of the upper arm, with the bladder above the brachial artery. The measurement was repeated five times at one minute intervals, and the average of the five readings was used as the conventional BP value for analysis. Participants were classified as normotensive, hypertensive or ISHC according to the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) criteria shown in Table 2.1.

Table 2.1 The ESC and ESH criteria for the classification of participants according to office (*conventional*) BP measurement. Adapted from Williams et al. (2018).

Category	**SBP (mm Hg)**		**DBP (mm Hg)**
Normotensive	< 140	and	< 90
Hypertensive	≥ 140	and/or	≥ 90
Isolated Systolic Hypertensive	≥ 140	and	< 90

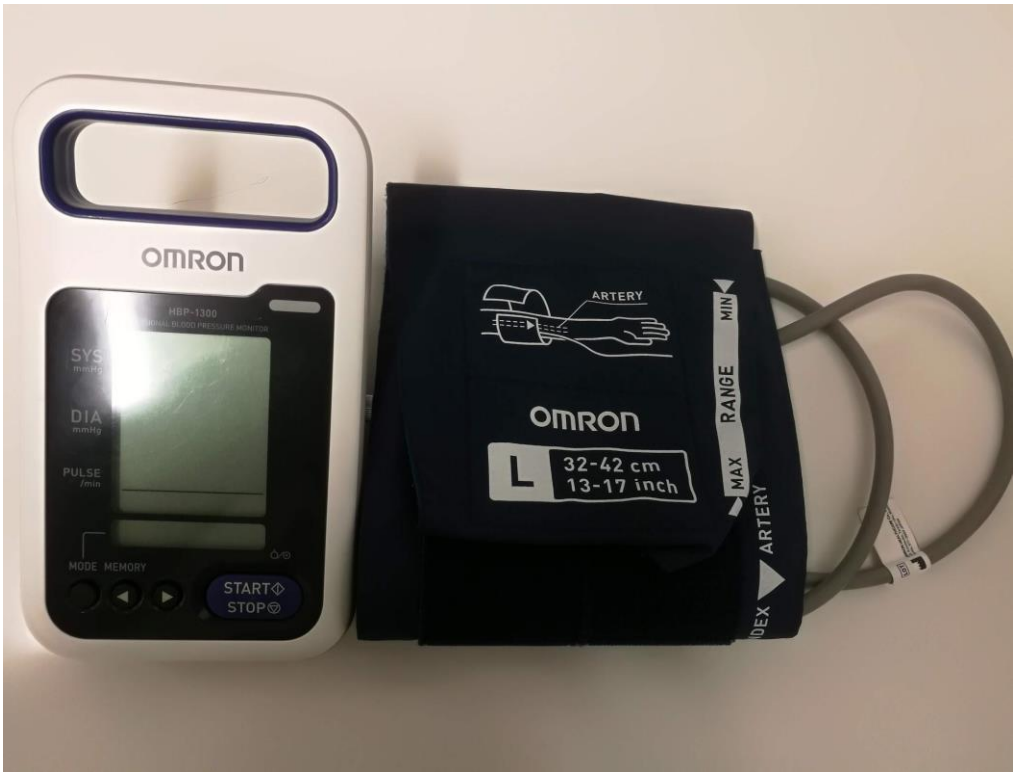

Figure 2.2 The Omron® HBP-1300 automated BP monitor used for conventional BP measurement.

2.4 Pulse Wave Assessment

A high fidelity tonometer interfaced with a SphygmoCor computer software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia - version 9.0) was used to perform pulse wave assessments of PWV, a measure of arterial stiffness. The applanation tonometry method used is considered a "gold standard" for pulse wave analysis (Zheng et al. 2015; Gavish and Izzo, 2016) and has been previously described by Shiburi et al. (2006) and Stoner et al. (2012).

Figure 2.3 Tonometer used in the determination of Pulse Wave Velocity

Participants were allowed to rest in the supine position with their legs uncrossed for 15 minutes prior to assessment. Using an inextensible measuring tape, distances (in mm) between the relative sampling sites (femoral and carotid) and the suprasternal notch were measured. The difference between the two distances was considered as the pulse wave distance. Applanation tonometry was then used to record sequential wave forms at the participant's dominant carotid and femoral regions. A three lead chest ECG was performed concurrently with the waveform sampling in order to assess the time differences in the generation of the waveforms. The pulse transit time was defined as the average of 10 consecutive beats. The PWV was automatically calculated as the difference between the aforementioned distances (i.e. the pulse wave distance) divided by the pulse transit time (Shiburi et al. 2006).

Figure 2.4 Computer screen output from a typical PWV measurement with the Sphygmocor® software. Pulse waveforms are traced in white and the corresponding ECG output is traced in yellow. The PWV is given in m/s (arrow).

2.5 Echocardiography

Echocardiography was used to determine the left ventricular mass index (LVMI) for the participants. All echocardiographic measurements were carried out by an experienced technician using an echocardiogram - the Acuson SC2000 Diagnostic Ultrasound System (Siemens Medical Solutions USA, Inc.) linked to a 10-MHz linear array transducer and electrocardiogram (ECG). The measurements were performed according to a method described by Bamaiyi et al. (2018) and Foppa et al. (2005). Participants were asked to lie in the left lateral decubitus position. M-mode images were taken at a frame rate of >110 frames per second.

M-mode echocardiography of the short axis of the heart was obtained as close to the tip of the mitral valve as possible using the parasternal long axis view (2D). The resulting images were used to measure left ventricular dimensions only when the endocardial surfaces of the septal and posterior walls, as well as both the left and right septal surfaces, could be clearly seen. Wall dimensions, namely the Left Ventricular Internal Diameter at end Diastole (LVIDD), the Posterior Wall Thickness in Diastole (PWTD) and the Interventricular Septal Thickness in Diastole (IVSTD) were obtained from M-mode images and analysed according to the American Society of Echocardiography (ASE).

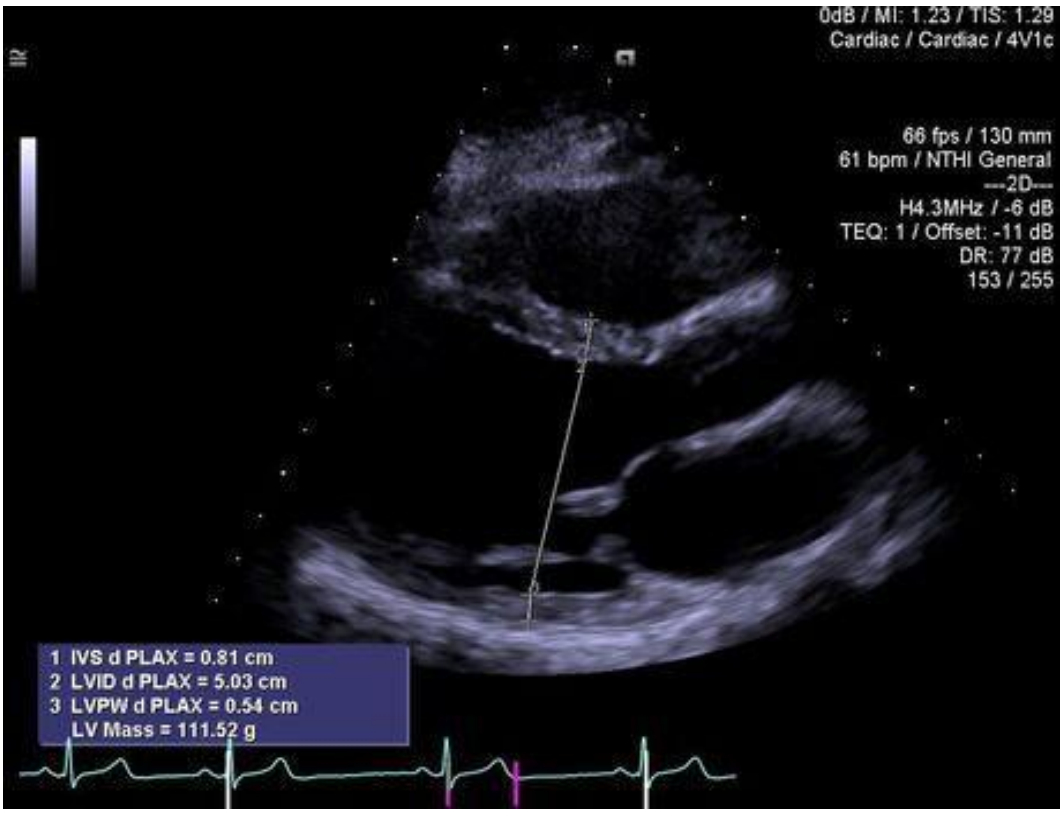

Figure 2.5 M-Mode ultrasound of the left ventricle showing measurement of dimensions for the calculation of LVM. *Courtesy of Siemens Healthineers.*

The LVM was obtained from the above-mentioned parameters using the following ASE formula:

$$\mathbf{LVM = 0.8\ (1.04\ ([LVIDD + PWTD + IVSTD]^3 - [LVIDD]^3)) + 0.6g}$$

Left Ventricular Mass Values were indexed for body size and categorised for LVH as shown below.

Table 2.2 Categories of LVH defined by LVMI. Adapted from Douglas and Bloomfield (2017).

Category	Left Ventricular Mass Index (g/m^2)	
	Male	**Female**
Mildly Abnormal	103-116	89-100
Moderately Abnormal	117-130	101-112
Severely Abnormal	>130	>112

2.6 Urinalysis

Each participant was asked to provide a spot urine sample. These samples were aliquoted into smaller labelled sample tubes and transported to the CLS where they were analysed to determine microalbumin and creatinine concentrations. Microalbumin to Creatinine ratios were then computed and used as an indication of renal pathology (Yuyun et al. 2005). Microalbuminuria was defined as a spot urine M:C ratio of 2.5 – 25 mg/mmol for women, and 3.5 – 25 mg/mmol for men (Yuyun et al. 2005).

2.7 Twenty-four-hour Ambulatory BP Monitoring

Participants were each fitted with an ambulatory BP monitor (Spacelabs, model 90207) on the non-dominant arm which measured their BP at regular intervals over a 24-hour period in their normal environment. The monitors were calibrated monthly against an automatic BP monitor (Omron, Kyoto, Japan). Standard adult cuffs (24 – 32 cm) with an inflatable bladder were used on participants with a MUAC <31 cm and large adult cuffs (32 - 42 cm) for those with a MUAC exceeding 31 cm. Monitors were set to measure BP every 15 minutes from 06:00 – 22:00 and every 30 minutes thereafter until 06:00 the next morning. On average, participant bedtime was 19:00 and wake up time was 05:00. Based on this, the 09:00–19:00 and 23:00–05:00 intervals were used to define daytime and night time respectively (Thijs et al. 1992, Fagard et al. 1996 and Fagard et al. 1997) in order to account for rapid fluctuations of BP that typically occur in the mornings and evenings. Participants were advised to continue with their normal day to day activities throughout the measurement period, but to keep the measurement arm steady during readings. Isolated Systolic Hypertension was expressed as conventional, 24-hour, day time as well as night-time ISH where only the systolic BP exceeded the diagnostic threshold in each case; in accordance with the ESH guidelines. Participants were asked to keep a record of bedtimes and wake-up times (to determine awake and sleep periods); periods of strenuous activity; medications and other

substances which might interfere with BP. Only data from participants with > 20 hours of measurement and at least 10 and 5 readings for calculation of daytime and night-time means respectively, were used in analysis.

2.8 Statistical Analysis

All data were analysed using STATA (StataCorp LLC Texas USA) data analysis and statistical software version 13.0. Data are expressed as mean ± standard deviation (SD) for continuous variables. Categorical variables are expressed as absolute or relative frequencies or as percentages. Age, gender, BMI, hypertension, diabetes smoking and alcohol consumption were corrected for. A P-value <0.05 was considered as statistically significant. The sample size was determined using sample calculator with confidence intervals at 95%.

A ROC curve was generated for each ISH subgroup by plotting True positive rate (sensitivity) against false positive rate (1-specificity) for each subgroup in relation to elevated PWV, LVMI and M:C. The area under the ROC curve was then calculated as an indication of the predictive ability of the respective ISH subtypes.

CHAPTER 3: RESULTS

Table 3.1 shows the demographic, general and clinical characteristics of the population under study. Of the 549 participants, 41 (7.5%) had ISHC. This figure is similar to those obtained for the ambulatory sub-types of ISH, namely ISH24, ISHN and ISHD which had 39 (7.1%), 42 (7.7%) and 41 (7.5%) participants respectively. Systolic-diastolic hypertension was observed in 161 (29%) of the participants. The mean age of the population was 45.3±18.5 years and the ISHC group was significantly older (65.3±13.5 years) than both normotensives (39.7±17.6 years) and hypertensives (52.1±15.5 years). Compared to ISHC, there were slight reductions in average age within the other ISH subtypes, with ISH24 at 57.8±20.1 years, ISHN at 55.4±24.6 years and ISHD at 53.7±20.9 years. We observed that all the ISH subgroups had greater proportions of female participants than the normotensive or hypertensive groups. Anthropometry revealed significantly higher waist circumference in the ISHC group than in the normotensives, this was also true for all the other ISH subgroups albeit of no statistical significance. In addition to this, the overall population was overweight with a BMI of 29.1±7.8 kg/m^2. Both ISHC and hypertensives were obese (BMI of 31.4±7.5 kg/m^2 and 30.9±7.5 kg/m^2 respectively), the former group having a significantly higher BMI than the normotensives (BMI = 28.0±7.7 kg/m^2). All other subgroups of ISH were also obese according to BMI. The average Conventional SBP (SBPC) of the ISHC group (153.1±11.7 mm Hg) was significantly higher than that of the normotensives (129.7±21.4 mm Hg). Overall, the SBPC values for all ISH sub-types were higher than the clinical upper limit of 140 mm Hg, satisfying the first condition in the clinical definition of ISH. Conventional ISH had an average Conventional DBP (DBPC) of 83.5±4.8 mm Hg, significantly higher than that of normotensives (77.6±7.2 mm Hg) and significantly lower than that of hypertensives (98.6±8.4 mm Hg). Similarly, ISH24, ISHN and ISHD all had DBPCs below those of hypertensives but above those of normotensives. For all ISH sub-types, the DBPCs fell below 90 mm Hg, satisfying the second condition in the clinical definition of ISH. All sub-types of ISH had higher PP values than both normotensives and hypertensive groups, significantly so for those participants with ISHC (PP = 69.7±12.3 mm Hg).

Table 3.1 Demographic and clinical characteristics of participants according to Blood Pressure status.

	Total sample population	NT	ISHC	ISH24	ISHN	ISHD	HT
Numbers (%)	549	347 (63.2)	41 (7.5)	39 (7.1)	42 (7.7)	41 (7.5)	161 (29.3)
Age (years)	45.3±18.5	39.7±17.6	65.3±13.5*#	57.8±20.1	55.4±24.6	53.7±20.9	52.1±15.5
Female gender (%)	36.6	34.0	51.2	51.3	47.6	56.1	38.5
Waist C (cm)	90.04±16.01	87.02±16.05	98.11±14.27*	90.04±60.01	96.86±18.11	95.87±16.23	94.40±14.67
BMI (kg/m^2)	29.1±7.8	28.0±7.7	31.4±7.5*	31.2±8.1	30.9±9.3	31.4±8.9	30.9±7.5
Smokers (%)	15.1	14.4	19.5	15.4	14.3	21.9	15.5
Alcohol usage (%)	23.3	19.6	24.4	20.5	33	26.8	31.1
SBPC (mm Hg)	129.7±21.4	117.6±11.8	153.1±11.7*	151.9±21.7	142.7±23.8	147.7±22.4	149.6±20.3
DBPC (mm Hg)	84.1±12.0	77.6±7.2	83.5±4.8*#	88.7±11.9	85.6±10.5	86.7±12.0	98.6±8.4
PP (mm Hg)	45.5±14.9	40.1±12.0	69.7±12.3*#	63.2±16.2	57.1±17.2	61.0±18.0	51.1±17.3

BMI, Body Mass Index; NT, Normotensive; ISHC, Conventional Isolated Systolic Hypertension; ISH24, 24 Hour Isolated Systolic Hypertension; ISHN, Night-time Isolated Systolic Hypertension; ISHD, Daytime Isolated Systolic Hypertension; HT, Hypertensive; PP, Pulse Pressure; DBPC, Conventional Diastolic Blood Pressure; SBPC, Conventional Systolic Blood Pressure; Waist C, Waist Circumference. Data is presented as mean ± SD or percentage. * depicts significant difference between ISHC and NT, # depicts significant differences between ISHC and HT. $P < 0.05$ for all significant differences.

The ROC curve analysis of the relationships between the sub-types of ISH and target organ changes is shown in Tables 3.2, 3.3 and 3.4. All subtypes of ISH were significantly associated with increased PWV, LVMI and M:C ratio in this population. Conventional ISH strongly predicts arterial stiffness and LVH, with area under the curve (AUC) values of 0.88±0.03 (CI: 0.83 to 0.93) and 0.86±0.03 (CI: 0.88 to 0.92), respectively. Moreover, conventional ISH is an excellent predictor of renal pathology based on the large AUC for the subtype (0.91±0.04, CI: 0.87 to 0.95). Twenty-four hour ISH and ISHN both moderately predict arterial stiffness and LVH with AUC values ranging between 0.71 and 0.78; both are good predictors of renal dysfunction (AUC values of 0.83 and 0.82 respectively). Daytime ISH was shown to be a strong predictor of all three organ changes under study (AUC values all exceeding 0.8). The pattern of association and the significance was maintained after adjusting for age.

Table 3.2 ROC Curve Analysis of the relationship between ISH subtypes and Pulse Wave Velocity

	Pulse Wave Velocity	
	AUC	CI
ISHC	0.88±0.03	0.83 to 0.93
ISH24	0.77±0.04	0.68 to 0.86
ISHN	0.78±0.04	0.70 to 0.85
ISHD	0.83±0.05	0.74 to 0.92

AUC, area under the curve; CI, confidence intervals; ISHC, conventional isolated systolic hypertension; ISH24, 24-hour Isolated systolic hypertension; ISHN, Night-time isolated systolic hypertension; ISHD, Daytime isolated systolic hypertension $P < 0.05$ for all associations. Age, gender, BMI, hypertension, diabetes smoking and alcohol consumption were corrected for.

Table 3.3 ROC Curve Analysis of the relationship between ISH subtypes and LVMI

	Left Ventricular Mass Index	
	AUC	CI
ISHC	0.86±0.03	0.88 to 0.92
ISH24	0.76±0.03	0.67 to 0.86
ISHN	0.71±0.05	0.62 to 0.80
ISHD	0.80±0.06	0.68 to 0.91

AUC, area under the curve; CI, confidence intervals; ISHC, conventional isolated systolic hypertension; ISH24, 24-hour Isolated systolic hypertension; ISHN, Night-time isolated systolic hypertension; ISHD, Daytime isolated systolic hypertension $P < 0.05$ for all associations. Age, gender, BMI, hypertension, diabetes smoking and alcohol consumption were corrected for.

Table 3.4 ROC Curve Analysis of the relationship between ISH subtypes and M:C ratio

	Microalbumin:Creatinine Ratio	
	AUC	CI
ISHC	0.91±0.04	0.87 to 0.95
ISH24	0.83±0.05	0.72 to 0.91
ISHN	0.82±0.04	0.75 to 0.90
ISHD	0.81±0.05	0.72 to 0.90

AUC, area under the curve; CI, confidence intervals; ISHC, conventional isolated systolic hypertension; ISH24, 24-hour Isolated systolic hypertension; ISHN, Night-time isolated systolic hypertension; ISHD, Daytime isolated systolic hypertension $P < 0.05$ for all associations. Age, gender, BMI, hypertension, diabetes smoking and alcohol consumption were corrected for.

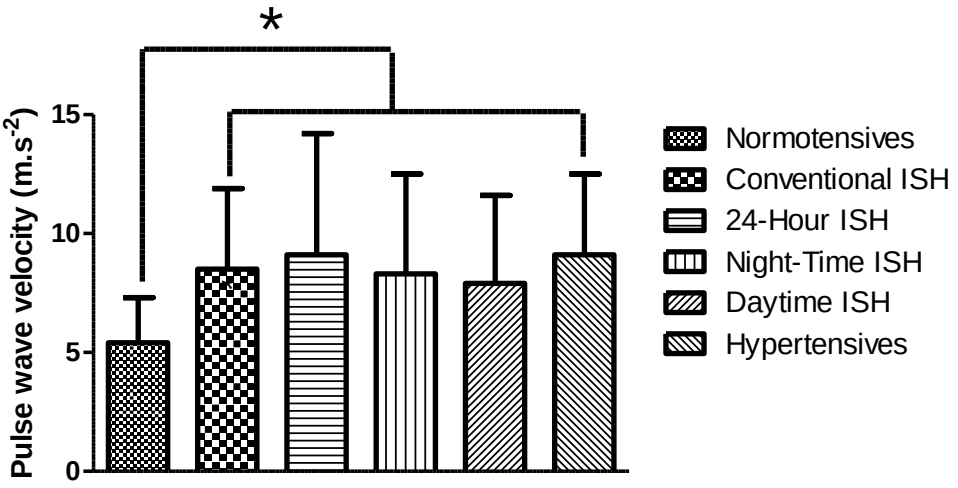

Figure 3.1 Comparison of PWV of ISH subgroups, the hypertensives and the normotensives.

Figure 3.1 Shows data of PWV expressed as adjusted means ± SD. The differences between the means was calculated using the General Linear Model and adjustments were made for the following covariates; age, gender, BMI, alcohol intake and cigarette smoking. There was no significant difference in the PWV of the different ISH subtypes and none of the ISH subtypes was significantly different from the hypertensives. However, the PWV of all the ISH subtypes and hypertensives was significantly higher than that of the normotensives. * = p value < 0.05.

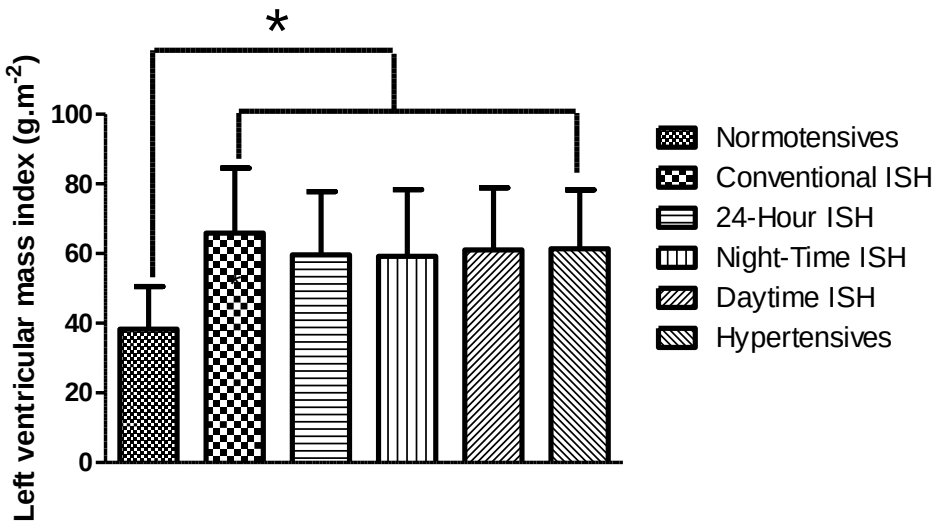

Figure 3.2 Comparison of the LVMI of the ISH subtypes, the normotensives and the hypertensives.

Figure 3.2 Shows data of LVMI expressed as adjusted means ± SD. The differences between the means was calculated using the General Linear Model and adjustments were made for age, gender, BMI, alcohol intake, cigarette smoking and presence of diabetes. There was no significant difference in the LVMI of the different ISH subtypes and none of the ISH subtypes was significantly different from the hypertensives. However, the LVMI of all the ISH subtypes and hypertensives was significantly higher than that of the normotensives. * = p value < 0.05.

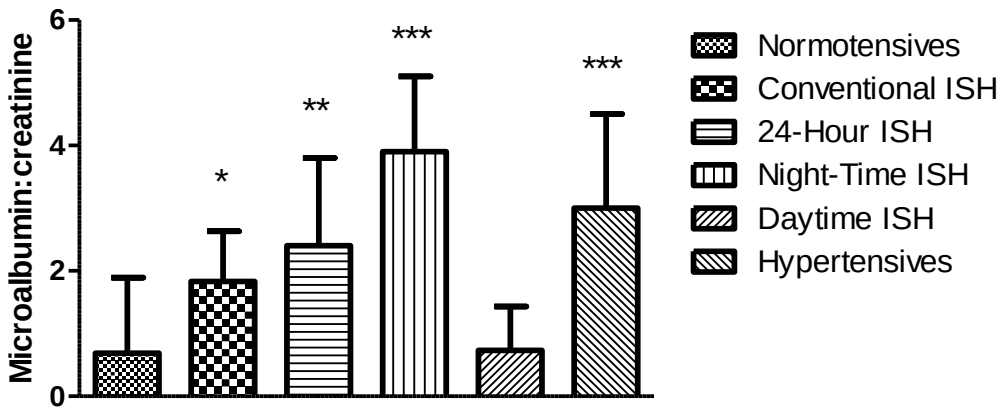

Figure 3.3 Comparison of the microalbumin-to-creatinine ration of the different ISH subtypes, normotensives and hypertensives.

Figure 3.3 Shows data of microalbumin-to-creatinine ratio (MC) expressed as adjusted means ± SD. The differences between the means was calculated using the General Linear Model and adjustments were made for age, gender, BMI, alcohol intake, cigarette smoking and presence of diabetes. The data shows that the MC of conventional ISH was significantly higher than that of the normotensives, the MC of 24-Hour ISH was significantly higher than that of the normotensives and ISHC, the MC of the night-time ISH and hypertensives were significantly higher than the normotensives and all ISH subtypes, and the MC of the daytime ISH was not significantly different from the normotensives.

$P < 0.05$ was considered statistically significant.

*$p < 0.05$ vs normotensive and daytime ISH

**$p<0.01$ vs normotensives and daytime ISH

***$p<0.0001$ vs normotensives and daytime ISH

CHAPTER 4: DISCUSSION

4.1 Introduction

In the present study, we determined the general characteristics of ISH and went on to divide it into four subtypes namely ISHC, ISH24, ISHN and ISHD. We proceeded to investigate the associations between each of these subtypes and PWV, LVMI as well as M:C ratio; representing preclinical artery, cardiac and kidney pathologies respectively. We further investigated the extent to which each of the ISH subtypes predicted the target organ changes mentioned. Our main findings suggest that while all subtypes of ISH are significantly associated with increased PWV and LVMI in measures comparable to general hypertension, ISHN is even more strongly associated with an elevated M:C ratio than hypertension.

A number of studies have investigated ISH, however, to the best of our knowledge there are no studies to date that have investigated the subtypes of ISH based on 24-hour ABPM and how these impact on target organs; particularly in a South African population. There is limited documentation of such studies in other populations, yet these still differ considerably from the present research (Ming et al. 1993; Franklin et al. 2012). Franklin et al. (2012) carried out analysis of ambulatory ISH data from populations in Europe, Asia and South America (Fan et al. 2010) in relation to cardiovascular events, rather than cardiovascular damage in itself, which often precedes the former. Ming et al. (1993) used ambulatory techniques to investigate renal function in ISH, however, their defining values for ISHC were ≥160 mm Hg for SBP and ≤95 mm Hg for DBP unlike the current values as defined by the ESC/ESH (SBP ≥ 140 mm Hg and DBP ≤ 90 mm Hg) which were used in this study. Earlier studies by other researchers who studied ISH by ambulatory measurement also used similar clinic BP reference values to those employed by Ming et al. (1993) and did not investigate target organ damage in this context (Silagy et al. 1990; Cox et al. 1991; Thijs et al. 1992), moreover ambulatory techniques have evolved since then (Nobre and Mion Junior, 2016).

Other studies have only focused on the relationships between ISHC and target organ damage (Cirillo et al. 2000; Voyaki et al. 2001; Young et al. 2002; Verhave et al. 2005; Wallace et al. 2007), and did not factor in ambulatory subtypes of the condition. Cirillo et al. (2000) added PP as another variable in their investigation of the association of ISH with microalbuminuria. In addition to this, their cohort was made up of senior-aged participants (ages 45-64), similar to that of Verhave et al. (2005) which had individuals over the age of 40. In another study, Voyaki et al. (2001) also focused on subjects older than 60 years in their study of renal function among ISH patients, as did Young et al. (2002); whose participants were all above the age of 65. Wallace et al. (2007) and Antza et al. (2015) measured arterial stiffness in ISH patients diagnosed by conventional BP measurements. Wallace et al. (2007) also measured endothelial dysfunction in

their population, an outcome which was not part of this study. While the present study investigated conventional and ambulatory ISH in relation to arterial stiffness within a general adult population, Safar et al. (2006) only investigated arterial stiffness in ISHC of the elderly.

Of all these studies, none involved comparisons of the ISH subtypes with those of HT in order to fully understand the relative magnitude of target organ damage; we have not found any studies investigating all three target organs that we studied in this research. Furthermore, none were carried out in a South African population or similar.

4.2 Demographic and clinical characteristics

The results of the present study show that 7.5% of the cohort had ISHC and the same percentage had ISHD. Night-time ISH was found in 7.7% of the population, while 7.1% of the participants had ISH24. The percentage of participants with ISHC in our study is consistent with the work of Gupta et al. (2006) who found a similar (7.78%) prevalence of the condition following their study in a North Indian town. Huang et al. (2004) also found a similar prevalence of ISH (7.6%) in a Chinese study.

Ntuli et al. (2015) investigated a population ethnically similar to our study cohort and their study revealed a much higher prevalence of ISHC (21%). While their much larger population sample size (n = 1281) (Ntuli et al. 2015) could be a factor in this vast difference, the most likely explanation for this is the socioeconomic difference between their sample population and ours. The study by Ntuli et al. (2015) was conducted in rural Limpopo (Dikgale), where unemployment and poverty is high and there is limited access to adequate healthcare (Alberts et al. 2005; Kanjala et al. 2010; Ntuli et al. 2015).

All these socioeconomic factors have been implicated in contributing to the high prevalence of hypertension in developing countries (Seedat, 1999; Seedat et al. 2018; Gomez-Olive et al. 2017), and it would not be surprising that ISHC would follow the trend. The mean age of participants in the present study (45.3 years) was similar to that of subjects in the study by Ntuli et al. (2015) (44.2 years). Gupta et al. (2006) did not report a mean age for their population which was limited to the working age-group under 58 years, while Huang et al. (2004) carried out their investigation on participants in the 35-74 age group. The bulk of studies on ISHC have been focused on specific age groups, usually the young (under 35 years of age) or the old (over 50 years old) (Grodzicki et al. 1998; Chaudhry et al. 2004; Lurbe and Redon, 2016; Eeftinck Schattenkerk et al. 2018) unlike our population which included all consenting persons over the age of 18.

While several studies in recent years have shown that the condition is not at all restricted to the older population (Jangid et al. 2015; Grebla et al. 2010; Lurbe and Redon, 2016), the relatively high average age associated with ISH (especially the conventional subtype) in our study is consistent with the findings of a number of researchers and with the widely accepted notion that ISH is predominant and naturally occurring in the elderly population (Stokes, 2006; Chobanian, 2007; Singh, 2012; Emeriau and Kalula, 2013; Egan et al. 2015). A study by Huang et al. (2004) showed an increase in ISHC with age and moreover a tendency toward stage 2 ISHC with increasing age. Martins et al. (2001) observed an increase in PP and SBP from the age of 45 upward in their analysis of data from the NHANES.

Indeed, the most commonly described pathophysiological mechanism for ISH involves changes occurring to the large arteries owing to ageing (Kocemba et al. 1998). With age progression, elastin in the media decreases, leading to a fragmented media (Kocemba et al. 1998; Emeriau and Kalula, 2013) which is susceptible to calcium and lipid accumulation. Along with this media calcification occurs the accumulation of smooth muscle cells within the intima, collagen cross linking occurs and all this leads to the thickening and fibrosis of the arterial wall (Kocemba et al. 1998; O'Rourke and Nichols, 2005; Emeriau and Kalula, 2013). These changes culminate in arterial stiffness, an increased wall-to-lumen ratio and a reduced cross-sectional area of the lumen of the greater arteries (Kocemba et al. 1998; Bavishi et al. 2016; Tan and Thakur, 2019).

Due to poor compliance, the large arteries fail to expand and subsequently recoil effectively in systole and diastole of the cardiac cycle, respectively. There is a resultant increase in aortic PP and PWV. Consequently, the reflected wave which would normally return during diastole, returns during late systole and augments systolic pressure; SBP increases while the DBP decreases (O'Rourke and Nichols, 2005; Tan and Thakur, 2019). In line with this, we observed higher values of average SBPC in the ISH groups than in the normotensive group, and these were comparable to that of hypertensive participants. This was coupled with relatively low DBPC for all ISH sub-types when compared to the hypertensive group.

By definition, PP is the difference between SBP and DBP, thus its normal value is approximately 40 mm Hg (Homan and Cichowski, 2019). Pulse Pressure values exceeding 60 mm Hg are associated with target organ damage which may or may not be asymptomatic (Williams et al. 2018). In the present study, PP was markedly increased in participants with ISHC, with an average of 69.7 mm Hg. Wallace et al. (2007) also observed similar elevated SBP and PP (67 mm Hg) in their ISHC group. This finding was as expected based on the definition and underlying physiology of the condition (Hall, 1999; Stokes, 2006: Emeriau and Kalula, 2013) since PP is the difference

between systolic and diastolic BPs; and an increase in the former and/or decrease in the latter would raise PP.

In general, all the ISH groups in this study were obese. Average BMI values ranging from 30.9 to 31.4 were recorded for these groups, all of which exceed the obesity threshold of 30 for BMI (Janssen et al. 2004). The role of obesity as a risk factor for ISH is well documented (Seedat, 1999; He et al. 2005; Grebla et al. 2010; Park et al. 2015; Tan and Thakur, 2019). Erhun et al. (2005) observed the highest prevalence of ISH among the extremely obese group in their study. The ISH subgroup in the research by Grebla et al. (2010) was overweight, and these authors suggested that obesity may be an important determinant of ISH in young adults. A study by (Nemes et al. 2008) showed that obesity is associated with increased arterial stiffness and that this is true even for young obese adults, whose arterial stiffness they found comparable to that of elderly non-obese individuals. Although all of these studies investigated obesity in ISH by conventional BP measurement, their findings may extend to all the ambulatory subtypes of the condition as well. Our results show that in all participants with any forms of ISH, arterial stiffness as measured by PWV was increased in comparison to normotensives.

Several mechanisms have been described that may explain the role of obesity in ISH. Hyperinsulinaemia and insulin resistance, which are both strongly associated with obesity (Brunzell and Hokanson, 1999), may mediate aortic stiffness through glycation of vascular wall proteins and subsequent increased cross-linking (Nemes et al. 2008). Insulin has also been associated with smooth muscle hypertrophy and increased endothelial dysfunction of large arteries likely resulting from oxidant stress, causing increased susceptibility to atherosclerosis (Arcaro et al. 2002; Nemes et al. 2008).

One other significant mechanism that has been implicated in the relationship between obesity and ISH is the activity of leptin (Nemes et al. 2008). Hyperleptinaemia is associated with endothelial dysfunction in obese individuals (Leung and Kwan, 2008), which is an underlying cause of arterial stiffness (Emeriau and Kalula, 2013). Schutte et al. (2005) reported a strong negative correlation between leptin and arterial compliance coupled with a strong positive relationship between leptin and SBP as well as leptin and PP in obese/overweight hypertensive African women. The high-leptin state of overweight/obese women in our study population, which was predominantly African, has been previously described (Maseko et al. 2018) and may play an important role in ISH.

While a number of studies have investigated the relationship between ISHC and target organ damage, very few (to the best of our knowledge) have explored the extent of target organ changes

that may arise from other subtypes of ISH which may well be missed by conventional diagnosis. For this reason, we used 24-hour ABPM to study ISH24, ISHN and ISHD in addition to ISHC; and their relationship to changes in arterial stiffness, left ventricle morphology and renal function.

4.3 Isolated Systolic Hypertension and Arterial Stiffness

We measured PWV by applanation tonometry, a minimally invasive method which is widely recognised as the 'gold standard' in the determination of arterial stiffness (Wallace et al. 2007; Stoner et al. 2012. As far as we know there are no studies which have investigated PWV in ambulatory subtypes of ISH, however, the general association of ISHC with arterial and aortic stiffness has been reported (O'Rourke et al. 2005; Wallace et al. 2007; Antza et al. 2015). Antza et al. (2015) in their study of arterial stiffness in ISHC observed an increase in arterial stiffness in patients with the condition, and suggested that ISHC may have a role to play in large artery arteriosclerosis.

This observation can be explained in terms of the haemodynamic changes associated with ISH. Since ISH is characterised by elevated systolic and pulse pressures, these parameters exert increased mechanical stress on the arteries over time, leading to elastin fragmentation and subsequent calcification, collagen deposition and smooth muscle cell hypertrophy (O'Rourke, 1999; Steppan et al. 2011; AlGhatrif and Lakatta, 2015). In addition to this, endothelial dysfunction associated with the shear stress also triggers the inhibition of NO production and the release of proinflammatory cytokines and growth factors such as TGF-β (Wallace et al. 2007; Sanders, 2009; AlGhatrif and Lakatta, 2015; Gavish and Izzo, 2016). These augment arterial damage by promoting smooth muscle cell hypertrophy and the increased production of extracellular matrix proteins; moreover, TGF-β inhibits the activity of those metalloproteases (Sanders, 2009) which would otherwise assist by breaking down the collagen build-up, such as MMP-9 (Sanders, 2009; Ecobici and Stoicescu, 2017). All these factors culminate in arterial stiffening of mainly the central arteries (AlGhatrif and Lakatta, 2015; Zheng et al. 2015). In essence, ISH speeds up the rate of arterial ageing and increases arterial stiffness, thereby leading to its own exacerbation in a vicious cycle (Wallace et al. 2007). Several scholars agree that the causal relationship between arterial stiffness and ISH is bidirectional (AlGhatrif and Lakatta, 2015; Gavish and Izzo, 2016; Ecobici and Stoicescu, 2017).

With this in mind, it is not surprising that we observed significantly elevated PWV in all subtypes of ISH when compared to normotensives. Of interest, participants with ISH24 had considerably higher PWV than other subgroups of the condition to an extent that is comparable to the PWV increase observed in the hypertensive (SDH) group. This suggests that the arterial damage caused

by ISH24 may equal arterial stiffness arising from hypertension in this population. Unlike the other ambulatory subtypes, 24-hour ambulatory values factor in BPs from both daytime and night-time in a routine environment, implying that ISH of this nature is sustained throughout the day and night. Despite the scarcity of ambulatory ISH literature to support this claim we deduce that since both ISHD and ISHN are associated with increased arterial stiffness, the cumulative effect of prolonged elevated SBP and PP on the arterial walls would be greatest in the ISH24 group especially since arterial stiffness is generally believed to increase at night (Syrseloudis et al. 2011).

Receiver Operating Characteristic (ROC) Curve analysis is used in clinical prediction to assess how well a test can discriminate between absence or presence of a condition. The analysis yields a curve of sensitivity versus 1-specificity, where the Area Under the Curve (AUC) is a measure of predictive power of the test to a maximum of 1 (Chung et al. 2014). The closer the AUC is to 1, the greater the ability of the test in question to discriminate whether the presence of a condition is associated with a change in a given parameter (Hajian-Tilaki, 2013; Chung et al. 2014). We used ROC curve analysis to determine how well the different subgroups of ISH would predict an increased PWV in this population. In this respect, ISHC and ISHD emerged as the best discriminators with AUC of 0.88 and 0.83 respectively, followed closely by ISHN (AUC = 0.78) and ISH24 (AUC = 0.77). This implying that 88% of the time, a positive ISHC result predicts an increase in PWV, and so on. To the best of our knowledge, no researchers have used ROC curve analysis in assessing predictive power of conventional or ambulatory subtypes of ISH over increased PWV or arterial stiffness, however, Chung et al. (2014) used ROC analysis to show that brachial-ankle PWV was a good predictor of resistant hypertension (AUC = 0.687) – a result which supports the cyclic nature of the PWV-Hypertension relationship.

4.4 Isolated Systolic Hypertension and Left Ventricular Hypertrophy

Left ventricular mass index has been used as an indication of LVH, a major independent predictor of cardiovascular mortality and morbidity (Savage et al. 1987; Levy et al. 1990; Ofili et al. 1998). We used echocardiography, a well-accepted, efficient and non-invasive tool for the estimation of LVMI (Levy et al. 1990; Ofili et al. 1998). In this study, there were no clear differences in LVMI values obtained for the ambulatory ISH sub-types (ISHD, ISHN and ISH24), suggesting that there are no major differences in the development of LVH among these three subtypes; although the extent of cardiac damage they caused is similar to that associated with hypertension. There are no studies thus far which have investigated left ventricle pathologies caused by ambulatory ISH.

Of note, ISHC participants exhibited elevated LVMI over and above hypertensives. The SBP component which is amplified in these individuals appears to be more influential in cardiac

morphology than DBP (Lip et al. 1999; Davy and Gentile, 2007). The premature return of the reflected wave in ISH is probably the most significant cause of LVM increase (Karpetas et al. 2015) in this condition. The augmentation of SBP by said reflected wave places a strain on the left ventricle to pump harder in order to compensate for the poor arterial compliance and recoil. As the left ventricle adapts to the increased workload (Nichols and Edwards, 2001; Stokes, 2006), concentric hypertrophy of surrounding tissue occurs, resulting in thickening and increase in mass of the left ventricle wall (Steppan et al. 2011; Douglas et al. 2017). Poor coronary perfusion owing to low DBP (Stokes, 2006) may also exacerbate the effects of increased LVM in ISH as increased oxygen demand of the myocardium becomes difficult to meet (Nichols and Edwards, 2001).

Our results bear some similarity to those obtained by Pearson et al. (1991), who reported that ISHC patients exhibited increased LVMI arising from thickened septal and posterior walls of the left ventricle. Lip et al. (1999) had related outcomes, they found that LVMI and other echographic parameters were similar between ISHC and full hypertension (SDH) groups. Some scholars carried out a randomised double blind trial on the effects of drug therapy on LVMI in ISHC, and found that after three years, the placebo group had increased LVM (Ofili et al. 1998), supporting the view that ISH leads to LVH.

The LVMI values associated with ISH and hypertension in this study are pre-clinical yet significantly elevated in comparison to the normotensive control group. Some research has shown that increased LVMI even within the “normal” range is clinically relevant i.e. it is associated with significant cardiovascular risk (Foppa et al. 2005). Since ISH increases the risk of LVH at least twofold (Egan et al. 2015), even the moderately increased LVM in this population may progress to LVH over time as the elevated SBP persists.

Most ISH studies in the past have been carried out on elderly participants, however, our results show that even after correcting for age the associations and predictions remain unchanged, suggesting that ISH is just as detrimental to the elderly as it is to younger age groups with respect to left ventricle structure (Psaty et al. 1992) and consequently, cardiovascular function. Levy et al. (1990) also found that the relationship between increased LVMI and cardiovascular morbidity and mortality was applicable to the middle-aged study group as much as the elderly study group, although their focus was not particularly on ISH. Obesity, which was identified in this ISH population, is thought to increase the risk of LVM and LVH by its tendency to attract other risk factors such as metabolic syndrome and diabetes mellitus (Foppa et al. 2005; Rayner and Becker, 2006; Douglas et al. 2017). Genetics also plays an important and complex role in the increase of LVM and development of LVH (Douglas et al. 2017). This was outside the scope of our investigation, however, the population under study - being predominantly black, may be at higher

risk of LVH (Douglas et al. 2017). Skelton et al. (2003) reported a very high prevalence of increased LVM in an African-American population.

In terms of predictive ability, again ISHC and ISHD were the strongest predictors of increased LVMI according to ROC analysis (AUC = 0.86 and 0.80 respectively), followed by ISH24 (AUC = 0.76) and ISHN (AUC = 0.71). There is no comparable research on ISH predictive power on increased LVMI, however some scholars recently found that central SBP was a stronger predictor of LVH (AUC = 0.6090) than 24 hour SBP (AUC = 0.5840) (Litwin et al. 2019). This work of Litwin et al. (2019) differs from our study in that it was carried out in a population of hypertensive children (mean age 15 years) whereas our population was exclusively comprised of adults of varied hypertensive states. In addition to this, we did not define ISH by central BPs. Despite this, the AUC values we obtained for all ISH subtypes are significantly larger than those obtained by Litwin et al. (2019) for SBP, this suggests that the predictive power of the SBP component (which is amplified in ISH) increases with age.

4.5 Isolated Systolic Hypertension and Renal Pathology

In order to investigate renal function in ISH, we measured 24-hour urinary microalbumin and creatinine concentrations and calculated the M:C ratio which was used to define presence or absence of microalbuminuria – a primary indicator of glomerular damage (Cirillio et al. 2000). As with the other target organ damage indicators, all sub-types of ISH emerged as strong predictors of impaired renal function in this population. This result is supported by Young et al. (2002) who showed that SBP, a defining component of ISH, is the strongest predictor of a decline in kidney function.

Furthermore, our results show that ISHC, ISH24 and ISHN had significantly increased M:C ratio. Of these subtypes, ISHN had the largest M:C ratio, even exceeding that for hypertensives. In fact, the average M:C ratio associated with ISHN in this study is indicative of microalbuminuria. This suggests that Night-time ISH has detrimental effects on the renal system above and beyond those of hypertension, i.e. night-time ISH predicts renal dysfunction more strongly than hypertension. Some researchers have found an association between albuminuria and night-time SBP (Mehta and Drawz 2011; Oliveras et al. 2011; Ruiz- Hurtado et al. 2016). Ruiz- Hurtado et al. (2016) in their study found that of all BP variables under investigation, only Night-time SBP was significantly associated with high and very high albuminuria.

While the exact mechanism responsible for this is not yet fully understood, several researchers have hypothesised possible physiological links between night-time SBP and microalbuminuria which may be applicable in our case (Cirillio et al. 2000; Lurbe et al. 2002; Verhave et al. 2005;

de la Sierra et al. 2014; Laurent and Boutouyrie, 2015). There is a possibility that ISHN in this population could be a form of nocturnal hypertension or non-dipping although we did not carry out analysis in support of this theory. The elevated night-time SBP associated with these phenomena would be responsible for microalbuminuria indicative of renal damage (Ruiz- Hurtado et al. 2016).

Complex disturbances in the sympathetic nervous system are thought to mediate nocturnal dipping and rising (de la Sierra et al. 2014; Ivy and Bailey, 2014). These may involve the circadian rhythm of kidney function, activity of the RAAS system and pressure natriuresis (Ivy and Bailey, 2014) which is of particular importance in salt sensitive populations (Kimura, 2001; Fukuda et al. 2004). In such populations, increased salt intake is associated with diminished natriuresis and reduced daytime sodium excretion. In order to compensate for this, night time pressure natriuresis and therefore night time blood pressure is increased (Kimura et al. 2010). The high salt intake, non-dipping and tendency towards pressure natriuresis in the present population have been previously reported (Maseko et al. 2006; Nyundu, 2016). These factors present a possible explanation for the observed normalcy of microalbumin excretion in the ISHD subtype versus marked microalbuminuria in the ISHN subtype. Whatever the cause, it appears that the renal damage caused by elevated SBP and PP in these scenarios may be cumulative and persistent, hence it could be detected in spot urinalysis.

Elevated night-time SBP and associated PP may cause structural changes to renal vasculature (Verhave et al. 2005), which may in turn lead to an impairment of the myogenic tone responsible for autoregulation of renal blood flow (Laurent and Boutouyrie, 2015). Without this protective effect, the high systemic pressures can be translated to intrarenal haemodynamic changes which can cause injury to the glomerulus evidenced by microalbuminuria (Cirillio et al. 2000; Lurbe et al. 2002; Laurent and Boutouyrie, 2015).

Our findings raise major concerns given that Night-time ISH can only be detected by ambulatory BP monitoring which remains a non-routine tool in hypertension diagnosis in most parts of the world including SA, this means this condition could easily be underdiagnosed yet it appears to contribute significantly to kidney damage. Night-time BPs generally carry the highest cardiovascular risk and prognosis than any other ABPM subtype (Ruiz- Hurtado et al. 2016), and the same appears to be true of ISH and renal pathology risk in this study.

All ISH subtypes in the present study were demonstrated to be strong predictors of microalbuminuria as determined by M:C ratio. Conventional ISH in particular showed very strong ability to predict an abnormal M:C ratio (AUC = 0.91), while the other subtypes exhibited similar

predictive strength to each other (ISH24 AUC = 0.83, ISHN AUC = 0.82 and ISHD AUC = 0.81). The present study appears to be the first to employ ROC Curve analysis to investigate clinical prediction of microalbuminuria by conventional and ambulatory ISH subtypes. The ROC has previously shown that resistant hypertension strongly predicts microalbuminuria with 0.776 as the AUC (da Rocha Nogueira et al. 2007). Based on our AUC values, ISH in all its subtypes may be an even stronger predictor of microalbuminuria than resistant hypertension in this population.

CHAPTER 5: CONCLUSION

5.1 Conclusion

Our overall findings are that ISHC, ISHN, ISHD and ISH24 are all present and equally prevalent in this population. The elderly (over the age of 50) are seemingly the most affected by all forms of ISH, however this finding must be interpreted with caution as this study sample did not have equal representation of all adult ages, and we did not stratify data according to age. Increased PP accompanies ISH in this population, as does obesity.

All ISH subtypes emerged as good predictors of elevated PWV, LVMI and M:C ratio, which are markers of arterial stiffness, LVH and renal dysfunction, respectively. Out of all the subtypes, ISHC had the strongest predictive power for all aforementioned markers. Another finding of this study is that all forms of ISH are associated with elevated PWV and LVMI of a magnitude comparable to the hypertensives of this population. Moreover, while ISHC, ISH24 and ISHN are all associated with M:C ratios that are significantly higher than those of normotensives, ISHN in particular is strongly associated with clinical microalbuminuria exceeding that observed in the hypertensive control group.

Evidently, the detrimental effects of ISH subtypes on target organs are at the very least similar to those caused by hypertension (SDH). Our findings suggest that the effects of Night-time ISH in particular may be worse; it may lead to declining kidney function in this population. We suspect that obesity may play a significant role in exacerbating end organ damage in ISH. The further investigation, diagnosis and treatment of ISH deserves more attention in this population in order to minimise overall cardiovascular and renal risk, considering that elevated SBP and PP are both major risk factors in this regard.

5.2 Limitations

Our population sample size was relatively small and thus not truly representative of the South African population. Based on the average age of the population we deduce that the younger age groups may have been underrepresented hence this study cannot draw any conclusions on the effects of ISH on the young. The analysis of a single spot urine sample for microalbuminuria instead of a 24-hour sample limited the conclusions that can be drawn regarding the circadian patterns of ISH on the kidney.

5.3 Recommendations & future perspective

We recommend the routine use of 24-hour ABPM in the diagnosis of ISH for all individuals, especially for the elderly aged 50 and older who are at a higher risk of the condition. This would minimise the possible underdiagnoses of nocturnal forms of ISH. The measurement of microalbuminuria may be considered as the first indication of target organ damage in this population, and is particularly useful in monitoring damage due to night-time ISH. We also propose that future investigations of ISH make use of ambulatory Pulse Wave Analysis tools to define ISH by central pressures rather than peripheral measurements. In future, longitudinal studies would be beneficial in establishing the degree of causality between arterial stiffness and ISH. We encourage further research into circadian interrelationships of ISH, RAAS hormones, salt metabolism and renal function in this population. Furthermore, there is a need to investigate interventions that may eliminate or at the very least reduce the impact of ISH on target organs in South African populations.

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APPENDICES

Appendix 1: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Mrs Bongubuhle Mlambo et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180201

NAME: (Principal Investigator)	Mrs Bongubuhle Mlambo et al
DEPARTMENT:	School of Physiology Medical School
PROJECT TITLE:	Impact of Dietary Salt Intake on Isolated Systolic Hypertension in an African Population
DATE CONSIDERED:	23/02/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Joseph M. Maseko
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/06/2018

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **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 26/06/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Informed Consent form

D#: _____

South African Hypertension and Diet Study (SAHDS)

Written Consent Form

Full Name of participant : _____

Participant code (D#) : _____

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 : _____

SIGNATURE : _____

DATE : _____

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 3: Standardised questionnaire

SOWETO SALT STUDY

STANDARD QUESTIONNAIRE

PARTICIPANT IDENTIFICATION

Surname: .....

Name(s): .....

Identification number: .....

Sex: .....

Date of birth: .....

House number: .....

Apartment number or postal box number: .....

Street: .....

Town: .....

Postal code (zipcode): .....

Telephone number: .....

HOW TO COMPLETE THE QUESTIONNAIRE

The participants may complete the questionnaire themselves. However, they may also request the help of the team of fieldworkers. After completion, the questionnaire should be inserted in the envelope which should then be closed and sealed. All information provided will be treated confidentially and will be used anonymously in the statistical analysis.

For further information or help, please do not hesitate to contact the team of fieldworkers.

[Store this section separate from remainder of questionnaire.]

Question 1: Specify your current marital state. (*Tick appropriate box*)

- Unmarried ☐

- Unmarried, but living together with partner ☐

- Married and living together with "legal" wife/husband ☐

- Married, but living together with a partner, other than "legal" husband or wife ☐

- Divorced and not living together with a new partner ☐

- Divorced, but living together with a new partner ☐

- Widow or widower, not living together with a new partner ☐

- Widow or widower, but living together with a new partner ☐

- Other (please specify)

……..

Question 2: Are you still attending school?

yes ☐ no ☐

- If no: proceed to question 3.

- If yes: please, provide the name and address of your school or the institution where you take courses.

  .....

- Is taking courses a secondary activity for you? For instance, are you combining further education with an occupational or professional activity?

  yes ☐ no ☐

Question 3: Do you currently exert any professional or occupational activity?

yes ☐ no ☐

- If no: proceed to question 4.

- If yes:

- What is your present occupation?

  Please, provide a detailed description of your current job.

  .....

  .....

  .....

  .....

- When did you start your current professional activity?

  Since: .....

- Where do you exert your current professional activity?

  Please, provide the name(s) of the street(s) and town(s). Please also specify the factory, firm or institution where you are working.

  .....

  .....

  .....

- If you would have to grade your physical activity at work, which of the following would best describe the intensity of your physical work? (*Tick Appropriate box*)

  * Sitting ☐
  * Driving a car ☐
  * Pushing a wheelbarrow ☐
  * Loading a large lorry without any mechanical help ☐

Question 4: If you presently don't have any professional activity, please specify the reason.

- Have you ever been employed before yes ☐ no ☐

- Long-lasting health problems yes ☐ no ☐

- Permanently incapacitated yes ☐ no ☐
- Are you retired? yes ☐ no ☐
- Are you currently unemployed? yes ☐ no ☐
- Are you working at home, doing the housekeeping? yes ☐ no ☐
- Are you currently serving in the army? yes ☐ no ☐

Question 5: If you currently do not exert any professional activity, what was the last job you had and for how many years?

- Last occupation

  Please, provide a detailed description of your activities at work.

  .....

- For how long did you practice your <u>last</u> job?

  Years? .....

- Where did you exert your last professional activity?

  Please, provide the name(s) of the street(s) and town(s). Please, also specify the factory, firm or institution where you were working.

  .....

  .....

Question 6: Do you practice your current occupation (see question 3) or did you practice your last job (see question 5) as an independent self-supporting worker or professional?

Please, tick the correct answer.

yes ☐ no ☐

- If no: proceed to question 7.

- If yes: if you do work as an independent self-supporting worker or professional, how many persons are working (or were working) in your company?

  ..... persons

- Please, specify the sort of business you are (or were) in. (*Tick appropriate box*)

  * Trade ☐
  * Industry ☐
  * Services ☐
  * Handicraft ☐
  * Agriculture ☐
  * Other ☐ *(please specify)*……

- If you are (or were) an independent farmer, please, specify in km² the surface of your farming lands.

  ..... km²

- If you are (or were) an independent farmer, which sort of farming activity are you (or were) you involved in? (mixed agriculture, cattle breeding, florist, vegetable-growing, fruit-growing, poultry etc.)

  .....

Question 7: Do you practice your present job or occupation (see question 3) or did you practice your former job or occupation (see question 7) as an employee, receiving a salary?

yes ☐ no ☐

- If no: proceed to question 8.

- If yes:

- Did you (or do you currently) work -

  * For a private person or company? yes ☐ no ☐
  * For a municipal, provincial, public or interurban service? yes ☐ no ☐

∗ Did you (or do you currently) work -

◊ On a full-time basis? yes ☐ no ☐

◊ On a part-time basis? yes ☐ no ☐

∗ Did you have (or do you currently have) -

◊ a blue collar job? (manual labour) yes ☐ no ☐

◊ a white collar job? (office/administration) yes ☐ no ☐

◊ a pink collar job? (customer interaction) yes ☐ no ☐

∗ If you worked (or currently work) as an employee in a private company, which sort of business was it conducting?

◊ Trade yes ☐ no ☐

◊ Industry yes ☐ no ☐

◊ Services yes ☐ no ☐

◊ Handicraft yes ☐ no ☐

◊ Agriculture yes ☐ no ☐

∗ If you were (or currently are) employed by a private person or company, how many persons worked (or work) for the same person or company ?

..... persons

- If you were (or are) working as an employee, how many persons were (or are) directly or indirectly subordinate to you?

..... persons

- Please, specify the official name of your present job or occupation.

.....

.....

Question 8: Which is the highest level of education which you successfully completed and for which you hold a certificate/diploma/degree?

.....

Question 9: Please, specify whether some of your relatives currently suffer (or have suffered) from high blood pressure (hypertension).

Please, tick ***one*** 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 ☐
- Your grandfather (mother's side) yes ☐ no ☐ unknown ☐
- Your grandmother (mother's side) yes ☐ no ☐ unknown ☐
- 1 or more of your own children yes ☐ no ☐ unknown ☐
- 1 or more of your own grandchildren yes ☐ no ☐ unknown ☐
- 1 or more brothers or sisters of your father yes ☐ no ☐ unknown ☐
- 1 or more brothers or sisters of your mother yes ☐ no ☐ unknown ☐

- 1 or more of your own brothers or sisters yes ☐ no ☐ unknown ☐

Question 10: Did you ever, or do you now suffer from a disease affecting your heart or blood vessels?

Please, tick the correct answer.

yes ☐ no ☐

- If no: proceed to question 11.
- If yes: please, specify the diseases affecting your heart or blood vessels. Please, provide for each disease the date (month/year) on which the first symptoms occurred, if applicable, and the date (month/year) on which you were cured.

Disease/Condition	**starting date (month/year)**	**date of cure (month/year)**

Question 11: Did you ever, or do you now suffer from a disease affecting your kidneys or urinary tract?

Please, tick the correct answer.

yes ☐ no ☐

- If no: proceed to question 12.
- if yes: please, specify the diseases of your kidney or urinary tract. Please, provide for each diease the date (month/year) on which the first symptoms occurred, if applicable, and the date (month/year) on which you were cured.

Disease/Condition	**starting date (month/year)**	**date of cure (month/year)**

Question 12: Did you ever or do you currently suffer from kidney stones or stones in your urinary tract ?

yes ☐ no ☐

- If no: proceed to question 13.
- If yes:
  - Did/do you have repeated pain attacks? yes ☐ no ☐
  - Did/do you ever pass a stone with urine? yes ☐ no ☐
  - Did/do you ever undergo surgical/endoscopic/ultrasound treatment to remove the stones? yes ☐ no ☐
  - Do you still have kidney/urinary tract stones? yes ☐ no ☐

Question 13: Do you have diabetes?

yes ☐ no ☐

- If no: proceed to question 14.

- If yes:

  - do you follow a diet and avoid eating sweet foodstuffs ? yes ☐ no ☐
  - are you taking pills, which lower blood sugar ? yes ☐ no ☐
  - are you being treated with insulin injections ? yes ☐ no ☐

Question 14: Were you ever told by a doctor or health professional that you have an elevated blood pressure?

yes ☐ no ☐

- If no: proceed to question 15.

- If yes:

  - When was the diagnosis of high blood pressure established for the first time? ..... (month/year)

  - Did you ever receive a treatment for an elevated blood pressure (hypertension)?

yes ☐ no ☐

Question 15: Are you currently in good health?

yes ☐ no ☐

- If yes: proceed to question 16.

- If no: please, specify the diseases you currently have or previously had. Please, do not repeat the diseases you already mentioned in reply to questions 10-14. Please, also specify the date

(month/year) on which the first symptoms occurred, if applicable, and the date (month/year) on which you were cured.

Disease/Condition	**starting date (month/year)**	**date of cure (month/year)**

Question 16: Did you ever take or are you taking now drugs to lower your blood pressure?

yes ☐ no ☐

- If no: proceed to question 17.

- If yes:

  - Are you <u>currently</u> taking blood pressure lowering drugs? yes ☐ no ☐
  - Please, specify the name of the drug(s) and the number of tablets that you are taking each day.

Name of drug	**Tablets/Times/Day**

Question 17: Did you ever take or are you taking now drugs which eliminate salt and make you pass urine more frequently or in larger amounts?

yes ☐ no ☐

- If no: proceed to question 18.

- If yes:

  - Are you <u>currently</u> taking these drugs? yes ☐ no ☐
  - Please, specify the name of the drug(s) and the number of tablets that you are taking each day.

Name of drug	Tablets/Times/Day

Question 18: Did you ever take pain-killers on a regular basis, for instance against headaches, tooth pain, painful periods, etc... ?

yes ☐ no ☐

- If no: proceed to question 20.

- If yes:

  - During how many years ? ..... years
  - Please, specify the name of the tablets which you are currently taking (or were taking) in the past on a regular basis.
  - Please, specify also the amount of tablets or powders per week.

Name of pain-killer	Amount/Week

Question 19: Did you take medicines during the past 2 weeks?

yes ☐ no ☐

- If no: proceed to question 20.
- If yes: please, specify the drugs that you have been taken as well as the daily dose of each medicine.

Name of drug	Tablets/Times/Day

Question 20: Do you currently smoke?

yes ☐ no ☐

- If no: proceed to question 21.

- If yes:

  - How much do you smoke?
    - ◊ Cigarettes with filter per day .....
    - ◊ Cigarettes without filter per day .....
    - ◊ Grams of tobacco per day for hand-rolled cigarettes .....
    - ◊ Grams of tobacco per week for pipe .....
    - ◊ Small cigars per week .....
    - ◊ Cigars per week .....
  - At what age did you start smoking regularly? .....
  - Do you inhale the smoke? yes ☐ no ☐

Question 21: Did you smoke in the past?

yes ☐ no ☐

- If no: proceed to question 22.

- If yes:

  - Did you smoke at least one cigarette per day during one year? yes ☐ no ☐
  - At what age did you smoke for the first time? .....
  - How much did you smoke in the past?
    - ◊ Cigarettes with filter per day .....
    - ◊ Cigarettes without filter per day .....
    - ◊ Grams of tobacco per day for hand-rolled cigarettes .....
    - ◊ Grams of tobacco per week for pipe .....
    - ◊ Small cigars per week .....
    - ◊ Cigars per week .....
  - Please, specify the reason(s) why you stopped smoking.

.....

.....

Question 22: Do you consume alcoholic beverages ?

yes ☐ no ☐

- If no: proceed to question 23.

- If yes:

  - How much alcohol do you currently consume?
    - ◊ Number of glasses of beer per day .....
    - ◊ Number of bottles of wine per week .....
    - ◊ Number of bottles of aperitives or fortified wine per week .....
    - ◊ Number of bottles of liquor per week .....
  - At what age did you start drinking alcohol regularly? .....

Question 23: Did you regularly consume alcoholic beverages in the past?

yes ☐ no ☐

- If no: proceed to question 24.

- If yes:

  - At what age did you stop consuming alcohol regularly? .....
  - How much alcohol did you consume in the past?
    - ◊ Number of glasses of beer per day .....
    - ◊ Number of bottles of wine per week .....
    - ◊ Number of bottles of aperitives or fortified wine per week .....
    - ◊ Number of bottles of liquor per week .....
  - Please, specify the reason(s) why you stopped consuming alcoholic beverages on a regular basis.

    .....

    .....

Question 24: Do you drink coffee or caffeine-containing beverages (cola/energy drinks) on a regular base ?

yes ☐ no ☐

- If no: proceed to question 25.

- If yes:

  - Specify the number of cups of coffee and the number of glasses of cola/energy drinks you consume on average per day.

    ◊ Cups of coffee .....

    ◊ Glasses of cola .....

    ◊ Other (*specify*) .....

  - Do you use decaffeinated coffee ?

    yes ☐ no ☐

    ◊ If yes, specify number of cups of decaffeinated coffee you drink on average per day: .....

Question 25: Please grade on a scale from 1 to 10 the physical efforts in your daily life, including your job, sports, and activities at leisure time.

..... points (please, provide a value ranging from 1 to 10)

A few examples:

- A civil servant who is doing only sitting work, but who walks to his work place and in his leisure time engages in gardening could rate his physical efforts at 4-5 points.
- An older person who spends the whole day resting in his chair, could rate his physical effort at 1 point.
- A manual worker who each day has to load a truck with sand, just using a spade, cycles 20 km to and from his work place and in his leisure time has an additional job as a construction worker, could rate his physical efforts at 9-10 points.

Question 26: Do you practice any sports activities on a regular basis?

yes ☐ no ☐

- If no: proceed to question 27.

- If yes:

    - Which sport(s) do you practice on a regular basis?

      .....

    - At what age did you start practicing sports regularly?

      At age: .....

    - At present, how many hours per week do you spend practicing sport?

      Average number of hours per week: .....

Question 27: Do you walk regularly?

yes ☐ no ☐

- If no: proceed to question 28.

- If yes :

    - How many hours do you walk on average per day?

      Number of hours: .....

    - How many kilometers do you walk per day?

      Number of kilometers per day: .....

Question 28: Please grade on a scale from 1 to 10 the psychological tensions and stress that you are currently facing in your daily life.

..... points (please, provide a value from 1 to 10)

A few examples:

- A student who is well taking care of by his parents, maintains friendly relations with his fellow students and does not have to fear exams, because he is very bright, might rate his stress level at 1-2 points.
- A housewife who has to care for many children, who hardly gets her work done and who in addition has marital problems with her husband, could rate her stress level at 9-10 points.
- An employee with a quiet job, without problems in his family, but who is not completely sure that he will keep his job, and therefore feels insecure, could rate his stress level at 5-6 points.

QUESTIONS 29-33 (FOR WOMEN ONLY)

Question 29: Did you already have your periods?

yes ☐ no ☐

Question 30: Did you ever take "the pill"?

Please, note that "the pill" can be prescribed, not only for birth control, but also against irregular or abundant periods and/or after natural or surgically induced menopause.

yes ☐ no ☐

- If no: proceed to with question 31.

- If yes:

  - Are you <u>currently</u> taking "the pill"? yes ☐ no ☐
  - Please, specify the name of "the pill" you are taking now

    .....

  - Overall, how long did you take "the pill"?

    ..... years; if less than 1 year: ..... months

Question 31: Are you pregnant at present?

yes ☐ no ☐

Question 32: Have you been pregnant before?

yes ☐ no ☐

- If no: proceed to question 33.

- If yes:

  - How many times have you been pregnant ? .....
  - How many miscarriages did you have ? .....
  - How many children were born alive ? .....

- How many children were stillborn ? .....

Question 33: (<u>Only for women older than 30 years</u>)

Do you still have your periods ?

yes ☐ no ☐

- If yes: proceed to question 34.

- If no:

  - Please, specify since when (month/year) your periods became irregular.
    Since: .....

  - Please, specify since when (month/year) your periods completely disappeared.
    Since: .....

    ◊ Did your periods disappear spontaneously? (if your periods disappeared spontaneously and if only later you underwent surgery involving your reproductive organs, please, reply "yes" to this question)
    Please, tick the correct answer.

    yes ☐ no ☐

  - Please, specify the operations that you have undergone and also provide the date of surgery (month/year) and the reason for the surgical intervention.

Removal of -	**Date (month/year)**	**Reason**
only womb		
only right ovary		
only left ovary		
both ovaries		

right ovary together with womb		
left ovary together with womb		
both ovaries and womb		

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

yes ☐ no ☐

- If yes: Please, specify the name of "the pill" and the number of months that you are taking this "pill".

  Name of "the pill": .....

  Number of months: .....

Please provide your signature to attest your approval or disapproval.

Signature: .....

Date: .....

Appendix 4: 24 hour ABPM Diary

South African Hypertension and Diet Study (SAHDS)

24-Hour Ambulatory Blood Pressure Monitoring Diary card

Name and Surname:_____

Participant code | | | | | | |

Date of Birth | | | | | | | | | |

Gender | | 1= Male, 2= Female

Date | | | | | | | | | |

Time | | :

Initial BP

SBP1 | | | | DBP1 | | | | mmHg

HR | | | | Bpm

Kindly indicate the time (HH:MM) of the following activities:

1. Main Meal | | :

2. Start of night rest | | :

3. Getting up: | | :

Please list any medication you are taking. Should you also take any medication during the blood pressure monitoring, indicate them as well.

Name of medication	Quantity per day	Time taken

Should you experience any of the following symptoms during the ABPM please indicate the time, and/or any medication taken to alleviate them.

Symptom/ Complication	Time
1. Palpitations, Fast pulse, Irregular heart rhythm	
2. Fatigue	
3. Visual disorder	
4. Headaches	
5. Hot flushes	
6. Nausea or Vomiting	
7. Syncope	
8. Dizziness	
9. Other (Please specify)	

Directives

Please keep your arm still during inflation of the cuff. The monitor is programmed to measure blood pressure at regular interval. During the day each measurement is announced by a beep. If after a measurement there are several beeps, the reading will be repeated two minutes later.

Appendix 5: Turnit In Report (attached)