THE ASSOCIATION BETWEEN ISOLATED CENTRAL SYSTOLIC HYPERTENSION AND TARGET ORGAN DAMAGE

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Declaration

I, Olwethu Blassin Ndlazi, declare that this dissertation, except were acknowledged on and referenced accordingly, is my own work. It is being submitted for the degree of Master of Science in Medicine at the University of Witwatersrand, Johannesburg. It has not been previously submitted for any degree to the current or any other institution.

I certify that the assessments contained in this dissertation have approval of the Committee for Research in Human Subjects (Medical) of the University of the Witwatersrand, Johannesburg. The ethics approval number is **M240809**.

I certify that the above statement is correct:

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Dedication

This dissertation is dedicated to my family, whose unwavering support, sacrifices and encouragement has carried me throughout this journey. To my supervisor who guided me with wisdom and patience, forever grateful for your invaluable insights and support. To my best friend and colleagues, I somehow managed to drag all of you into this degree, your words of motivation and encouragement, made this journey more meaningful. To myself, this path started as a vague dream, that led to purpose, and I have proven to myself that dreams can be a reality.

Abstract

Isolated systolic hypertension (ISH) is a well-known hypertension subtype that is mainly found in older individuals. It has been shown to be associated with target organ damage including arterial stiffness and left ventricular hypertrophy. On the other hand, there is no available data on isolated central systolic hypertension. It is not clear whether this hypertension phenotype exists or not. If it exists, is it associated with any target organ damage? Therefore, the aim of this study was to determine whether isolated central systolic hypertension is an existing hypertension subtype, and whether this clinical entity requires intervention, or it is just benign. In this cross-sectional study we recruited 1216 individuals of African ancestry who were (≥18 years) and categorized into five groups based on blood pressure profiles: normotensive (NT), isolated central systolic hypertension (ICSH), isolated brachial systolic hypertension (IBSH), isolated central and brachial systolic hypertension (ICBSH), and hypertensive (HT). Clinical and demographic data were collected using standardized questionnaires at the University of the Witwatersrand, Johannesburg, South Africa, with ethical approval (MED24-02-475). Anthropometric assessments, conventional and central blood pressure measurements, pulse wave velocity (PWV), and echocardiographic left ventricular mass index (LVMI) were obtained. Additionally, 24-hour ambulatory blood pressure monitoring was used to assess blood pressure throughout the whole day. Statistical analyses, including multivariate-adjusted linear regression models, were performed using SAS 9.4, adjusting for confounders such as age, sex, alcohol consumption, tobacco use, and diabetes. Our results show that the prevalence of people with both central and peripheral hypertension in this population is 27.6%. When we categorised these hypertensives according to isolated systolic hypertension status, the prevalence was 5.9%, 6.7%, 18.9% and 68.5% for IBSH, ICSH, ICBSH and HT respectively. The PWV of ICSH was significantly higher than that of the normotensives but it was similar to IBSH, but the LVMI of ICSH was significantly higher than that of IBSH. These results show that ICSH is a clinical entity that requires intervention since it increases arterial stiffness similar to IBSH. Most importantly its negative impact on the left ventricle is worse than that of IBSH.

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Contents

List of abbreviations

ABPM	Ambulatory blood pressure monitor
ACE	Angiotensin-converting enzyme
AGTR1	Angiotensin II type 1 receptor
BMI	Body mass index
BP	Blood Pressure
C_DBP	Central diastolic blood pressure
C_SBP	Central systolic blood pressure
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DBP24	24-Hour diastolic blood pressure
DBPC	Conventional diastolic blood pressure
DBPN	Night-time diastolic blood pressure
E/A	Early-to-late diastolic filling
ED	Endothelial dysfunction
ENaC	Epithelial Sodium Channel
HT	Hypertension
IBSH	Isolated brachial systolic hypertension
ICBSH	Isolated central and brachial systolic hypertension
ICSH	Isolated central systolic hypertension
ISH	Isolated systolic hypertension
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
mm Hg	Millimetre mercury

NO	Nitric Oxide
NT	Normotensive
PP	Pulse pressure
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system
SBP24	24-Hour systolic blood pressure
SBPN	Night-time systolic blood pressure
SNS	Sympathetic nervous system
SV	Stroke volume
SVR	Systemic vascular resistance
TOD	Target organ damage

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Preface

Hypertension remains a critical global health concern and leading cause of cardiovascular morbidity and mortality. Despite extensive research, the complexity of this disease, continues to challenge medical researchers and physicians, particularly as its prevalence rises worldwide. This non-communicable disease is estimated to be most prevalent in the African region, where approximately 46% of the population at the age of 25 years and older are hypertensive as compared to 35-40% in other parts of the world (Dzudie *et al.*, 2017). This statistic suggests that nearly half of the adult African population is affected by hypertension.

Over the past decade, numerous research and intervention programs have been implemented to reduce the prevalence of hypertension (HT) in Africa by at least 25%, however these efforts have not yielded the desired outcome (Kamara *et al.*, 2024; WHO, 2025). Hypertension, commonly referred to as high blood pressure (BP), is a chronic medical condition characterized by elevated arterial BP exceeding established systolic and/or diastolic BP thresholds (Gabb, 2020). Beyond being a clinical condition, HT is also a major risk factor for cardiovascular disease and is recognized as the leading cause for premature deaths worldwide. Given the clinical definition of hypertension, the accurate diagnostic criteria are critical for its classification and management. However, its complex pathophysiology influenced by various factors such as genetic, lifestyle and environmental factors, makes effective management particularly challenging. The pathophysiology of HT involves an interaction between genetics, and physiological mechanisms that result in increased total peripheral resistance and increased volume after load (Iqbal and Jamal, 2025). These mechanisms contribute to the remodelling of vasculature and the organs they supply. Hypertension is present in various subtypes, distinguished by differences in pathophysiological mechanisms, vascular remodelling and anatomical factors. One subtype is isolated systolic hypertension (ISH), defined by an elevated systolic blood pressure (SBP) (≥140mm Hg) while diastolic blood pressure (DBP) remains within normal range (<90mm Hg) (Dominiczak *et al.*, 2009).

Although ISH is commonly diagnosed in elderly patients due to reduced or loss of arterial compliance and arterial stiffness, recent studies indicate an increasing prevalence among young adults (Saladini and Palatini, 2017). Emerging evidence suggests that this trend is attributed to increased sympathetic hyperactivity (Masuo *et al.*, 1997). Implying that sympathetic activity plays a crucial role in the isolated elevation of SBP. While peripheral vascular remodelling is well documented, recent studies highlight that structural and functional changes extend beyond peripheral vasculature, affecting central blood vessels such as the aortic and carotid arteries (Humphrey, 2020). However, these alterations often remain undetected due to limitations in

current primary clinical diagnostic tools, underscoring the critical gap in the diagnostic capabilities for HT. Although peripheral BP measurements have been instrumental in routine primary health, this diagnostic measure fail to fully capture key cardiovascular biomarkers that reflect central haemodynamics (Terentes-Printzios, Gardikioti and Vlachopoulos, 2021). Target organs such as the heart, large arteries and kidneys are directly exposed to central compared to brachial BP which suggests that central BP has better predictive value to clinical events compared to brachial BP(Kollias *et al.*, 2016). Advancements in medical technology have facilitated the concept of central BP and its clinical significance to be taken into consideration in primary healthcare because it made the non -invasive assessment of central haemodynamics possible. A pilot study by Maseko et. al (2022)showed that approximately 14% of the Gauteng population had isolated central hypertension, indicating that a potentially more concerning form of hypertension is often overlooked due to limitations of conventional diagnostic tools. Although HT is not a recent threat in the health space, it remains a financial and health burden in most countries despite being one of the most researched topics (Iqbal and Jamal, 2025). Among various subtypes, the phenomenon in which central systolic BP increases independently of central diastolic BP has not been explored. Therefore, the aim of the study is to determine the impact of isolated central systolic hypertension on blood pressure and target organ damage in people of African ancestry. By contributing to the existing body of knowledge this study seeks to enhance understanding of this association and improve current risk stratification methods to support therapeutic interventions in HT management.

CHAPTER 1

Introduction

1.1 Introduction

Hypertension (HT) generally defined as an increase in blood pressure (BP) is the leading cause of comorbidities and premature mortality globally, disproportionately affecting populations of African ancestry. This is the highest risk factor for cardiovascular morbidity, exhibiting a higher prevalence (47%), much earlier onset and severe hypertension compared to other ethnic groups. This means that approximately half of the adult African population is hypertensive, and it is quite a challenge to manage their type of hypertension. Among various types of hypertensions, isolated central systolic hypertension (ICSH) has emerged as a clinically significant subtype. This type of hypertension is characterisECed by elevated central systolic blood pressure (C_SBP) with normal brachial systolic and diastolic BP. Although peripheral BP measurements have been used to assess and diagnose hypertension for years, studies have determined that central BP is a better predictor of cardiovascular events (Terentes-Printzios, Gardikioti and Vlachopoulos, 2021). Central blood pressure is measured at the ascending aorta, and reflects the pressure exerted on vital organs, particularly the heart, brain and kidneys more accurately compared to brachial BP (Zuo *et al.*, 2020). Despite diagnostic tools for central BP becoming more accessible, it remains underutilized in primary health care, especially in populations of African ancestry.

Studies suggest that elevated central systolic BP is associated with target organ damage (TOD), particularly in the vasculature and the heart. These are the organs that are directly exposed to central BP. However, the impact of ICSH in individuals of African ancestry has not been investigated, because it has never been established whether this hypertension subtype exists. If indeed it exists, its impact on people of African ancestry could be substantial because of their susceptibility to hypertension complications. This study aims to address this gap by first determining whether ICSH exists, then its association with TOD.

1.2 African population's susceptibility to hypertension

1.2.1. Genetic predisposition in African population

Hypertension is highly prevalent among individuals of African ancestry, and studies have indicated that this population has a significantly higher risk of developing the condition compared to other ethnic groups. Notably, individuals of African ancestry are more likely to develop hypertension at an earlier age whilst exhibiting lower rates of BP control through treatment compared to Caucasian populations (Howard *et al.*, 2006). This disproportion suggests the integrated involvement of various genetic, physiological, and environmental factors contributing to the increased susceptibility to hypertension in this population. The regulation of BP (homeostasis, SBP 120 mm Hg, DBP 90 mm Hg) is a complex physiological process influenced by genetic predisposition. One key genetic factor implicated in hypertension among the population of African ancestry is the angiotensin II type 1 receptor (AGTR1) gene, which encodes for the angiotensin II receptor. This gene has been associated with hypertension in African cohorts, particularly those located in South Africa (Kalideen, Rayner and Ramesar, 2024). Angiotensin II plays a crucial role in the regulation of BP through physiological cascades inducing vasoconstriction and increasing vascular resistance, ultimately contributing to elevated BP. A specific genetic variant of AGTR1, distinguished by an A-to-C substitution in the untranslated region, has been associated with increased arterial stiffness, elevated BP and a high cardiovascular risk in this population through defective function and receptor expression (Kalideen, Rayner and Ramesar, 2024). The presence of the C allele has been associated with severe, early-onset, and treatment resistant hypertension.

The Renin-angiotensin-aldosterone system (RAAS) is central to BP homeostasis, and anti-hypertensive medication to inhibit angiotensin-converting enzyme (ACE) and block angiotensin II receptors and calcium blockers have been developed to mitigate this system. However, individuals of African ancestry often exhibit genetic variations that reduce the efficacy of these therapeutic agents (Mabhida *et al.*, 2021). The genetic variability in this population could be the reason why this population experiences more severe and difficult to manage hypertension.

In addition to the AGTR1 polymorphism, genetic variants of the epithelial Sodium Channel (ENac), particularly mutations to the SCNN1B genes which encodes for a subunit of the ENac, which is important for sodium reabsorption in the kidney have been investigated in relation to hypertension (Spence and Rayner, 2018). Although these mutations have been associated to a

Liddle-like phenotype, which is a rare monogenic form of hypertension, characterized by decreased aldosterone and renin levels, and increase sodium retention, studies have shown that such mutations occur at similar frequencies across racial groups and are not unique to individuals of African ancestry. Nevertheless, individuals of African ancestry often exhibit a high sensitivity to sodium intake, predisposing them to volume-dependent hypertension that responds well to diuretic therapy in comparison to other populations.

While genetic predisposition plays a critical role in hypertension susceptibility, lifestyle and environmental factors contribute to the high prevalence of hypertension in individuals of African ancestry. Socioeconomics disproportions, especially low-income levels, limited access to quality education and healthcare, have been identified as major contributors to the increased prevalence of hypertension in this population (Marden *et al.*, 2016). Most individuals of African ancestry reside in developing countries where healthcare services are poor, and access to healthy dietary choices is limited. Additionally, urbanization has been associated with sedentary lifestyles and increased consumption of foods high in sugar and fats, further exacerbating the risk of obesity and hypertension (Sidahmed, Geyer and Beller, 2023).

1.2.2. Social, economic, lifestyle and diabetes

According to the World Bank Group (2022), South Africa is one of the major transitioning economies and has experienced an increase in the availability and consumption of high-sugar beverages. A recent a study by Mukhovha *et al.* (2025) found that over half of South African beverages contain excessive sugar contents and thus will require warning labels to indicate this health hazard. The widespread availability of unhealthy food options has contributed significantly to the rising prevalence of obesity, which, increases risk of non-communicable diseases (NCDs), including hypertension.

Furthermore, the prevalence of diabetes continues to rise across the African continent, with approximately 38% of South Africans estimated to have undiagnosed diabetes (Mutyambizi *et al.*, 2019). Diabetes significantly contributes to hypertension through various related mechanisms particularly insulin resistance and endothelial dysfunction. Insulin resistance, a key feature of type 2 diabetes, leads to hyperinsulinemia which stimulates the sympathetic nervous system (SNS) and consequently, increases heart rate and vascular resistance thereby

elevating BP (Spence and Rayner, 2018). Additionally, individuals of African ancestry with diabetes usually exhibit lower baseline of nitric oxide bioavailability which leads to increased vascular resistance, making them susceptible to increased hypertension. The coexistence of all these factors, genetics, socioeconomic disadvantages, unhealthy lifestyle and high prevalence of diabetes lead to a higher incidence of hypertension among individuals of African ancestry.

1.3. Central and peripheral hypertension

1.3.1. Peripheral blood pressure

The measure of blood pressure is integral to the assessment of risk for cardiovascular disease. Traditionally, BP has been measured at the brachial artery, using the sphygmomanometer. This measurement gives the representation of peripheral BP. This type of BP represents the pressure exerted by the circulating blood on the walls of peripheral blood vessels and is an aspect of the combined effects of cardiac output and vascular resistance in the arteries (Laurent, Sharman and Boutouyrie, 2016). However , recent studies have emphasized the importance of central BP, which describes the pressure in the aorta and central arteries (carotid, subclavian) during the cardiac cycle (Kollias *et al.*, 2016). The disparities between central and peripheral BP is crucial as central BP has been shown to reflect the pressure load exerted on the heart and vasculature more accurately, therefore showing better predictions of target organ damage (TOD) compared to peripheral BP (Zuo *et al.*, 2020).

1.3.2. Central blood pressure

The concept of measuring central BP has evolved over years. In the 1700s central BP measurements were taken invasively by inserting a glass tube directly into a mare's artery and observing the pulsing of blood into the 12-foot glass tube, this was marked as the first recorded measurement of arterial BP (Lewis, 1994). Furthermore, this BP measurement technique was refined by introducing the mercury manometer to obtain precise arterial pressure quantification. (Booth, 1977). This emphasises the development of BP to allow for better treatment as advancements occur. Consequently, advancements in technology coupled with a deeper understanding of cardiovascular physiology, particularly pressure wave reflections and augmentation, facilitated the developments of non-invasive methods to estimate central BP

(McEniery *et al.*, 2014). Moreover, mathematical modelling and techniques such as applanation tonometry allowed health care workers to assess central haemodynamics without direct arterial access. Central BP has become a crucial determinant of cardiovascular risk event. In contrast to peripheral BP, which can be influenced by multiple factors, central BP specifically reflects the properties of the central arterial tree, including its compliance and wave reflections that occur during the cardiac cycle (Terentes-Printzios, Gardikioti and Vlachopoulos, 2021). The ability of central arteries to expand and contract in response to pressure plays an important role in lessening pulsatile blood flow from the heart and ensuring a steady perfusion to vital organs (Marchais *et al.*, 1993). This suggests that when the heart contracts during systole and the left ventricle ejects blood into the compliant aorta, the aorta expands to accommodate the increased volume. The aorta then reduces the central systolic pressure (C_SBP) and pulse pressure (PP) produced during systole. This modulating effect minimizes damage to capillary networks in organs such as the heart, brain and kidneys (Marchais *et al.*, 1993). Although compliance is widely distributed across the arterial tree, the total systemic compliance is predominated by the aorta and the major branches (Dart and Kingwell, 2001). Arterial compliance is not only important during the systole but is crucial for diastole (heart relaxation). During diastole, the elastic recoil of the aorta and large arteries prevents the steep drop in diastolic pressure ensuring a continuous perfusion despite the relaxation phase (Sheikh *et al.*, 2023). Reduced compliance of the central arteries impairs their ability to buffer pulsatile blood flow, leading to altered perfusion of vital organs. This loss of arterial elasticity contributes to elevated central systolic blood pressure (C_SBP) and widened pulse pressure (PP), both of which are key mechanisms in the development of hypertension. The pulse wave generated during systole, travels through the arterial system at a particular speed that is influenced by the arterial compliance and diameter. Wave reflections are present throughout the arterial tree at the bifurcations or transitions between arterial elasticity of the arteries causing the forward travelling pulse wave to reflect back ward to the heart (Dart and Kingwell, 2001). The arterial buffering system plays a key role in modulating both the forward and reflected waves by dampening their frequency and amplitude. This modulation depends on factors such as the distance the wave travels and the mechanical properties of the vessel wall. This suggests that the augmentation of the C_SBP is due to the combination of the forward traveling wave generated by the left ventricle during systole and the reflected wave. The superimposition of these waves is particularly evident in the aortic pressure wave trace, leading to an increase in systolic pressure and, consequently, an elevated PP. This process contributes to the augmented workload on the heart (Dart and Kingwell, 2001). In contrast to this, wave reflections are an advantage aiding coronary perfusion when they arrive during diastole (Mitchell *et al.*, 2004). Studies have demonstrated

that increased C_SBP is an independent risk for TOD, particularly left ventricular hypertrophy (LVH), cerebrovascular events and kidney damage (Hashimoto, 2014). Central BP has been concluded to be a better predictor of cardiovascular events due to the direct pulsatile stress in exerts on these vital organs as compared to peripheral BP. Although peripheral PP is a valuable clinical measure, which can contribute to cardiovascular events and TOD, especially in isolated systolic hypertensive individuals, it has been recognized that peripheral BP can underestimate the risk associated with central haemodynamics (Pini *et al.*, 2008; McEniery *et al.*, 2014).

1.4. Isolated hypertension and target organ damage

Isolated systolic hypertension is defined as a SBP ≥ 140 mm Hg with a DBP of < 90 mm Hg, and it's distinguished from other hypertensive forms that involves concurrent increases in both the SBP and DBP (Bavishi, Goel and Messerli, 2016). This type of hypertension is particularly prevalent in elders due to aging and pathological changes in arterial structure particularly elastin fibre fragmentation and increased collagen deposition which contribute to arterial remodelling (Sun, 2015). These structural alterations reduce arterial compliance and impair the artery's ability to buffer the pulsatile pressure from the heart, leading to an isolated elevation in systolic pressure. The pathophysiological basis of ISH primarily involves arterial stiffening, which accelerates the return of the reflected wave from the periphery to the heart. Whereas in a compliant arterial system, reflected waves return during diastole, assisting coronary perfusion. However, in individuals with arterial stiffness, these reflected waves return earlier, simultaneously with systole and leading to further elevation of SBP while DBP remains relatively stable. This haemodynamic phenomenon underlies the BP pattern observed in ISH.

1.4.1. Endothelial Dysfunction

Endothelial dysfunction is a key contributor to ISH, as the endothelium is responsible for vascular regulation through the release of vasoactive substances such as nitric oxide (NO), which facilitate vasodilation (Laurent and Boutouyrie, 2020). This vasodilator is essential for maintaining vascular homeostasis by relaxing the smooth muscle within the arterial wall. Consequently, the presence of dysfunction reduces NO bioavailability significantly, leading to impaired vasodilation, increased vascular resistance, heightened arterial stiffness, all of which

contribute to elevated SBP (Konukoglu and Uzun, 2017; Laurent and Boutouyrie, 2020). While biological in origin, endothelial dysfunction disrupts the mechanical balance between vasoconstrictive and vasodilative factors, promoting sustained vascular smooth muscle contraction and arterial stiffening. In older individuals, this process is further exacerbated by chronic inflammation and oxidative stress, which accelerate vascular remodelling and reduce NO bioavailability, thereby perpetuating ISH. Wallace *et al.* (2007) demonstrated that patients with ISH have a higher aortic pulse wave velocity (PWV) and a lower flow-mediated dilation compared to their age matched controls. This relationship further emphasises the role of endothelial dysfunction in arterial stiffness and ISH pathogenesis.

1.4.2. Influence of ISH on arterial stiffness and haemodynamics

While ISH is commonly associated with aging, younger individuals may also develop this condition due to distinct pathophysiological mechanisms. One proposed mechanism involves increased stroke volume (SV), particularly in individuals of African ancestry, who tend to have a more volume-dependent hypertension (Woodiwiss *et al.*, 2020; Franklin *et al.*, 1997). Elevated SV result in the ejection of a larger blood volume with each cardiac cycle, which when coupled with the low arterial compliance, lead to exaggerated systolic pressures elevations. Additionally, ISH in younger individuals may be characterised by increased cardiac preload, defined as the stretching of cardiac muscle prior to the contraction due to the volume of blood in the ventricles at the end of diastole. The Frank-Starling principle suggests that increased preload leads to enhanced myocardial contractility and stroke volume, contributing to elevated SBP (Franklin *et al.*, 1997). Unlike in older individuals, where ISH is primarily associated with arterial stiffness, younger individuals with ISH may not exhibit significantly increased systemic vascular resistance (SVR) or arterial stiffness, making this mechanism particularly relevant in this population. Another key contributor to ISH in younger individuals is increased sympathetic nervous system (SNS) activity, which increases cardiac output and myocardial contractility, further elevating SBP without corresponding increase in DBP (Lurbe *et al.*, 2016; DeLalio, Sved and Stocker, 2020). Elevated SNS activity leads to increased norepinephrine release, promoting vasoconstriction and elevating central BP. However, in other cases, genetic predisposition, sensitivity to sodium and a sedentary lifestyle reduces arterial compliance in individuals of African ancestry, increasing their susceptibility to ISH (Nilsson, 2020).

A study by Lurbe *et al.* (2016) showed the role of premature wave reflections among younger individuals with ISH. Increased vascular tone or stiffened peripheral arteries lead to early return of reflected waves, amplifying SBP and mimicking the haemodynamic pattern observed in elderly individuals with ISH. This suggests that ISH in younger individuals is driven by a combination of increased cardiac output, early wave reflections and altered vascular properties.

With central BP, gaining recognition over the years as a superior and more accurate predictor of cardiovascular events compared to peripheral BP measurements, a possibility exists that if a hypertension phenotype like central systolic hypertension (ICSH) exists, it could predict cardiovascular target organ damage above the well-known isolated brachial hypertension (IBSC). However, the impact of this hypertension subtype on cardiovascular health remains unknown because its existence has never been established. Therefore, if ICSH exists, it may provide a new insight into the pathogenesis of hypertension related target organ damage.

1.5 Arterial stiffness

Arterial stiffness refers to the structural alterations within the arterial wall, primarily involving changes to extracellular matrix components such as collagen and elastin. It serves as a crucial marker for hypertension risk, particularly in relation to central haemodynamics, and has been positively associated with systolic hypertension, coronary disease and heart failure (Palatini *et al.*, 2011). Clinically, arterial stiffness has been widely utilized to assess the initiation progression of cardiovascular events in hypertensive patients. Non-invasive measurement techniques such as applanation tonometry, pulse analysis and pulse wave velocity (PWV) assessment, in conjunction with general transfer software, have become validated approaches for quantifying arterial stiffness (Spronck and Humphrey, 2019; Jin *et al.*, 2023). Applanation tonometry involves the use of a high-fidelity pressure sensor applied to a superficial artery (carotid, radial or femoral) compressing it against underlying structures to capturing pressure waveforms that reflect each cardiac cycle (Kim and Braam, 2013). These waveforms include both the forward travelling pulse wave, originating from the heart, and the reflected wave from the periphery vasculature. Due to the disparities between central and peripheral arteries, general transfer function software mathematically reconstructs the central aortic waveform from the radial wave form, thereby estimating central arterial stiffness and augmentation index (London and Pannier, 2010; Palatini *et al.*, 2011; Spronck and Humphrey, 2019). In contrast to this, research indicated the underestimation of arterial stiffness through this technique, as PWV

measurements can be easily affected by the constraint of external tissue surrounding the arterial wall such that, increased tethering of the arterial walls may reduce radial arterial movements, potentially leading to an underestimation of arterial stiffness (Hodis and Zamir, 2011). This suggests that normal PWV values may not always accurately reflect the absence of arterial stiffness, particularly in the case where an individual presents with significant tethering. However, PWV is the golden standard for arterial stiffness measurement. It is determined by assessing the transit time between two arterial sites, with a higher PWV indicating greater arterial stiffness due to faster wave transmission in rigid arteries (Spronck and Humphrey, 2019). Mechanical factors play a crucial role in arterial health, as altered blood flow and pressure can change luminal radius and wall thickness. Consequently, quantifying the mechanoregulation of arterial structures is essential (Spronck and Humphrey, 2019).

Structural and functional alterations in arteries occur as a result of various pathophysiological mechanisms that increase cardiovascular risk (Safar, Frohlich and Borer, 2007). The most common mechanism involves a loss of arterial elasticity. The arterial wall is composed of elastin, collagen and vascular smooth muscle cells all of which contribute to vascular compliance (Laurent, Boutouyrie and Lacolley, 2005; London and Pannier, 2010). Throughout the cardiac cycles, arterial expansion and recoil depend primarily on elastin, a highly extensible protein that undergoes degradation via matrix metalloproteinases enzymes due to oxidative stress, inflammation and aging (London and Pannier, 2010). The degradation of elastin reduces arterial compliance, therefore increasing pulse wave velocity and central systolic BP. As a compensatory response mechanism, collagen synthesis is elevated (Safar, Frohlich and Borer, 2007). Since collagen is stiffer than elastin, its accumulation contributes to arterial rigidity.

Additional pathophysiological mechanisms contributing to arterial stiffness include metabolic disorders such as diabetes. In individuals of African ancestry, non-enzymatic glycation process promotes advanced glycation end products (AGES) which enhance collagen cross-linking and arterial rigidity (Schutte *et al.*, 2020; Li *et al.*, 2024). Vascular calcification associated with AGES further contributes to arterial stiffening and elevated central systolic pressure.

Moreover, endothelial dysfunction, inflammation, vascular remodelling and lipid accumulation, contribute to atherosclerosis, a unique determinant of arterial stiffness (Libby, Ridker and Maseri, 2002). Endothelial dysfunction plays a pivotal role in the initiation of atherosclerosis, primarily due to impaired local synthesis and availability of NO. Nitric oxide (NO), a vasodilator with anti-inflammatory properties is crucial for regulating blood flow, vascular tone and immune response. In ED, diminished NO bioavailability leads to increased oxidative stress and vascular permeability (De Caterina *et al.*, 1995). Accumulated lipids form plaques which

undergo oxidation and promote vascular smooth muscle cell migration from the media to the intima. This process leads to collagen deposition and extracellular matrix remodelling within the arteries, reducing arterial compliance. As plaque accumulation progresses and calcifies, the arterial lumen narrows, causing a reduction in arterial compliance, increasing vascular resistance and enhancing pulse wave reflections. Ultimately, the stiffening of arteries accelerates pulse wave transmission, causing the reflected waves to return earlier in systole instead of diastole. This phenomenon results in the amplification of central systolic pressure and pulse pressure, while maintaining a normal diastolic pressure. It could be the main determinant of ICSH. Therefore, if the ICSH phenotype exists, studies are that could establish its relationship with arterial stiffness are required.

1.6. LVH

Left ventricular hypertrophy (LVH) is a significant complexity of hypertension where structural adaptation of the myocardium occurs in response to chronic pressure overload or volume overload. This adaptation is characterized by an increase in myocardial mass and extracellular remodelling (Yildiz *et al.*, 2020). Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality and has been associated with arrythmias, heart failure and sudden cardiac death (Cohen-Solal *et al.*, 1994). Even though hypertension has been established to playing a major role in the development and progression of LVH, ICSH may be an emerging risk factor. Although LVH develops through a combination of mechanical, neurohormonal and molecular pathways, the primary driver in hypertension is the increased afterload due to elevated BP, requiring a compensatory myocardial hypertrophy to maintain cardiac output. Hypertensive individuals have been associated with arterial stiffness, leading early return of reflected waves during systole, consequently increasing ventricular afterload and stoke volume as a compensatory mechanism (Palatini *et al.*, 2011). The chronic wall stress due to prolonged exposure to afterload results in adaptive concentric hypertrophy, where the LV wall thickens without proportional chamber dilation (De Simone, 2004). Moreover, studies by Verdecchia *et al.* (1996) and Krumholz *et al.* (1995) found that concentric LVH is associated with a greater LV mass. However, a study by Verdecchia *et al.* (1995) also identified that there were patients with normal LV mass, who exhibited concentric LV remodelling showing that a normal pressure overload plays an important role in prognosis, even in the absence of hypertrophy. Notable, the same study demonstrated that although the LV mass was normal for

patients with concentric LV remodelling, these patients had higher values of LV mass than patients with normal LV geometry emphasising the association between concentric LV and a greater LV mass. The presence of arterial stiffness-further amplifies SBP in the aorta, increasing LV workload and promoting myocardial hypertrophy. Increased mechanical stress leads to fibrosis and extracellular matrix deposition, which reduce myocardial compliance and possibly contribute to diastolic dysfunction. Given that individuals of African ancestry are more prone to SNS hyperactivity and volume dependent hypertension, hypertrophy and fibrosis may be exacerbated, worsening diastolic function (DeLalio, Sved and Stocker, 2020; Woodiwiss *et al.*, 2020). Since ventricular geometry cannot be measured using conventional brachial or central BP measurements, LVH is diagnosed using imaging, primarily echocardiographic techniques which produce parameters that are associated to LVH (Gosse *et al.*, 1999). The echocardiographic index for assessing LVH is the left ventricular mass index (LVMI), which provides valuable insight to cardiac structural alteration and cardiovascular risk stratification which has been normalized to account for individual body size. Additionally, relative wall thickness (RWT) is used to classify hypertrophy patterns which have different prognostic implications.

1.7 Justification

Numerous studies have exhibited the impacts of elevated central blood pressure on TOD. In South Africa, a pilot study indicated that approximately 14% of this population has isolated central hypertension. This finding suggests that a significant proportion of individuals may have a hypertensive status that remain undetected when assessed using conventional clinical assessments. Given the heightened susceptibility of this population to hypertension and related complications, the high incidence and prevalence of hypertension could be largely contributed to this undetected hypertensive subtype. Isolated central systolic hypertension remains unknown because of the current diagnostic tools in primary health care that rely mainly on peripheral BP measurements rather than central BP assessment. As a result, the current diagnostic and management strategies for HT in South Africa and African populations in primary health care may be inadequate. This diagnostic and knowledge gap is a challenge because if the ICSH phenotype exists, it will remain undiagnosed while it causes substantial damage to cardiovascular target organs. Investigating the existence of ICSH could enhance risk stratification and provide crucial insight into early detection of central hypertension. Moreover,

this research could inform target therapeutic strategies aimed at mitigating cardiovascular complications associated with ICSH, thereby enhancing hypertension management and reducing the cardiovascular disease burden in this high-risk population.

1.8 Aim and objectives

This study aims to determine the association between isolated central systolic hypertension and cardiovascular target organ damage in a cohort population of African ancestry. We aim to do this by

- First establishing whether a hypertension phenotype exists where individuals have elevated central systolic BP while central diastolic BP remains normal.
- Comparing the prevalence of ICSH to the well-known brachial isolated systolic hypertension phenotype.
- Determine the impact of ICSH on LVMI using echocardiography.
- Determine the impact of ICSH on PWV using applanation tonometery.

CHAPTER 2

Method Section

2.1 Study group

This study was conducted at the University of the Witwatersrand, Health Science Campus, Johannesburg, South Africa, in accordance with the principles outlined in the Declaration of Helsinki. Ethical clearance (M240809) was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, in Johannesburg. A total of 1216 individuals of African ancestry, residing in Gauteng during the study were recruited in Johannesburg. Both female and male participants aged 18 years and older, with no upper age limit, were included in the study.

2.2 Clinical and demographic data

Participants were recruited and invited to the Xihlovo Xa Vutomi Clinic, where the study objectives, procedures, and requirements were explained in detail. Prior to any data collection, the participants were required to provide written consent (Appendix 5) then the standardized questionnaire was administered. The questionnaire (Appendix 6) was designed such that the participants could answer the question with a 'yes' or 'no', and a few sections requiring short answers. The questionnaire captured information on the participants family history of hypertension and cardiovascular events, their medical history and lifestyle factors.

2.3 Anthropometric measurements

Anthropometric measurements were conducted according to the international standards for anthropometric assessments (Norton, 2018). Participants were required to be barefoot and wear a light-weight medical gown for all the measurements. Height measurements were taken using a stadiometer and the participants were asked to place their head in a Frankfort plane position, with their feet flat onto the ground and the body up straight. The headboard of the stadiometer was placed firmly on the vertex of the head, compressing the hair and the measurements were recorded to the nearest 0.1 cm. Weight measurements were recorded using a Health Professional electronic scale and the participants were required to step onto the scale without using an object to support themselves, measurements were recorded to the nearest 0.1 kilogram (kg). The

obtained height and weight were used to calculate the participants body mass index (BMI). Calculation:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

2.4 Conventional blood pressure measurements

Participants were left to sit comfortably with their back against the chair and feet uncrossed, in a rested position five minutes prior to the BP measurements being taken. Brachial BP measurements were recorded using an Omron Kyoto, Japan automated sphygmomanometer. Participants were required to rest the arm at which the BP was measured on the arm rest that was elevated close to heart level. A cuff suitable to the participant's arm circumference was used. Blood pressure measurements were taken five consecutive times at one-minute intervals. The measurements were then averaged to determine the average systolic and diastolic BP as well as the participant's resting heart rate.

2.5 Central blood pressure measurements

Central BP measurements were recorded using a high-fidelity SPC-301 micromanometer, interfaced with a computer using SphygmoCor software version 9.0 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). Participants were required to rested in a supine position, with their legs uncrossed and their arms along their body. An applanation tonometry probe, attached to the SphygmoCore device was used to do a pulse wave analysis. Firstly, the participants anthropometric and conventional BP measurements are inputted into the software, then the tonometry probe was used to obtain the participant's stable radial pulse. These parameters were then converted to central BP using a general transfer function.

2.6 Pulse wave velocity

The SphygmoCor software was used to obtained pulse wave velocity (PWV), a measure of arterial stiffness. The applanation tonometry method is a 'gold standard' for pulse wave

analysis. While the participant remained in the supine position, using an inextensible measuring tape we measured the distance between their suprasternal notch to the radial pulse (labelled distance A). We also measured the distance between their suprasternal notch and the femoral artery pulse (labelled distance B). This measurement was used the calculate the pulse transit time between distance B and A.

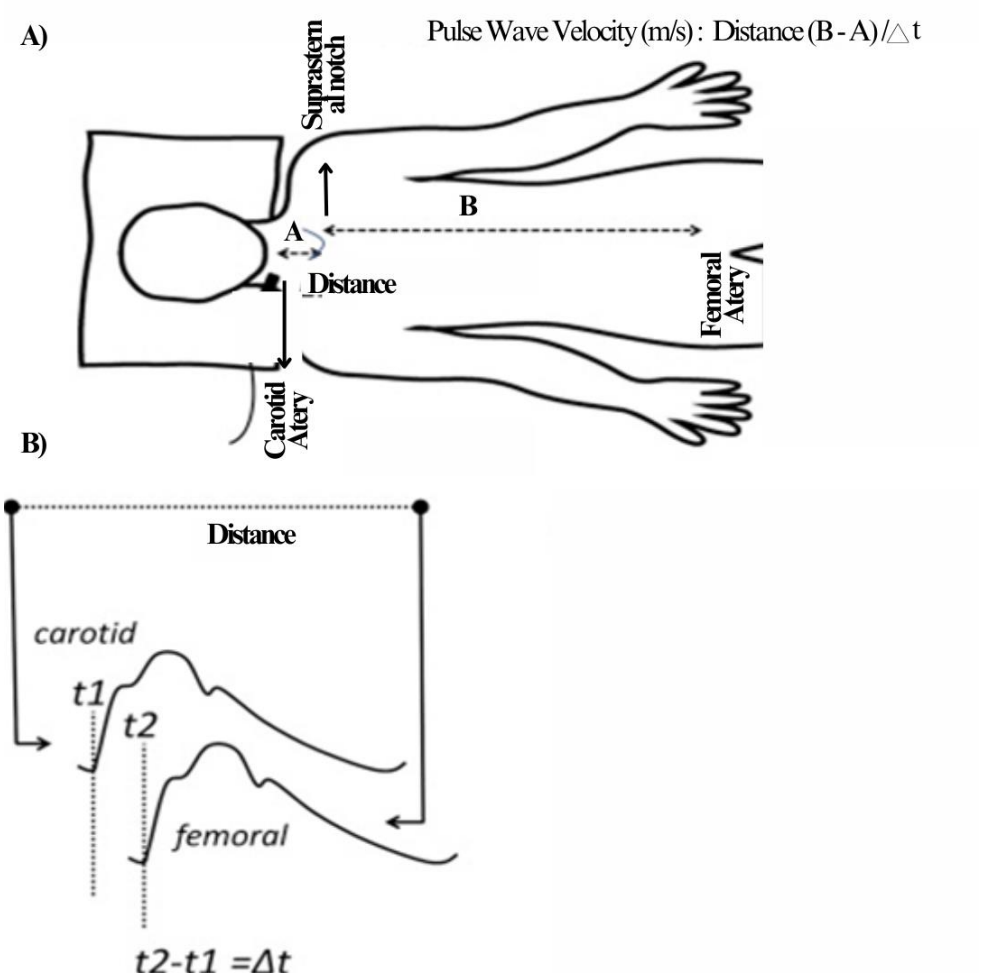

Figure 1: Example of how pulse wave velocity measurements are taken (adapted from Pacana and Michael, 2012).

This figure shows the supine position of a participant and the points (suprasternal notch, carotid artery and femoral artery) where the applanation tonometry probe will be placed and the distances taken from each point. B exhibits the appearance of carotid and femoral pulse waves once transferred using the Sphygmocor software and how change in time is calculated.

A three-lead chest ECG was performed during this procedure. Applanation tonometry was used to record the stable wave forms at the participant dominant femoral and carotid sites. Pulse transit time was defined as the average 10 over consecutive beats. Pulse wave velocity was

automatically calculated as the distance between label A and label B and divided by the pulse transit time

2.7 Echocardiography

Echocardiography was used to determine the left ventricular index (LMVI), a measure of left ventricular hypertrophy. Echocardiographic measurements were done by a qualified cardiologist Dr. Adamu, using a high-resolution ultrasound echocardiogram equipped with a 2.5-5MHz phased array transducer. The measurements were analysed according to the American Society of Echocardiographic convention. Participants were required to be in the left lateral decubitus position to get optimal image acquisition. Left ventricular dimensions were obtained at the parasternal long axis view and were taken during end-diastole. The following measurements were obtained: Intraventricular Septal thickness (IVSd), which was the distance between the endocardial surfaces of the interventricular septum. The Left ventricular internal diameter (LVIDd), which was the distance between the endocardial surfaces and the left ventricular wall. The posterior wall thickness (PWTd), which was the distance from the endocardial to the epicardial surface of the posterior wall. All these measurements were recorded in centimetres (cm). Left ventricular mass was calculated using the following Formula:

$$LVM\ (g) = 0.8 \times (1.04 \times [(IVSd + LVIDd + PWTd)^3 - (LVIDd)^3]) + 0.6$$

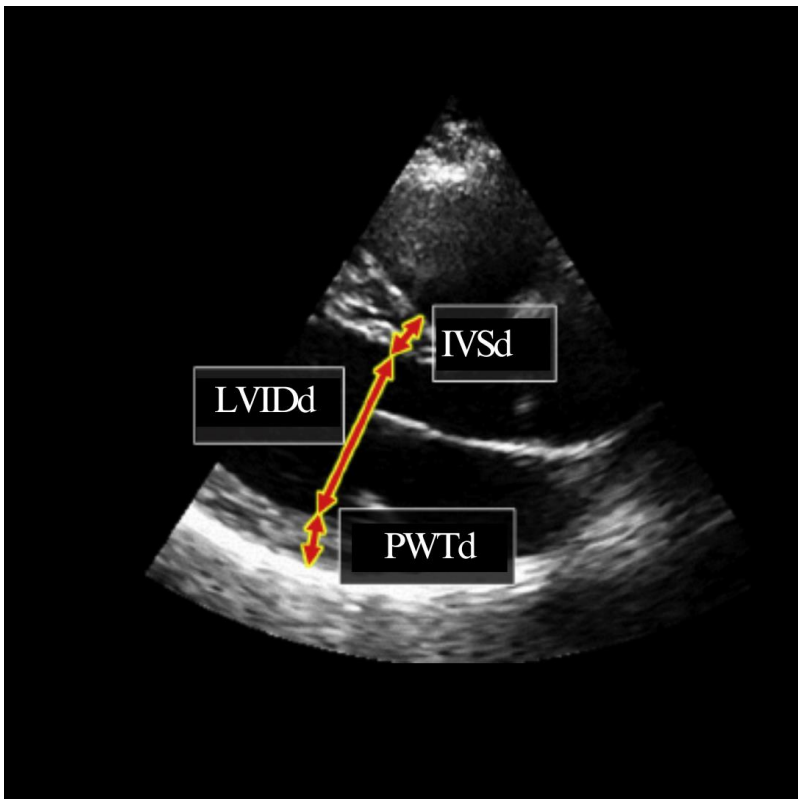

Figure 2: Example of echocardiographic measurements (adapted from Perperidis, 2015)

This figure shows example measurements of left ventricular internal diameter (LVIDd), intraventricular septal thickness (IVSd) and left ventricular posterior wall thickness (PWTd) during end diastole. Measurements were taken across the parasternal long axis.

Left ventricular mass was indexed to body surface area (BSA) to obtain left ventricular mass index (LVMI). Body surface area was calculated using the following Formula:

$$BSA\ (m^2) = \sqrt{(Height(cm) \times Weight\ (kg))/3600}$$

Then:

$$LVMI\ (g/m^2 = \frac{LVM(g)}{BSA(m^2)}$$

2.8 Twenty-four-hour ambulatory blood pressure measurements

To obtain 24-hour central and brachial BP measurements we used the 24-hour ambulatory monitor (ABPM). The same cuff size used for the conventional BP measurements was used and wrapped around the non-dominant hand. The monitors were programmed to take BP

measurements at 30-minute interval during the day (07h00 – 22h00) and at 1-hour intervals at night (22h00 – 07h00). Participants were also issued a dietary recall form, where they recorded the time, they went to sleep and woke up, foods and drinks, and medication they took during the monitoring duration. The ABPM and dietary recall were collected from the participants after 24-hours and the data was retrieved. Ambulatory BP data was expressed as 24-hr average systolic and diastolic BP.

2.9 Data Analysis

SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) was used for database management and statistical analysis. Normality was tested using the Shapiro-Wilk test. Categorical variables were expressed as percentages. Continuous variables were expressed as mean±SD. For independent relationships, we corrected for other variables using the multivariate adjusted linear regression. Adjustments were for sex, age, alcohol intake, tobacco intake and diabetes mellitus. Data was categorized into the following hypertensive subtypes: normotensives (NT), isolated central systolic hypertension (ICSH), isolated brachial systolic hypertension (IBSH), isolated central and brachial hypertension (ICBSH) and hypertensives (HT). Graphpad Prism version 10 was used to represent the association between LVMI, PWV and Serum creatinine with all the hypertension subtypes. P value < 0.05 was considered statistically significant.

CHAPTER 3

Results Section

Table 1: Demographic and general characteristics of the study population

	TP	NT	ICSH	IBSH	ICBSH	HT
Number	1216	709	18	16	51	185
Age	44.1±18.3	36.7±16.2	58.3±17.3[a]	62.5±13.5[a]	67.4±10.7[ab]	56.7±13.5[a]
BMI	29.5±8.0	27.9±8.1	31.4±6.9[a]	33.4±7.1[a]	31.8±6.8[a]	32.3±7.8[a]
Diabetic (%)	8.7	6.9	5.6	25.0	21.6	9.2
Cigarette smokers (%)	15.1	15.5	5.6	6.3	13.1	7.6
Alcohol intake (%)	20.2	20.3	16.7	12.5	21.6	23.2
Alcohol intake and smoking (%)	8.1	8.5	0	0	19.8	9.2

BMI, body mass index; TP, total population; NT, normotensive (normal brachial systolic and normal brachial diastolic blood pressure); ICSH , isolated central systolic hypertension (normal brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); IBSH, isolated central brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, normal central systolic blood pressure, normal central diastolic blood pressure); ICBSH, isolated central and brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); HT, hypertensive (increased brachial systolic blood pressure, increased brachial diastolic blood pressure, increased central systolic blood pressure, increased central diastolic blood pressure). Data expressed as a percentage or mean ± standard deviation. $P<0.05$ considered significant. a, significantly different to NT; b, significantly different to ICSH; c, significantly different to IBSH; d, significantly different to ICBSH.

Table 1 describes the demographic, anthropometric and general characteristics of the study sample according to hypertension subtypes.

A significant proportion of the total population was hypertensive. Of the population, 58% was normotensive and 22.2% of the population was hypertensive. Participants classified into the hypertensive subtypes (ICSH, IBSH, ICBSH, HT) were significantly older compared to the normotensive subtype. In addition, the hypertensive subtypes had a significantly higher BMI (> 31) compared to the normotensive subtype (27.9±8.1). The prevalence of ICSH was 1.5% and that of IBSH was 1.3%, while 4.2% had both isolated central and brachial hypertension (ICBSH). Isolation hypertensive subtypes IBSH and ICBSH had the highest prevalence of diabetes, 25% and 21.6 % respectively. Only 20.2% of the population consume alcohol. The HT and ICBSH hypertensive subtypes had the highest alcohol consumption compared to other hypertensive subtypes. Although the hypertensive (HT) subtype demonstrated elevated alcohol consumption, only 9.2% of participants in this group concurrently consumed alcohol and smoked cigarettes. In contrast, 19.8% of participants in the ICBSH subtype engaged in both alcohol consumption and cigarette smoking.

Table 2: Central and brachial blood pressure values (mm Hg) of the population categorized according to isolated systolic hypertension status

	NT	ICSH	IBSH	ICBSH	HT
SBP24	111.8±10.0	116.1±85.0	119.8±10.9[a]	130.4±16.3[abc]	135.4±16.8[abcd]
DBP24	68.4±7.1	70.4±6.5	69.5±6.9	73.4±8.9[a]	84.6±11.7[abcd]
SBPN	104.3±11.7	111.4±12.6[a]	115.8±9.9[a]	121.6±20.0[abc]	129.8±20.2[abcd]
DBPN	60.5±8.5	64.6±7.5	64.6±8.6	64.9±11.3	77.5±13.7[abcd]
SBPD	116.3±10.2	118.9±8.4	121.9±14.4	134.2±14.7[ab]	138.7±16.4[abcd]
DBPD	73.6±7.4	73.0±6.9	72.6±8.6	77.7±9.1[b]	89.3±11.8[abcd]
SBPC	115.8±10.9	133.0±8.6[a]	144.8±5.7[ab]	155.8±15.7[abc]	163.4±17.3[abcd]
DBPC	76.7±7.4	80.1±8.1[a]	80.5±5.9[a]	81.9±4.2[a]	102.7±10.6[abcd]
C_SP	105.8±10.6	140.3±23.5[a]	118.8±7.6[ab]	144.2±16.8[ac]	154.3±17.1[abcd]
C_DP	77.0±7.4	83.8±4.3[a]	78.0±6.4	82.7±4.5	104.3±11.8[abcd]

NT, normotensive (normal brachial systolic and normal brachial diastolic blood pressure); ICSH , isolated central systolic hypertension (normal brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); IBSH, isolated central brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, normal central systolic blood pressure, normal central diastolic blood pressure); ICBSH, isolated central and brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); HT, hypertensive (increased brachial systolic blood pressure, increased brachial diastolic blood pressure, increased central systolic blood pressure, increased central diastolic blood pressure). SBP24, 24-Hour systolic blood pressure; DBP24, 24-Hour diastolic blood pressure; SBPN, night-time systolic blood pressure; DBPN, night-time diastolic blood pressure; SBPD, daytime systolic blood pressure; DBPD, daytime diastolic blood pressure; SBPC, conventional systolic blood pressure; DBPC, conventional diastolic blood pressure; C_SP, central systolic

pressure; C_DP, central diastolic pressure. Data expressed as mean ± standard deviation. P<0.05 considered significant. a, significantly different to NT; b, significantly different to ICSH; c, significantly different to IBSH; d, significantly different to IBCS

Table 2 describes the central and brachial blood pressure values of the population categorized according to isolated systolic hypertension status.

Isolated hypertensive subtypes had significantly higher central and brachial BP compared to the normotensives. The average SBP24 in IBSH is significantly higher compared to NT. Moreover, ICBSH was significantly higher than NT and all the other isolated systolic hypertension subtypes (ICSH and IBSH). Whereas only ICBSH and HT had a significantly higher DBP24 compared to NT. All hypertension subtypes had a significantly higher SBPN compared to the NT subtype. However, subtype ICBSH was also significantly higher than both ICSH and IBSH. The hypertensive (HT) subtype had a significantly higher SBPN compared to all the isolated systolic hypertensive subtypes. There was no significant difference in DBPN across the hypertension subtypes despite the HT subtype. Only ICBSH and HT had a significantly higher SBPD compared to NT. Isolated central and brachial hypertension (ICBSH) subtype had a significantly higher SBPD compared to IBSH. Only the HT subtype had a significantly higher DBPD compared to the NT. Despite the lack of significant difference in SBPD and DBPD among the isolated systolic hypertensives (ICSH, IBSH, ICBSH), both SBPD and DBPD in the ICBSH subtype were significantly different to the IBSH subtype. Notably, SBPD was higher than SBPN across all the hypertension subtypes. All the hypertensive subtypes had significantly higher conventional systolic blood pressure (SBPC) compared to NT. However, ICBSH and HT also had a significantly higher SBPC compared to ICSH and IBSH. All the hypertensive subtypes had a significantly different DBPC compared to NT. All the hypertensive subtypes had a significantly higher central systolic blood pressure (C_SP) compared to NT. The IBSH had a significantly lower C_SP compared to ICSH. Only ICSH and HT had a significantly different C_DP compared to NT.

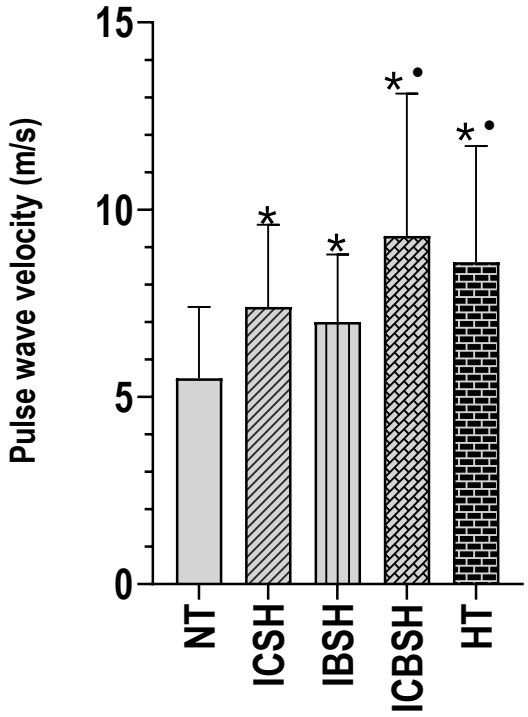

Figure 3: Differences in PWV in hypertension subtypes.

NT, normotensive (normal brachial systolic and normal brachial diastolic blood pressure); ICSH , isolated central systolic hypertension (normal brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); IBSH, isolated central brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, normal central systolic blood pressure, normal central diastolic blood pressure); ICBSH, isolated central and brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); HT, hypertensive (increased brachial systolic blood pressure, increased brachial diastolic blood pressure, increased central systolic blood pressure, increased central diastolic blood pressure). Data expressed as mean ± standard deviation. Means adjusted for age sex, BMI, alcohol intake and smoking. $P<0.05$ considered significant. *Significantly different from the NT; •Significantly different from IBSH.

All the hypertensive groups (ICSH, IBSH, ICBSH and HT) had a significantly higher PWV compared to the normotensive subgroup, but the ICSH and ICBSH were not significantly different from one another. However, ICBSH and the HT were significantly different from the IBSH.

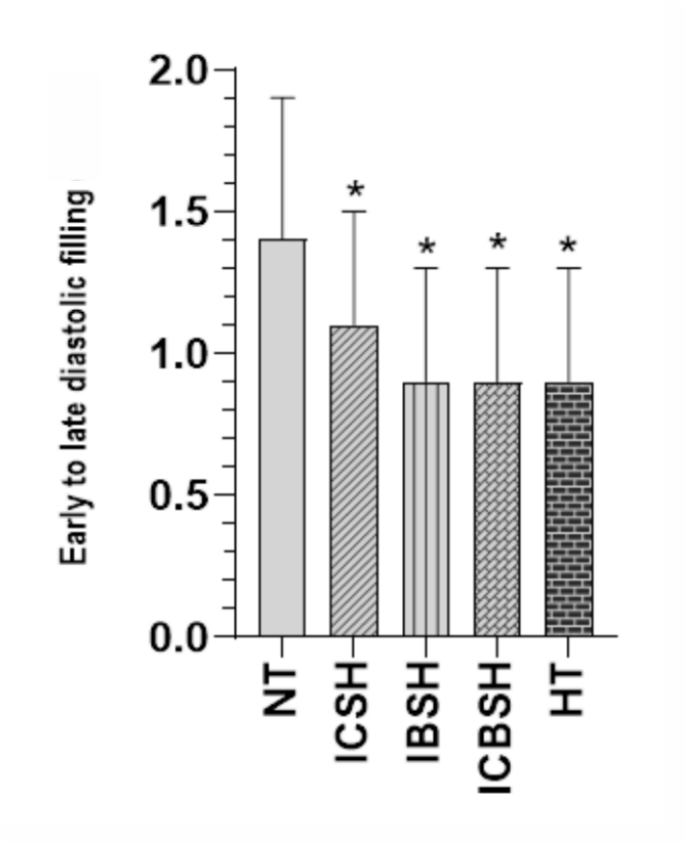

Figure 4: Differences in early to late diastolic filling in the hypertension subtypes.

NT, normotensive (normal brachial systolic and normal brachial diastolic blood pressure); ICSH , isolated central systolic hypertension (normal brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); IBSH, isolated central brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, normal central systolic blood pressure, normal central diastolic blood pressure); ICBSH, isolated central and brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); HT, hypertensive (increased brachial systolic blood pressure, increased brachial diastolic blood pressure, increased central systolic blood pressure, increased central diastolic blood pressure). Data expressed as mean ± standard deviation. Means adjusted for age sex, BMI, alcohol intake and smoking. $P<0.05$ considered significant. *Significantly different from the NT.

All the hypertensive groups (ICSH, IBSH, ICBSH and HT) had a significantly lower early to late diastolic filling compared to the normotensives. However, the ICSH, IBSH, ICBSH and HT were not significantly different from one another.

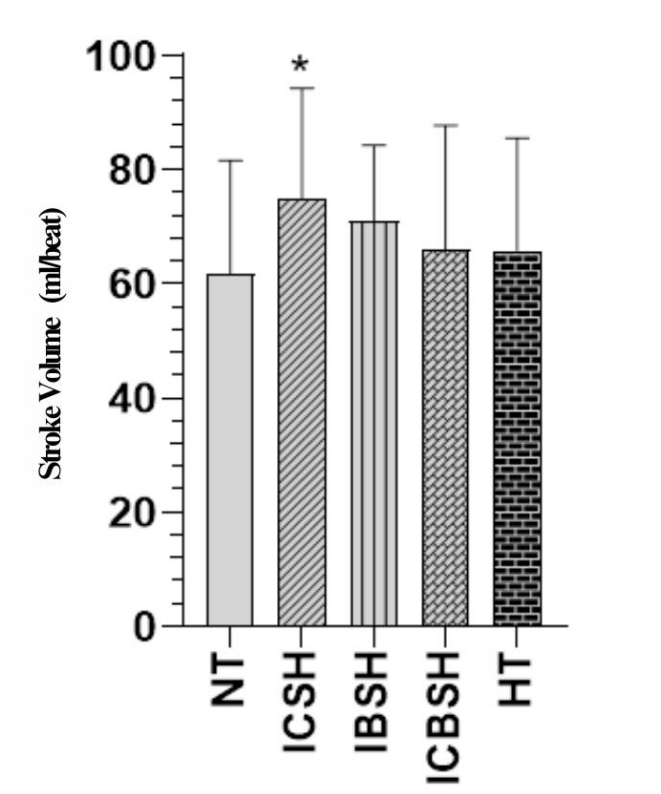

Figure 5: Differences in stroke volume in hypertension subtypes.

NT, normotensive (normal brachial systolic and normal brachial diastolic blood pressure); ICSH , isolated central systolic hypertension (normal brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); IBSH, isolated central brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, normal central systolic blood pressure, normal central diastolic blood pressure); ICBSH, isolated central and brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); HT, hypertensive (increased brachial systolic blood pressure, increased brachial diastolic blood pressure, increased central systolic blood pressure, increased central diastolic blood pressure). Data expressed as mean ± standard deviation. Means adjusted for age sex, BMI, alcohol intake and smoking. $P<0.05$ considered significant. *Significantly different from the NT.

Only ICSH had a significantly high stroke volume compared to the normotensives. However, IBSH, ICBSH and HT were not significantly different from one another.

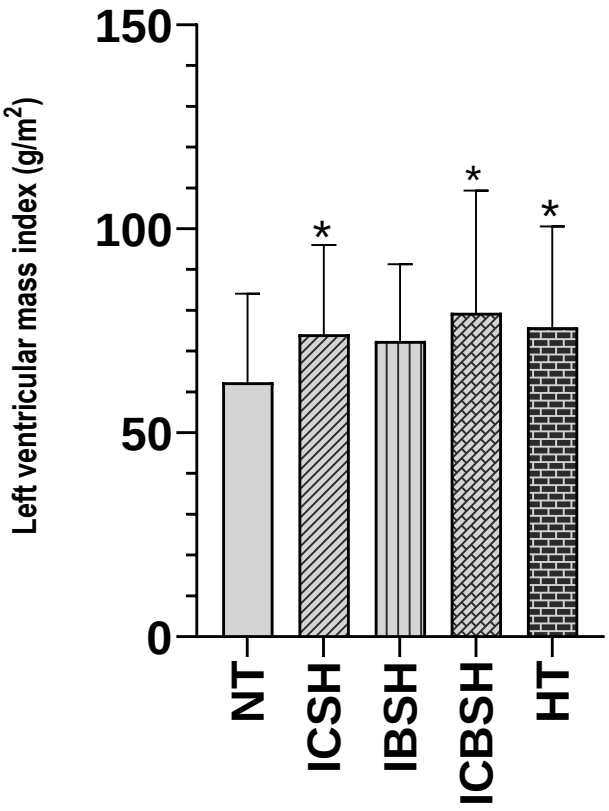

Figure 6: Differences in left ventricular mass index in hypertension subtypes.

NT, normotensive (normal brachial systolic and normal brachial diastolic blood pressure); ICSH , isolated central systolic hypertension (normal brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); IBSH, isolated central brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, normal central systolic blood pressure, normal central diastolic blood pressure); ICBSH, isolated central and brachial systolic hypertension (increased brachial systolic blood pressure, normal brachial diastolic blood pressure, increased central systolic blood pressure, normal central diastolic blood pressure); HT, hypertensive (increased brachial systolic blood pressure, increased brachial diastolic blood pressure, increased central systolic blood pressure, increased central diastolic blood pressure). Data expressed as mean ± standard deviation. Means adjusted for age sex, BMI, alcohol intake and smoking. $P<0.05$ considered significant. *Significantly different from the NT.

Only ICSH, ICBSH and HT had a significantly higher left ventricular mass index compared to the normotensives. However, ICSH, IBSH, ICBSH and HT were not significantly different from one another.

CHAPTER 4

Discussion

4.1 Discussion

4.1.1 The prevalence of hypertension in the African population

Our results show that the prevalence of people with both central and peripheral hypertension in this population is 27.6%. When we categorised these hypertensives according to isolated systolic hypertension status, the prevalence was 5.9%, 6.7%, 18.9% and 68,5% for IBSH, ICSH, ICBSH and HT respectively. Several studies have reported on isolated systolic hypertension and its relationship with cardiovascular target organ changes. The limitation of these studies is that none of them have looked at isolated central systolic hypertension. There is a lot of evidence that indicates that central BP is more closely associated with target organ damage than peripheral BP. Therefore, a possibility exists that isolated central hypertension is more closely associated with cardiovascular target organ damage than peripheral isolated systolic hypertension. Indeed, our results confirm this possibility. According to this study, individuals with IBSH had a higher clinic systolic BP compared to individuals with ICSH. Contrary, individuals with ICSH had a higher central systolic BP compared to individuals with IBSH. When the cardiac changes of these two groups were compared, there was no significant difference in the LVMI of the IBSH group compared to the normotensives group. On the other hand, those with ICSH had a significantly higher LVMI compared to those with IBSH. Interestingly, the LVMI of the ICSH group was not significantly different from that of the HT group, meaning that when central systolic BP is elevated, its negative impact on the left ventricle is similar to that of full hypertension (when both systolic and diastolic central and peripheral blood pressures are elevated). To the best of our knowledge, this is the first study to provide evidence that ICSH is more closely associated with LVMI than IBSH.

4.1.2 Factors influencing hypertension

There was no significant difference in age between the ICSH and IBSH groups. However, both groups were significantly older than the normotensive group. This suggests that age-related arterial changes are similar in the ICSH and IBSH groups. Structurally, when individuals get older, there is a loss in elasticity of the arterial wall resulting in increased stiffness (ONUH and QIU, 2020). Arterial stiffness is characterized by increased collagen deposition and fragmentation of elastin fibres (Singh *et al.*, 2025). This implies that these changes reduce arterial compliance therefore, accelerating the velocity of pressure wave reflection within the

arterial system. As a result, the pressure waves return to the heart earlier during systole. The distensibility of both central and peripheral blood vessels is altered, affecting the way they respond when blood is ejected out of the left ventricle into the systemic vasculature. Additionally, endothelial dysfunction occurs within arterial walls due to alteration in smooth muscles, fibroblasts and macrophages naturally occurring in the endothelial wall. These cells are hyper sensitive to their mechanical environment (Humphrey, 2008). The dysfunction of these cells impairs up- and downregulation of nitric oxide synthase —enzymes responsible for vasodilation and promotes aggregation of thrombocytes in vascular walls (Konukoglu and Uzun, 2017). Consequently, systemic vascular resistance increases as a response to altered haemodynamic loading. This process establishes a positive feedback mechanism that further elevates systolic BP thus contributing to the pathogenesis of ICSH and IBSH.

Similar to age, the body mass index (BMI) of the ICSH and IBSH did not differ significantly. However, both groups exhibited a significantly higher BMI compared to the normotensive group. This suggests that increased adiposity similarly affects central and peripheral blood vessels. Adipose tissues secrete plasma leptin, which stimulate the hypothalamus and increases SNS activity (Hall *et al.*, 2015). Consequently, individuals with high adiposity have sustained SNS activity which results in high systolic BP. Moreover, SNS activation promotes the release of the norepinephrine which works on the vascular tissue, causing vasoconstriction of both central and peripheral blood vessels (Hall *et al.*, 2015). This vasoconstriction contributes to increased systemic resistance, thus increasing BP. In addition to leptin, adipose tissue secretes pro-inflammatory cytokines that facilitates vascular remodelling and contribute to endothelial dysfunction (Simonds and Cowley, 2013). These factors collectively reduce arterial distensibility, promote arterial stiffness and vascular resistance. Several clinical studies have demonstrated that maintaining a BMI<25 Kg/ m^2 is an essential factor in the primary prevention of hypertension (Stevens *et al.*, 2001; Hall *et al.*, 2021). This implies that lifestyle changes aiding the loss of weight can significantly lower blood pressure in hypertensive patients. However, the validity of BMI for assessing adiposity as a sole metric has been debated. Studies by Ortega *et al.* (2016) and Nkoana (2021) have criticized this metric due to its inability to differentiate between muscle and fat mass, and inaccurate reflection of body fat. Despite these limitations, BMI remains the standardized method for comparing outcomes related to body weight across different studies and populations.

Since the contribution of age and BMI was similar between the ICSH and IBSH, we focused our attention on diabetes, a disease of lifestyle that is known to affect arterial function. Although diabetes is a common comorbidity in hypertensive individuals, our study revealed that it is more

prevalent in individuals with IBSH than those with ICSH. Studies suggest that the strong association between diabetes and ISH is attributed to the degradation and loss of elasticity in blood vessel in individuals with the disease (Dagnew and Yeshaw, 2019). Hyperglycaemia in diabetic patients activates the renin-angiotensin-aldosterone system (RAAS) by increasing the production of angiotensin II in both the systemic and local tissue, particularly vascular walls and the heart. The elevated levels of angiotensin II induce oxidative stress and inflammation in these areas compromising vessel wall elasticity, resulting in increased systemic vascular resistance and increased blood pressure (Balgobin *et al.*, 2024). We can assume that this impact is more pronounced in peripheral blood vessels, as they are less elastic than central blood vessels.

When lifestyle factors, alcohol intake and cigarette smoking, were scrutinized, the percentage of people who drink and smoke was similar between the two groups (ICSH and IBSH). However, those who drank alcohol did not smoke and vice versa. Interestingly, there was a high percentage of those who drank alcohol and smoked cigarettes in the group that developed both central and peripheral isolated systolic hypertension (ICBSH). Several studies have shown that cigarette smoking, and alcohol consumption are contributors in the development and exacerbation of isolated systolic hypertension (ISH) through many physiological mechanisms. Particularly, SNS activation through nicotine which acts as an adrenergic agonist, releasing catecholamines, leading to an elevated heart rate and vasoconstriction, which increases blood pressure acutely (Primatesta *et al.*, 2001). Although this relationship was scrutinized for only presenting acute BP rise, a study with 24-hour ambulatory BP monitoring confirmed that smokers maintained a higher ambulatory systolic daytime BP compared to non-smokers (Mann *et al.*, 1991). Moreover, cigarette smoke is rich in reactive compounds and free radicals which elevate oxidative stress in the body, damaging endothelial cells thus impairing endothelial function, through the reduction of NO a vasodilator (Neunteufl *et al.*, 2002; Talukder *et al.*, 2011). Therefore, long-term exposure to cigarette accelerates the loss of elasticity in blood vessels and reduces arterial compliance. Arterial stiffness is an independent contributor to increased SBP, primarily due to the accelerated pulse pressure and the early return of reflected pressure waves during systole. Ultimately, this mechanism leads to an increasing in both central and peripheral systolic BP. For any smoking category, alcohol further exacerbates the effects of smoking through the sympathetic activation which stimulates adrenaline release thus increasing heart rate and cardiac output (Husain, Ansari and Ferder, 2014). A study by Roerecke *et al.* (2017) exhibited a linear relationship between alcohol consumption and SBP, such that even moderate consumption lead to notable increases in SBP. This also implies that a reduction in

alcohol consumption decreases BP significantly. Both cigarette smoking and alcohol consumption are primary contributors to arterial stiffness and heightens SNS activation thus elevates central and peripheral systolic pressures.

4.1.3 Diagnosis of hypertension subtype

The next question we sought to answer was whether these hypertension subtypes can be easily diagnosed. The most widely used diagnostic tool in a clinic setting is conventional (clinic) BP measurement. Ambulatory and central BP measure are still limited to research because they are too expensive for normal clinical use. According to the most commonly used tool (conventional BP measurement), all the hypertension subtypes had significantly higher BP values than the normotensive group. According to the most commonly used tool (conventional BP measurement), all the hypertension subtypes had significantly higher BP values than the normotensive group, with the highest values observed in the full hypertensives (HT), followed by the ICBSH group, and then the IBSH group. The ICSH had the lowest BP. Notably, the HT, IBSH and the ICBSH were in the hypertensive range (systolic BP $\geq$ 140 mm Hg). Therefore, these hypertension subtypes could be easily diagnosed in a clinic setting using ambulatory BP techniques. On the other hand, the ICSH had a normal systolic BP < 140 mm Hg. Even with the more stringent 24-hour ambulatory BP monitoring, the 24-hour, night-time and daytime BP of these individuals were within the normal range. This raises a serious concern. The ICSH hypertension phenotype cannot be diagnosed with the widely used conventional BP measuring technique. The implication of this is that there is a number of people with undiagnosed central hypertension. That raises a more important question. Is ICSH a hypertension phenotype that requires clinical intervention or is it benign?

The analysis of central and brachial BP values according to ISH status provided us with critical insights into the differential impact of hypertension subtypes on 24-hour, nighttime, and conventional BP parameters, avoiding the discrimination of our findings based on the white coat hypertension and monitoring adverse dipping patterns, the variation in BP between daytime and nighttime. Our findings demonstrated that NT individuals had the lowest central and brachial BP values, as expected. However, the other hypertensive subtypes exhibited significantly higher systolic BP particularly in ICBSH and HT, which experienced the highest SBP across most parameters. Twenty -four-hour SBP (SBP24) was progressively higher across the group, with ICSH having the lowest SBP24 among the hypertensive groups and this could

be attribute to the normal peripheral BP this group experiences. The significantly elevated ICBSH and HT compared to NT and the other subtypes suggest that the combination of increased brachial and central BP are primary characteristics of these subtypes. This may be attributed to the more pronounced hypertensive burden, likely due to increased pulse wave reflecting and reduced arterial compliance (Palatini *et al.*, 2011; Laurent and Boutouyrie, 2020). A key observation is that ICBSH had significantly higher SBPN than both ICSH and IBSH, further emphasizing that individuals with concurrent central and brachial hypertension experience persistent systolic elevations over a 24-hour period. Kario (2018) similarly identified nocturnal hypertension as a marker of cardiovascular risk and vascular remodelling, although his findings did not show a consistent relationship between nocturnal hypertension and specific hypertension subtypes. This may suggest that non-dipping or reverse dipping patterns are present, particularly in these groups, thereby increasing the risk of target organ damage. Interestingly, there was no significant difference in DBPN across the hypertensive groups, except for the full hypertensives (HT) group which had the highest DBPN. This is consistent with the known pathophysiology of ISH, suggesting that systolic elevations dominate BP patterns, while DBP remains relatively normal (Kocemba *et al.*, 1998; Tan and Thakur, 2025). We observed that all hypertensive subtypes had a significantly higher SBPC compared to NT, however, ICBSH and HT had a higher SBPC compared to ICSH and IBSH, further confirming the burden of dual hypertension subtypes. These conventional measurements align with the ambulatory data, confirming that HT and ICBSH are the most severe hypertensive variants. Contrary to this, diastolic BP patterns were different, showing that only ICBSH and HT have a significantly higher DBPD compared to NT, this suggests that when central systolic hypertension is present, it may affect diastolic function, possibly due to increased late systolic pressure augmentation (Vest, 2019). Although, we noted that HT had a significantly higher DBPD than NT, confirming that diastolic hypertension is more characteristic of essential hypertension than the isolated systolic subtypes. Notably, IBSH had significantly lower C_SP than ICSH, confirming the suggestion that in ICSH individuals, central pressure increases independently of brachial pressure. Only ICSH and HT had significantly higher C_DP compared to NT, although it remained within the normal range for ICSH, confirming the relatively stable central diastolic pressure observed in this subtype.

4.1.4 Impact of ICSH on cardiovascular target alteration

To answer this question, we investigated the impact of ICSH on cardiovascular target changes. When we looked at PWV, an index of arterial stiffness, the PWV of the ICSH and IBSH

individuals were not significantly different but both subtypes were significantly different in the normotensives. Then when we compared the two subtypes to the other two hypertensive groups (ICBSH and HT), they were not significantly different from each other, but they were significantly different from the ICSH and IBSH and the normotensive. From these results a clear pattern regarding arterial stiffness is emerging. The first level of arterial stiffness was observed in the two groups who had only one hypertension subtype (ICSH and IBSH). So, whether isolated systolic hypertension is central or peripheral, the impact on arterial stiffness is the same. The second level of arterial stiffness was in the two groups which had both central and peripheral isolated systolic hypertension (ICBSH and HT). As expected, arterial stiffness was highest in this group as damage was both centrally and peripherally. Pulse wave velocity (PWV) reflects the speed at which pressure wave moves through the arterial system therefore, although the ICSH and IBSH subtypes may not be significantly different from each other, the mechanisms governing their increase in PWV compared to NT differ significantly. Given that ICSH is characterized by heightened central systolic BP with normal brachial BP, this suggests that central pressure increases mainly due to proximal aortic stiffness before brachial pressure increases (Palatini *et al.*, 2011). In contrast to this, IBSH exhibits elevated brachial systolic BP with the involvement of central pressures, suggesting that this subtype may be influenced by peripheral vascular resistance rather than central arterial stiffness. Despite the differing BP patterns and mechanisms, the wave reflections from stiffened arteries return to the heart earlier, thereby increasing central pressure which promotes vascular remodelling (Kim, 2023). Arterial stiffness is characterized by the breaking down of elastin in large arteries, thereby reducing their compliance leading to elevated PWV. Therefore, ultimately, the compliance of both arterial structures directly influenced by ICSH and IBSH are equally compromised. Additionally, both hypertensive subtypes are associated with early endothelial dysfunction leading to impaired NO synthesis and bioavailability. This results in an impaired vascular function thereby an increased vascular tone, further contributing to arterial stiffness (Konukoglu and Uzun, 2017). Heightened SNS activity, commonly observed in individuals with ISH and those of African ancestry, promote vasoconstriction through NA release, thereby increasing systemic vascular resistance and raising PWV (DeLalio, Sved and Stocker, 2020; Kalideen, Rayner and Ramesar, 2024). Although arterial stiffness in the ICSH and IBSH subtypes is elevated compared to NT, it is not as pronounced as in the dual subtypes (ICBSH and HT). In ICBSH individuals, both central and brachial systolic BP are elevated, suggesting that arterial stiffening is not limited to the aorta or peripheral arteries alone, but rather affects the entire arterial system. The HT group, which exhibits both systolic and diastolic hypertension, likely represents the most advanced form of arterial stiffening, where both large and small arteries have undergone structural

remodelling. The pathophysiological mechanism governing the higher PWV compared to NT and the single hypertensive groups (ICSH and IBSH) is that in the presence of high central systolic BP in ICBSH and HT leads to excessive pulsatile load on the aorta, increasing aortic stiffening through arterial calcification and fibrosis (Safar, Frohlich and Borer, 2007; Laurent and Boutouyrie, 2020). Concurrently, heightened brachial BP pressures contribute to systemic arterial stiffness due to pressure stress imposed on the endothelial cells. The increased stiffness in both accounts lead to earlier wave reflection which exacerbates central pressure thereby worsening the cycle of arterial stiffness. This pressure stress leads to chronic inflammation indicated by C-reative protein (CRP) and interleukin-6 (IL-6), which are linked to arterial stiffness in hypertensive individuals (Laurent and Boutouyrie, 2007). An elevation in pulse pressure (PP), the difference between systolic and diastolic BP can be expected, in ICBSH and HT contribute to increased mechanical stress on arterial walls thereby leading to vascular remodelling and further loss of elasticity. In a comprehensive meta-analysis with a large sample size, the authors demonstrated that a high aortic PWV was linked to an increase in coronary heart disease, independent of other cardiovascular risk factors (Libby et al.,2002). The underlying physiological mechanism involves sustained high systolic blood pressure (SBP) and chronic arterial wall stress, which contribute to endothelial dysfunction. This impairs the function of endothelial cells lining the coronary arteries supplying the heart, increasing vascular permeability and allowing low-density lipoprotein (LDL) cholesterol to infiltrate and become oxidized. The resulting inflammatory response promotes the development of atherosclerosis, along with platelet aggregation and activation of the coagulation cascade (Libby et al., 2002; Libby, 2021). Ultimately, there's a reduction in coronary perfusion increasing the risk of heart attacks. In terms of PWV, individuals with ICSH were similar to individuals with undiagnosed brachial hypertension. This means that individuals with ICSH who exhibit high PWV experience further elevations in SBP, which increases vascular wall stress and contributes to damage in vital organs such as the heart, brain, and kidneys (Kim, 2023). Because this hypertension subtype often goes undiagnosed, patients do not receive antihypertensive treatment to mitigate the resulting damage, and thus a vicious cycle of PWV elevating SBP and SBP preceding an increase in PWV. Moreover, increased PWV leads to widened pulse pressure difference between systolic and diastolic BP, which has been associated with a high incidence of stokes and other cardiovascular complications (Kim, 2023). The silent progression of ICSH possesses an even greater risk of cardiovascular events including heart attacks, heart failure and strokes as it remains undetected while progressively damaging vital organs. These results show us that to mitigate the risk of unexpected cardiovascular events, measurement of ICSH should be mandatory in general clinic practice.

If ICSH has such a significant impact on the vasculature, how does it impact the heart? To address this, we investigated the early-to-late diastolic (E/A) filling of the individuals. Our results show that all the hypertensive groups (IBSH, ICBSH and HT) had similar (E/A), but they were significantly different from the normotensive group. This means the impact of all hypertension subtypes on left ventricular diastolic function is similar. Regardless of whether hypertension is central, brachial, or both, the ultimate effect is an increase in LV workload. Elevated central systolic pressure (C_SP) in ICSH, ICBSH, and HT leads to greater LV afterload and increased myocardial oxygen demand. Additionally, increased arterial stiffness results in the early return of reflected pressure waves during late systole, amplifying systolic pressure and imposing further stress on the left ventricle. A higher pulse wave velocity (PWV) observed in hypertensive subtypes contributes to augmented systolic load and progressive ventricular remodelling. Since LV afterload is a primary determinant of early diastolic dysfunction, all hypertensive subtypes share a similar trajectory of diastolic impairment, which explains the comparable E/A ratios observed across groups. Another possible explanation for the similarity is that there is a likelihood that all hypertensive subtypes had already reached a threshold level of diastolic dysfunction, making it difficult to detect further differences using conventional echocardiographic markers. More sensitive diagnostic tools, such as tissue Doppler imaging (TDI) or left atrial strain analysis, may reveal subtle variations that the E/A ratio alone does not capture (Nagueh *et al.*, 2016). Additionally, compensatory mechanisms such as left atrial contractility may temporarily mask differences in E/A ratio among hypertensive subtypes, further contributing to the observed similarity across groups.

Furthermore, the assessment of cardiac function without a proper assessment of ventricular function would produce a biased conclusion on cardiac function. So, we looked at stroke volume SV) among the hypertensive subtypes and found that the stoke volume in the ICSH subtype was significantly higher than that of all the other groups including the normotensives. The higher SV in the ICSH group is very odd, but its underlying physiological mechanisms can be explained. Of the four hypertensive subtypes, it is the only one with normal brachial BP. In this group, systolic hypertension is only limited to the central arteries. During systole, the heart ejects blood into the aorta. With an increased aortic pressure, the heart must work hard to eject blood because of increased afterload to the left ventricle. To compensate for the increased afterload, the force of contraction increases. Since increased systolic BP is only limited to the central arteries, peripheral BP is normal. The normal peripheral BP allows normal venous

return. With a normal venous return and an increased force of contraction, the stroke volume increases. However, this explanation leads to another question. Why is the stroke volume of the other hypertension subtypes with increased central blood pressure (ICBSH and HT) not increased? The aortic pressure and the afterload is increased in these groups as well. The reason for the lower SV in the other two groups (ICBSH and HT) is that these two subtypes have increased systolic BP both centrally and peripherally. With increased peripheral BP, venous return is reduced due to increased total peripheral resistance. With a decrease in venous return, the force of contraction will decrease according to Starling's Law, resulting in a decreased stroke volume. The next question to answer is whether the increased afterload in these groups has implications on cardiac remodelling.

We answered this question by looking at left ventricular mass index (LVMI), a parameter for Left ventricular hypertrophy. We found that ICSH, ICBSH and HT groups has a significantly higher LVMI compared to the NT group. Notably, there was no significant differences in LVMI among the ICSH, ICBSH, and HT groups. However, contrary to our expectations, the LVMI of IBSH was not significantly different to that of the normotensives but it was significantly lower that of the other three hypertensive groups. The possible explanation is that isolated brachial systolic hypertension (IBSH) might result in less severe left ventricular afterload compared to ICSH, ICBSH, and HT. Given that left ventricular afterload and arterial stiffness are primary contributors in LVMI, a reduction in these factors are likely to cause the difference in IBSH (Tarazi and Levy, 1982). In IBSH, only the brachial systolic blood pressure is elevated, while central systolic pressure may remain relatively unaffected. This means that arterial stiffness and central pressure load, which are significant contributors to LV remodelling and hypertrophy in other hypertensive subtypes, might be less pronounced in IBSH. As a result, the LV mass index in IBSH may not be as elevated as in other hypertensive subtypes, where both central and peripheral pressure increases drive more substantial ventricular remodelling. Additionally, the IBSH group is only based on a single hypertensive pressure which is a less pronounced predictor of cardiovascular event, the results might be representing an earlier stage in the hypertensive process compared to ICBSH and HT thereby cardiac remodelling might be less advance. As a compensatory response, the left ventricle may adapt to isolated brachial systolic pressure by increasing contractility in the early stages, without showing myocardial cell alterations (Heinzel *et al.*, 2020). After a while, the ventricle could be less responsive to the stress caused by the brachial pressure, resulting in a lower LVMI compared to the other groups. These findings are consistent with existing literature by Sarnecki *et al.* (2022) who

demonstrated that individuals with isolated systolic hypertension exhibited a higher LVMI and increased aortic stiffness compared to their normotensives counterparts. Therefore, suggesting that raised SBP can lead to significant cardiac remodelling. Elevated SBP, characteristic of ICSH, contributes to afterload thereby, the chronic pressure overload stimulated myocardial hypertrophy as an adaptive response to maintain cardiac output (Yildiz *et al.*, 2020). Additionally, increased SBP induces the release of vasoactive substances, particularly angiotensin II and norepinephrine which promote myocardial cell growth and contribute to hypertrophic remodelling (Cacciapuoti, 2011). Due to the high pressure and extracellular matrix remodelling, myocardial fibrosis occurs as there is an increase in oxidative stress, which leads to structural alterations and contributes to increased LVMI and impairs ventricular compliance (Yildiz *et al.*, 2020).

4.1.5 Conclusion

This study provides significant evidence on the association between isolated central systolic hypertension (ICSH) and cardiovascular target organ changes, particularly focusing on the left ventricle and arterial stiffness. Our findings exhibit that ICSH is primarily characterized by elevated central systolic pressure, increased arterial stiffness, and a significantly high left ventricular mass index (LVMI) when compared to normotensive individuals. The finding reveals a clear pattern in arterial stiffness progression where ICSH and IBSH individuals show a moderate increase in PWV compared to normotensive, while those with dual hypertension (both central and peripheral hypertension exhibited the highest degree of arterial stiffness. Despite the difference in underlying mechanisms, in ICSH and IBSH, the total effect on arterial compliance is similar. Furthermore, our results indicates that all hypertensive subtypes have similar E/A ratio, suggesting a common path of left ventricular dysfunction or a common threshold level of diastolic dysfunction, making differences less detectable with conventional echocardiographic markers. Interestingly, stroke volume was higher in the ICSH group compared to the other groups suggesting an elevated aortic pressure leading to enhanced left ventricular contractility while maintaining normal venous return. In contrast, the elevated peripheral resistance in ICBSH and HT reduce venous return thereby decreasing stroke volume. The analysis of LVMI further confirms that ICSH, ICBSH and HT groups exhibit significant cardiac remodelling compared to normotensives, with no significant distinction among the three hypertensive groups. However, IBSH exhibited a surprisingly lower LMVI than the other hypertensive groups, potentially due to a lesser impact of left ventricular mass. Our results

ultimately highlighting the clinical importance of recognizing and addressing ICSH, because of the significant impact on cardiovascular health that may be ignored due to the lack of detection in conventional BP measurements. Age-related alteration, specifically arterial stiffness and increased BMI were found to similarly affect both ICSH and IBSH groups. Our findings also noted the influence of diabetes and lifestyle factors, such as cigarette smoking and alcohol consumption, on the development and progression of hypertension. These factors contribute to vascular remodelling and endothelial dysfunction, exacerbating the effects of central and peripheral hypertension. Moreover, the results emphasize the necessity to introduce advanced diagnostic tools, such as central BP measurements, for the early detection of ICSH. Given that ICSH individuals are usually undiagnosed with hypertension despite presenting with high central systolic pressure, this subtype may contribute to the rising burden of cardiovascular disease, potentially leading to heart failure, stroke and other cardiovascular events. More importantly, attention to this subtype will improve cardiovascular risk stratification. In conclusion, our study demonstrated that ICSH is associated with substantial cardiovascular changes, particularly in left ventricular mass and arterial stiffness, which are similar or possibly worse to the effects observed in full hypertension. It is crucial for future research and clinical practices to further explore the mechanisms underlying ICSH and the associated long-term cardiovascular implications. This may have a significant impact on antihypertensive therapeutics. Early detection and treatment strategies focused on reducing arterial stiffness and managing central systolic pressure may be essential in the mitigation of adverse effects of ICSH and decreasing the prevalence of hypertension at large, thereby preventing future unexpected cardiovascular events.

4.1.6 Study limitations and future perspective

Although our study population was confirmed accord to the sample size calculation, the study population may not fully represent all individuals of African ancestry, as regional, genetic and lifestyle difference could affect cardiovascular outcomes. Therefor a larger more diverse cohort would strengthen the generalizability of the findings. While adjustments for key confounders, unmeasurable variables such as sodium intake and physical activity genetic predisposition may have influenced the results. However, we adjusted for this limitation by looking at people residing in one province during the study and a dietary recall was also issued to participants where they indicated food and beverages they took during their 24-hour ambulatory BP

measurements. Another limitation would be the sole use of E/A ratio as a sole indicator of diastolic function because although E/A can be used to assess diastolic function, the evaluation is not comprehensive. Therefore, for future studies, other parameters such as left atrial volume and myocardial strain imaging should be included to provide a more comprehensive assessment. Despite these limitations, this study contributes to the growing understanding of central hypertension and its impact on cardiovascular events. Future research should address these limitations and incorporate larger, longitudinal studies to establish causality. Lastly, since our study was focused on individuals of African ancestry, further research should explore the genetic predispositions contributing to ICSH, this can help with tailored treatment approaches for different populations.

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APPENDICES

Appendix 1: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms OB Ndlazi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M240809

NAME: (Principal Investigator)	Ms OB Ndlazi **DEGREE:** MSc
SCHOOL:	School of Physiology Faculty of Health Sciences
PROJECT TITLE:	*The association between central blood pressure reverse dipping and target organ damage in people of African ancestry*
DATE CONSIDERED:	2024/08/30
DECISION:	Approved unconditionally
CONDITIONS:	Change of supervisor noted on 2024/12/20
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor M Maseko
APPROVED BY:	Professor Y Adam, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2024/12/06 **EXPIRY DATE:** 2029/12/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report** in the format available at https://wits.ac.za/research/researcher-support/research-ethics/ethics-committees/. This report is due annually, for the duration of the Clearance Certificate, beginning on the first anniversary of Date of Approval above. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

Appendix 2: Approved Title

*Please note that the application for a change of title was submitted to the faculty and will be attached once approved.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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

Reference: Ms Sandra Munesar
E-mail: Sandra.munesar@wits.ac.za

16 January 2025
Person No: 2096024
PAG

Miss OB Ndlazi
2779
Extension 9
Barberton
1300
South Africa

Dear Miss Olwethu Ndlazi

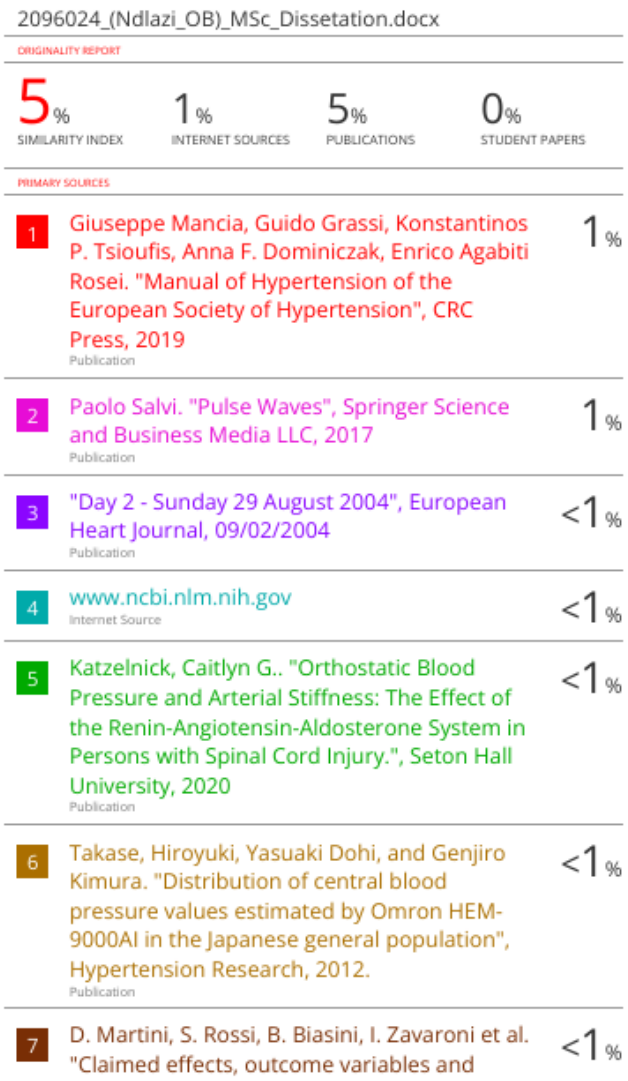
Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *The association between central blood pressure reverse dipping and target organ damage in people of African ancestry.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Ms Sandra Munesar
Faculty Registrar
Faculty of Health Sciences

Appendix 3: Similarity report



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ORIGINALITY REPORT

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Appendix 4: Plagiarism declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

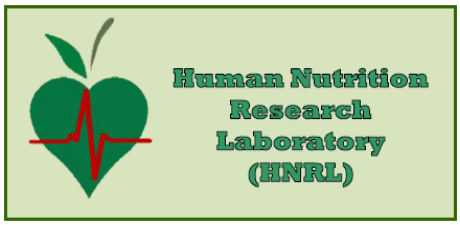
I _Olwethu Blassin Ndlazi_____ (Student number: _2096024_____) am a student registered for the degree of _Master of Science in Medicine_____ in the academic year _2025__.

I hereby declare the following:

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

Signature: _____ Date: _27/08/2025_____

Appendix 5: Consent form



Human Nutrition Research Laboratory
South African Hypertension and Diet Study (SAHDS)
Written consent form

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

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

Name of participant : _____

Participant code : _____

Signature : _____

Date : _____

To be filled by the investigators

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

Name : _____

Signature : _____

Date : _____

Appendix 6: Questionnaire

1.	**Personal information**								
	Participant No.		Gender	Male	Non-binary	Preferred not to say	Date of Birth		Ethnicity
				Female	Gender neutral	Pronouns	Age		
2.	**Medical History**								
2.1	**History of mm diseases?**	YES		NO		**Examples, Hypertension, Chronic Kidney disease, Diabetes**			
	If YES, specify								
2.2	**Are you using hypertension treatment or Medicinal plants?**	YES		NO					
2.2.1	**If YES, how long (in years)?**								
2.2.2	**Describe the regimen**								
2.3	**Please, specify whether some of your relatives currently suffer (or have suffered) from high blood pressure (hypertension)**								
2.3.1	**Your Father**	Yes		No		Unknown			
	Your grandfather (Father's side)	Yes		No		Unknown			
	Your grandmother (Father's side)	Yes		No		Unknown			
	Your mother	Yes		No		Unknown			

	Your grandfather (mother's side)	Yes		No		Unknown	
	Your grandmother (Mother's side)	Yes		No		Unknown	
	1 or more of your own children	Yes		No		Unknown	
	1 or more of your own grandchildren	Yes		No		Unknown	
	1 or more brothers or sisters of your father	Yes		No		Unknown	
	1 or more brothers or sisters of your mother	Yes		No		Unknown	
	1 or more of your own brothers or sisters	Yes		No		Unknown	

2.4	**Marital status**	Single		Married		Widowed	
2.5	**Are you still attending school?**	Yes		No			
2.6	**Which is the highest level of education which you successfully completed?**						
	Do you currently exert any professional or occupational activity?	**Yes**		**No**			
2.7	If yes: What is your present occupation? Please, provide a detailed description of your current job below.						
2.8	**If you currently do not exert any professional activity, which was the last job you had?**						

2.8.1			**Years**				
2.8.2	**Please, provide a detailed description of your activities at your previous work.**						
3.	**Please, specify whether you suffer from diseases affecting your:**						
3.1.1	**Heart**	Yes		No		Unknown	
3.1.2	**Kidneys**	Yes		No		Unknown	
4.	**Were you ever told by a doctor or health professional that you have an elevated blood pressure?**	Yes		No		Unknown	
5.	**Are you currently in good health?**	Yes		No		Unknown	
6	**Did you ever take or are you taking now drugs which eliminate salt and make you pass urine more frequently or in larger amounts? If yes, explain below**	Yes		No		Unknown	
7.	**Did you ever take pain-killers on a regular basis, for instance against headaches, tooth pain, painful periods, etc... ? If yes, explain below**	Yes		No			
8.	**Did you take medicines during the past 2 weeks? if yes, explain below**	Yes		No			

9.1	**Do you currently smoke? If yes, explain the frequency, type and amount per day**	Yes		No	
9.2	**Did you smoke in the past? If yes, explain below**				
10.1	**Do you currently consume alcoholic beverages? If yes, explain the frequency, type and amount per day below**	Yes		No	
10.2	**Did you consume alcohol beverages in the past? If yes, explain**	Yes		No	
11	**Do you drink coffee or caffeine-containing beverages (cola) on a regular base? If yes, give details below**	Yes		No	
12.	**Do you practice any sports activities on a regular basis? If yes, explain the frequency, type and intensity below**	Yes		No	
Please note that this section is for females only					
13.1	**Did you already have your periods?**	Yes		No	
13.2	**Have you ever taken "The Pill"? If yes, explain the regimen below**	Yes		No	

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

DECLARATION

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

Signature: _____ Date: _____